AstraZeneca

EU RMP	
Drug Substance	Quetiapine fumarate
Version Number	15
Edition No	3
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EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® AND SEROQUEL XR®)

Active substance (INN or common name)	Quetiapine fumarate
Pharmaco-therapeutic group (ATC Code)	N05A H04
Name of Marketing Authorization Holder or Applicant	AstraZeneca
Number of medicinal products to which this RMP refers:	2
Products concerned (brand names)	SEROQUEL® and SEROQUEL XR®, ALZEN SR®

Plan Approved by: [redacted]

EU RMP Part I	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	14
Data lock point for this module	12 June 2014

PART I: PRODUCT OVERVIEW

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
5-HT_2	5-hydroxytryptophan type 2
ADR	Adverse drug reaction
AE	Adverse event
AMI	Acute myocardial infarction
AUC	Area under the curve
BP	Blood pressure
CDS	Core Data Sheet
C_{max}	Maximum plasma concentration
CMS	Concerned member state
CYP	Cytochrome P450
DM	Diabetes mellitus
DUS	Drug Utilization Study
EPS	Extrapyramidal symptoms/side effect
EU	European Union
FDA	Food and Drug Administration
GAD	Generalised anxiety disorder
GGT	Gamma-glutamyltransferase
GPRD	General Practice Research Database
HDL	High-density lipoprotein
HEM	Hospital-event monitoring
ICH	International Conference on Harmonisation
IHD	Ischemic heart disease
IR	Immediate release
LDL	Low-density lipoprotein
LLN	Lower limit of normal
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
m-PEM	Modified prescription-event monitoring
MR	Mutual recognition
MRP	Mutual recognition procedure

Abbreviation or special term	Explanation
NET	Norepinephrine transporter
OR	Odds ratio
PASS	Post-authorization safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PhV	Pharmacovigilance
PIL	Patient Information Leaflet
PK	Pharmacokinetic/Pharmacokinetics
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SE-RLS	Swedish Record Linkage Study
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SOC	System organ class
TD	Tardive dyskinesia
UK	United Kingdom
US	United States
VTE	Venous thromboembolism
XL/XR	Extended release

I: PART I: PRODUCT OVERVIEW

I: 1 INTRODUCTION

The objectives of this European Union (EU) Risk Management Plan (RMP) are to document the identification of safety concerns (defined as important identified risks, potential risks, and missing information) and the assessment of their significance, provide a framework for the pharmacovigilance plan, and provide details of the implementation of risk-minimising measures.

The purpose of this EU RMP is to ensure that the benefits and risks of SEROQUEL® and SEROQUEL extended release (XR/XL)®, hereafter SEROQUEL/SEROQUEL XR, are well understood and properly communicated, and that the benefits exceed the risks by the largest feasible margin.

The safety profile of quetiapine is generally similar between the two formulations and among its multiple approved indications. As such, trends observed for special populations and drug interactions that impact clearance should be similarly observed with, and relevant to, both formulations. With a few exceptions, analyses for the various risk topics presented in the RMP did not distinguish between formulations or indications.

Inclusion of information relating to a potential risk within this plan should not be taken to imply that causal association with the use of SEROQUEL® or SEROQUEL XR® has been established.

I: 2 SUMMARY OF CHANGES SINCE LAST EDITION

A summary of changes since the last edition can be found in Part VI: 2.7, Summary of changes to the RMP over time.

I: 3 ADMINISTRATIVE INFORMATION

Table I-1 Date and version number of each Module/Annex

PART	MODULE/ANNEX	Date when the module or part was last signed off	Version Number of RMP when last submitted/or Not Applicable
PART II Safety Specification	SI Epidemiology of the indication and target population(s)	September 2013	12
	SII Non-clinical part of the safety specification	September 2014	13

Table I-1 Date and version number of each Module/Annex

PART	MODULE/ANNEX	Date when the module or part was last signed off	Version Number of RMP when last submitted/or Not Applicable
	SIII Clinical trial exposure	September 2014	13
	SIV Populations not studied in clinical trials	September 2014	13
	SV Post-authorisation experience	February 2016	13
	SVI Additional EU requirements for the safety specification	September 2014	13
	SVII Identified and potential risks	February 2016	13
	SVIII Summary of the safety concerns	February 2016	13
Part III Pharmacovigilance Plan		February 2016	13
PART IV Plan for post-authorisation efficacy studies		September 2014	13
PART V Risk Minimisation Measures		02 December 2016	14.1
PART VI Summary of RMP		02 December 2016	14.1
PART VII Annexes	ANNEX 2 Current or proposed SmPC/PIL	September 2014	13
	ANNEX 3 Worldwide marketing status by country	September 2014	13
	ANNEX 4 Synopsis of clinical trial programme	September 2014	13
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	February 2016	13
	ANNEX 6 Protocols for proposed and on-going studies in Part III	February 2016	13

Table I-1 Date and version number of each Module/Annex

PART	MODULE/ANNEX	Date when the module or part was last signed off	Version Number of RMP when last submitted/or Not Applicable
	ANNEX 7 Specific adverse event follow-up forms	September 2014	Not applicable
	ANNEX 8 Protocols for studies in Part IV	September 2014	13
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	February 2016	Not applicable
	ANNEX 10 Details of proposed additional risk minimisation activities	02 December 2016	14.1
	ANNEX 11 Mock up examples	September 2014	Not applicable
	ANNEX 12 Other supporting data	September 2014	13

EU European Union; PIL Patient Information Leaflet; RMP Risk Management Plan; SmPC Summary of Product Characteristics.

Table I-2 Contact details

European Union Qualified Person responsible for Pharmacovigilance	[redacted]
Contact Person for this RMP	[redacted]
Email address or telephone number of contact person	[redacted]

RMP Risk Management Plan.

I: 3.1 Overview of versions

Table I-3 Version number of last agreed RMP

Version number	14.1 (dated 02 December 2016)
Agreed within	NL/H/xxxx/WS/127

DCP Decentralized Procedure; MRP Mutual Recognition Procedure; RMP Risk Management Plan.

The RMP version under evaluation is shown in Table I-4.

Table I-4 Current RMP versions under evaluation

RMP version number	Submitted on	Submitted within
NA	NA	NA

NA Not applicable; RMP Risk Management Plan.

I: 4 PRODUCT INFORMATION

Quetiapine is an atypical antipsychotic agent, which exhibits affinity for brain serotonin (5-hydroxytryptophan type 2 [5-HT_2]) and dopamine D_1 and D_2 receptors. It also has high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 receptors, but no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Quetiapine's major active metabolite, norquetiapine (Winter et al 2008), has been shown to exhibit a higher affinity than quetiapine for several serotonin receptors that have been implicated in the pharmacology of mood regulation, eg, $5HT_{1A}$ (partial agonism), $5HT_{2A}$ (antagonism), and $5HT_{2C}$ (antagonism). However, in addition to the inhibition of dopamine and serotonin receptors, norquetiapine has been shown to also be a potent inhibitor of the norepinephrine transporter (NET) (IC_{50}=35 nM) (Jensen et al 2008), which is a well-established mode of action for many antidepressants (eg, reboxetine and imipramine). This MoA has not been demonstrated with any other antipsychotic drug at standard doses. Quetiapine's major active metabolite, norquetiapine, is therefore thought to be an important contributor to the antidepressant effect seen in study programs with quetiapine in bipolar depression and major depressive disorder (MDD).

In adult patients, the safety of quetiapine has been demonstrated in comprehensive clinical development programs in schizophrenia, bipolar mania, bipolar depression, recurrence prevention in bipolar disorder, and MDD, which have led to approval for these indications in many countries worldwide. In addition, safety data from the generalised anxiety disorder (GAD) clinical program has been included in the overall assessment of the safety of quetiapine. While GAD is not an approved indication in the EU, it has been approved in 9 countries globally.

SEROQUEL XR is a modified release formulation of SEROQUEL. Studies have shown SEROQUEL XR to have a similar efficacy and safety profile to that of the current SEROQUEL formulation across the dose range. SEROQUEL XR is registered in most European countries and in the United States (US) for treatment of schizophrenia, moderate to severe manic episodes in the framework of bipolar disorder and major depressive episodes in bipolar disorder, and recurrence prevention in bipolar disorder. Applications have also been approved in the US and in some European countries for add-on treatment in patients with MDD.

Table I-5 Product Information

Invented names in the EEA	SEROQUEL (IR), XEROQUEL(IR)SEROQUEL XR (XL)
Authorisation procedure	Mutual recognition, decentralized and national procedure
Brief description of the product	Quetiapine/quetiapine XR is an atypical antipsychotic. Quetiapine and the active human plasma metabolite, norquetiapine, interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to dopamine D_2 receptors which is believed to contribute to the clinical antipsychotic properties and low EPS liability of SEROQUEL compared to typical antipsychotics. Quetiapine has no affinity for the NET and low affinity for the serotonin $5HT_{1A}$ receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at $5HT_{1A}$ sites by norquetiapine may contribute to SEROQUEL's therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine have high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptor subtypes.
Current Indications in the EEA	Quetiapine and quetiapine XR: • Treatment of schizophrenia • Treatment of moderate to severe manic episodes in bipolar disorder • Treatment of major depressive episodes in bipolar disorder • Prevention of recurrence of manic or depressed episodes in patients with bipolar disorder, who previously responded to quetiapine treatment Quetiapine XR only: • Add-on treatment of major depressive episodes in patients with MDD who have had sub-optimal response to antidepressant monotherapy

Table I-5 Product Information

Posology and routes of administration in the EEA	SEROQUEL can be administered with or without food. Different dosing schedules exist for each indication.
SEROQUEL	**Adults:** **For the treatment of schizophrenia** SEROQUEL should be administered twice a day. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). From Day 4 onwards, the dose should be titrated to the usual effective dose of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day. **For the treatment of moderate to severe manic episodes in bipolar disorder** SEROQUEL should be administered twice a day. The total daily dose for the first 4 days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3), and 400 mg (Day 4). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg/day. The usual effective dose is in the range of 400 to 800 mg/day. **For the treatment of major depressive episodes in bipolar disorder** SEROQUEL should be administered once daily at bedtime. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600-mg group compared to the 300-mg group. Individual patients may benefit from a 600-mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. **For preventing recurrence in bipolar disorder** For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may be adjusted depending on clinical response and tolerability of the individual patient within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy. **Elderly:** As with other antipsychotics, SEROQUEL should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly subjects when compared to younger patients. Efficacy and safety have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder. **Pediatric population :** SEROQUEL is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1, and 5.2 of the SmPC.

Table I-5 Product Information

	Renal impairment: Dosage adjustment is not necessary in patients with renal impairment. **Hepatic impairment:** Quetiapine is extensively metabolised by the liver. Therefore, SEROQUEL should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25 to 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.
Posology and routes of administration in the EEA **SEROQUEL XR**	**Adults:** **For treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder** SEROQUEL XR should be administrated at least 1 hour before a meal. The daily dose at the start of therapy is 300 mg on Day 1 and 600 mg on Day 2. The recommended daily dose is 600 mg; however, if clinically justified, the dose may be increased to 800 mg daily. The dose should be adjusted within the effective dose range of 400 to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia, no dosage adjustment is necessary. **For the treatment of major depressive episodes in bipolar disorder:** SEROQUEL XR should be administered at bedtime. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600-mg group compared to the 300-mg group. Individual patients may benefit from a 600-mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. **For preventing recurrence in bipolar disorder:** For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to SEROQUEL XR for acute treatment of bipolar disorder should continue on SEROQUEL XR at the same dose administered at bedtime. SEROQUEL XR dose can be adjusted depending on clinical response and tolerability of the individual patient within the dosage range of 300 to 800 mg/day. It is important that the lowest effective dose is used for maintenance therapy. **For add-on treatment of major depressive episodes in MDD:** SEROQUEL XR should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine) and at 50 mg/day in short-term monotherapy trials. There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.

Table I-5 Product Information

Elderly:

As with other antipsychotics and antidepressants, SEROQUEL XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of SEROQUEL XR may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients. Elderly patients should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. The lowest effective dose, starting from 50 mg/day should be used. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment.

Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Pediatric population:

SEROQUEL is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1, and 5.2 of the SmPC.

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

Quetiapine is extensively metabolised by the liver. Therefore, SEROQUEL XR should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with known hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

Table I-5 Product Information

Pharmaceutical forms and strengths	Pharmaceutical form: Film-coated tablet
	Strengths:
SEROQUEL	SEROQUEL 25 mg contains 25 mg quetiapine (as quetiapine fumarate)
	Excipient: 18 mg lactose (anhydrous) per tablet
	SEROQUEL 100 mg contains 100 mg quetiapine (as quetiapine fumarate)
	Excipient: 20 mg lactose (anhydrous) per tablet
	SEROQUEL 150 mg contains 150 mg quetiapine (as quetiapine fumarate)
	Excipient: 29 mg lactose (anhydrous) per tablet
	SEROQUEL 200 mg contains 200 mg quetiapine (as quetiapine fumarate)
	Excipient: 39 mg lactose (anhydrous) per tablet
	SEROQUEL 300 mg contains 300 mg quetiapine (as quetiapine fumarate)
	Excipient: 59 mg lactose (anhydrous) per tablet
	SEROQUEL 3-Day Starter pack (Combined pack) contains 6 tablets SEROQUEL 25 mg and 2 tablets SEROQUEL 100 mg
	SEROQUEL 4-Day Starter pack contains 6 tablets SEROQUEL 25 mg, 3 tablets SEROQUEL 100 mg, and 1 tablet SEROQUEL 200 mg
SEROQUEL XR	Pharmaceutical form: Prolonged release tablet
	Strengths:
	SEROQUEL XR 50 mg contains 50 mg quetiapine (as quetiapine fumarate)
	Excipient: 119 mg lactose (anhydrous) per tablet
	SEROQUEL XR 150 mg contains 150 mg quetiapine (as quetiapine fumarate)
	Excipient: 71 mg lactose (anhydrous) per tablet
	SEROQUEL XR 200 mg contains 200 mg quetiapine (as quetiapine fumarate)
	Excipient: 50 mg lactose (anhydrous) per tablet
	SEROQUEL XR 300 mg contains 300 mg quetiapine (as quetiapine fumarate)
	Excipient: 47 mg lactose (anhydrous) per tablet
	SEROQUEL XR 400 mg contains 400 mg quetiapine (as quetiapine fumarate)
	Excipient: 15 mg lactose (anhydrous) per tablet

EEA European Economic Area; IR immediate release; MDD Major Depressive Disorder; NET norepinephrine transporter; XL/XR prolonged release.

Table I-6 Authorisation and launch dates

	Country	Date
First authorisation worldwide	UK	31 July 1997
First launch worldwide	UK	22 September 1997
First authorisation in the EEA	UK	31 July 1997
First launch in the EEA	UK	22 September 1997

EEA European Economic Area; UK United Kingdom.

This product is not subject to additional monitoring in the EU.

EU RMP Part II, Module SI	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	12
Data lock point for this module	12 June 2013

Part II SAFETY SPECIFICATION

MODULE SI: EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATION

II: 1.1 Indication: Schizophrenia

II: 1.1.1 Epidemiology of the disease

Table II-1 Epidemiology of schizophrenia

Indication/ target population	Schizophrenia
Incidence	Estimates of the risk of developing schizophrenia over a lifetime range from 0.3-2.0% with an average of approximately 0.7% (Saha et al 2005). In the WHO 10-nation study, the annual incidence rate of schizophrenia ranged from 16 to 40 cases per 100,000 using broad criteria (ICD-9, WHO 1978 criteria) and 7 to 14 cases per 100,000 using more narrow diagnostic criteria (CATEGO class S+) (Sartorius et al 1986, Jablensky et al 1992). The US NIMH Epidemiologic Catchment Area study found a 10-fold higher incidence; however, cases were defined based upon survey research methods and not clinician-provided diagnoses or services (Tien and Eaton 1992). Variation in incidence rates of schizophrenia with urbanicity, migration, and male gender was observed in a meta-analysis of 55 studies (published between 1965 through 2001) across 35 countries in which a median incidence of 15.2 cases per 100,000 was determined with 10th and 90th deciles for incidence rates corresponding to rates of 8 and 43 per 100,000, respectively (McGrath et al 2004).
Prevalence	The median point prevalence of schizophrenia estimated on the basis of a meta-analysis of 21 studies was 4.6 cases per 1000 persons with the 10th and 90th decile for prevalence rates ranging from 1.9 to 10 per 1000 (Saha et al 2005). Median period prevalence (up to 1 year) was estimated as 3.3 per 1000 based upon a meta-analysis of 34 studies. The median lifetime prevalence of estimate of 4.0 per 1000 was based upon 24 studies with the 10th and 90th decile for prevalence rates ranging from 1.6 to 12.1 per 1000.
Demographics of the target population	The peak age of onset of schizophrenia for males is between 18 and 25 years of age; in females a latter and broader peak age of onset occurs from age 26 to 45 (Wyatt et al 1988). A second peak in incidence for women occurs during the ages 55 to 64 years. Prevalence rates are found to be similar among genders and rural and urban dwellers.
Risk factors for the disease	Higher prevalence rates of schizophrenia are observed among more developed as compared to lesser developed countries and higher rates are observed among lower versus higher socioeconomic classes within communities. Higher incidence rates of schizophrenia are associated with urbanicity and higher rates are observed among migrants. The relative odds of having a marital status of single in individuals with schizophrenia, as compared to those never diagnosed with schizophrenia, peak at the time of hospital admission, at more than 15 and remain elevated for decades. The effect of being unmarried is greater for males. In a similar vein, individuals who are eventually diagnosed are more likely than others to have been unemployed years earlier (Messias et al 2007). It is well known that schizophrenia aggregates strongly in families. Adoption studies have described a genetic basis for schizophrenia, and twin studies consistently find a three-fold greater concordance of the disease among monozygotic twins than dizygotic twins (Bromet and Fennig 1999). However the precise mode of genetic transmission and nature of what is transmitted is unknown (Tandon et al 2008b).
Main treatment options	Typical antipsychotics, atypical antipsychotics, psychotherapy, psycho-education, social support, counselling (European Medicines Agency 2012).
Mortality and morbidity	Studies of patients with schizophrenia have demonstrated substantially higher levels of natural and unnatural mortality compared to the general population (Brown 1997). Brown

Table II-1 Epidemiology of schizophrenia

Indication/ target population	Schizophrenia
	found an aggregate SMR of 134 (95% CI: 131-137) in a meta-analysis of studies performed between 1986 and 1996. In this meta-analysis, 80% of people with schizophrenia were found to die from natural causes, compared to 97% of the general population; with natural deaths accounting for 59% of the excess mortality (Brown 1997). Suicide was found to represent 12% of all deaths in Brown's analysis representing 28% of excess deaths. It has been suggested that the SMRs observed in more recent studies of individuals with schizophrenia are increasing in magnitude, ranging as high as SMR of 320 in mortality studies conducted through the 1990's (Saha et al 2007). Other record linkage studies have found elevated mortality rates for nearly all causes of death in schizophrenia including accidents and injuries (suicides and poisonings included), and major organ systems including: mental, circulatory, respiratory, digestive and genitourinary disorders (Newman and Bland 1991). Deaths attributable to CHD is one of the primary causes of mortality occurring in 50% to 75% of patients with schizophrenia even though the relative risk of CHD in schizophrenia compared to the general population is approximately 2 (Saha et al 2007, Hennekens et al 2005). The reasons for the elevated multiple causes of death in schizophrenia are complex and likely to be multifactorial. The lives of patients with schizophrenia are, on average, approximately 20% shorter than those of the general population and some authors have claimed that the gap is continuing to increase (Newman and Bland 1991, Hennekens et al 2005). Investigators (Tiihonen et al 2009) found that the differential mortality gap widened between people with schizophrenia and the general population in Finland between the 1970's and 1990's, but the gap has grown smaller since then.

CHD Coronary heart disease; CI Confidence interval; ICD International Classification of Diseases; NIMH National Institute of Mental Health; SMR Standardized mortality ratio; WHO World Health Organization; US United States.

II: 1.1.2 Concomitant medication(s) in the target population

The most frequently prescribed concomitant medications in schizophrenia are anticholinergics, benzodiazepines, antidepressants, lithium and anticonvulsants (Novick et al 2005).

II: 1.1.3 Important co-morbidities found in the target population

Table II-2 Co-morbidity in the target population (Schizophrenia)

Important co-morbidity	Incidence, prevalence, and mortality
Psychiatric conditions	Estimated rates of comorbid psychiatric conditions vary widely across studies. A study examining psychiatric comorbidity rates among a sample of 184 schizophrenia patients found anxiety disorder present in 31.5% of patients, OCD in 5.4%, and social phobia in 8.2% (Goodwin et al 2003). In contrast, a study evaluating psychiatric comorbidity in 80 outpatients with schizophrenia found social anxiety in 36.3% of patients, panic disorder in 13.8%, OCD in 22.5%, and GAD in 2.5% (Pallanti et al 2004). Much higher rates for both comorbid GAD (26.7%) and social phobia (23.3%) were reported in another study (Tibbo et al 2003).
CVD	Schizophrenia patients with cardiovascular disease have 2.2-fold increased risk of dying from the disease compared to the general population with cardiovascular disease (Saha et al 2007).The etiology of this excess CVD is considered multifactorial and includes genetic and lifestyle factors as well as disease specific and treatment effects. The excess risk in schizophrenia (which is similar in patients with bipolar and unipolar depression) is attributed to a 1-5 fold relative risk of modifiable CVD risk factors, obesity, smoking, diabetes, hypertension and dyslipidemia in this group of patients compared to the general population (De Hert et al 2009).
Diabetes	The prevalence of diabetes is approximately 1.5 to 2.0 times greater among patients diagnosed with schizophrenia than in the general population (American Diabetes Association 2004), although the extent to which other risk factors contribute to this increase is unclear. Increased rates of insulin resistance and diabetes have been reported in association with diabetes, including limited observations in unmedicated patients (Haupt and Newcomer 2002).
Drug and/or alcohol use disorder	The proportion of individuals with schizophrenia with a comorbid drug and/or alcohol use disorder varies in published studies from 10% to 70% (Dixon 1999). The observed range is the result of variability in the diagnosis of schizophrenia, patient characteristics, types of populations studied and ways of defining drug and alcohol disorders. In the Epidemiologic Catchment Area study, 37% of persons with a lifetime diagnosis of schizophrenia or schizophreniform disorder met the criteria for an alcohol abuse disorder and 27.5% met the criteria for another drug abuse disorder (Regier et al 1990). A common drug of abuse is cannabis and it has even been suggested that cannabis use may lead to schizophrenia or expedite disease onset. Cannabis has been shown to nearly double the deterioration of gray matter in the brains of schizophrenia patients and is associated with many other severe side effects (Volkow 2009).

CVD Cardiovascular disease; GAD Generalised anxiety disorder; OCD Obsessive-compulsive disorder.

II: 1.2 Indication: Bipolar disorder

II: 1.2.1 Epidemiology of the disease

Table II-3 Epidemiology of bipolar disorder

Indication/ target population	Bipolar disorder: Bipolar mania (Bipolar I) and Bipolar depression (Bipolar I and Bipolar II)
Incidence	**Bipolar disorder**: Incidence rate of bipolar disorder is difficult to assess because bipolar disorder cannot be diagnosed until sometime after initial presentation (Bebbington and Ramana 1995). Per the APA (APA 2000), annual incidence of bipolar disorder ranges from 0.5 to 5.0 per 10000 in the general population. **Bipolar mania:** Reported incidence of bipolar mania varies greatly depending on how a case is identified, from 2.6 hospital admissions for mania to 20.8 contacts with psychiatric services for mania per 100,000 person-years in studies conducted in the 1960's to 1980's (Bebbington and Ramana 1995). Incidence may have increased over time (1.7 admissions for mania per 100,000 person-years in 1965 to 1969 to 3.4 per 100,000 person-years in 1985 to 1989, in London) (van Os et al 1996). **Bipolar depression**: Bipolar disorder often initially presents in a depressive phase; 54.5% of first episodes of bipolar disorder are depressive (Kupfer et al 2005).
Prevalence	In a review of literature, the lifetime prevalence for bipolar spectrum disorder varied across 12 countries from 0.2% in Iceland to 6.5% in Germany. The lifetime prevalence rate for bipolar I disorder varied across 11 countries from 0.3% in Taiwan to 2.6% in Israel. The lifetime prevalence rate for bipolar II disorder varied across 8 countries from 0.1% in Taiwan to 2.0% in Hungary (Noaghiul and Hibbeln 2003). Across studies in 6 countries using similar diagnostic assessment tools, the 12-month prevalence averaged 0.9% (Pini et al 2005). Recent US population-based studies reported the lifetime prevalence of bipolar I disorder to range from 1% to 3.3%; 12-month prevalence estimates of this disorder range from 0.6% to 2.0% (Merikangas et al 2007, Grant et al 2005). Bipolar II disorder lifetime prevalence was 1.1% with a 12-month prevalence of 0.8%; lifetime prevalence of bipolar spectrum disorders (including subthreshold bipolar disorder) was 4.4% with a 12-month prevalence of 2.8% (Merikangas et al 2007). Bipolar patients spend more time depressed than manic. In one study, bipolar patients were rated by their clinicians as depressed on 121 days, or 33.2% of the year; in contrast, they were rated manic on 39.6 days or 10.8% of the year. In addition to showing 3 times as many days depressed as days manic, approximately 60% of the patients in this cohort showed a pattern of illness morbidity that included a more prominent depressive than manic course (Post et al 2002). Another study found that patients with bipolar I reported being symptomatically ill 47.3% of weeks during a mean follow-up of 12.8 years. Depressive symptoms (31.9% of total follow-up weeks) predominated over manic/hypomanic symptoms (8.9% of weeks) or cycling/mixed symptoms (5.9% of weeks) (Judd et al 2002).

Table II-3 Epidemiology of bipolar disorder

Indication/ target population	Bipolar disorder: Bipolar mania (Bipolar I) and Bipolar depression (Bipolar I and Bipolar II)
Demographics of the target population	The NCSR reports age at onset of approximately 18.2 years for bipolar I disorder and 20.3 years for bipolar II disorder (Merikangas et al 2007). Similar ages at onset were found using the NESARC, which also showed that the age of onset peaks at 16 to 18 years, then declines steadily over the next 5 decades. The age at onset of a depressive episode was 23.6 years (23.7 for men and 23.5 for women) (Grant et al 2005). Post et al reported the age of onset to be 20.8±10.6 years with the average initiation of treatment occurring approximately 1 decade later (Post et al 2002). From onset, bipolar disorder is a lifelong illness, though prevalence appears to decrease with age and is unrelated to race/ethnicity, and family income (Merikangas et al 2007). Bipolar I disorder affects men and women with equal frequencies. However, Bipolar II appears to be more common in women.
Risk factors for the disease	Lifetime prevalence rates of comorbid psychiatric and medical conditions are increased in people with bipolar disorder. The etiology of the compromised health status in patients with bipolar disorder is multifactorial. Strong associations between bipolar disorder and a variety of psychiatric and medical conditions have been found, but directionality is unknown.
Treatment options	Polytherapy, including mood stabilizers (lithium and anticonvulsants), atypical and typical antipsychotics, and antidepressants. Neuroleptics and benzodiazepines (acute management of mania) Psychotherapy, Psychoeducational treatment Electroconvulsive therapy (European Medicines Agency 2001)
Mortality and morbidity	Bipolar disorder is associated with increased risk for a variety of comorbid psychiatric and medical conditions, as well as an increased risk for mortality, especially suicide. Globally, 9.7 million disability-adjusted life years are lost due to bipolar disorder (Hyman et al 2006). Bipolar depression is the leading cause of impairment and death among patients with bipolar disorders (Perlis et al 2006, Post et al 2003). Among 15386 psychiatric inpatients in Sweden with a bipolar disorder diagnosis in 1973 to 1995, there were 3463 deaths (203 per 10000 person-years). The SMR (observed/expected number of deaths based on the general population) was 2.5 in males and 2.7 times in females. For natural causes of death, the SMR was 1.9 and 2.1 in males and females, respectively; for unnatural causes of death, the SMR was 8.6 and 12.7, respectively (Osby et al 2001). Other studies report SMRs ranging from 1.58 (Angst et al 2002) to 4.5 for all causes of death (Schneider et al 2001) and SMR of 22.2 for unnatural causes (Schneider et al 2001).

APA American Psychiatric Association; NCSR National Comorbidity Survey-Replication; NESARC National Epidemiologic Survey on Alcohol and Related Conditions; SMR Standardized mortality ratio; US United States.

II: 1.2.2 Concomitant medication(s) in the target population

The most frequently prescribed concomitant medications in bipolar disorder are polytherapy, including mood stabilizers (lithium and anticonvulsants), atypical and typical antipsychotics, and antidepressants. Neuroleptics and benzodiazepines are commonly used for acute management of mania. Lithium is used for the prevention of recurrence of both mania and depression in Bipolar Disorder. Carbamazepine is approved for prophylaxis of manic

depressive illness unresponsive to lithium and divalproex for manic episodes (European Medicines Agency 2001).

II: 1.2.3 Important co-morbidities found in the target population

Among patients seen at Veterans Administration healthcare settings in the US, 82.2% of those with a diagnosis code for bipolar disorder in 2000 to 2001 had at least 1 comorbid medical condition or substance use disorder, compared to 71.8% in the general veterans population ($p<0.001$) (Kilbourne et al 2004). A greater proportion of bipolar patients than non-bipolar patients had history of allergies, asthma, diabetes, emphysema/chronic obstructive pulmonary disorder, gastric (acid-related) disorders, Hepatitis C, human immunodeficiency virus infection, hypertension, lower back pain, migraine, and seizure disorders (Hirschfeld et al 2003, Kilbourne et al 2004).

Table II-4 Co-morbidity in the target population (Bipolar disorder)

Important co-morbidity	Incidence and prevalence
Psychiatric comorbidities	Regarding psychiatric comorbidities, 97.7% of bipolar I patients and 95.8% of bipolar II patients have at least 1 additional DSM-IV disorder; and 86.2% of bipolar I patients and 85.8% of bipolar II patients have 3 or more additional DSM-IV disorders (Merikangas et al 2007). Among those with a lifetime history of bipolar I (bipolar II), the lifetime prevalence of an anxiety disorder is 86.7% (89.2%); impulse control disorder, 71.2% (70.4%), and substance use disorder, 60.3% (40.4%) (Merikangas et al 2007). In another study, among those with lifetime prevalent bipolar I disorder, 58.0% had lifetime prevalence of alcohol use disorder; 37.5%, drug use; 56.4%, any anxiety disorder; and 64.7%, any personality disorder (Grant et al 2005). A review of the literature found that the average reported prevalence of any axis I disorder across studies of bipolar patients is 65%, including substance use disorder (56%); alcohol use disorder (49%); other drug abuse (44%); and anxiety disorder (71%) (Krishnan 2005). Epidemiologic studies have consistently shown excess CVD morbidity and mortality in patients with bipolar disorder (De Hert et al 2009). Modifiable cardiovascular risk factors are increased in patients with bipolar disorder. The excess risk in bipolar disorder is attributed to a 1-3 fold relative risk of modifiable CVD risk factors, obesity, smoking, diabetes, hypertension and dyslipidemia in this group of patients compared to the general population (De Hert et al 2009).

CVD Cardiovascular disease; DSM-IV Diagnostic and Statistical Manual of Mental Disorders IV.

II: 1.3 Indication: Major Depressive Disorder

II: 1.3.1 Epidemiology of the disease

Table II-5 Epidemiology of Major Depressive Disorder

Indication/ target population	MDD
Incidence	Estimates of the incidence and lifetime prevalence of MDD vary widely across countries due to cultural differences, varying methods of assessment, and heterogeneous samples with multiple comorbidities (Weissman et al 1996). A recent meta-analysis of 4 studies derived from English language reports in the world literature estimated the 1-year incidence of MDD to be 2.9 per 100 persons (Waraich et al 2004).
Prevalence	A recent meta-analysis of representative population-based studies derived from English language reports in the world literature estimate the lifetime prevalence of MDD to be 6.7% (Waraich et al 2004). In other estimates, 1-year prevalence has been placed at about 6.9% within the EU population (Wittchen and Jacobi 2005). In the US, 12-month prevalence has been estimated to be 5.3% and lifetime prevalence to be 13.2% of the adult population (Hasin et al 2005).
Demographics of the target population	Risk of MDD is fairly low until the early teen years (Hasin et al 2005). The peak age of onset ranges from 18 to 30, at which point the risk of developing MDD begins to decline (Weissman et al 1996, Hasin et al 2005). One year and lifetime prevalence estimates for MDD are 1.5- to 2.5-fold greater in women than men (Waraich et al 2004).
Risk factors for the disease	Marital status has been found to be highly associated with the onset and prevalence of depression, but not with treatment outcome. Married and never married persons have lower rates of depression than those divorced, separated, and widowed. Clinicians have long described a relationship between life events (particularly adverse interpersonal events) and the onset of depressive episodes. Early life trauma, particularly sexual abuse, is associated with early-onset depression in women. Increased rates of depression have been reported among patients with several general medical illnesses. Among these are cardiovascular disease, AIDS, respiratory disorders, cancer, and several neurologic conditions (Parkinson's disease and stroke in particular). The risk of depression is higher among the relatives of probands with early-onset recurrent MDD. Genetic factors may also influence the risk of MDD in part by influencing the susceptibility of individuals to the depressive effect of life events.
Treatment options	Antidepressants, augmentation strategies (e.g. combination therapy, lithium and other mood stabilizers, thyroid hormones, atypical antipsychotics, etc.) or even monotherapy with second generation antipsychotics has been considered within the psychopharmacologic options. In many clinical treatment guidelines electroconvulsive therapy is an option for patients suffering from severe treatment resistant depression (European Medicines Agency 2013).

Table II-5 Epidemiology of Major Depressive Disorder

Indication/ target population	MDD
Mortality and morbidity	MDD is associated with excess mortality even after controlling for age, sex, and comorbid medical illness (Vythilingam et al 2003). A meta-analysis of 25 community studies including 106,628 subjects with a follow-up of 1.25 to 16 years reported mortality rates of 17% vs 7% in depressed vs nondepressed subjects, respectively, and a RR of dying in depressed subjects of 1.81 (95% CI: 1.58 to 2.07) (Cuijpers and Smit 2002). In a prospective study of affective disorder patients (recurrent depression, n=137) with a follow-up of 5 years, SMR for unnatural death was 46.7 for subjects with recurrent major depression, and was higher for women than men (Schneider et al 2001). Much of the excess mortality has been attributed to suicide, with rates in depressive disorders ranging from 3.4% in community outpatients to 15% in inpatient populations (Guze and Robins 1970, Morrison 1982, Blair-West et al 1999, Angst et al 2002). MDD is associated with a 15.9% lifetime risk of suicide attempt (Chen and Dilsaver 1996). In addition to death from suicide, studies have been cited associating depression with death from accidents, substance abuse, CVD, cerebrovascular disease, respiratory infections, thyroid disorders, homicide, and cancer (Zheng et al 1997, Angst et al 2002).

AIDS Acquired Immunodeficiency Syndrome; CI Confidence interval; CVD Cardiovascular disease; EU European Union; MDD Major Depressive Disorder; RR Risk ratio; SMR Standardized mortality ratio; US United States.

II: 1.3.2 Concomitant medication(s) in the target population

The most frequently prescribed concomitant medications in MDD include combination therapy, lithium and other mood stabilizers, antidepressants, and thyroid hormones (European Medicines Agency 2013).

Table II-6 Co-morbidity in the target population (MDD)

Indication/ target population	Incidence, prevalence, and mortality
Psychiatric disorders	MDD has been strongly associated with other psychiatric disorders, especially alcohol and drug abuse and/or dependence, anxiety disorders, and personality disorders (Hasin et al 2005). Results from the US National Comorbidity Survey-Replication reported that nearly 3/4^{ths} of respondents with lifetime MDD met criteria for at least one other psychiatric disorder, including 59% with anxiety disorder, 30% with impulse control disorder, and 24% with substance use disorder (Kessler et al 2003).
CVD	There is strong supporting evidence of an association between MDD and CVD (Glassman 2007, Glassman et al 2002). MDD occurs in 15% to 23% of patients with acute coronary syndrome and is a risk factor for associated morbidity and mortality. Post-MI depression is associated with a 3-fold increase in cardiac mortality, with increasing risk as a function of depressive symptom severity. Depression is associated with increased risk of ischemic stroke and with increased mortality after ischemic stroke or congestive heart failure. There is evidence, although inconclusive, that treating depression reduces these medical risks.
Other medical conditions	MDD has been associated with a number of other medical conditions including cancer (20% to 45%), cerebrovascular accidents (26% to 34%), chronic pain (33% to 35%), and Parkinson's disease (40%) (Warrell 2003), as well as death from accidents, substance abuse, CVD, cerebrovascular disease, respiratory infections, thyroid disorders, homicide, and cancer (Zheng et al 1997, Angst et al 2002).

CVD Cardiovascular disease; MDD Major Depressive Disorder; MI Myocardial infarction; US United States.

EU RMP Part II, Module SII	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	12 June 2014

Part II SAFETY SPECIFICATION

MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II: 2.1 Summary of key safety findings from non-clinical data

Nonclinical safety studies of quetiapine in animals included safety pharmacology, single and repeat-dose toxicity, genotoxicity, carcinogenic potential, reproductive toxicity, and a variety of investigative studies. Table II-7 lists the key nonclinical safety findings and clinical findings that potentially relate to the nonclinical results.

Table II-7 Key safety findings from non-clinical studies

Non-clinical findings	Relevance to human usage
Acute toxicity	
Quetiapine has low acute toxicity. Findings in mice and rats after oral (500 mg/kg) or intraperitoneal (100 mg/kg) dosing were typical of an effective neuroleptic agent and included decreased motor activity, ptosis, loss of righting reflex, fluid around the mouth and convulsions.	Section 4.4 of the SmPCs has cautionary statements for somnolence and seizures. Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation. In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered. In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures Section 4.8 of the SmPC lists somnolence in the frequency category of very common and seizure as uncommon.
Repeat dose toxicity	
Posterior triangular cataracts were seen after 6 months in dogs at 100 mg/kg/day and were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in cynomolgus monkeys dosed up to 225 mg/kg/day, or in rodents.	A Phase IV open-label safety study (D1441C00089) to evaluate the relative cataractogenic potential of SEROQUEL and risperidone with respect to nuclear opalescence and cortical or posterior subcapsular opacification over 2 years of exposure. According to the treatment blinded ophthalmologists' assessments the increase in lens opacification in patients receiving quetiapine was not inferior to that in patients receiving risperidone over the 2-year study period. There were numerically more identified cataractogenic events in the risperidone treatment group (17 events, 16 patients) than the quetiapine group (6 events, 6 patients). The results of this study are found in the SmPCs Section 5.1 Clinical Safety.

Table II-7 Key safety findings from non-clinical studies

Non-clinical findings	Relevance to human usage
In multiple-dose studies in rats, dogs and monkeys, anticipated CNS effects of an antipsychotic drug were observed with quetiapine (eg, sedation at lower doses and tremor, convulsions or prostration at higher exposures)	Section 4.4 of the SmPCs has cautionary statements for somnolence and seizures. Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation. In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered. In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures Section 4.8 of the SmPCs lists somnolence in the frequency category of very common and seizure as uncommon.
Thyroid follicular cell hypertrophy and concomitant changes in plasma thyroid hormone levels occurred in rat and monkey. Pigmentation of a number of tissues, particularly the thyroid, was not associated with any morphological or functional effects	Section 5.1 Clinical Safety of the SmPCs states: Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. The incidences of shifts in TSH was 3.2 % for quetiapine versus 2.7 % for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T3 or T4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were not associated with clinically symptomatic hypothyroidism. The reduction in total and free T 4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration Section 4.8 of the SmPCs lists hypothyroidism and decreases in free T_3 in the frequency category of uncommon. Decreases in total T_4 decreases in free T_4, decreases in total T_3, increases in TSH are listed in the frequency category of common.

Table II-7 Key safety findings from non-clinical studies

Non-clinical findings	Relevance to human usage
Reproductive and developmental toxicity	
Effects related to elevated prolactin levels (marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate) were seen in rats. Quetiapine had no teratogenic effects.	Elevated prolactin levels in rats are not directly relevant to humans because of species differences in hormonal control of reproduction. As a class, atypical antipsychotics have not been studied extensively in pregnancy; pregnant women were excluded from quetiapine clinical trials. Exposure to quetiapine will be classified as missing information for pregnant women and neonates Section 4.6 (Fertility, pregnancy and lactation) of the SmPCs states: The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests. Quetiapine should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed. There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine. Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Table II-7 Key safety findings from non-clinical studies

Non-clinical findings	Relevance to human usage
Hepatotoxicity	
Reversible morphological and functional effects on the liver, consistent with hepatic enzyme induction, were seen in mouse, rat and monkey. Serum transaminase activities were generally decreased in animals.	Sections 4.2, 4.4, and 5.2 of the SmPCs have information for patients with hepatic impairment. Quetiapine is extensively metabolised by the liver. Therefore, SEROQUEL should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. For SEROQUEL IR, Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg/day to an effective dose, depending on the clinical response and tolerability in the individual patient. For SEROQUEL XR, patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient. Section 4.8 of the SmPC lists elevations in serum transaminases (ALT, AST), and elevations in gamma-GGT levels in the frequency category of common. Jaundice and hepatitis are listed in the frequency category of rare.
Metabolic	
Daily oral administration of quetiapine for 6 months reduced body weight gain in rats and dogs. Administration for 12 months reduced body weight gain in rats and monkeys, whereas weight gain in dogs was not affected. Quetiapine did not affect glucose levels in rats, dogs, or monkeys.	NA
Hepatocyte fat deposition was observed in rats and monkeys. Oral administration of norquetiapine, an active metabolite, also caused hepatocyte deposition in rats. Quetiapine and norquetiapine generally decreased plasma cholesterol and triglycerides in animals.	Unknown
Genotoxicity	
Genetic toxicity studies with quetiapine show that it is not a mutagen or clastogen.	No evidence of genotoxicity in humans

Table II-7 Key safety findings from non-clinical studies

Non-clinical findings	Relevance to human usage
Carcinogenicity	
Two-year rat and mouse studies were conducted. In the rat study (doses 0, 20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, regarded as secondary to prolonged hyperprolactinemia. In male rat (250 mg/kg/day) and mouse (250 and 750 mg/kg/day), there was an increased incidence of thyroid follicular cell benign adenomas, consistent with known rodent-specific mechanisms resulting from enhanced hepatic thyroxine clearance.	In clinical and post-marketing data there is no evidence of carcinogenicity in humans.
Cardiovascular	
In dogs, oral quetiapine (25 mg/kg) reduced blood pressure, increased heart rate, and slightly increased the PR interval. Transient increases in heart rate, unaccompanied by an effect on blood pressure, have been observed in repeat dose dog studies. Combined evaluation of preclinical ECG data from in vivo studies and from in vitro activity in a depolarising Purkinje fibre model does not indicate that quetiapine has the potential to prolong QT interval.	Sections 4.4, 4.5 and 4.9 of the SmPCs include information on hypotension, tachycardia and QT prolongation. Based on non-clinical, clinical and class effect data, tachycardia has been observed as with other antipsychotics that have alpha$_1$ adrenergic blocking activity, tachycardia associated with orthostatic hypotension and syncope and may be seen especially during the initial dose-titration period. Additionally hypotension and tachycardia may be seen in overdose as part of the drug's known pharmacologic effect. Increases in QT have also been observed in the setting of quetiapine overdose. Section 4.8 of the SmPCs list Tachycardia and Orthostatic hypotension in the frequency category of common; QT prolongation as uncommon.
CNS	

Table II-7 Key safety findings from non-clinical studies

Non-clinical findings	Relevance to human usage
Quetiapine is a CNS-active drug. The main overt behavioural effect in animals is sedation. Convulsions in animals have been observed.	Section 4.4 of the SmPCs has cautionary statements for somnolence and seizures. Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation. In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve; treatment discontinuation may need to be considered. In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures. Section 4.8 of the SmPCs lists somnolence in the frequency category of very common and seizure as uncommon.
Respiratory	
Quetiapine (up to 10 mg/kg IV) had no effect on pulmonary resistance or dynamic respiratory compliance in dogs.	Unknown
Gastrointestinal Quetiapine (50 mg/kg, po) reduced gastrointestinal motility in mice. Norquetiapine (9 mg/kg, po) reduced gastrointestinal motility in rats.	Section 4.8 of the SmPC lists constipation in the frequency category of common. Intestinal obstruction is in the frequency category of rare (pending approval).
General Pharmacology	
Quetiapine and several metabolites are weak inhibitors of human CYP activity, and at therapeutic plasma concentrations should have little effect on in vivo drug metabolism mediated by CYP450 1A2, 2C9, 2C19, 2D6, and 3A4. Evidence of enzyme induction occurred only with supra therapeutic exposures.	Section 5.2 (Pharmacokinetic Properties) of the SmPC states: From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine

Table II-7 Key safety findings from non-clinical studies

Non-clinical findings	Relevance to human usage
Other toxicity related information or data	
Like other D2 dopamine antagonists, quetiapine caused hyperprolactinemia in rats and monkeys. Secondary effects of hyperprolactinemia in rats included mammary hyperplasia in both sexes.	Section 4.4 of the SmPC has a precautionary statement for children and adolescents (10 to 17 years of age): Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents. Section 4.8 of the SmPC lists hyperprolactinemia in the frequency category of common for adults and Elevations of prolactin is very common for children and adolescents 10-17 years of age.

D1441C00089: A Multicenter, Open label, Flexible dose, Parallel group Evaluation of the Cataractogenic Potential of Quetiapine Fumarate (SEROQUEL™) and Risperidone (RISPERDAL™) in the Long term Treatment of Patients with Schizophrenia or Schizoaffective Disorder [CLEARS]

ALT Alanine aminotransferase; AST Aspartate aminotransferase; CNS Central nervous system; CYP Cytochrome P450; ECG Electrocardiogram; GGT Gamma glutamyltransferase; NA Not applicable; SmPC Summary of Product Characteristics; T_3 Triiodothyronine; T_4 Thyroxine; TBG Thyroxine-binding globulin; TSH Thyroid stimulating hormone.

II: 2.2 Conclusions on non-clinical data

Table II-8 Safety concerns

Important identified risks (confirmed by clinical data)	Behavioral sedation Hypotension Alteration of thyroid hormones Seizure Hyperprolactinemia
Important potential risks (not refuted by clinical data or which are of unknown significance)	None
Missing information	Use in pregnant or lactating women

EU RMP Part II, Module SIII

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	12 June 2014

Part II SAFETY SPECIFICATION
MODULE SIII: CLINICAL TRIAL EXPOSURE

II: 3.1 Brief overview of development

SEROQUEL was first approved for marketing in the UK on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 July 2014 SEROQUEL has been approved in 104 countries for schizophrenia, in 100 countries for bipolar mania, in 75 countries for bipolar depression, and in 54 countries for bipolar maintenance. SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base.

SEROQUEL XR was first approved for marketing in the US for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 July 2014, SEROQUEL XR has been approved in 91countries for schizophrenia, in 86 countries for bipolar mania, in 79 countries for bipolar depression, in 68 countries for bipolar maintenance, in 75 countries for MDD, and in 9 countries for GAD. SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base.

II: 3.2 Clinical trial exposure

Approximately 28576 subjects have been exposed to SEROQUEL or SEROQUEL XR in clinical studies. Version 27 (data cutoff: 20 June 2014) of the integrated clinical study safety database includes 137 studies in patients with diagnoses including schizophrenia, schizoaffective disorder, bipolar disorder (including manic, depressed, and mixed), MDD, GAD, and other disorders including dementia-related psychosis.

In this RMP, clinical study exposure is characterized for the following 3 populations:

- quetiapine-treated patients in short-term placebo-controlled studies-9474 subjects as follows: 9042 adult subjects [age ≥18 years] with-1024.3 patient-years of exposure to SEROQUEL/SEROQUEL XR and 432 pediatric patients [age <18 years] with 39.5 patient-years of exposure to SEROQUEL/SEROQUEL XR)

- quetiapine-treated patients in longer-term, randomized withdrawal studies (placebo-controlled withdrawal phase only) (includes 2043 adult subjects [age ≥18 years] with 1026.0 patient-years of exposure to SEROQUEL/SEROQUEL XR)

- quetiapine-treated subjects in all clinical studies, including open-label extension phases (the all-studies group) (includes 28576 patients with 8587.92 patient-years of exposure to quetiapine)

To facilitate an understanding of the database limitation and of the exposure data, an overview of the clinical studies included in the clinical development program for SEROQUEL and SEROQUEL XR and their designs are presented below. All studies referred to in this section are included in the quetiapine integrated clinical-study safety database version 27.

Human safety database of patients with MDD treated with SEROQUEL XR

The clinical program for the development of SEROQUEL XR for the treatment of patients with MDD comprised 8 studies: 4 double-blind, placebo-controlled, monotherapy studies in non-elderly adults (D1448C00001, D1448C00002, D1448C00003, and D1448C00004), 1 similarly designed study in elderly patients (D1448C00014), 2 double-blind, placebo-controlled, adjunct therapy studies (D1448C00006 and D1448C00007), and 1 longer-term randomized withdrawal study (D1448C00005). The program included 3796 patients with MDD treated with SEROQUEL XR in the MDD program. Both sexes, as well as the adult age range, including elderly patients, were well represented. More information on these studies is provided in Annex 12.

Human safety database of patients with bipolar depression treated with SEROQUEL

The clinical program for the development of SEROQUEL in bipolar depression comprised 4 placebo-controlled efficacy studies: Studies D1447C00001 (0001), D1447C00134 (0134), 5077US/0049 (0049), and D1447C00135 (0035). The first 8 weeks of the 4 studies were similar, comparing the effects of 2 doses of quetiapine (300 or 600 mg daily) with placebo in outpatients with major depressives episodes. Studies 0001 and 0134 differed from the other 2 studies in that they also incorporated active controls (lithium in Study 0001, paroxetine in Study 0134). Further, the acute phases of Studies 0001 and 0134 were followed by continuation phases to assess prevention of recurrent mood episode. Data from these continuation phases are generally considered together with data from the controlled phases of the randomized withdrawal studies throughout the RMP. This program included 1712 patients with bipolar depression who were treated with SEROQUEL. Both sexes, as well as the adult age range, were well represented. More information on these studies is provided in Annex 12.

Human safety database of patients with bipolar disorder treated with SEROQUEL for recurrence prevention

The clinical program for the development of SEROQUEL for recurrence prevention in adult patients with manic, depressed, or mixed mood episodes comprised 3 double-blind, placebo-controlled studies, with each preceded by an open-label stabilization period: Studies D1447C00144, D1447C00126, and D1447C00127. This program included 5802 patients treated with SEROQUEL. Both sexes, as well as the adult age range, were well represented. More information on these studies is provided in Annex 12.

Human safety database of patients with bipolar disorder (mixed or manic episodes) treated with SEROQUEL XR

The clinical program for the development of SEROQUEL XR in bipolar disorder (both bipolar depression and bipolar mania) comprised 2 placebo-controlled efficacy studies (Studies D144CC00002 and D144CC00004) and 1 double-blind, placebo-controlled adjunct therapy study (D144AC00003). The program included 137 patients with bipolar depression and 507 patients with bipolar mania who were treated with SEROQUEL XR. Both sexes, as well as the adult age range, were well represented. More information on these studies is provided in Annex 12.

Human safety database of patients with schizophrenia treated with SEROQUEL XR

The clinical program for the development of SEROQUEL XR in schizophrenia included the following: 3 short-term, placebo-controlled efficacy studies (D1444C00132, D1444C00133, and 5077IL/0041), 1 switching study (D1444C00146), and 1 relapse prevention study (D1444C00004). This program included 2173 patients treated with SEROQUEL XR; both sexes, as well as the adult age range, were well represented. More information on these studies is provided in Annex 12.

Human safety database of elderly patients treated with SEROQUEL/SEROQUEL XR

The AstraZeneca integrated clinical-study safety database for quetiapine includes 1465 elderly patients treated with SEROQUEL or SEROQUEL XR (519.0 patient-years exposure); 849 of these patients were exposed to quetiapine in Phase III studies specifically designed to assess treatment in elderly patients. More information on these studies is provided in Annex 12.

The efficacy and safety of quetiapine have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Human safety database of pediatric patients treated with SEROQUEL/SEROQUEL XR

The AstraZeneca integrated clinical-study safety database for quetiapine includes 6 studies in pediatric patients. Across 6 studies, 601 pediatric patients were exposed to SEROQUEL (204.6 patient-years exposure). SEROQUEL XR was not evaluated in this patient population. Both sexes were represented, with slightly more male than female patients treated and more adolescents (patients 13 to 17 years) than children (patients <13 years) treated. Study D144AC00001 was an 8-week study with SEROQUEL XR in children and adolescents (aged 10 to 17 years) with bipolar depression, in which efficacy was not established.

An additional 18 pediatric patients (12 to 17 years) with psychotic disorders were exposed to open-label SEROQUEL in a pilot efficacy and safety study (Study 5077US/0018) (Shaw et al 2001). These patients are not included in the integrated quetiapine clinical-study safety database and are not discussed further in this RMP.

No pediatric patients were exposed to quetiapine in the randomized withdrawal studies.

Human safety database of patients with GAD treated with SEROQUEL XR

The clinical program for the development of SEROQUEL XR in the treatment of patients with GAD comprised 6 studies: 3 short-term, placebo-controlled monotherapy studies (D1448C00009, D1448C00010, and D1448C00011) in non-elderly adults, 1 similarly designed study in elderly patients (D1448C00015), 1 adjunct study (D1441L00016), and 1 longer-term randomized withdrawal study (D1448C00012). Across those studies, 3229 patients with GAD were treated with SEROQUEL XR. Both sexes, as well as the adult age range, including elderly patients, were well represented. More information on these studies is provided in Annex 12).

Table II-9 Duration of exposure by indication - short-term placebo-controlled trial population of quetiapine and quetiapine XR

Indication 1	**Schizophrenia**	
Duration of exposure (at least)	**Persons**	**Person-time**
≥ 1 day	1875	156.9
≥ 2 weeks	1498	149.7
≥ 1 month	1120	128.6
≥ 3 months	NA	NA
≥ 6 months	NA	NA
≥ 12 months	NA	NA
≥ 24 months	NA	NA
≥ 36 months	NA	NA

Indication 2	**Bipolar depression**	
Duration of exposure (at least)	**Persons**	**Person-time**
≥ 1 day	1996	257.3
≥ 2 weeks	1719	252.2
≥ 1 month	1501	239.2
≥ 3 months	1	0.3
≥ 6 months	NA	NA
≥ 12 months	NA	NA
≥ 24 months	NA	NA
≥ 36 months	NA	NA

Indication 3	**Bipolar mania**	
Duration of exposure (at least)	**Persons**	**Person-time**
≥ 1 day	732	79.3
≥ 2 weeks	580	76.8
≥ 1 month	326	62.3
≥ 3 months	7	1.8
≥ 12 months	NA	NA
≥ 24 months	NA	NA
≥ 36 months	NA	NA

Note: Person-time = patient-years.
NA Not applicable; XR Prolonged release.

Table II-10 Duration of exposure by indication - longer-term, randomized withdrawal trial population

Indication 1	**Schizophrenia (SEROQUEL XR only)**	
Duration of exposure (at least)	**Persons**	**Person-time**
≥ 1 day	95	31.3
≥ 2 weeks	94	31.2
≥ 1 month	87	30.8
≥ 3 months	52	24.9
≥ 6 months	19	11.6
≥ 12 months	NA	NA
≥ 24 months	NA	NA
≥ 36 months	NA	NA

Indication 2	**Bipolar depression**	
Duration of exposure (at least)	**Persons**	**Person-time**
≥ 1 day	291	164.8
≥ 2 weeks	281	164.6
≥ 1 month	261	163.4
≥ 3 months	221	156.7
≥ 6 months	175	139.4
≥ 12 months	14	14.2
≥ 24 months	NA	NA
≥ 36 months	NA	NA

Indication 3	**Bipolar mania**	
Duration of exposure (at least)	**Persons**	**Person-time**
≥ 1 day	732	79.3
≥ 2 weeks	580	76.8
≥ 1 month	326	62.3
≥ 3 months	7	1.8
≥ 12 months	NA	NA
≥ 24 months	NA	NA
≥ 36 months	NA	NA

Note: Person-time = patient-years.
NA Not applicable; XR Prolonged release.

Table II-11 Duration of exposure by indication (totals) - all clinical trial population (including open extension)

Indication	**Schizophrenia[a]**	
Duration of exposure	**Persons[b]**	**Person-time**
Up to 1 day	10055	3593.5
Up to 2 weeks	8488	3564.2
Up to 1 month	7255	3492.9
Up to 3 months	2924	2795.7
Up to 6 months	1548	2304.3
Up to 9 months	1179	2078.7
Up to 12 months	855	1786.9
Up to 24 months	288	912.2
Up to 36 months	140	559.0
~~Total person-time~~		

Indication	**Bipolar depression**	
Duration of exposure	**Persons[b]**	**Person-time**
Up to 1 day	2242	557.7
Up to 2 weeks	1950	552.4
Up to 1 month	1708	538.1
Up to 3 months	433	333.2
Up to 6 months	339	297.1
Up to 9 months	234	230.7
Up to 12 months	91	101.1

Indication	**Bipolar mania/mixed[b]**	
Duration of exposure	**Persons[b]**	**Person-time**
Up to 1 day	7117	2368.0
Up to 2 weeks	6187	2352.8
Up to 1 month	5322	2302.3
Up to 3 months	3346	1974.7
Up to 6 months	1375	1236.1
Up to 9 months	637	788.6
Up to 12 months	394	580.3
Up to 24 months	52	116.1
Up to 36 months	1	3.1

Table II-11 Duration of exposure by indication (totals) - all clinical trial population (including open extension)

Total person-time		11722
Indication	**MDD**	
Duration of exposure	**Persons[b]**	**Person-time**
Up to 1 day	3796	820.1
Up to 2 weeks	3350	812.9
Up to 1 month	2943	788.9
Up to 3 months	955	518.3
Up to 6 months	341	300.6
Up to 9 months	213	219.3
Up to 12 months	107	125.6
Indication	**GAD**	
Duration of exposure	**Persons[b]**	**Person-time**
Up to 1 day	3226	612.5
Up to 2 weeks	2802	605.7
Up to 1 month	2490	587.2
Up to 3 months	633	285.2
Up to 6 months	178	127.1
Up to 9 months	59	55.5
Up to 12 months	16	17.2
Indication	**Mixed**	
Duration of exposure	**Persons[b]**	**Person-time**
Up to 1 day	86	0.9
Indication	**Other[c]**	
Duration of exposure	**Persons[b]**	**Person-time**
Up to 1 day	1453	430.9
Up to 2 weeks	997	422.5
Up to 1 month	811	412.0
Up to 3 months	291	321.6
Up to 6 months	153	266.2
Up to 9 months	127	250.3
Up to 12 months	103	228.6

Table II-11 Duration of exposure by indication (totals) - all clinical trial population (including open extension)

Up to 24 months	66	171.8
Up to 36 months	4	12.9

Indication	**Pediatric schizophrenia[d]**	
Duration of exposure	**Persons**	**Person-time**
Up to 1 day	220	100.2
Up to 2 weeks	213	100.0
Up to 1 month	200	99.2
Up to 3 months	163	94.0
Up to 6 months	120	76.6
Up to 9 months	7	9.2
Up to 12 months	5	7.7

Indication	**Pediatric Bipolar mania/mixed**	
Duration of exposure	**Persons**	**Person-time**
Up to 1 day	381	104.5
Up to 2 weeks	324	103.0
Up to 1 month	278	100.3
Up to 3 months	157	82.1
Up to 6 months	107	62.0
Up to 9 months	3	3.7
Up to 12 months	2	2.7

Total patient population Duration of exposure	**Persons**	**Person-time**
Up to 1 day	28576	8587.92
Up to 2 weeks	24311	8513.5
Up to 1 month	21007	8321.0
Up to 3 months	8902	6404.8
Up to 6 months	4161	4669.7
Up to 9 months	2459	3636.1
Up to 12 months	1573	2850.1
Up to 24 months	406	1200.1
Up to 36 months	145	575.0

Note: Person-time = patient-years. Person-time calculated as total exposure/365.25. Only quetiapine-treated patients are included.
[a] Or schizoaffective disorders (pediatric studies excluded).
[b] Pediatric studies excluded.
[c] Including dementia-related psychoses.
[d] Or schizoaffective disorders.
GAD Generalised anxiety disorder; MDD Major depressive disorder; NA Not applicable.

Table II-12 Exposure by dose (by indication) - short-term placebo-controlled trial population

Indication 1	**Schizophrenia[a]**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	85	3.6
100-199	112	6.0
200-299	246	19.0
300-399	495	43
400-499	118	6.7
500-599	407	38.4
600-699	70	5.2
700-799	342	34.9
>799	NA	NA
Indication 2	**Bipolar depression**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	55	0.4
100-199	62	1.0
200-299	1099	146.8
300-399	54	1.9
400-499	100	9.6
500-599	625	97.5
600-699	1	0.1
700-799	NA	NA
>799	NA	NA
Indication 3	**Bipolar mania/mixed[b]**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	15	0.1
100-199	33	1.4
200-299	91	7.7
300-399	141	18.8

Table II-12 Exposure by dose (by indication) - short-term placebo-controlled trial population

400-499	103	9.5
500-599	152	15.3
600-699	93	10.6
700-799	103	15.9
>799	1	0.1
Indication 4	**MDD**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	267	21.0
100-199	1009	114.7
200-299	666	76.5
300-399	NA	NA
400-499	NA	NA
500-599	NA	NA
600-699	NA	NA
700-799	NA	NA
>799	NA	NA
Indication 5	**GAD**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	551	65.2
100-199	930	120.7
200-299	520	74.7
300-399	NA	NA
400-499	NA	NA
500-599	NA	NA
600-699	NA	NA
700-799	NA	NA
>799	NA	NA
Indication 6	**Other[a]**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	201	29.2
100-199	289	27.9
200-299	6	1.1
300-399	NA	NA
400-499	NA	NA

Table II-12 Exposure by dose (by indication) - short-term placebo-controlled trial population

500-599	NA	NA
600-699	NA	NA
700-799	NA	NA
>799	NA	NA
Indication 7	**Pediatric schizophrenia**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	1	0.0
100-199	1	0.0
200-299	3	0.1
300-399	71	8.0
400-499	NA	NA
500-599	4	0.2
600-699	15	1.6
700-799	52	6.3
>799	NA	NA
Indication 8	**Pediatric bipolar mania/mixed**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	3	0.0
100-199	58	6.7
200-299	49	6.2
300-399	87	5.2
400-499	55	3.2
500-599	33	2.1
600-699	NA	NA
>799	NA	NA

Note: Person-time = patient-years.
a Includes schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychosis.
GAD Generalised anxiety disorder; MDD Major depressive disorder; NA Not applicable.

Table II-13 Exposure by dose (by indication) - longer-term, randomized withdrawal trial population[a]

Indication 1	**Schizophrenia**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	NA	NA
100-199	NA	NA
200-299	1	0.3
300-399	NA	NA
400-499	14	4.9
500-599	3	0.8
600-699	29	9.6
700-799	1	0.2
>799	NA	NA
Indication 2	**Bipolar depression**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	NA	NA
100-199	NA	NA
200-299	NA	NA
300-399	141	80.0
400-499	NA	NA
500-599	NA	NA
600-699	150	84.8
700-799	NA	NA
>799	NA	NA
Indication 3	**Bipolar mania/mixed[b]**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	NA	NA
100-199	5	3.5
200-299	21	8.3
300-399	73	39.3
400-499	415	251.5
500-599	131	70.3
600-699	237	130.3
700-799	66	37.6
>799	102	47.1

Table II-13 Exposure by dose (by indication) - longer-term, randomized withdrawal trial population[a]

Indication 4	**MDD**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	95	43.8
100-199	158	68.6
200-299	17	10.3
300-399	121	56.2
400-499	NA	NA
500-599	NA	NA
600-699	NA	NA
700-799	NA	NA
>799	NA	NA
Indication 5	**GAD**	
Dose of exposure mg/day	**Persons**	**Person-time**
<100	54	16.2
100-199	106	30.8
200-299	8	3.0
300-399	48	13.1
400-499	NA	NA
500-599	NA	NA
600-699	NA	NA
700-799	NA	NA
>799	NA	NA

Note: Person-time = patient-years.
a There were no longer-term randomized withdrawal pediatric studies.
GAD Generalised anxiety disorder; MDD Major depressive disorder; NA Not applicable.

Table II-14 Exposure by dose (totals) - all clinical trial population (including open extension)

Indication	**Schizophrenia[a]**	
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	494	59.4
100 to 199	643	142.1
200 to 299	1276	403.2
300 to 399	1851	607.5

Table II-14 Exposure by dose (totals) - all clinical trial population (including open extension)

400 to 499	1584	666.5
500 to 599	1867	728.1
e600 to 699	903	402.6
700 to 799	1182	514.6
More than 799	255	69.6
Indication	**Bipolar depression**	
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	57	0.4
100 to 199	67	1.0
200 to 299	1338	362.4
300 to 399	54	1.9
400 to 499	100	9.6
500 to 599	625	182.2
600 to 699	1	0.1
Indication	**Bipolar mania/mixed[b]**	
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	34	0.5
100 to 199	528	18.3
200 to 299	658	104.3
300 to 399	1793	647.6
400 to 499	1334	553.1
500 to 599	1351	512.9
600 to 699	615	237.8
700 to 799	712	262.4
More than 799	91	31.1
Indication	**MDD**	
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	763	154.4
100 to 199	1778	373.2
200 to 299	1251	291.7
300 to 399	3	0.8
400 to 499	NA	NA
500 to 599	NA	NA
600 to 699	1	0.1

Table II-14 Exposure by dose (totals) - all clinical trial population (including open extension)

Indication	**GAD**	
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	968	157.2
100 to 199	1482	290.8
200 to 299	776	164.5
Indication	**Mixed**	
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	26	0.3
100 to 199	28	0.3
200 to 299	15	0.2
300 to 399	17	0.2
Indication	**Other[c]**	
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	673	148.0
100 to 199	569	145.9
200 to 299	109	66.7
300 to 399	52	31.5
400 to 499	18	17.9
500 to 599	29	18.5
600 to 699	2	1.8
700 to 799	1	0.6
Indication	**Pediatric Schizophrenia[d]**	
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	1	0.0
100 to 199	1	0.0
200 to 299	8	1.8
300 to 399	33	10.3
400 to 499	26	13.2
500 to 599	40	18.9
600 to 699	52	27.6
700 to 799	59	28.3
Indication	**Pediatric Bipolar mania/mixed**	
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	4	0.0

Table II-14 Exposure by dose (totals) - all clinical trial population (including open extension)

100 to 199	59	6.8
200 to 299	59	9.0
300 to 399	41	8.8
400 to 499	81	18.0
500 to 599	67	26.5
600 to 699	40	19.8
700 to 799	30	15.5
Total patient population		
Dose of exposure (mg)	**Persons**	**Person-time**
Less than 100	3020	520.2
100 to 199	5155	978.4
200 to 299	5490	1403.8
300 to 399	3844	1308.5
400 to 499	3143	1278.3
500 to 599	3979	1487.1
600 to 699	1614	689.8
700 to 799	1984	821.4
More than 799	346	100.8

Note: Person-time = patient-years. Person-time calculated as total exposure/365.25. Only quetiapine-treated patients are included.
[a] Or schizoaffective disorders (pediatric studies excluded).
[b] Pediatric studies excluded.
[c] Including dementia-related psychoses.
[d] Or schizoaffective disorders.
GAD Generalised anxiety disorder; MDD Major depressive disorder; NA Not applicable.

Table II-15 Exposure by age group and gender (by indication) - short-term placebo-controlled trial population

Indication	**Persons**		**Person-time**	
Age group	**Male**	**Female**	**Male**	**Female**
Schizophrenia				
Adult 18-65	1334	541	109.6	47.3
Elderly >65	NA	NA	NA	NA
Elderly ≥75	NA	NA	NA	NA
Bipolar depression				

Table II-15 Exposure by age group and gender (by indication) - short-term placebo-controlled trial population

Indication	Persons		Person-time	
Age group	**Male**	**Female**	**Male**	**Female**
Adult 18-65	819	1177	106.6	150.7
Elderly >65	NA	NA	NA	NA
Elderly ≥75	NA	NA	NA	NA
Bipolar mania/mixed				
Adult 18-65	405	316	43.9	33.9
Elderly >65	2	9	0.3	1.2
Elderly ≥75	NA	2	NA	0.5
MDD				
Adult 18-65	633	1143	66.0	121.0
Elderly >65	50	116	7.8	17.4
Elderly ≥75	12	24	1.6	3.3
GAD				
Adult 18-65	623	1154	77.8	147.6
Elderly >65	63	161	9.8	25.3
Elderly ≥75	8	29	1.1	4.2
Other				
Adult 18-65	90	47	2.0	1.3
Elderly >65	90	269	14.0	40.9
Elderly ≥75	75	239	11.7	36.1
Pediatric Schizophrenia				
<13	NA	NA	NA	NA
13-17	87	60	9.9	6.3
<18	87	60	9.9	6.3
Pediatric Bipolar mania/mixed				
<13	58	52	4.5	3.9
13-17	92	83	7.9	7.1
<18	150	135	12.4	10.9

Note: Person-time = patient-years. Person-time calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
GAD Generalised anxiety disorder; MDD Major depressive disorder; NA Not applicable.

Table II-16 Exposure by age group and gender (by indication) - longer-term, randomized withdrawal trial population

Indication	Persons		Person-time	
Age group	**Male**	**Female**	**Male**	**Female**
Schizophrenia				
Adult 18-65	57	38	18.3	13.0
Elderly >65	NA	NA	NA	NA
Elderly ≥75	NA	NA	NA	NA
Bipolar depression				
Adult 18-65	124	167	71.3	93.5
Elderly >65	NA	NA	NA	NA
Elderly ≥75	NA	NA	NA	NA
Bipolar mania/mixed				
Adult 18-65	468	562	259.8	314.5
Elderly >65	9	11	5.5	8.0
Elderly ≥75	1	1	0.1	1.1
MDD				
Adult 18-65	135	256	55.7	123.2
Elderly >65	NA	NA	NA	NA
Elderly ≥75	NA	NA	NA	NA
GAD				
Adult 18-65	71	145	23.6	39.6
Elderly >65	NA	NA	NA	NA
Elderly ≥75	NA	NA	NA	NA

Note: Person-time = patient-years. Person-time calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
BP Bipolar depression; F Female; GAD Generalised anxiety disorder; M Male; MDD Major depressive disorder; NA Not applicable.

Table II-17 Exposure by age group and gender (by indication) – all clinical trial population (adult patients >= 18 years)

Indication	Persons		Person-time	
Age group	**Male**	**Female**	**Male**	**Female**
Schizophrenia				
Adult 18-65	6564	3422	2281.1	1277.0

Table II-17 Exposure by age group and gender (by indication) – all clinical trial population (adult patients >= 18 years)

Indication	Persons		Person-time	
Age group	**Male**	**Female**	**Male**	**Female**
Elderly >65	37	32	18.7	16.7
Elderly ≥75	10	9	5.1	2.2
Bipolar depression				
Adult 18-65	924	1318	233.5	324.2
Elderly >65	NA	NA	NA	NA
Elderly ≥75	NA	NA	NA	NA
Bipolar mania/mixed				
Adult 18-65	3336	3673	1072.0	1248.3
Elderly >65	50	58	24.3	23.4
Elderly ≥75	5	7	2.0	2.3
MDD				
Adult 18-65	1305	2324	275.2	519.8
Elderly >65	50	117	7.8	17.4
Elderly ≥75	12	24	1.6	3.3
GAD				
Adult 18-65	1066	1936	203.4	373.9
Elderly >65	63	161	9.8	25.3
Elderly ≥75	8	29	1.1	4.2
Mixed				
Adult 18-65	61	25	0.7	0.3
Elderly >65	NA	NA	NA	NA
Elderly ≥75	NA	NA	NA	NA
Other				
Adult 18-65	448	108	42.7	12.7
Elderly >65	281	616	124.5	251.0
Elderly ≥75	204	518	74.5	191.3

Note: Person-time = patient-years. Person-time calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
GAD Generalised anxiety disorder; MDD Major depressive disorder; NA Not applicable.

Table II-18 Exposure by age group and gender (by indication) – all clinical trial population (pediatric patients < 18 years)

Indication / Age group	Persons		Person-time	
	Male	**Female**	**Male**	**Female**
Pediatric Schizophrenia				
<13	2	NA	1.2	NA
13-17	124	94	56.9	42.1
<18	126	94	58.1	42.1
Pediatric Bipolar mania/mixed				
<13	84	68	29.3	17.6
13-17	123	106	33.1	24.4
<18	207	174	62.4	42.0

Note: Person-time = patient-years. Person-time calculated as total exposure/365.25. Only quetiapine-treated patients are included. Patient's age is given at the start of the clinical trial.
NA Not applicable.

Table II-19 Exposure by age group and gender (totals) - all clinical trial population (including open extension)

Age group (years)	Persons		Person-time	
	Male	**Female**	**Male**	**Female**
Adult 18-65	13704	12806	4108.5	3756.2
Elderly >65	481	984	185.1	333.9
Elderly ≥75	239	587	84.2	203.3
Total Adult	**14185**	**13790**	**4293.6**	**4090.1**
Pediatric <13	86	68	30.5	17.6
Pediatric 13-17	247	200	90.0	66.5
Total Pediatric	**333**	**268**	**120.5**	**84.1**
Total population	**14518**	**14058**	**4414.1**	**4174.2**

Note: Person-time = patient-years.

Table II-20 Exposure by age group and gender (by product) - short-term placebo-controlled trial population

	Persons		Person-time	
Age group	**Male**	**Female**	**Male**	**Female**
Total population by medicinal product: SEROQUEL (quetiapine)				
18-65	1687	1530	184.3	181.9
>65	92	278	14.3	42.1
>74	75	241	11.7	36.5
10-<13	46	39	2.8	2.1
13-17	146	109	13.2	9.0
Total population by medicinal product: SEROQUEL XR (quetiapine XR)				
18-65	2217	2848	221.6	319.9
>65	113	277	17.6	42.7
>74	20	53	2.7	7.5
10-<13	12	13	1.8	1.8
13-17	33	34	4.6	4.4

Note: Person-time = patient-years.
XR prolonged release.

Table II-21 Exposure by age group and gender (by product) - longer-term, randomized withdrawal trial population

	Persons		Person-time	
Age group	**Male**	**Female**	**Male**	**Female**
Total population by medicinal product SEROQUEL (quetiapine)				
18-65	592	729	331.2	408.0
>65	9	11	5.5	8.0
>74	1	1	0.1	1.1
Total population by medicinal product SEROQUEL XR (quetiapine XR)				
Age group	Persons		Person-time	
	M	F	M	F
18-65	263	439	97.6	175.7
>65	NA	NA	NA	NA
>74	NA	NA	NA	NA

Note: Person-time = patient-years.
NA not applicable; XR prolonged release.

Table II-22 Exposure by age group and gender (by product) - all clinical trial population (including open extension)

	Persons		Person-time	
Age group	**Male**	**Female**	**Male**	**Female**
Total population by medicinal product SEROQUEL (quetiapine)				
18-65	9298	7330	3367.6	2689.0
>65	345	662	165.0	286.5
>74	199	498	79.3	191.9
10-<13	74	55	28.8	15.8
13-17	214	165	85.4	62.1
Total population by medicinal product SEROQUEL XR (quetiapine XR)				
18-65	4631	5648	740.9	1067.2
>65	136	322	20.1	47.3
>74	40	89	5.0	11.4
10-<13	12	13	1.8	1.8
13-17	33	35	4.6	4.4

Note: Person-time = patient-years.
XR prolonged release.

Table II-23 Exposure by ethnic or racial origin (by indication) - short-term placebo-controlled trial population

Indication **Ethnic/racial origin**	**Persons**	**Person-time**
Schizophrenia		
White	992	83.1
Black	573	45.0
Asian	190	19.6
Hispanic	76	5.6
Other	44	3.5
Bipolar depression		
White	1375	176.7
Black	262	32.4
Asian	233	31.0
Hispanic	70	10.6
Other	56	6.6

Table II-23 Exposure by ethnic or racial origin (by indication) - short-term placebo-controlled trial population

BP mania/mixed		
White	501	55.1
Black	106	6.1
Asian	76	13.4
Hispanic	10	0.9
Other	39	3.7
MDD		
White	1566	170.0
Black	278	30.7
Asian	52	6.2
Hispanic	32	3.7
Other	14	1.6
GAD		
White	1740	226.4
Black	190	24.9
Asian	16	2.3
Hispanic	32	4.0
Other	23	3.0
Other		
White	326	46.9
Black	79	6.3
Asian	3	0.6
Hispanic	83	4.2
Other	5	0.1
Pediatric Schizophrenia		
White	89	9.7
Black	16	1.7
Asian	29	3.3
Hispanic	9	1.1
Other	4	0.3
Pediatric Bipolar mania/mixed		
White	214	17.2
Black	42	3.5
Asian	4	0.5

Table II-23 Exposure by ethnic or racial origin (by indication) - short-term placebo-controlled trial population

Hispanic	12	0.7
Other	13	1.4

Note: Person-time = patient-years.
GAD Generalised anxiety disorder; MDD Major depressive disorder.

Table II-24 Exposure by ethnic or racial origin (by indication) - longer-term, randomized withdrawal all clinical trial population (including open extension)

Indication **Ethnic/racial origin**	**Persons**	**Person-time**
Schizophrenia		
White	95	31.3
Black	NA	NA
Asian	NA	NA
Hispanic	NA	NA
Other	NA	NA
Bipolar depression		
White	222	121.9
Black	31	22.7
Asian	20	11.9
Hispanic	16	7.3
Other	2	0.9
Bipolar mania/mixed		
White	828	467.0
Black	71	36.8
Asian	69	35.3
Hispanic	53	33.8
Other	29	14.9
MDD		
White	339	154.0
Black	33	18.6
Asian	2	0.7
Hispanic	13	4.4
Other	4	1.1

Table II-24 Exposure by ethnic or racial origin (by indication) - longer-term, randomized withdrawal all clinical trial population (including open extension)

GAD		
White	183	53.4
Black	13	4.5
Asian	16	4.3
Hispanic	3	0.7
Other	1	0.2

Note: Person-time = patient-years.
GAD Generalised anxiety disorder; MDD Major depressive disorder.

Table II-25 Exposure by ethnic or racial origin (totals) - all clinical trial population (including open extension)

Ethnic/racial origin	Persons	Person-time
White	20545	6540.9
Black	3753	937.6
Asian	2442	606.3
Hispanic	1127	336.6
Other	709	166.7

Note: Person-time = patient-years.

Table II-26 Exposure by special populations (by indication) - randomised, blinded trial population

Indication **Special population**	**Persons**	**Person-time**
All indications		
Pregnant women	unknown	unknown
Lactating woman	unknown	unknown
Renal impairment	unknown	unknown
Hepatic impairment	unknown	unknown
Cardiac impairment	unknown	unknown
Sub populations with genetic polymorphism	unknown	unknown
Immuno-compromised	unknown	unknown

Note: Person-time = patient-years.

Table II-27 Exposure by special populations (by indication) - all clinical trial population (including open extension)

Indication **Special population**	**Persons**	**Person-time**
All indications		
Pregnant women	unknown	unknown
Lactating woman	unknown	unknown
Renal impairment	unknown	unknown
Hepatic impairment	unknown	unknown
Cardiac impairment	unknown	unknown
Sub populations with genetic polymorphism	unknown	unknown
Immuno-compromised	unknown	unknown

Note: Person-time = patient-years.

Table II-28 Exposure by special populations (totals) - randomised, blinded trial population

Special population	**Persons**	**Person-time**
Pregnant women	unknown	unknown
Lactating woman	unknown	unknown
Renal impairment	unknown	unknown
Hepatic impairment	unknown	unknown
Cardiac impairment	unknown	unknown
Sub populations with genetic polymorphism	unknown	unknown
Immuno-compromised	unknown	unknown

Note: Person-time = patient-years.

Table II-29 Exposure by special populations (totals) - all clinical trial population (including open extension)

Special population	**Persons**	**Person-time**
Pregnant women	unknown	unknown
Lactating woman	unknown	unknown
Renal impairment (open-label pharmacokinetic study)	8	.022

Table II-29 Exposure by special populations (totals) - all clinical trial population (including open extension)

Special population	Persons	Person-time
Hepatic impairment (open-label pharmacokinetic study)	8	.022
Cardiac impairment	unknown	unknown
Sub populations with genetic polymorphism	unknown	unknown
Immuno-compromised	unknown	unknown

Note: Person-time = patient-years.

EU RMP Part II, Module SIV

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	12 June 2014

PART II SAFETY SPECIFICATION
MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II: 4.1 Limitations of adverse drug reaction detection common to clinical trial development programmes

Table II-30 Limitations common to clinical trial development programme

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare but not very rare (<1 in 10000) ADRs.	Approximately 28576 patients were exposed over the whole clinical trial programme.	ADRs with a frequency greater than approximately 1 in 9000 could be detected if there were no background incidence
Due to prolonged exposure	The duration of treatment in the longer-term SEROQUEL/SEROQUEL XR trial programme was 6 to 12 months. Patients (N=4161) were exposed to quetiapine IR or XR for ≥6 months in any AstraZeneca study.	Due to the duration of treatment ADRs due to prolonged exposure were not captured in clinical studies.
Due to cumulative effects	The duration of treatment in the longer-term SEROQUEL/SEROQUEL XR trial programme was 6 to 12 months. Patients (N=4161) were exposed to quetiapine IR or XR for ≥6 months in any AstraZeneca study.	Due to the duration of treatment, ADRs due to cumulative effects were not captured in clinical studies
Which have a long latency	The duration of treatment in the longer-term SEROQUEL/SEROQUEL XR trial programme was 6 to 12 months. Patients (N=4161) were exposed to quetiapine IR or XR for ≥6 months in any AstraZeneca study.	Due to the duration of treatment, ADRs which have a long latency were not captured in clinical studies

ADR Adverse drug reaction; IR Immediate release; XR Extended release.

II: 4.2 Effect of exclusion criteria in the clinical trial development plan

II: 4.2.1 Effect of exclusion criteria in the clinical trial development plan

Table II-31 Exclusion criteria which will remain as contraindications

Criterion	Implications for target population
Hypersensitivity to the active substance or to any of the excipients.	In Section 4.3 (Contraindications) Hypersensitivity to the active substance or to any of the excipients of this product is contraindicated. In Section 4.8 (Undesirable effects) Hypersensitivity is uncommon. Patients with hypersensitivity to quetiapine fumarate will be limited to treatment with other medications, excluding SEROQUEL/SEROQUEL XR.
Use of any of the following CYP3A4 inhibitors in the 14 days preceding enrollment including but not limited to: ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, fluvoxamine, and saquinavir	In Sections 4.3 (Contraindications) and 4.5 (Interaction with other medicinal products and other forms of interaction) concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. Patients on therapy with strong CYP3A4 inhibitors will either have to stop therapy with the CYP3A4 inhibitor or the patients will be limited to treatment with other medications, excluding SEROQUEL/SEROQUEL XR.

CYP Cytochrome P450; XR prolonged release.

Table II-32 Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Elderly patients with a history of orthostatic reactions causing clinically-significant symptoms, or requiring medication for symptomatic or neurogenic orthostatic hypotension.	In the clinical trial program, this exclusion was specific to patients >65 years of age to avoid injury and falls.	The risk of occurrence cannot be predicted and the benefit of treatment can outweigh the risk. Section 4.4 of the SmPCs states: Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see Section 4.8) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.
History of recurrent aspiration, significant swallowing difficulties, or in the investigator's opinion, at high risk of aspiration	In the clinical trial program this exclusion was specific to patients > 65 years of age to avoid the risk of aspiration and the sequelae of aspiration.	For all patients there is a warning in the SmPC section 4.4 Special warnings and precautions that SEROQUEL/SEROQUEL XR should be used with caution in patients at risk for aspiration pneumonia. Additionally, dysphagia is a listed event in section 4.8. The risk of occurrence cannot be predicted and the benefit of treatment can outweigh the risk.

Table II-32 Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Elderly Patients meeting the DSM-IV Diagnostic Criteria for Dementia of the Alzheimer's type; DSM-IV Diagnostic Criteria for Vascular Dementia; DSM-IV Diagnostic Criteria for Dementia Due to Other General Medical Conditions (e.g., head trauma, intracranial structural abnormality, etc.); Practice Parameter for Mild Cognitive Impairment (Neurology 2001;56: 1133-1142); Diagnostic Criteria of The Consortium for Dementia with Lewy Bodies; and the Consensus Diagnostic Criteria for Frontotemporal Dementia.	An FDA meta-analysis of atypical antipsychotics showed an increased risk of death from all causes in this population.	Included in the SEROQUEL/SEROQUEL XR SmPCs Section 4.4 Special warnings and precautions for use: Quetiapine is not approved for the treatment of dementia-related psychosis. In a meta-analysis of atypical antipsychotics, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo-controlled quetiapine studies in the same patient population (n=710); mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia. The risk of occurrence cannot be predicted and the benefit of treatment can outweigh the risk.
Patients who, in the opinion of the investigator, pose imminent risk of suicide or a danger to themselves or others.	Patients who posed an imminent risk required acute treatment outside of a clinical study.	The risk of occurrence cannot be predicted and the benefit of treatment can outweigh the risk. Suicide is an identified risk in the population for all approved indications for SEROQUEL/SEROQUEL XR. A cautionary statement is contained in the SmPCs in section 4.4 (Special warnings and precautions for use) and in the PIL.

Table II-32 Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
An ANC of ≤ 1.5 X 109/L.	Patients with decreased ANCs ≤ 1.5 X 109/L required monitoring and/or treatment outside of a clinical study	The risk of occurrence/worsening cannot be predicted and the benefit of treatment can outweigh the risk. Included in the SEROQUEL/SEROQUEL XR SmPCs Section4.4 (Special Warnings and precautions for use), Severe Neutropenia (neutrophil count <0.5 X 109/L) has been reported in quetiapine clinical trials. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 109/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 109/L. Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g. fever, weakness, lethargy, or sore throat) at any time during Seroquel therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.) Section 4.5 Interaction with other medicinal products and other forms of interaction and 4.8 Undesirable effects has Leucopenia and Decreased neutrophil count, (common); Agranulocytosis (rare) and Neutropenia (unknown).
Use of any of the following CYP3A4 inducers in the 14 days preceding enrollment including but not limited to: phenytoin, carbamazepine, barbiturates, rifampin, St. John's Wort, and glucocorticoids.	A known drug interaction, such as this, could confound the efficacy and safety results of a clinical trial.	In section 4.5 (Interaction with other medicinal products and other forms of interaction) concomitant use of quetiapine with hepatic enzyme inducers is not considered a contraindication if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer.

Table II-32 Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
History of seizure disorder, except febrile convulsions	Seizures have been reported with the atypical antipsychotic class and were observed at higher doses in rat, monkey and dog pre-clinical studies.	The risk of occurrence cannot be predicted and the benefit of treatment can outweigh the risk. In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. Seizure is an uncommon event in section 4.8 and there is a cautionary statement for patients with a history of seizure in section 4.4 of the SEROQUEL/ SEROQUEL XR SmPCs and in the PIL.
Current or past diagnosis of stroke	Quetiapine has the potential to cause hypotension and tachycardia and should be used with caution in patients with known cardiovascular disease. A class warning exists for the elderly demented population who have an approximately 3-fold increased risk of cerebrovascular AEs in randomised placebo controlled trials. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.	Cautionary statements are contained in the SmPCs in section 4.4 (Special warnings and precautions for use) and in the PIL. An approximately 3-fold increased risk of cerebrovascular AEs has been seen in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke. The risk of occurrence cannot be predicted and the benefit of treatment can outweigh the risk. Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension especially during the initial dose titration period and therefore dose reduction or more gradual titration should be considered if this occurs. A slower titration regimen could be considered in patients with underlying cardiovascular disease

Table II-32 Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Pregnancy and lactation	The safety and efficacy of quetiapine during human pregnancy has not yet been established.	Included in the SEROQUEL/SEROQUEL XR SmPCs section 4.6: Fertility, pregnancy and lactation. SEROQUEL/SEROQUEL XR should only be used during pregnancy if the benefits justify the potential risks. First trimester: The moderate amount of published data from exposed pregnancies (i.e. between 300-1000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks. Third trimester Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Breastfeeding Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent.

Table II-32 Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
		Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue Seroquel therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
A patient with DM fulfilling one of the following: Unstable DM defined as enrollment HbA1c >8.5%. Admitted to hospital for treatment of DM or DM related illness in past 12 weeks. Not under physician care for DM Physician responsible for patient's DM care has not indicated that patient's DM is controlled. Physician responsible for patient's DM care has not approved patient's participation in the study Has not been on the same dose of oral hypoglycaemic drug(s) and/or diet for the 4 weeks prior to randomisation. For thiazolidinediones (glitazones) this period should not be less than 8 weeks. Patient taking insulin with a daily dose on one occasion in the past 4 weeks which has been more than 10% above or below their mean dose in the preceding 4 weeks.	Patients with uncontrolled diabetes required acute treatment outside of a clinical study.	The risk of occurrence or worsening of diabetes cannot be predicted and the benefit of treatment can outweigh the risk. DM is an uncommon event in section 4.8 (and blood glucose increased to hyperglycaemic levels is a common event in section 4.8 (Undesirable effects) in the SmPCs. Additionally, a cautionary statement which suggests appropriate clinical monitoring is contained in the SmPCs in section 4.4 (Special warnings and precautions for use) and in the PIL.

AE Adverse event; ALT Alanine aminotransferase; ANC Absolute neutrophil count; AST Aspartate aminotransferase; CDS Core Data Sheet; CYP Cytochrome P450; DM Diabetes mellitus; DSM IV Diagnostic and Statistical Manual of Mental Disorders IV; FDA Food and Drug Administration, GGT Gamma glutamyltransferase; HbA1c Glycosylated hemoglobin; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone; ULN Upper limit of normal; XR Extended release.

II: 4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Pregnancy and lactation

In clinical studies, patients were screened for pregnancy and excluded from participation if the pregnancy test was positive; however, 89 patients with negative urine pregnancy tests at baseline tested positive during the study and were inadvertently exposed to quetiapine.

Outcomes of 89 pregnancies were as follows: 29 healthy babies, with an additional 3 babies that were considered healthy but one baby had symptoms of muscle rigidity at birth and 2 babies were premature; 7 unhealthy babies including a baby with neonatal withdrawal syndrome and a mother with placenta previa; 23 elective terminations; 4 spontaneous miscarriages and 23 reports with an unknown outcome.

Accepted class labelling regarding this population has been incorporated into the Core Data Sheet (CDS) and Patient Information Leaflet (PIL). SEROQUEL/SEROQUEL XR should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed. Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue SEROQUEL/SEROQUEL XR therapy.

Patients on concomitant cardiovascular medications

Section 4.5 of the SmPCs states:
Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.
Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval

Patients on concomitant valproic acid

A dedicated open-label PK drug interaction study (50771L/0120) was performed to evaluate the effect of SEROQUEL and divalproex sodium in schizophrenic/schizoaffective or bipolar subjects (33 evaluable subjects). It was demonstrated that neither SEROQUEL nor divalproex sodium produced any clinically relevant effect on the PK of the other. Furthermore, the co-administration of these products was found to be generally safe and well tolerated.
AstraZeneca will continue to review the potential for an interaction between quetiapine and valproate.

II: 4.4 Conclusions on the populations not-studied and other limitations of the clinical trial development programme

Table II-33 Safety concerns due to limitations of the clinical trial programme

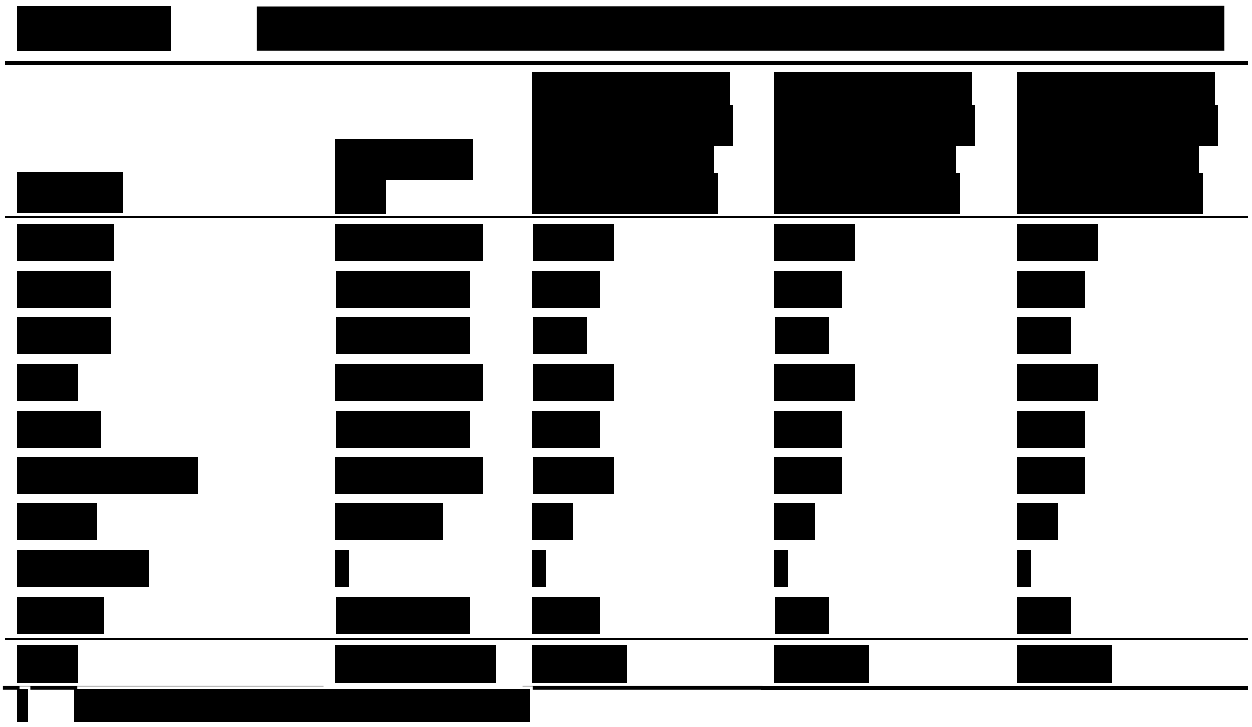
Safety concerns due to limitations of the clinical trial programme		**Outstanding Concern?**
Safety concern	**Comment**	**Yes/No**
Use in pregnant or breastfeeding women	Missing information	Yes ~~There are 2 pregnancy registries involving women receiving antipsychotics that are currently being conducted from which AstraZeneca is receiving reports. (Both of these registries are no longer supported financially in part by AstraZeneca). Information from these registries is reviewed periodically in the PBRER.~~ A cumulative review of use during the third trimester of pregnancy and EPS and/or withdrawal symptoms of newborns was submitted to Switzerland October 2011.
Use in patients on concomitant cardiovascular medications	Missing information	Yes A cumulative review of cardiovascular events was submitted to the MEB February 2010~~.~~
Use in patients on concomitant valproic acid	Missing information	Yes

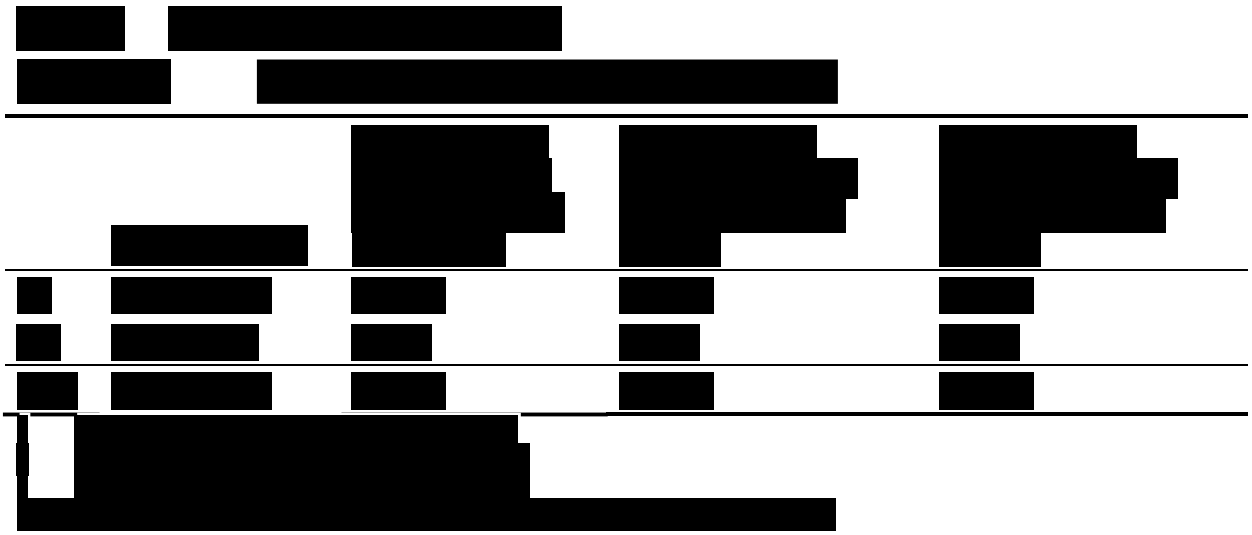
EPS Extrapyramidal symptoms; MEB Medicines Evaluation Board; PBRERPeriodic Benefit-Risk Evaluation Report.

EU RMP Part II, Module SV

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	14
Data lock point for this module	06 December 2016

PART II SAFETY SPECIFICATION
MODULE SV: POST-AUTHORISATION EXPERIENCE





II: 5.3 Post-authorisation use in populations not studied in clinical trials

Exposure data for SEROQUEL/SEROQUEL XR is based on AstraZeneca's Enterprise Performance Visibility database, as described in Part II: 5.2. Detailed demographic data or data on special patient populations are not available.

II: 5.4 Post-authorisation off-label use

A review of post-authorisation off–label use with SEROQUEL/SEROQUEL XR use has not identified any safety issues. AstraZeneca will continue to monitor off-label use as part of ongoing pharmacovigilance processes.

Non-interventional studies

Table II-41 presents data related to off-label use from 5 SEROQUEL/SEROQUEL XR post-authorisation safety studies (PASS). In addition, information from a manuscript, submitted for publication, representing work separate from SEROQUEL/SEROQUEL XR Post-Authorization Safety Studies conducted to fulfill regulatory commitments, is presented below.

Table II-41 European Union off-label use

Off-label category	Country	Source of information	Comment
Use in MDD prior to Marketing Authorization	Sweden	Swedish Record Linkage Study: Retrospective assessment from Pilot (feasibility) study linking Swedish Prescription Drug Register to National Patient Register	During the period July 1, 2006 – December 31, 2010, the IR and XR formulation of quetiapine was used to treat patients with a recent diagnosis of MDD in 1344 and 606 patients, respectively
Prescribed dosing of quetiapine outside recommended range in MDD (by indication).	Sweden	Swedish Record Linkage Study (SE RLS)	In the retrospective assessments performed to date, the proportion of patients receiving a prescription of quetiapine XR at doses below and above the recommended dosing for MDD (50mg/d, 300mg/d) were 2% and 5.1%, respectively
		SE RLS First Drug Utilisation Report (treatment period 2011 there were 2065 pts in the unrestricted cohort and 943 pts in the restricted cohort	In the unrestricted MDD cohort: 0.2% and 0.1%, respectively In the restricted MD cohort (Dx <1 yr from a psychiatric clinic): 0.0% and 0.1%
		SE RLS Second Drug Utilisation Report (treatment period 2011-2012 there were 3983 pts in the unrestricted cohort and 1751 pts in the restricted cohort)	In the unrestricted MDD cohort: 0.2% and 0.1%, respectively In the restricted MDD cohort (Dx <1 yr from a psychiatric clinic): 0.0% and 0.1%, respectively
		EU DU Interim Report 30 pts in Sweden	Doses of Seroquel XR below and above recommended dosing for MDD were: 0% and 3.3%, respectively

Table II-41 European Union off-label use

Off-label category	Country	Source of information	Comment
	UK	GPRD study 5,564 users of Seroquel XR 10 Sept 2008 – 30 Dec 2012	Doses of Seroquel XR higher than recommended were: Schizophrenia 0.1% Bipolar disorder 0.4% MDD 19.3%
		mPEM study 13,276 pts prescribed Seroquel XR Feb 2010 – Feb 2013	Maintenance doses of Seroquel XR higher than recommended were: Schizophrenia 1.12% Bipolar disorder 0.42% MDD 28.4%
		HEM/OASIS study 869 pts prescribed Seroquel XR Feb 2010 – 25 Apr 2013	Maintenance doses of Seroquel XR and IR higher than recommended (doses in mg) were: Schizophrenia XR (800): 0%; IR (750): 3.4% Manic episodes in Bipolar disorder XR (800): 0.3%; IR (800): 0%
Prescribed dosing of quetiapine outside recommended range (by indication).	UK	HEM/OASIS	Maintenance doses of Seroquel XR and IR lower than recommended (doses in mg) were Schizophrenia XR (< 400): 36.8%; Schizophrenia IR(< 150): 22.1% Manic episodes in Bipolar disorder XR(< 300): 29.7% IR (< 200): 29.1%
	Germany Italy Romania Spain	EU DU Interim Report Patients with MDD under psychiatrists care: 150 pts in Germany 63 pts in Italy 327 pts in Romania 187 pts in Spain	Doses of Seroquel XR below and above recommended dosing for MDD were: 1.3% and 10%, respectively 1.6% and 4.8%, respectively 0.9% and 10.7%, respectively 0.5% and 5.3%, respectively
Use outside of approved indications (Other than licensed indications)	UK	GPRD 1065 pts for whom indication was unknown or undetermined	19.1%
		m-PEM 3750 pts with other indications reported	29.3%
		HEM/OASIS misclassification of indication	5.4%

Table II-41 European Union off-label use

Off-label category	Country	Source of information	Comment
(Monotherapy at initiation of treatment for MDD)	Sweden	SE RLS First Drug Utilisation Report (treatment period 2011)	Unrestricted MDD cohort: 34.5% Restricted MD cohort (Dx < 1 yr from a psychiatric clinic): 22.4%
		SE RLS Second Drug Utilisation Report (treatment period 2011-2012)	Unrestricted MDD cohort: 27.8% Restricted MD cohort (Dx < 1 yr from a psychiatric clinic): 15.5%
		EU DU Final Report 31 pts in Sweden	25.8%
	UK	GPRD study - 2758 pts	22.9%
	Germany	EU DU Interim Report 152 patients	15.8%
	Italy	EU DU Interim Report 105 patients	35.2%
	Romania	EU DU Interim Report 327 patients	12.8%
	Spain	EU DU Interim Report 196 patients	8.2%

EU European Union; IR immediate release; MDD Major depressive disorder; m-PEM Modified prescription event monitoring; UK United Kingdom; XR prolonged release.

Non-interventional study HOME

A retrospective, non-interventional cohort study (HOME), funded by AstraZeneca, was conducted to study hospital stay in patients admitted for acute bipolar manic episodes prescribed quetiapine immediate release (IR) or XR. This involved 659 IR and 571 XR patients in 8 European countries (Belgium, Croatia, Denmark, Finland, Germany, Italy, Turkey, and the UK) for whom data was collected between November 2010 and March 2011. While the primary study objectives were to compare the length of hospital stay for the 2 patient cohorts, and to describe demographic and other relevant patient-related factors, information on dosing was also collected. Of patients in the IR and XR cohorts receiving quetiapine for the first time, 78.7% and 68.9% respectively, received only 1 total daily dose, and only 14.4% and 23.9% received dose titration during the first 7 days of hospitalization, as per the labeled recommendation. Most received a daily quetiapine dose >400 mg. As no AE reports were collected, it is not possible to assess the impact of the lack of titration in individual patients in this particular study. No new safety information was identified.

Non-interventional studies from RECONNECT-S program

The RECONNECT-S program consisted of 3 non-interventional studies in schizophrenia: RECONNECT-S Alpha, RECONNECT-S Beta, and RECONNECT-S Gamma. These protocols had similar content, but were conducted in different geographic areas. This cross sectional study concerns antipsychotic prescribing patterns in schizophrenia. It was not a specific SEROQUEL study, but data from each atypical antipsychotic was presented individually. No efficacy outcome or proactive safety data was collected.

Study reports for RECONNECT-S Alpha and Gamma were completed. Both studies showed that the mean daily dose for quetiapine is within the therapeutic range. The manuscripts for these studies are still pending as they have not yet been finalized,.

RECONNECT-S Alpha

This non-interventional study was conducted in Russia at 8 study sites. The primary objective was to describe the use of atypical antipsychotics in schizophrenic patients during hospitalization due to an acutely agitated psychotic episode by evaluation of type, dose, and mode of administration of the medication.

The results of the analysis showed that approximately 2 out of 3 patients received atypical antipsychotics during hospitalization. However, atypicals were used mostly in combination with typical antipsychotics, not as monotherapy, as usually recommended. Only 74 of 600 patients (12.3%) received atypical antipsychotic monotherapy during hospitalization. The atypical antipsychotics most prescribed—either alone or in combination with another antipsychotic—were clozapine, risperidone, and quetiapine. The mean daily dose of risperidone in the "atypical antipsychotic group" was at the upper limit of the therapeutic dose range recommended in the Sm PC for "standard" patients (4-6 mg). The median dose of clozapine was slightly lower than the recommended dose (200 450 mg/day). The mean dose of quetiapine was within the therapeutic dose interval recommended for the treatment of schizophrenia (400-800 mg/day).

RECONNECT-S Gamma

This non-interventional study was conducted in Hungary (8 sites), Latvia (10 sites), and Romania (15 sites). The primary objective was to describe the use of atypical antipsychotics in subjects with schizophrenia during hospitalization due to an acutely psychotic episode by evaluation of drug, dose, and mode of administration of the medication.

The results of the primary analysis showed that, of the 496 subjects, 96% (479) were treated with atypical antipsychotics. The most frequently used medications were quetiapine (n=129; 27.4%), oral risperidone (n=95; 20.2%), oral olanzapine (n=104; 22.1%), and clozapine (n=73; 15.5%). The overall mean daily dose ±standard deviation was 601.7 ± 219.51 mg for quetiapine (range 200-800 mg/day), 4.7 ± 1.93 mg for oral risperidone (range 4-6 mg/day; maximum 16 mg/day), and 16.2 ± 5.96 mg for oral olanzapine (range 5-20 mg/day).

II: 5.5 Epidemiological study exposure

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
PHARMO: SEROQUEL Safety Study (cohort study)	The study was conducted in 2 Parts. Part I involved the comparison of users of quetiapine vs. users of other antipsychotics in terms of indications for SEROQUEL use, comorbidities, drug utilization, treatment switches and discontinuations, to assess feasibility of evaluating outcomes Part II: Evaluation of patient characteristics, drug utilization and the incidence of safety outcomes (all cause mortality, acute MI, stroke, suicide, EPS, diabetes, hypo-thyroidism) in patients treated with quetiapine compared with those treated with olanzapine and risperidone.	The data source for this study was the PHARMO Record Linkage System a patient-centric database linking patient demographics, drug dispensing hospital morbidity, and general practitioner information on approximately 2 million inhabitants of the Netherlands. Part I of the retrospective cohort study included patients who received antipsychotics. Part II of the study included naive users of quetiapine and atypical antipsychotics specifically olanzapine and risperidone.	The duration of Part I of the study included all patients who received antipsychotic medications during the period January 1, 1998 to December 31, 2009. Part II of the study included naive users of quetiapine and atypical antipsychotics (specifically olanzapine and risperidone) treated from January 1, 2000 to November 30, 2009	4,658 naive users of quetiapine; 7229 naive user of risperidone and 5856 naive users of olanzapine	Original Protocol: Dec 2008 Part 1 Report: 21 Nov 2009 Part 2 Protocol: 20 May 2010 Part 2 Report: 26 April 2011
D144AC00004 m-PEM study (exposure only cohort study with nested case control studies) m-PEM study on extended-release quetiapine (SEROQUEL XR)	Examine the safety and use of quetiapine XL prescribed in general practice (as a treatment for schizophrenia, bipolar disorder and as add-on treatment for MDD) in adult patients, using m-PEM methodology. a) Quantify both the incidence of new and worsening of pre existing type II DM, metabolic syndrome and EPS and explore the patterns of these events over time	Physician completed survey characterizing patients treated with quetiapine XL in the general practice setting in England for the treatment of schizophrenia, manic and depressive episodes associated with bipolar disorder, and as add-on therapy for MDD.	12 months following first treatment with quetiapine XL	13,276 patients treated with XL;3127 elderly patients (i.e., age > 65 yrs) treated with XL for bipolar disorder and MDD Nested case control study will include cases of EPS and somnolence/sedation (including drowsiness)	Original protocol: 9 Dec 2009 Protocol amendment: 22 June 2010 (revised questionnaire included date of BMI measurement) Annual Progress Rpt:

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
	b) Determine the dose dependent characteristics of EPS and somnolence/sedation (including drowsiness) c) Quantify the incidence of rarely and frequently reported events d) Quantify drug utilization characteristics e) Identify previously unrecognized ADRs f) Quantify, follow-up and causally assess reports of neutropenia (including agranulocytosis), metabolic syndrome and events related to raised blood glucose The study questionnaire captures the primary indication for starting treatment, the secondary indication, if applicable, and date (in Item 4) as well as the start dose, maintenance dose (the date achieved), and dose frequency or time of day administered) (in Item 5). To examine the incidence of EPS and somnolence in relation to the prescribed dose.				21 Jan 2011 Interim PEM Report: 31 Jan 2011 Expanded case definition to include all cases of bipolar disorder initiated: Oct 2011 Protocol amendment: December 2011 (to include 1000 patients with MDD including 500 elderly) Annual Progress Report: Feb 2011 Annual Progress Report: Feb 2012 Annual Progress Report: Feb 2013 Final report: December 2013 Interpretation report: December 2013.

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
					Nested case control study report on EPS: Oct 2013 Nested case control study report on somnolence: Dec 2014 The submissions to be made following the completion of the renewal (licensing) procedure in 2016
D1444C00006 GPRD study (cohort study with nested case-control studies)	1) to characterize new users of quetiapine XL as well as new users of other study drugs (i.e. the comparison group) with regard to the indication for which they receive the study drug, diagnosed comorbidities and drug utilization patterns prior to receiving a study drug, and the duration of treatment prior to discontinuation, 2) to quantify the risk of developing newly diagnosed outcomes of interest in new users of SEROQUEL XR and in the	UK-based computerized database of anonymized longitudinal medical records from primary care, specifically, the General Practice Research Database (GPRD); patients treated with quetiapine XL	Patients treated with quetiapine XL for approved indications - from earliest use of quetiapine XL for schizophrenia in November 2008 through June 2012 (cohort definitions to allow optimizing number of patients treated with XL only with a minimum follow-up period of six months; also to include patients with a	5564 patients received quetiapine XL 10 Sept 2008 through 30 December 2012 31,808 users of non-quetiapine comparator drugs. In nested case-control studies there were varying numbers of patients experiencing events of interest and varying numbers of matched controls.	Original protocol dated: 14 Dec 2007 Annual Progress Report: April 2010 Protocol amendment: 7 October 2010 (to include patients treated with quetiapine XL for MDD) Annual Progress Report:

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
	comparison group(s), namely: • death of all causes • suicide/suicide attempt/ suicide ideation • acute MI • thrombotic or hemorrhagic stroke • DM • hypothyroidism • neuroleptic malignant syndrome • fractures • syncope • EPS associated with new use of parasympatholytic drugs • seizures • cataract		minimum follow-up of 12 months)		April 2011 Annual Progress Report: May 2012 Annual Progress Report: May 2013 Study Report: September 2013 Interpretation Report: November 2013
D144C00011 HEM/OASIS (exposure only cohort study) HEM study. A cohort study to monitor the safety and use of prolonged release (SEROQUEL XL) in the mental health trust setting.	To monitor the short-term (up to 12 weeks) use and safety of quetiapine XL and quetiapine IR prescribed to patients with a clinical diagnosis of schizophrenia, plus manic episodes associated with bipolar disorder by psychiatrists under normal conditions of use a) to compile a cohort of all eligible psychiatrists b) to recruit cohorts of patients newly initiated on quetiapine (IR and XL formulations)	Physician completed survey characterizing patients treated with quetiapine XL in the mental health trust setting in the UK	12 weeks from date of first treatment with quetiapine XL	869 patients from the mental health trusts in England evaluable for drug utilisation; 845 evaluable for outcomes. There was lower than planned recruitment, especially of patients treated with high dose XL and IR 42 (18.8%) received IR > 600 mg/d. 279 (43.1%) had received high dose XL at any time during the	Protocol date: 31 May 2009 Interim Report: August 2010 Revised protocol: 25 December 2011 (recruitment of add'l junior psychiatrists Interim and Annual Report: Feb 2011 Annual Report:

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
	c) to examine the safety and use in new users of both quetiapine formulations with particular interest in the following: i) drug utilisation characteristics ii) to compare rates of events reported by psychiatrists for patients taking high dose (> 600mg) quetiapine XL to high dose (> 600mg) quetiapine IR iii) to compare event rates between patients receiving low dose quetiapine XL (< 600mg) and patients receiving high dose quetiapine XL (> 600 mg). iv) to further quantify and explore the pattern of selected events reported by psychiatrists for patients taking quetiapine over time			12 week study period.– IR had received a dose > 600 mg/d. 612/809= 76% had been treated with XL.	Feb 2012 Annual Report: Mar 2013 Final report: September 2013 Interpretation report: November 2013
D1443C00056 Swedish Record Linkage study (population-based cohort study with nested case-control studies included) Swedish Record-Linkage Study-three register-based studies, pilot (Methodology): Drug	1.To assess the feasibility of using a record linkage approach to studying the use and safety of SEROQUEL XR through a pilot study prior to approval in the MDD indication. 2a.To characterize patients dispensed SEROQUEL XR for the treatment of MDD, in add-on therapy, in monotherapy (if any), and compare with patients treated for MDD with other antidepressants either as add-on therapy or in	Cases of MDD treated with SEROQUEL XR or other antidepressants within Sweden from January2011. Data linkage of the following population-based data registers in Sweden is to be performed: Prescription Drug Register, including all purchases of prescribed drugs at pharmacies (dispensed drugs), National Patient Register which	The drug utilization study started three months after launch in Sweden (Q1, 2011) and collected data for the following 2 years. The observation period for the Safety study started at the date of launch in Sweden (Q1, 2011) and continued during	The second DU Report, applied less stringent criteria for defining the patient population observed 3983 patients having received treatment with Seroquel XR for MDD (with an average of 0.35 p-yrs of exposure) based upon diagnosis codes (ICD10 F32-F33) during the years 2011-2012; Using	Protocol date: 18 June 2010 Protocol amendment: 10 October 2010 Annual Report: July 2011 Annual Report : July 2012 Final Report: Dec 2012

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
Utilization; Safety Utilization	monotherapy. 2b.To characterize doses, durations of treatments, treatments changes in patients dispensed SEROQUEL XR or other antidepressants for MDD, as well as trend over time in usage, and specialty of prescriber. 3. To study the incidence rates of specific outcomes of interest and compare MDD patients treated with SEROQUEL XR as add-on to those treated with other antidepressants. The outcomes of interest: acute MI, Stroke, Suicide, DM, EPS, Somnolence, and death from all causes.	contains information on hospitalizations, outpatient visits at hospitals, including day surgery carried out by both private and public caregivers. Cause of Death Register which contains data on all deaths from 1961. The data collected includes underlying and contributing causes of death, in addition to about 30 other variables (however, there is a lag time of up to 2 years). Population Register contains information on dates of emigration and death for all patients. It is to be used to ascertain time at risk for all patients included in the study.	the following 2-4 years.	more restrictive criteria (having a diagnoses from a psychiatric clinic within the past year) 1751 patients received treatment with Seroquel XR for MDD (with an average of 0.37 p-yrs of exposure).	DU Part 1 Report: Sept 2013 DU Part 2 Report: May 2014 Part III safety report: Annual Report: July 2014 Annual Report: July 2015 Final Report : July 2016

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
D144CC000057 EU Drug Utilisation study (drug utilisation cohort study) A multinational, Multicenter, Retrospective, Observational Drug Utilisation Study of SEROQUEL Extended Release Prescribed by Psychiatrists as Treatment for Major Depressive Disorder in Selected Countries in the European Union	1. Document characteristics of patients under specialist (psychiatric) care who are prescribed SEROQUEL XR as treatment for MDD in each of the selected countries over a 9 month period, starting 3 months following the launch of the product for its approved indication. 2. Describe differences between countries concerning treatment practices involving use of SEROQUEL XR through the use of a drug utilisation questionnaire of psychiatrist in 5 European countries	Data is abstracted from the medical records of patients with MDD who were treated with quetiapine XL by psychiatrists from different practice settings in Germany, Spain, Italy, Romania and Sweden. Data abstracted includes characteristics of the participating psychiatrist, patients' medical and psychiatric history, and the drugs utilised in the medical management of MDD.	An inception cohort defined by patients initiating SEROQUEL XR (as add-on therapy or as monotherapy) during a 9 month period corresponding to 3 to 12 months following the launch of the product in each country for the MDD indication	757 patients were included in the interim analysis: 30 from Sweden, 150 from Germany, 63 from Italy, 327 from Romania and 187 from Spain There were 811 patients included in the Final EU DU Report: 31 from Sweden, 152 from Germany, 105 from Italy, 327 from Romania and 196 from Spain.	Protocol: 16 June 2010 Protocol amendment: 14 April 2011 SAB meeting 5 July 2011 Pilot study completed: 13 April 2012 Protocol amendment and Annual Report: July 2011 SAB meeting: 9 Mar 2012 Protocol amendment and Annual Report: July 2012 Annual Report: July 2013 Interim Analysis Report: Feb 2014 Annual Report: July 2014 Final Report: May 2015

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
D1443C00091 (cohort study) A naturalistic study of Quetiapine XR use in France	To describe patient characteristics (demographic and clinical) and the patterns of use of Quetiapine XR in patients receiving the drug for the first time in real-life practice. Secondary objectives: - to assess the patient's health and healthcare utilization up to one year after receiving Quetiapine XR -to evaluate representa-tiveness of the schizo-phrenia or acute bipolar disease Quetiapine XR treated patients in the context of all schizo-phrenia or acute bipolar disease patients and identify the potential level of channeling bias. - the proportion of patients experiencing AEs & SAEs possibly related to Quetiapine XR, including those leading to discon-tinuation of treatment are presented	Patients of psychiatrists receiving Quetiapine XR for the first time in the inclusion period with a diagnosis of schizophrenia or bipolar disorder. The prescription of the medicinal product is clearly separated from the decision to include the subject in the study.	12 months	From the sampling frame of 7715 psychiatrists, there were 263 active physicians who were prescribers in the Seroquel group and 141 in the reference group. 1877 patients (994 with bipolar disease, 672 with schizophrenia, 164 with MDD and 47 with another diagnosis) received Seroquel XR for the first time during the inclusion period in France.	Protocol date: 19 Dec 2011 Interim report: January 2015 Final Report: November 2015

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
D1443C00127 Physician survey on monitoring of patients treated with quetiapine	Survey physicians' receipt of educational materials and assess through self-report their activity monitoring patients treated with SEROQUEL®, SEROQUEL® XL or quetiapine fumarate. The evaluation of monitoring includes the recording of weight at initiation and during treatment, testing of lipids, evaluation of signs and symptoms of hyperglycemia, testing of plasma glucose of patients with diabetes, and in a similar fashion testing blood glucose for worsening of glycemic control in patients with risk factors for diabetes.	Survey responses from General Practitioners and specialist physicians (i.e., psychiatrists and neurologists) from each of eight selected countries representing the geographic diversity of the EU (UK, Germany, Sweden, Romania, Spain, Hungary, Italy and Netherlands)	This is a cross sectional survey that was conducted over the course of 3-4 months	100 physicians in each of eight EU countries	Completed FVAR received

Table II-42 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person-time (if appropriate)	Comment
D1443C00128 EMR data to assess monitoring of patients treated with quetiapine	Evaluate EMR data to assess the medical monitoring performed by physicians during encounters with patients diagnosed with schizophrenia, bipolar disorder or major depressive disorder who were being treated with SEROQUEL, SEROQUEL XL or quetiapine fumarate. Assessment of the monitoring includes: ~~t~~recording of weight at initiation and during treatment, testing of lipids, evaluation of signs and symptoms of hyperglycemia, testing of plasma glucose of patients with diabetes, and in a similar fashion testing for worsening of glycemic control in patients with risk factors for diabetes.	IMS's LifeLink EMR-EU comprised of longitudinal patient-level data from physician-practice data systems of office-based physicians in the UK and Germany. The data includes basic demographics, medical diagnoses, linked prescriptions, lab tests and notes (entered in fixed fields) related to patient status as recorded during medical encounters	Patient encounters recorded in IMS Disease Analyzer in Germany during the calendar period 13 February 2012 - 31 August 2012 and for patient encounters with in the UK during 11 January 2012 - 31 July 2012	Electronic Records on 887 patients from 93 General Practitioner practices in the UK; 6,153 patients from 42 psychiatrists and 145 neurologists from Germany	Completed FVAR received

ADR Adverse drug reaction; BMI Body mass index; DM Diabetes mellitus; EMR Electronic medical record; EPS Extrapyramidal symptoms; EU European Union; GPRD General Practice Research Database; HEM Hospital-event monitoring; IR Immediate release; MDD Major depressive disorder; m-PEM Modified prescription-event monitoring; PEM Prescription-event monitoring; UK United Kingdom; XL/XR extended release.

EU RMP Part II, Module SVI

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	06 December 2016

PART II SAFETY SPECIFICATION

MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

II: 6.1 Potential for harm from overdose

The possibility of a suicide attempt with a drug overdose is inherent in the diseases that SEROQUEL/SEROQUEL XR is used to treat (ie, schizophrenia, bipolar depression, bipolar mania, MDD, and GAD).

An overdose of SEROQUEL or SEROQUEL XR would be expected to result in signs and symptoms from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia, and hypotension. In addition, death or coma, or QT prolongation could be expected.

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 51 grams. In postmarketing experience, there have been reports of overdose of quetiapine alone resulting in death or coma. Additionally, the following events have been reported in the setting of monotherapy overdose with quetiapine: QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium, and/or agitation. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. While the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered. Refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

Close medical supervision and monitoring should be continued until the patient recovers.

Routine pharmacovigilance is performed to monitor the effects of SEROQUEL and SEROQUEL XR and overdose. Milestones for evaluation and reporting for this topic include any new data identifying a change in the safety profile for overdose with SEROQUEL/SEROQUEL XR. A comprehensive review of all AEs occurring in the setting of a monotherapy overdose with SEROQUEL/SEROQUEL XR was performed June 2010. No new significant safety information regarding AEs of SEROQUEL/SEROQUEL XR in the setting of an overdose was identified.

II: 6.2 Potential for transmission of infectious agents

No issue is expected. Compliance with applicable regulations relating to transmissible spongiform encephalopathy is achieved as follows:

All excipients except lactose monohydrate are produced from non-animal sources. The magnesium stearate used in the manufacture of SEROQUEL sustained release tablets is vegetable based.

Lactose monohydrate used in SEROQUEL XR tablets is derived from milk fit for human consumption. Lactose monohydrate meets the requirements of the Public Statement: Lactose prepared using calf rennet: Risk assessment in relationship to bovine spongiform encephalopathies (EMEA/CPMP/571/02, published London, 27 February 2002).

II: 6.3 Potential for misuse and abuse

As requested by PRAC on 8 May 2014, Astrazeneca conducted a cumulative overview of the signals for possible misuse and abuse. In the 12 November 2016 response, Astrazeneca asked for the inclusion of a comment that a causal relationship has not been established and that it concerns a class effect for all atypical antipsychotics, as follows:

> "Cases of misuse and abuse with quetiapine and other atypical antipsychotic drugs have been reported although a causal relationship has not been established. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse."

The MEB did not agree to Astrazeneca's proposal and imposed a warning to be included in section 4.4 of SmPC. Following the imposition of MEB, Astrazeneca added the following text in section 4.4 of the SmPC:

> "Misuse and abuse
>
> Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse. "

In July 2016, Astrazeneca conducted a safety information review committee (SIRC) review for the topic of misuse and abuse with SEROQUEL/SEROQUEL XR. Based on the available information SIRC considered that a reasonable possibility of a causal relationship between Seroquel and misuse or abuse has not been established. No amendment of the undesirable effects section (4.8) of the Core Data Sheets (CDSs) was recommended. SIRC recommended that wording on misuse and abuse is added to the warnings and precautions section (4.4) of the CDSs. Following the recommendation of SIRC, Astrazeneca added text below to section 4.4 of the CDS.

> "Misuse and abuse
>
> Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse. "

While AstraZeneca maintains that there is insufficient evidence to support a causal relationship between Seroquel and drug abuse and misuse, abuse and misuse will be maintained in this EU RMP as a potential risk.

Routine pharmacovigilance is performed to evaluate and mitigate any risk of misuse and abuse of SEROQUEL/SEROQUEL XR. In addition, this topic is routinely reviewed in the SEROQUEL/SEROQUEL XR PBRER and, as such, all reports of misuse and abuse are reviewed. Milestones for evaluation and reporting for this topic include any new data identifying a change in the safety profile for SEROQUEL/SEROQUEL XR. A cumulative review was completed August 2014. In May 2015, Health Canada requested a cumulative Issue-Related Summary Report (IRSR) from 1997 to 31 July 2016 of adverse drug reactions and serious adverse drug reactions related to quetiapine containing products, pertaining to drug abuse and related events. This information was submitted in October 2016.

II: 6.4 Potential for medication errors

Potential name confusion

The potential for name confusion between SEROQUEL or SEROQUEL XR and any other medication exists. These errors can be made in the course of filling and/or dispensing medications. Examples could include: selecting the wrong bottle from the shelf, misreading prescriptions, misinterpreting verbal medication orders, transcribing errors, filling out a pharmacy card incorrectly, mishandling a transferred prescription from another pharmacy, and correctly hand writing and entering the prescription but incorrectly filling it. Medication errors involving name confusion can result from inattention to normal pharmacy and institutional practices and procedures.

The introduction of SEROQUEL XR into the marketplace may theoretically result in cases of name confusion with the currently marketed SEROQUEL [IR] tablets. The IR formulation is currently approved as 25 mg, 100 mg, 150 mg, 200 mg, and 300 mg. The XR formulation is available in the 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg tablet strength.

Based on the results of Study 5077IL/0097, which compared the steady-state PK of equivalent total daily doses of quetiapine (administered as SEROQUEL [IR]; given twice daily) and SEROQUEL XR (administered once daily), both formulations are similar with respect to area under the curve (AUC) over a 24-hour time period. The maximum plasma concentration (C_{max}) for SEROQUEL XR is 13% lower than for the morning dose of SEROQUEL [IR]. Additionally, in Studies 5077IL/0086 and 5077IL/0118, both dose and dose unit proportionality has been demonstrated up to total daily doses of 800 mg with respect to C_{max} and AUC. The elimination half-life is the same for SEROQUEL XR and SEROQUEL [IR], approximately 6 hours. Thus, with repeated dosing, the bioavailability of a once-daily dose of SEROQUEL XR is expected to be similar to that of the same total daily dose of SEROQUEL [IR] administered in divided doses every 12 hours. Therefore, in the event a patient's therapy is inadvertently switched from SEROQUEL [IR] twice daily to SEROQUEL XR once daily at the same total daily dose (or vice versa), it is unlikely to result in a major safety issue.

Potential dosing errors

SEROQUEL and SEROQUEL XR require dose escalation at the initiation of therapy so that patients can adapt to the known side effects, such as somnolence and sedation, that can occur during therapy initiation. However, the titration schedule for each formulation is not exactly the same; thus, there is the potential for dosing errors between the IR and XR formulations.

II: 6.4.1 Description of medication errors during the clinical trial programme

Excluding reports of overdose, medication errors have not been collected as AEs, and no potential risk has been identified during the clinical trial programme.

Table II-43 Description of medication errors during the clinical trial programme

Description of error	Number of occurrences	Analysis of cause	Steps taken to prevent	Comment
NA	NA	NA	NA	NA

NA Not applicable.

II: 6.4.2 Preventive measures for the final products being marketed

Prevention of error due to name confusion

To minimize the potential for medication error, SEROQUEL XR and SEROQUEL [IR] are packaged in such a manner that visual differences between the 2 formulations are easily apparent. The outer cartons are distinct and clearly labeled for easy recognition. The unit-dose blister packs also look significantly different. The [IR] formulation has silver foils with different colored print for each strength, while the XR formulation has black print on different colored foils for each strength. Furthermore, the engraving on the tablets is different. All IR tablets are engraved with strength and trade name (SEROQUEL), while the XR tablets (most strengths being of different shapes and all being of different colors) are engraved with the strength and the letters XR. Lastly the use of blisters formed from white, opaque film removing visibility of the contents reduces the attractiveness of the pack to children.

Prevention of dosing errors

Section 4.2 (Posology and method of administration) of the MR-SmPCs for SEROQUEL and SEROQUEL XR includes specific instructions for initiating therapy. Instructions are presented on an indication-by-indication basis because of differences in dose titration among the various indications.

In conjunction with launch for use in bipolar depression in MR countries, educational pieces providing treatment path guidance were developed for distribution to 100% of physicians visited. (see Part V: 1).

II: 6.4.3 Effect of device failure

Not applicable.

II: 6.4.4 Reports of medication errors with the marketed products

At this time, additional risk minimization activities (outside of routine risk minimization activities, ie, robust labeling) are not warranted for this topic. Milestones for evaluation and reporting include any new data identifying a change in the current assessment for SEROQUEL and SEROQUEL XR regarding medication error. As appropriate, the RMP for SEROQUEL/SEROQUEL XR will be updated.

Table II-44 Reports of medication errors with the marketed products

Description of error	Number of occurrences	Analysis of cause	Steps taken to prevent	Comment
Product name: SEROQUEL				
Confusion between IR and XR formulations	Unknown	The introduction of SEROQUEL XR into the marketplace may theoretically result in cases of name confusion with the currently marketed SEROQUEL [IR] tablets	To minimize the potential for medication error, SEROQUEL XR and SEROQUEL [IR] are packaged in such a manner that visual differences between the 2 formulations are easily apparent; Section 4.2 (Posology and method of administration) of the MR-SmPCs for SEROQUEL and SEROQUEL XR includes specific instructions for initiating therapy	Based on the results of Study 5077IL/0097, which compared the steady-state pharmacokinetics of equivalent total daily doses of quetiapine (administered as SEROQUEL [IR]; given twice daily) and SEROQUEL XR (administered once daily), both formulations are similar with respect to AUC over a 24-hour time period and thus in the event a patient's therapy is inadvertently switched from SEROQUEL [IR] twice daily to SEROQUEL XR once daily at the same total daily dose (or vice versa), it is unlikely to result in a major safety issue.
Name confusion with Serzone (nefazodone; Bristol Myers-Squibb)	Unknown	Matching first three letters of brand names.	In 2002 letters were sent to healthcare professionals and the products were differentiated by modification of the appearance of the trade name and packaging.	Bristol Myers-Squibb has ended worldwide distribution of Serzone. Issue resolved due to withdrawal of Serzone from the market.

AUC Area under the curve; IR Immediate release; MR Mutual recognition; SmPC Summary of Product Characteristics; XR prolonged release.

II: 6.5 Potential for off-label use

SEROQUEL is approved for schizophrenia and bipolar disorder, including moderate to severe manic episodes in bipolar disorder, major depressive episodes in bipolar disorder, and prevention of recurrence of manic or depressed episodes in patients with bipolar disorder, who previously responded to quetiapine treatment.

SEROQUEL XR is approved for treatment of schizophrenia and bipolar disorder, including moderate to severe manic episodes in bipolar disorder, major depressive episodes in bipolar disorder, prevention of recurrence of manic or depressed episodes in patients with bipolar disorder, who previously responded to quetiapine treatment. It is also approved as add-on treatment of major depressive episodes in patients with MDD who have had sub-optimal response to antidepressant monotherapy. Prior to initiating treatment, clinicians should consider the safety profile of SEROQUEL XR.

The potential for off-label use exists for all medicines including SEROQUEL and SEROQUEL XR. In particular, there is the potential for healthcare professionals to (a) prescribe SEROQUEL or SEROQUEL XR for other types of depression and other psychiatric conditions or (b) prescribe treatment at the wrong dose.

As with other drugs, there is also the potential for physicians to prescribe SEROQUEL/SEROQUEL XR to take advantage of known side effects (eg, sedation) to treat conditions in non-psychiatric populations.

Activities adopted to minimize the potential for off-label use and misdosing, particularly in the bipolar depression indication, include indication-specific educational pieces and activities and robust SmPC language related to dose titration. Following the interim EUDU report, it was proposed by AstraZeneca that educational materials should be sent to relevant EU physicians reminding them that SEROQUEL XR is only approved as add-on therapy in MDD. No further additional risk minimisation activities have been proposed following AZ's review of the final study report.

II: 6.6 Specific paediatric issues

II: 6.6.1 Issues identified in paediatric investigation plans

Not applicable.

II: 6.6.2 Potential for paediatric off-label use

There is the potential for healthcare professionals to prescribe treatment for paediatric patients because the diseases that SEROQUEL and SEROQUEL XR are approved for in adults are also found in pediatric patients. Additionally, there is physician awareness of the SEROQUEL clinical development program in the pediatric population. SEROQUEL and SEROQUEL XR are not approved for use in the pediatric population in the EU.

The available evidence from placebo-controlled clinical trials concerning the pediatric population is found in Sections 4.4, 4.8, 5.1 and 5.2 of the SEROQUEL/SEROQUEL XR SmPCs. A separate table in section 4.8 for children and adolescents summarises ADRs that occur in a higher frequency category in children and adolescent patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population: Increased appetite, elevations in prolactin, increases in blood pressure (BP), vomiting and extrapyramidal symptoms (EPS) (very common); irritability, rhinitis and syncope (common).

Part II: 3.2 of the EU-RMP contains tables with pediatric clinical trial data from the integrated quetiapine clinical study safety database.

An additional 18 pediatric patients (12 to 17 years) with psychotic disorders were exposed to open-label SEROQUEL in a pilot efficacy and safety study (Study 5077US/0018) (Shaw et al 2001). These patients are not included in the integrated quetiapine clinical-study safety database and are not discussed further in this RMP.

A comprehensive review of pediatric data was submitted in October 2010. There are no pediatric studies planned in the PASS program.

II: 6.7 Conclusions

No new safety concerns have been identified with SEROQUEL/SEROQUEL XR relating to overdose, transmission of infectious agents and medication errors.

While AstraZeneca maintains that there is insufficient evidence to support a causal relationship between Seroquel and drug abuse and misuse, abuse and misuse will be maintained on this EU RMP as a potential risk. Following the imposition of MEB and recommendation from SIRC, the following amendments were added to the Product Information in section 4.4 of the SmPC and CDS :

“Misuse and abuse

Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.”

There is potential for healthcare professionals to prescribe off-label use for paediatric patients Additionally, there is physician awareness of the SEROQUEL clinical development program in the pediatric population. Currently, SEROQUEL and SEROQUEL XR are not approved for use in the pediatric population in the EU.

EU RMP Part II, Module SVII

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	06 December 2016

PART II SAFETY SPECIFICATION
MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II: 7.1 Newly identified safety concerns (since this module was last submitted)

Suicide and Suicidality have been added back into the RMP (version 15, edition 2) as an important identified risk at the request of the RMS (MEB).This was previously classified as an important potential identified risk and removed from version 14 per the MEBs request.

II: 7.2 Recent study reports with implications for safety

The final clinical study report for the Swedish record linkage study (SE-RLS) PASS (part 3, safety) was submitted to the health authority in December 2016. The RMS has requested that the potential identified risk of Suicide and Suicidality (removed per MEB request version 14) be added back as an important identified safety concern (version 15, edition 3) based on the SE-RLS PASS results.

II: 7.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

This section provides details of the important identified and potential risks that may have a bearing on the product's benefit-risk assessment and/or may have a potential public health impact, and that require either further characterisation or evaluation, or implementation of specific risk minimisation activities to protect patients.

On the basis of data from the SEROQUEL/SEROQUEL XR clinical development programme and ongoing post marketing experience, the known risks of SEROQUEL/SEROQUEL XR treatment are described in section 4.8 of the SEROQUEL/SEROQUEL XR SmPCs.

II: 7.3.1 Important identified risks

The following safety concerns, categorized by Medical Dictionary for Regulatory Activities (MedDRA) (Version 15.0) System Organ Class (SOC), are important identified risks:

Nervous system disorders

- EPS, as identified in Table II-45.
- Somnolence, as identified in Table II-46.

Metabolism and nutritional disorders

- Weight gain, as identified in Table II-47.
- Lipid changes (Increased cholesterol [including increased low-density lipoproteins {LDLs}, increased triglycerides, and decreased high-density lipoproteins {HDLs}]), as identified in Table II-48.

- Hyperglycemia and diabetes mellitus (DM) (Note: DM included per mutual recognition procedure [MRP] outcome), as identified in Table II-49.
- Metabolic risk factors, as identified in Table II-50.

Psychiatric disorder

- Suicide and suicidality, as identified in Table II-51

Nervous system disorders

Table II-45 Important identified risks - EPS

Identified risk	EPS
Frequency/ seriousness/ outcomes	**Placebo-controlled trials** 657 (6.93%) quetiapine and 247 (4.95%) placebo patients had TEAEs; MH relative risk: QTP vs PLA (95% CI) 1.43 (1.23, 1.67) 2 events were considered serious by the investigators Recovered 486 patients (73.97%); Not recovered 171 patients (26.03%) **All studies (including OLEs) QTP exposure** 2764 (9.67%) had TEAEs. 35 events were considered serious by the investigators Recovered 1807 patients (65.38%); Not recovered 805 patients (29.12%); Unknown 152 patients (5.51%) **Long-term (≥6 months) QTP exposure** 204 (4.90%) had TEAEs 7 events were considered serious by the investigators Recovered 100 patients (49.02%); Not recovered 92 patients (45.10%); Unknown 12 patients (5.88%)
Severity and nature of risk	Antipsychotic-induced EPS include a variety of different iatrogenic movement disorders that can be divided into acute and tardive syndromes. Acute syndromes are those that develop within hours or days of antipsychotic treatment and include acute dystonia, akathisia, and parkinsonism. There were a total of 35 (1.27%) serious events in the all-study data. The majority of TEAEs of EPS were considered mild to moderate by the investigators.
Background incidence/ prevalence	Occurrence of movement disorders, specifically the components of EPS associated with symptoms of parkinsonism and akathisia are influenced by the large variety of assessment methods using more or less strict criteria. Rates of EPS and its component symptoms drawn from randomized clinical trials and meta-analyses may not be comparable, as they are drawn from different samples; they are reported as ranges here due to space constraints. **Schizophrenia:** Spontaneous dyskinetic movements in untreated adults with schizophrenia have been reported as ranging from 0% to 28.5% and in 0% to 71% of children and adolescents with psychiatric disorders, and in 19.9% of young healthy controls (Gebhardt et al 2006). In adults with schizophrenia the prevalence of parkinsonism is generally stated as 20% to 36% with a range in reports from 8.6% to 72% (Gebhardt et al 2006). In the CATIE study, the prevalence of parkinsonism symptoms ascribed to previous treatment with typical and atypical antipsychotics were 6% and 4-8%, respectively; however, in other settings prevalence rates in adults treated with atypical antipsychotics are reported as approximating 16% with a range of 4.4% to 66.7% (Gebhardt et al 2006). In children and adolescents treated with typical and atypical antipsychotics prevalence rates of Parkinsonism symptoms

Table II-45 Important identified risks - EPS

Identified risk	EPS
	have been reported as ranging from 20% to 25% and 0% to 19%, respectively (Gebhardt et al 2006). The prevalence of akathisia symptoms for typical and atypical antipsychotic use in adults is reported as ranging from 5.5% to 75% and 3% to 18%, respectively. In children and adolescents, the prevalence of akathisia symptoms found with typical and atypical antipsychotic use is reported as ranging from >30% and 1.8% to 11.1%, respectively (Gebhardt et al 2006). In acute schizophrenia, use of second-generation atypical antipsychotics imparts a lower risk of EPS compared to older antipsychotics (Tandon et al 2008a). EPS is estimated to occur in 60% to 65% of patients receiving conventional antipsychotics (McIntyre et al 2005a). A large (n=4939) observational study of patients with schizophrenia who started a new antipsychotic at baseline reported that EPS was present at baseline in 31.6% to 44.4% of patients, related to medications received before baseline. Decreases in the incidence of EPS were recorded in all treatment groups receiving atypical antipsychotics over the 36-month follow-up (Novick et al 2009). An evaluation of the incidence of EPS in 50 elderly patients with schizophrenia found that the incidence of EPS was low and similar to that in 25 matched controls (Evans et al 1999). The authors hypothesize that this may reflect habituation to the parkinsonian side effects among patients, while control subjects had EPS score consistent with aging. **Bipolar disorder:** Of particular significance in bipolar disorder is the evidence from meta-analysis of clinical trial results that indicates that EPS (especially the occurrence of motor-side effects) occurs less frequently with second-generation antipsychotics (Goodwin et al 2009). In RCTs in bipolar disorder, placebo-level occurrence of EPS has been noted with quetiapine (McIntyre et al 2005a). In a real-world study in 37 bipolar patients treated with atypical neuroleptics, the incidence of any EPS was 62.7%; Parkinsonian symptoms (tremor or rigidity), 45.1%; and akathisia, 35.3% (Ghaemi et al 2006). **MDD:** Although there are limited data on occurrence of EPS in MDD, EPS have been reported with the TCAs and selective SSRIs (Mamo et al 2000). In a study of 130 affective disorder patients (110 bipolar, 18 unipolar depression, 2 atypical affective disorder) previously treated with lithium, typical neuroleptics, or antidepressants, the prevalence of tremor was 20.8%; hypokinetic parkinsonism, 7.7%; akathisia, 4.6%; dystonia, 3.8%; and TD, 9.2%. **GAD:** A literature review did not reveal any data on the incidence or prevalence of EPS in the GAD population.
Risk groups or risk factors	The development of EPS may be influenced by multiple and interrelated factors, such as duration of illness and its treatment, age of the patient, and age at onset of illness. Ghaemi et al 2006 reported there were no predictors of EPS in general, but akathisia occurred more frequently with high-potency agents (risperidone, ziprasidone, aripiprazole) and in a younger age group as each increasing year of age was associated with a 5% lower odds of akathisia). In contrast, a systematic review of EPS in bipolar disorder and schizophrenia (Gao et al 2008b) found that there was no higher risk for akathisia with aripiprazole, olanzapine, quetiapine or ziprasidone compared with their respective placebo. Overall, patients with bipolar disorder were more vulnerable to developing EPS than patients with schizophrenia (Gao et al 2008b). In the Ghadirian study (Ghadirian et al 1996), tremor was associated with lithium and neuroleptic intake, hypokinesia was associated with neuroleptic treatment and age. In a study of 100 inpatients receiving stable neuroleptic medication, a family history of EPS was significantly related to the lifetime prevalence of EPS (Lencer et al 2004). A genotypic analysis of 119 patients with schizophrenia, 63 of whom had current or previous EPS,

Table II-45 Important identified risks - EPS

Identified risk	EPS
	identified the presence of the Taq1A A1 allele of the dopamine D2 receptor and the 9 repeat allele of the dopamine transporter (DAT1) VNTR as possible risk factors for antipsychotic drug-induced EPS (Güzey et al 2007). Although this study was exploratory, it supports the hypothesis that there may be genetic factors involved in the development of EPS.
Potential mechanisms	Neuroleptics can cause extrapyramidal disorder by blocking dopaminergic receptors. Quetiapine exhibits affinity for brain serotonin (5-HT_2) and dopamine D_1 and D_2 receptors. It is this combination of receptor antagonism with a higher selectivity for 5-HT_2 relative to dopamine D_2 receptors, which is believed to contribute to the low extrapyramidal side effect liability of SEROQUEL/SEROQUEL XR.
Preventability	Common medical practice would be to provide treatment and/or medication adjustments if there are presenting signs and symptoms of EPS. Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: **Extrapyramidal symptoms:** In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder and major depressive disorder (see sections 4.8 and 5.1). The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental. Section 4.6, Fertility, pregnancy and lactation, of the SEROQUEL/SEROQUEL XR MR-SmPC states: Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. Section 4.8, Undesirable Effects, lists EPS as a Very Common (frequency is ≥1/10) ADR event for all patients, including children and adolescents (10 to 17 years of age).
Potential public health impact of Safety Concern/ Impact on individual patient	EPS limits clinical effectiveness of antipsychotics because of the high noncompliance rate and eventual treatment failure associated with these symptoms when severe. Atypical antipsychotics are thought to be associated with a significantly reduced EPS risk. EPS has been associated with antipsychotic medications since their first use in 1950. EPS has also been associated with lithium and SSRIs/SNRIs. EPS can lead to serious disability and therefore may impact public health (Pierre 2005, Reilly and Kirk 2007). A study of patients with MDD (n=1014) reported that akathisia was a risk factor for the emergence of suicidal ideation (Seemüller et al 2009).
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.
MedDRA terms	Akathisia, akinesia, athetosis, bradykinesia, buccoglossal syndrome, chorea, choreoathetosis, cogwheel rigidity, drooling, dyskinesia, dyskinesia esophageal, dystonia, extrapyramidal disorder, freezing phenomenon, grimacing, hyperkinesia, hypertonia, hypokinesia, masked facies, micrographia, movement disorder, muscle contractions involuntary, muscle rigidity, nuchal rigidity, oculogyric crisis, opisthotonus, parkinsonian gait, parkinsonism, pleurothotonus, posturing, psychomotor hyperactivity, restlessness, torticollis, and tremor.

5-HT2 5 hydroxytryptophan type 2; CATIE Clinical Antipsychotic Trials of Intervention Effectiveness; CI Confidence interval; EPS Extrapyramidal symptoms; GAD Generalised anxiety disorder; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; OLE Open-label extension; PLA Placebo; QTP Quetiapine; RCT Randomized controlled trial; SSRI Selective serotonin reuptake inhibitor; TCA Tricyclic antidepressant; TEAE treatment-emergent adverse event.

Table II-46 Important identified risks - Somnolence

Identified risk	Somnolence
Frequency/ Seriousness/ outcomes	**Placebo-controlled trials** 4187 (44.19%) quetiapine and 732 (14.66%) placebo patients had TEAEs; MH relative risk: QTP vs PLA (95% CI) 5.00 (4.62, 5.41) 0 events were considered serious by the investigators Recovered 3077 patients (74.31%); Not recovered 1059 patients (25.57%); unknown ~~5~~ 5(0.12%) **All studies (including OLEs) QTP exposure** 11925 (41.73%) had TEAEs. 18 events were considered serious by the investigators Recovered 8751 patients (73.38%); Not recovered 2875 patients (24.11%); Unknown 296 patients (2.49%) **Long-term (≥6 months) QTP exposure** 347 (8.34%) had TEAEs 7 events were considered serious by the investigators Recovered 218 patients (62.82%); Not recovered 98 patients (28.24%) ; Unknown 29 patients (8.36%)
Severity and nature of risk	Somnolence is sleepiness or an inclination to sleep during periods of the day when the subject prefers or is required to be awake and alert, eg, during working hours of the day. It may or may not be related to amount of sleep actually experienced. There were a total of 18 (0.15%) serious events in the all-study data. The majority of TEAEs of somnolence in the all-trial data were considered mild to moderate.
Background incidence/ prevalence	Self-reported sleep problems co-occur with DSM-IV mental disorders with high prevalence (16% to 25%) and are associated with substantial self-reported role impairment (Roth et al 2006). **Schizophrenia**: Widely varying estimates suggest 30% to 80% of patients with schizophrenia experience disturbed sleep; forming part of the pathophysiology of the disorder (Cohrs 2008). Somnolence in schizophrenia is reported with atypical antipsychotics, including olanzapine (20-39%), risperidone (3-9%), and ziprasidone (14%) (Miller 2004). The CATIE trial found no statistically significant differences in the proportion of subjects experiencing hypersomnia or sleepiness as moderate or severe AEs among the antipsychotics studied (Lieberman et al 2005). In a placebo-controlled study in 302 adolescents with schizophrenia, somnolence incidence with aripiprazole was 11% and 22%, with 10 mg and 30 mg doses, respectively (Findling et al 2008). **Bipolar disorder**: Somnolence has been associated with most of the medications used to treat bipolar disorder, including atypical antipsychotics, lamotrigine, lithium, divalproex, carbamazepine, and SSRIs/SNRIs. The incidence of somnolence in bipolar mania for other atypical antipsychotics (aripiprazole, olanzapine) is very common (>10%). In a meta-analysis of 24 clinical studies in acute mania of varying designs and various control groups, all of the second-generation antipsychotics were associated with increased somnolence (Scherk et al 2007). In a study of 348 patients with bipolar II disorder, hypersomnia was reported in 37.6% of patients (Akiskal and Benazzi 2005). An analysis of data from acute trials (10 in mania, 3 in bipolar depression, and 8 in schizophrenia) plus 2 maintenance studies in bipolar disorder and 2 in schizophrenia found that atypical antipsychotics caused a significantly greater incidence of somnolence than placebo in mania and depression, with the number needed to harm of between 5 to 8 for mania and 2 to 6 for bipolar depression (Gao et al 2008a). A large (n=438) community study in children found the prevalence of sleep disturbances in pediatric bipolar disorder to be approximately 3% (Mehl et al 2006). In adolescents and children with bipolar disorder, common side effects with antipsychotic

Table II-46 Important identified risks - Somnolence

Identified risk	Somnolence
	agents include somnolence (Heaton et al 2006). Incidence of somnolence in adolescents with schizophrenia or bipolar I disorder treated with olanzapine (n=454) was 19.8% (Kryzhanovskaya et al 2009). The incidence of somnolence in a double-blind study of olanzapine-fluoxetine combination for bipolar depression was 18.5% olanzapine-fluoxetine combination vs 8.3% lamotrigine (Brown et al 2006). **MDD**: Polysomnographic sleep research has shown alterations of sleep architecture in depression. The relationship between poor sleep quality and depression is bidirectional; depression increases the risk of poor sleep quality, and poor sleep quality is a predictor of future depressive episodes (van den Berg et al 2009). Somnolence has been associated with most of the medications used to treat MDD, including SSRIs/SNRIs, tricyclics, and atypical antipsychotics. The incidence of somnolence in placebo-controlled clinical studies of SSRIs for major depression ranged from 2% to 10% in the placebo group and from 6% to 23% in the treatment group (PDR 2008). **GAD**: Poor sleep can also be a consequence or symptom of an anxiety disorder. It is reported that 60% to 70% of patients with GAD experience trouble sleeping (Papadimitriou and Linkowski 2005). Somnolence has been associated with most of the medications used to treat GAD, including SSRIs/SNRIs and benzodiazepines. **General**: The National Ambulatory Medical Care Survey estimates approximately 18.6 million visits (weighted population size) were made to physicians for sleep-related difficulties in children 17 years of age or less (US; 1993-2004) (Stojanovski et al 2007). A survey of 174 children attending psychiatric services concluded that sleep problems are highly prevalent among children with psychiatric disorders (Ivanenko et al 2006). In the elderly, excessive daytime sleepiness was significantly associated severity of depression and lifetime prevalence of manic and hypomanic episodes (Tsuno et al 2007).
Risk groups or risk factors	Patients with schizophrenia or bipolar disorder experience disturbances in their sleep-wake cycle; this may be due to the disorder itself, pharmacotherapy, or a comorbid sleep disorder (Kane and Sharif 2008). Insomnia is known to be more frequent in women than men for all age groups; however, gender differences in the prevalence of insomnia are likely caused by gender differences in the prevalence of anxiety and depression (Voderholzer et al 2003). When taking antipsychotic medications, children and adolescents seem to have a higher risk than adults for experiencing AEs including sedation (Correll 2008, Kumra et al 2008).
Potential mechanisms	Quetiapine, olanzapine, and ziprasidone all have an affinity for serotonergic 5-HT2 histaminergic receptors in addition to their antidopaminergic effects; blockade of these wakefulness-promoting receptors are likely involved in the sedative side effects of these agents (Cohrs 2008).
Preventability	Section 4.4, Special Warnings and Precautions for Use (SEROQUEL/SEROQUEL XR MR-SmPC) states: Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8). In clinical trials for treatment of patients with bipolar depression, and MDD (XR only) onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve, and treatment discontinuation may need to be considered. **Section 4.5** Interaction with other medicinal products and other forms of interaction In a 6-week, randomised, study of lithium and SEROQUEL XR versus placebo and SEROQUEL XR in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the

Table II-46 Important identified risks - Somnolence

Identified risk	Somnolence
	lithium add-on group compared to the placebo add-on group (see section 5.1). Section 4.6, Fertility, pregnancy and lactation, of the SEROQUEL/SEROQUEL XR MR-SmPC states: Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Section 4.7, Effect on Ability to Drive and Use Machines, of the MR-SmPC states: Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known. Section 4.8, Undesirable Effects, states: The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine are somnolence, …
Potential public health impact of Safety Concern/ Impact on individual patient	Excessive daytime somnolence is a prevalent problem in society. It has a substantial impact on public health through increased safety risks (eg, increased potential for falls) and the disruption of education, work, productivity, and the quality of life for affected patients. The 2002 Sleep in America Poll revealed that 37% of adults reported that daytime sleepiness interfered significantly with their daily activities (National Sleep Foundation 2002). Somnolence could contribute to increased frequency of motor vehicle accidents and therefore impact public health (Pandi-Perumal et al 2006). Section 4.7, Effect on Ability to Drive and Use Machines, of the MR-SmPC addresses this concern (as noted earlier). It has been suggested that sleep disturbance in the general population is a risk factor for the onset of a formal psychiatric diagnosis at a later time (Gillin 1998).
Evidence source	Clinical studies integrated safety database Version 27) and literature sources.
MedDRA terms	Lethargy, sedation, sluggishness, somnolence, fatigue, and hypersomnolence

5-HT2 5 hydroxytryptophan type 2; AE Adverse event; CATIE Clinical Antipsychotic Trials of Intervention Effectiveness; CI Confidence interval; DSM-IV Diagnostic and Statistical Manual of Mental Disorders IV; GAD Generalised anxiety disorder; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; MR Mutual recognition; OLE Open-label extension; PLA Placebo; QTP Quetiapine; SmPC Summary of Product Characteristics; SNRI Serotonin-norepinephrine reuptake inhibitor; SSRI Selective serotonin reuptake inhibitor; TCA tricyclic antidepressant; TEAE Treatment-emergent adverse event; US United States.

Metabolism and nutritional disorders

Table II-47 Important identified risks - Weight gain

Identified risk	Weight gain
Frequency of weight gain ≥ 7% increase/ Seriousness/ Outcomes	Data for this risk consists of vital sign measurements performed routinely during clinical studies and does not have seriousness or outcome data associated with it. **Placebo-controlled trials** 878 (10.0%) quetiapine and 178 (3.8%) placebo patients had weight gain ≥ 7% ; MH relative risk: QTP vs PLA (95% CI) 2.67 (2.26, 3.14) **All studies (including OLEs) QTP exposure** 4615 (18.4%) had weight gain ≥ 7%. **Long-term (≥6 months) QTP exposure** 1524 (40.1%) had weight gain ≥ 7%.
Severity and nature of risk	Weight gain is described in this RMP as potentially clinically important if it involved a weight increase of ≥7% compared with baseline. Relevant weight parameters include weight increase ≥7% compared with baseline and mean weight change from baseline to end of treatment. Data for this risk consists of vital sign measurements performed routinely during clinical studies and does not have severity data associated with it.
Background incidence/ prevalence	**Schizophrenia:** Obesity rates in patients with schizophrenia are at least as high, if not higher, than in the general population (Allison et al 1999). An analysis of time trends over ten years of data collection (1987-1996) of the annual National Health Interview Survey in the US determined that mean BMI for individuals with schizophrenia was higher than for individuals who were not schizophrenic (Homel and Casey 2002). Females aged 18 to 30 had a dramatic increase in BMI, whereas for most other age gender groups there was little evidence of a trend for BMI. In one European study, 74% of individuals with schizophrenia for 10 to 20 years met IDF metabolic syndrome risk factor criteria for excessive waist circumference (De Hert et al 2006). Rates of obesity in adolescents and young adults with schizophrenia treated at a single German center were 51% in males and 64% in females (Theisen et al 2001). **Bipolar disorder:** The prevalence of obesity in patients with bipolar disorders is reported to range from 20% to 35%, exceeding that in the general population (Kim et al 2008). In a study conducted at a major bipolar treatment center (n=377), 55% were either overweight (28% BMI = 25 to 30 kg/m^2) or obese (27% BMI >30 kg/m^2) (Wang et al 2006). Another group found that 58% of 644 bipolar patients were overweight, 21% were obese, and 5% were extremely obese. American patients had significantly higher mean ($p<0.0001$) BMIs and significantly higher rates of obesity ($p<0.001$) and extreme obesity ($p<0.001$) than European patients (McElroy et al 2002). Of 171 patients with bipolar disorder, 49% met the NCEP ATP III metabolic syndrome criterion for abdominal obesity (Fagiolini et al 2005). Comparative studies find that bipolar patients are more likely to be overweight and obese than matched controls (Elmslie et al 2000, Shah et al 2006). **MDD:** Both weight loss and weight gain are associated with depression (DSM-IV 2000). In a study of 93 untreated patients with a unipolar depressive episode, 37% gained weight during the course of illness (Weissenburger et al 1986). Weight gain may also be associated with remission of depression. In a study of 100 remitted outpatients with unipolar or bipolar depression, 72% gained weight upon remission of their depressive episode (Benazzi 1998). **GAD:** In the 20-year Zurich Cohort Study, GAD was found to be negatively associated with overweight; the reported prevalence of overweight in GAD patients was 13.1% (Hasler et al 2004).

Table II-47 Important identified risks - Weight gain

Identified risk	Weight gain
	Pediatric patients: The prevalence of overweight and obesity in children and adolescents has been rising across the US and Europe. A recent study of 137593 youths aged 10 to 16 years from 34 nations estimated the prevalence of overweight to range from 5.1% to 25.4% (Janssen et al 2005). Overweight was most prevalent in North America, Great Britain, and southwestern Europe. In chart-review studies of children and adolescents who were psychiatric in-patients in the US, approximately one-third had BMI ≥ the 95th percentile for their age group (Hasnain et al 2008, Vieweg et al 2005). The majority of patients in these studies had a primary mood disorder diagnosis; the remaining had a primary psychotic or bipolar disorder diagnosis. Most patients had multiple comorbidities and extensive psychiatric treatment histories. Studies suggest that some atypical antipsychotic medications may cause weight gain in youth (Laita et al 2007). A review of short-term clinical studies conducted among children and adolescents found that extreme weight gain (>7% weight increase from baseline) was differentially associated with the various atypical antipsychotics (Ratzoni et al 2002, Stigler et al 2004). Short-term clinical studies in children and adolescents diagnosed with bipolar depression or mania suggest that patients taking an atypical antipsychotic medication in combination with mood stabilizers had increased risk of weight gain compared to patients treated with 1 or 2 mood stabilizers (Correll 2007). Even in preschool-age children (4 to 6 years), weight gain >10% of baseline has been reported with olanzapine and risperidone (Biederman et al 2005).
Risk groups or risk factors	Obesity is a result of a complex variety of social, behavioral, cultural, environmental, physiological, and genetic factors. The risk for being overweight or obese has increased substantially for all age groups including children and is associated with adverse effects on almost every organ system (US DHHS 2001). A longitudinal study in Finland reported that the risk of individuals with a psychotic disorder becoming overweight between the ages of 14 and 31 years was higher in females than males (ORs 3.5 vs 2.1, respectively) (Hakko et al 2006). It has been reported that lower BMI at baseline and a diagnosis of undifferentiated schizophrenia are associated with antipsychotic-induced weight gain (Saddichha et al 2008). Weight gain is associated with most psychotropic medications used to treat depression, including TCAs, SSRIs, MAOIs, mood stabilizers, and atypical antipsychotics (Pi-Sunyer et al 2007). One study showed admission to a psychiatric inpatient unit to be a contributing factor, and among those admitted, those who gained more weight were patients with bipolar disorder or schizophrenia, smokers, males, and those treated with atypicals (Megna et al 2006). Studies in adults, adolescents and children have shown that different antipsychotics have different propensities to cause weight gain (Citrome 2007, Correll 2008). Olanzapine has a greater potential for weight gain than other antipsychotics (Nasrallah 2006, Karagianis et al 2007). Data from the CATIE schizophrenia study show that if 100 patients were treated with olanzapine rather than SEROQUEL or other antipsychotics, 14 to 23 more patients would experience weight gain >7% (Karagianis et al 2007).
Potential mechanisms	Although there are many theories, the exact mechanism of action is unknown. The serotonergic, adrenergic, and/or histaminergic neurotransmission may be involved. Olanzapine and clozapine, which appear to cause increased weight gain, have been found to raise leptin levels, which is associated with the increase in BMI.
Preventability	Common medical practice would be to recommend a healthy diet and exercise for patients at risk for weight gain. Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states:

Table II-47 Important identified risks - Weight gain

Identified risk	Weight gain
	Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilized antipsychotic guidelines (see Sections 4.8 and 5.1). Metabolic Risk Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patients' metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also section 4.8).
Potential public health impact of Safety Concern/ Impact on individual patient	Weight gain presents a serious public health Safety Concern; approximately 65% of adults are considered overweight or obese. The adverse effects of overweight and obesity on health and longevity are well documented. Obesity and its complications cause as many as 300,000 premature deaths each year, making it second to cigarette smoking as a cause of death. Overweight and obesity increase risk of morbidity and/or mortality from numerous chronic conditions including Type 2 DM, coronary heart disease, hypertension, hyperlipidemia, osteoarthritis, and certain cancers (Merck Manual 2007).
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.
MedDRA terms	For this RMP, weight gain was assessed on relevant laboratory weight parameters and not on adverse event reports.

AE Adverse event; BMI Body mass index; CATIE Clinical Antipsychotic Trials of Intervention Effectiveness; CI Confidence interval; DM diabetes mellitus; DSM-IV Diagnostic and Statistical Manual of Mental Disorders IV; GAD Generalised anxiety disorder; IDF International Diabetes Foundation; MAOI monoamine oxidase inhibitor; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III; OLE Open-label extension; OR Odds ratio; PLA Placebo; QTP Quetiapine; RMP Risk Management Plan; SSRI Selective serotonin reuptake inhibitor; TCA Tricyclic antidepressant; TEAE Treatment-emergent adverse event; US United States.

Table II-48 Important identified risks - Lipid changes (increased cholesterol [predominantly low-density lipoprotein], increased triglycerides, or decreased high-density lipoprotein)

Identified risk	Lipid changes (increased cholesterol [predominantly LDL], increased triglycerides, or decreased HDL)
Frequency/ Seriousness/ Outcomes	For this RMP, increased cholesterol, increased triglycerides, increased LDL and decreased HDL were assessed on relevant laboratory data and not on AE reports. The laboratory data does not have seriousness and outcome data. **Increased cholesterol:** **Placebo-controlled trials** 563 (8.9%) quetiapine and 215 (6.5%) placebo patients had increased cholesterol ; MH relative risk: QTP vs PLA (95% CI) 1.42 (1.21, 1.67) **All studies (including OLEs) QTP exposure** 1644 (10.3%) **Long-term (≥6 months) QTP exposure** 315 (13.8%) **Increased triglycerides:** **Placebo-controlled trials** 920 (14.9%) quetiapine and 299 (9.4%) placebo patients had increased triglycerides; MH relative risk: QTP vs PLA (95% CI) 1.70 (1.48, 1.94) **All studies (including OLEs) QTP exposure** 2696 (18.8%) 2708 (18.7%) **Long-term (≥6 months) QTP exposure** 508 (26.0%) **Increased LDL** **Placebo-controlled trials** 291 (5.8%) quetiapine and 137 (5.1%) placebo patients had increased LDL ; MH relative risk: QTP vs PLA (95% CI) 1.14 (0.92, 1.40) **All studies (including OLEs) QTP exposure** 896 (7.2%) **Long-term (≥6 months) QTP exposure** 212 (9.9%) **Decreased HDL** **Placebo-controlled trials** 657 (11.6%) quetiapine and 281 (10.2%) placebo patients had decreased HDL ; MH relative risk: QTP vs PLA (95% CI) 1.18 (1.02,1.36) **All studies (including OLEs) QTP exposure** 2069 (15.3%) **Long-term (≥6 months) QTP exposure** 430 (21.6%)

Table II-48 Important identified risks - Lipid changes (increased cholesterol [predominantly low-density lipoprotein], increased triglycerides, or decreased high-density lipoprotein)

Identified risk	Lipid changes (increased cholesterol [predominantly LDL], increased triglycerides, or decreased HDL)
Severity and nature of risk	Hypercholesterolemia can occur from either the overproduction of VLDL or its defective clearance as well as from the excessive conversion of VLDL to LDL. Lipoprotein metabolism, kinetics, the concentration of subclasses, and other genetic factors affecting functionality may all contribute to the atherogenic properties of LDL cholesterol and the anti-atherogenic properties of HDL; thus, standard plasma measurement may not capture the full range of LDL and HDL effects (Link et al 2007). For LDL, there is no apparent threshold value below which risk does not increase. Although a direct relationship between LDL and CHD shows no inflection points, any reduction in LDLs from population means is accompanied by a decreased risk for CHD. Higher risk for CHD at lower HDL levels is multifactorial in causation. Although an inverse relationship between HDL and CHD shows no inflection points, any reduction in HDL from population means is accompanied by increased risk for CHD. Relevant laboratory parameters include the following: For increased cholesterol: total cholesterol ≥6.21 mmol/L; for increased triglycerides: triglycerides ≥2.26 mmol/L; for increased LDLs: fasting levels ≥4.2 mmol/L; and for decreased HDLs: ≤1.04 mmol/L in patients who were normal at enrollment/baseline. Data for this risk are based on laboratory measurements performed routinely during clinical studies and do not have severity data associated with them.
Background incidence/ prevalence	**Schizophrenia:** In the CLAMORS study (a retrospective study of Spanish outpatients with schizophrenia, schizophreniform or schizoaffective disorder aged 18 to 74 years who were taking selected oral antipsychotics for at least 12 weeks), 49.3% of males and 52.6 % of females had total cholesterol values >200 mg/dL (Bobes et al 2007). In a Singaporean study, in which 71% of 160 patients had a diagnosis of schizophrenia spectrum disorder, a low prevalence of increased LDL cholesterol (>3.4 mmol/l) was observed in drug-naive patients with first-episode psychosis (21.3%) compared with age-, gender- and ethnicity-matched controls (32.5%) [p<0.05] (Verma et al 2009). **Bipolar disorder:** Most studies suggest bipolar patients have lower cholesterol levels than the national norm (Cassidy and Carroll 2002, Girardin and Gaspoz 2007, Glueck et al 1994) or than healthy controls (Swartz 1990, Atmaca et al 2002, Pae et al 2004). Of 171 patients with bipolar disorder participating in a research diagnostic interview using the Structured Clinical Interview, 23% met the NCEP ATP III metabolic syndrome criterion for low HDL cholesterol (Grundy et al 2004, Fagiolini et al 2005). A cross-sectional study of patients diagnosed with bipolar disorder in the Veterans Administration Health system showed a prevalence of hyperlipidemia at 23% (Kilbourne et al 2004). **MDD:** The association between total cholesterol levels and affective disorders is not consistently reported in different studies. In depressed patients, both high and low cholesterol levels have been found compared with healthy controls (Jow et al 2006). Other investigators cite studies associating low cholesterol levels with depression as well as increased risk of suicide (Papakostas et al 2004). In another report, significantly lower total cholesterol levels were observed in patients with MDD before and following recovery following admission to the central mental health hospital in Kuwait compared to sex-, age-, and weight-matched healthy controls (Olusi and Fido 1996). However, in another study, psychiatric outpatients with MDD who had been drug free for 1 month had similar total cholesterol levels as compared to age-, sex-, and BMI-matched healthy controls (Sevincok et al 2001).

Table II-48 Important identified risks - Lipid changes (increased cholesterol [predominantly low-density lipoprotein], increased triglycerides, or decreased high-density lipoprotein)

Identified risk	Lipid changes (increased cholesterol [predominantly LDL], increased triglycerides, or decreased HDL)

GAD: In the previously described study of psychiatric outpatients, those with comorbid GAD and MDD had higher total cholesterol levels compared with patients with GAD, MDD, and healthy control subjects (Sevincok et al 2001).

Pediatric population: Elevated levels of total cholesterol were observed in 9.6% to 10.7% of children 6 to 17 years of age, depending upon the cutpoints for elevated levels applied to participants in the US NHANES surveys conducted from 1999 to 2006 (Ford et al 2009). The National Cholesterol Education Program Panel on Cholesterol in Children and Adolescents guideline for elevated total cholesterol is >200 mg/dL (American Academy of Pediatrics 1992). The cutpoints for abnormal values of total cholesterol based on the 95th percentile in the Lipid Research Clinics Pediatrics Prevalence Study published in 1979 were 201 mg/dL for boys 10 to 14 years of age, 191 mg/dL for boys 15 to 19 years of age, 205 mg/dL for girls 10 to 14 years of age, and 208 mg/dL for girls 15 to 19 years of age.

General: According to the US NHANES surveys (2005-2006), the percentage of US men and women aged 20 years and older with total cholesterol >240 mg/dL was 13.8% and 17.3%, respectively (Schober et al 2007).

Increased triglycerides

Schizophrenia: In the CLAMORS study, the prevalence of hypertriglyceridemia was 37.3% (Bobes et al 2007). It was more prevalent in men than in women (40.7% [95% CI: 37.2–44.2] vs 32.4% [95% CI: 28.3–36.5], respectively, p<0.01). The 3-month results of non-fasting triglycerides in patients treated with antipsychotics in the CATIE schizophrenia trial found increases in fasting triglycerides with olanzapine (+21.5 mg/dL), quetiapine (11.9 mg/dL), and perphenazine (11.5 mg/dL) while decreases were observed with risperidone (-18.4 mg/dL) and ziprasidone (-32.1 mg/dL) (Meyer et al 2008).

Bipolar disorder: A small number of studies over the past 4 decades have suggested higher than normal levels of triglycerides in bipolar patients (Brandrup and Randrup 1967). Of 171 patients with bipolar disorder, 41% met the NCEP ATP III metabolic syndrome criterion for hypertriglyceridemia (Grundy et al 2004, Fagiolini et al 2005).

MDD: Patients hospitalized for affective disorders (depression, bipolar disorder, and schizoaffective disorder) had significantly higher triglyceride concentrations than community-based controls (p<0.03) (Glueck et al 1994).

GAD: A literature review did not reveal any information on the incidence or prevalence of increased triglycerides in the GAD population.

Increased LDLs:

Schizophrenia: A literature review found no reported studies of the occurrence of hyperlipidemia in untreated patients with schizophrenia. A study of Medicaid recipients with schizophrenia determined that 4.6% of a subgroup aged 20 to 34 years treated with clozapine received a diagnosis or treatment indicative of hyperlipidemia. Treatment with clozapine vs conventional antipsychotics was associated with a 2.4-fold elevated risk of hyperlipidemia (Lund et al 2001). Two case-control studies of patients with schizophrenia (conducted in the GPRD and in US Medicare recipients) found a significant association between the development of hyperlipidemia and previous use of antipsychotic drugs (Koro et al 2002, Lambert et al 2005). The study conducted in the GPRD determined that olanzapine and clozapine, but not risperidone or combination therapy, were significantly associated with a diagnosis of hyperlipidemia (Koro et al 2002). The study in US Medicare recipients determined that a diagnosis of hyperlipidemia was associated with an elevated OR (1.2; 95%

Table II-48 Important identified risks - Lipid changes (increased cholesterol [predominantly low-density lipoprotein], increased triglycerides, or decreased high-density lipoprotein)

Identified risk	Lipid changes (increased cholesterol [predominantly LDL], increased triglycerides, or decreased HDL)

CI=1.08,1.33) of having received treatment with olanzapine vs. older antipsychotic medications during the previous 12 weeks. No increase in risk for hyperlipidemia was observed for risperidone or quetiapine (Lambert et al 2005). In a study conducted in Singapore, in which 71% of 160 patients had a diagnosis of schizophrenia spectrum disorder, a low prevalence of increased LDL cholesterol (>3.4 mmol/l) was observed in drug-naive patients with first-episode psychosis (21.3%) compared with age-, gender- and ethnicity-matched controls (32.5%) [p<0.05] (Verma et al 2009).

Bipolar disorder: Most studies suggest bipolar patients have lower cholesterol levels than the national norm (Cassidy and Carroll 2002, Girardin and Gaspoz 2007, Glueck et al 1994) or than healthy controls (Swartz 1990, Atmaca et al 2002, Pae et al 2004).

MDD: The association between LDL levels and affective disorders is not consistently observed in different studies. In one report, significantly lower LDL levels were observed in patients with MDD before and following recovery following admission to the central mental health hospital in Kuwait compared to sex-, age-, and weight- matched healthy controls (Olusi and Fido 1996). However, in another study, psychiatric outpatients with MDD who had been drug free for 1 month had higher LDL levels than age-, sex-, and BMI-matched healthy controls (Sevincok et al 2001). Outpatients with comorbid GAD and MDD had higher levels of LDL than patients with MDD alone (Sevincok et al 2001).

GAD: In the previously described study of psychiatric outpatients, those with comorbid GAD and MDD had higher LDL levels compared with patients with GAD, MDD, and healthy control subjects (Sevincok et al 2001).

Pediatric population: Elevated levels of LDL were observed in 5.2% to 6.6% of children 6 to 17 years of age, depending upon the cutpoints for elevated levels applied to participants in the US NHANES surveys conducted from 1999 to 2006 (Ford et al 2009). The National Cholesterol Education Program Panel on Cholesterol in Children and Adolescents guideline on elevated LDL is >130 mg/dL. The cutpoints for abnormal values of LDL based on the 95th percentile in the Lipid Research Clinics Prevalence Study published in 1979 were 133 mg/dL for boys 10 to 14 years of age, 130 mg/dL for boys 15 to 19 years of age, 136 mg/dL for girls 10 to 14 years of age, and 137 mg/dL for girls 15 to 19 years of age.

Decreased HDLs

Schizophrenia: The 3-month results for HDL in patients treated with antipsychotics in the CATIE schizophrenia trial found mean decreases in HDL with olanzapine (–2.3 mg/dL), quetiapine (-1.0 mg/dL), risperidone (-0.7 mg/dL), ziprasidone (0.1 mg/dL), and perphenazine (-0.1 mg/dL) (Meyer et al 2008). Mean changes according to race were -0.2 mg/dL and 0.1 mg/dL in white and non-white patients, respectively. The proportion of patients who received quetiapine meeting ATP III criteria for low HDL at baseline and at 3 months was 56.9% and 57.4%, respectively.

Bipolar disorder: Of 171 patients with bipolar disorder participating in a research diagnostic interview using the Structured Clinical Interview, 23% met the NCEP ATP III metabolic syndrome criterion for low HDL (Fagiolini et al 2005).

MDD: The association between HDL levels and affective disorders is inconsistent. In one series, lower HDL levels were observed in men with MDD (Maes et al 1997); however, in other studies in women, either lower levels of HDL were observed (Sagud et al 2009) or no significant differences were observed (Huang et al 2003). Significantly higher HDL levels were observed in patients with MDD before and following recovery following admission to

Table II-48 Important identified risks - Lipid changes (increased cholesterol [predominantly low-density lipoprotein], increased triglycerides, or decreased high-density lipoprotein)

Identified risk	Lipid changes (increased cholesterol [predominantly LDL], increased triglycerides, or decreased HDL)
	the central mental health hospital in Kuwait compared to sex-, age-, and weight- matched healthy controls (Olusi and Fido 1996). However in another study, psychiatric outpatients with MDD who had been drug free for 1 month had lower HDL than age-, sex-, and BMI-matched healthy controls (Sevincok et al 2001). Outpatients with comorbid GAD and MDD had slightly lower levels of HDL than patients with MDD alone (Sevincok et al 2001). **GAD:** In the previously described study of psychiatric outpatients, outpatients with GAD had HDL levels that were not statistically different from healthy controls. Those with comorbid GAD and MDD had significantly lower HDL compared with patients with GAD only and healthy control subjects (Sevincok et al 2001). **Pediatric population:** The Lipid Research Clinics Prevalence Study determined the median values of HDL in mg/dL for boys aged 5 to 9, 10 to 14 and 15 to 19 to be 56, 57, and 47 with corresponding median values for girls as 54, 54, and 53, respectively. At puberty, HDL levels (and total cholesterol levels) decrease for boys. Non-Hispanic black children and adolescents had significantly higher mean HDL levels compared to non-Hispanic white and Mexican American children and adolescents. In linear regression models of these data, age, sex, and race have significant effects on lipid levels questioning the utility of fixed screening cut points (Hanley et al 2007).
Risk groups or risk factors	**Increased cholesterol, triglycerides, or LDL:** Risk factors for hypercholesterolemia and hypertriglyceridemia include sex, race/ethnicity, genetic predisposition, diet high in cholesterol, excess weight, inactivity, older age, and stress (Grundy et al 2004). High serum total cholesterol (>240 mg/dL) is found in 23% of US women aged 60 years and older compared to 10% of men of similar age (Schober et al 2007). In the US NHANES survey (2003-2006), the age-adjusted patterns of hypertriglyceridemia for race and ethnicity varied by sex. Males had a higher age-adjusted prevalence of hypertriglyceridemia than females (35.6% vs 26.5%). Non-Hispanic white and Mexican-American males had a higher prevalence of hypertriglyceridemia (36.6% and 43.7%, respectively) than non-Hispanic black males (21.2%) (Ervin 2009). US males 40 to 59 years of age were more likely than those 20 to 39 years of age to have hypertriglyceridemia (41.5% vs 29.6%), but the prevalence among males 60 years of age and over (36.7%) was not significantly different from that of the other two age groups. For females, the prevalence of hypertriglyceridemia increased with each succeeding age group. Mexican-American females had a higher prevalence of hypertriglyceridemia (34.6%) than either non-Hispanic white or non-Hispanic black females (27.3 and 14.4%, respectively). The Copenhagen Heart study determined that nonfasting triglyceride levels independently predict MI, IHD, and death, particularly in women (Nordestgaard et al 2007). Other meta-analyses have found a gradation of risk for both fasting and nonfasting triglycerides such that a relative risk of risk of coronary heart disease of 1.72 (95% CI: 1.56, 1.90) was observed comparing individuals in the upper vs lower tertiles of usual triglyceride levels among 262525 participants in 29 Western prospective studies (Sarwar et al 2007). Review of the medical records of 96 patients with schizophrenia or schizoaffective disorder showed that triglycerides increased during treatment with clozapine, with a linear coefficient of 0.5 mg/dL/month; in contrast, total cholesterol levels did not change during treatment (Henderson et al 2005). Switching between atypical antipsychotics has effects on both triglycerides and LDL cholesterol that vary depending on the choice of agent (Garman et al 2007).

Table II-48 Important identified risks - Lipid changes (increased cholesterol [predominantly low-density lipoprotein], increased triglycerides, or decreased high-density lipoprotein)

Identified risk	**Lipid changes (increased cholesterol [predominantly LDL], increased triglycerides, or decreased HDL)**

According to the US National Cholesterol Education Program ATP III, the following factors contribute to risk of elevated LDL and are recognized as major risk factors that modify LDL goals: age 45 years or older for males and 55 years or older for females; cigarette smoking; low HDL (<40 mg/dL); and family history of early CHD disease if in a male first degree relative under age 45 years or a female first-degree relative under age 55 years. Other factors include overweight condition and obesity, which are associated with elevated LDL cholesterol), prior history of coronary heart disease and diabetes; hypertriglyceridemia and elevated remnant lipoprotein (VLDL) levels, which are associated with arthrogenic potential. Sex differences in risk of elevated LDL generally follow that females have higher levels than males in childhood and adolescence, during pregnancy and after menopause, with males having higher risk during adult middle ages. Diets high in saturated fat, cholesterol, trans fats, and low in fiber and sedentary lifestyle are also considered risk factors. Secondary hyperlipidemia can be caused by diabetes, hypothyroidism, obstructive liver disease, chronic liver failure, and drugs that increase LDL (ie, progestins, anabolic steroids, and corticosteroids).

Decreased HDL: In the US NHANES survey (2003-2006), the age-adjusted patterns of low HDL for race and ethnicity varied by sex. Females had a higher age-adjusted prevalence of low HDL than males (27.8% and 21.6%, respectively). Non-Hispanic white and Mexican-American males had a higher prevalence of low HDL (22.6% and 26%, respectively) than non-Hispanic black males (11.5%) (Ervin 2009). Mexican-American females had a higher prevalence of low HDL cholesterol (39.6%) than either non-Hispanic white or non-Hispanic black females (27.6 and 26.8%, respectively).

Evidence from several prospective observational studies has reported an inverse relationship between plasma HDL levels and coronary heart disease risk. The risk for myocardial infarction increased about 25% for every 5-mg/dL decrease in serum HDL below median values for men and women in the Framingham Heart Study (Gordon et al 1977). Analyses of 4 large prospective studies—the Framingham Heart Study, the Multiple Risk Factor Intervention Trial (MRFIT), the Lipid Research Clinics Prevalence Mortality follow-up study, and the Coronary Primary Prevention Trial—has indicated that each 1 mg/dL decrease in HDL is associated with a 2% increase in CHD risk in men and a 3% increase in CHD risk in women with no prior history of CHD (Link et al 2007). There is evidence supporting an independent association of baseline HDL and decreased coronary event rates in patients with CHD.

Table II-48 Important identified risks - Lipid changes (increased cholesterol [predominantly low-density lipoprotein], increased triglycerides, or decreased high-density lipoprotein)

Identified risk	Lipid changes (increased cholesterol [predominantly LDL], increased triglycerides, or decreased HDL)
Potential mechanisms	**Increased cholesterol, triglycerides, or LDLs:** The liver may cause an overproduction of VLDL by obesity, excessive alcohol use, diabetes mellitus, and nephrotic syndrome. Any of these conditions can cause an increase in LDL and total cholesterol levels, and these are often associated with hypertriglyceridemia. Alterations in lipid metabolism have been identified for other members of the antipsychotic class. Excessive alcohol has been identified in the some populations treated with SEROQUEL/SEROQUEL XR. An exact potential mechanism for SEROQUEL/SEROQUEL XR and increased total cholesterol (predominantly increased LDL) and increased triglycerides has not been established. Potential mechanisms are likely to be multifactorial. **Decreased HDL:** The contribution of serious psychiatric conditions to aberrant lipid profiles is not well described, especially given that most studies have included previously treated patients. The development of dyslipidemia, including the observed changes in HDL among patients with serious psychiatric disorders treated with atypical antipsychotics, remain to be elucidated. Potential mechanisms are likely to be multifactorial and include environmental, behavioral, genetic, and other metabolic factors (eg, elevated serum triglycerides, overweight condition/obesity, physical inactivity, cigarette smoking, very high carbohydrate intake [>80% of total energy], type 2 diabetes, genetic factors, and use of certain drugs, ie, beta-blockers, anabolic steroids, and progestational agents).
Preventability	Common medical practice would be to recommend a healthy diet and exercise for patients at risk for increased lipids as well as a lipid-lowering medication for some patients. The Special Warnings and Precautions for Use section 4.4 of the MR-SmPC states: Metabolic Risk Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also section 4.8). **Lipids:** Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid changes should be managed as clinically appropriate.

Table II-48 Important identified risks - Lipid changes (increased cholesterol [predominantly low-density lipoprotein], increased triglycerides, or decreased high-density lipoprotein)

Identified risk	Lipid changes (increased cholesterol [predominantly LDL], increased triglycerides, or decreased HDL)
Potential public health impact of Safety Concern/ Impact on individual patient	Increased cholesterol: Elevated total cholesterol values are associated with CHD mortality. In the US, 20% of adults have high total cholesterol levels (≥200 mg/dL). In 2005-2006, the percentage of men and women aged 20 years and older with total cholesterol >240 mg/dL was 13.8% and 17.3%, respectively (Schober et al 2007). The proportion of men and women with total cholesterol at these levels who had never been told that they had high cholesterol by a physician was 7.1% and 8.0%, respectively. Increased triglycerides: Increased triglycerides have a serious public health impact due to the link between lipoprotein disorders and atherosclerosis, and its clinical manifestations of myocardial infarction, stroke, and sudden cardiac death. In addition, marked elevations of triglycerides are associated with acute pancreatitis, diabetes, and metabolic syndrome. Increased LDLs and decreased HDLs: Elevated LDL levels and low levels of HDL are each associated with an increase in risk for atherosclerotic disease and its clinical sequelae, including myocardial infarction, stroke, and sudden death. Several studies have demonstrated that approximately two-thirds of patients with coronary artery disease have low serum levels of HDL. These diseases contribute to the elevated mortality observed among patients with schizophrenia compared to the general population. Given the long-term impact of untreated hyperlipidemia on cardiovascular mortality, especially in populations with multiple cardiovascular risk factors, there is a need to insure that mental health professionals are cognizant of these problems in these patients. They need to take on an active role in monitoring changes in lipids especially when they are associated with antipsychotic treatments.
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.
MedDRA terms	For this RMP, increased cholesterol, increased triglycerides, increased LDLs, and decreased HDLs were assessed on relevant laboratory data and not on AE reports.

AE Adverse event; BMI Body mass index; CATIE Clinical Antipsychotic Trials of Intervention Effectiveness; CHD Coronary heart disease; CI Confidence interval; GAD Generalised anxiety disorder; GPRD General Practice Research Database; HDL High-density lipoprotein; IHD Ischemic heart disease; LDL Low-density lipoprotein; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; MI Myocardial infarction; NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III; NHANES National Health and Nutrition Examination Survey; OLE Open-label extension; OR Odds ratio; PLA Placebo; QTP Quetiapine; RMP Risk Management Plan; SSRI selective serotonin re-uptake inhibitors; TEAE Treatment-emergent adverse event; US United States; VLDL Very low-density lipoprotein.

Table II-49 Important identified risks - Hyperglycemia and diabetes mellitus (included per MRP outcome)

Identified risk	Hyperglycemia and DM (included per MRP outcome)
Frequency/ Seriousness/ Outcomes	**AE reports (MedDRA PTs)** **Placebo-controlled trials** 44 (0.46%) quetiapine and 24 (0.48%) placebo patients had TEAEs; MH relative risk: QTP vs PLA (95% CI) 1.05 (0.63, 1.76) 1event was considered serious by the investigators Recovered 18 patients (40.91%); not recovered 26 (59.09%) **All studies (including OLEs) QTP exposure** 225 (0.79%) had TEAEs. 16 events were considered serious by the investigators Recovered 75 patients (33.33%); Not recovered 144 patients (64.00%); Unknown 5 patients (2.22%) **Long-term (≥6 months) QTP exposure** 50 (1.20%) had TEAEs 6 events were considered serious by the investigator. Recovered 16 patients (32.00%); Not recovered 33 patients (66.00%) **Fasting blood glucose ≥7.0 mmol/L (≥126 mg/dL) in patients who met specified criteria at baseline)** **Placebo-controlled trials** 75 (2.0%) quetiapine and 29 (1.5%) placebo patients; MH relative risk: QTP vs PLA (95% CI) 1.46 (0.94, 2.28) **All studies (including OLEs) QTP exposure** 265 (2.9%) . **Long-term (≥6 months) QTP exposure** 55 (4.1%) **Random blood glucose ≥11.1 mmol/L (≥200 mg/dL) in patients who met specified criteria at baseline)** **Placebo-controlled trials** 16 (1.0%) quetiapine and 5 (0.5%) placebo patients; MH relative risk: QTP vs PLA (95% CI) 2.26 (0.81, 6.30) **All studies (including OLEs) QTP exposure** 52 (1.2%) . **Long-term (≥6 months) QTP exposure** 13 (2.9%)

Table II-49 Important identified risks - Hyperglycemia and diabetes mellitus (included per MRP outcome)

Identified risk	Hyperglycemia and DM (included per MRP outcome)
Additional information	AstraZeneca evaluated glucose metabolism in patients with schizophrenia in Study D1441C00125, which was a 24-week, international, multicenter, open-label, flexible-dose, randomized, parallel-group, Phase IV study to compare the effects of quetiapine, olanzapine, and risperidone (study report submitted to the MEB in June 2007). Results showed certain differential treatment effects on glucose excursion after glucose load. Specifically, the difference between quetiapine and olanzapine groups in mean change in $AUC_{0\text{-}2h}$ for plasma glucose was statistically significant in favor of quetiapine, and the difference between quetiapine and risperidone groups was numerically in favor of quetiapine. Additionally, the quetiapine group showed no change from randomization at Week 24 in mean 2-hour glucose values, while increases were seen in both the olanzapine and risperidone groups. Moreover, a shift to a higher 2-hour glucose category (ie, from normal to impaired/high or from impaired to high) was seen in about twice as many patients in the risperidone group compared with the quetiapine group, and in about 50% more patients in the olanzapine group than in the quetiapine group. In the absence of glucose load, there was no meaningful difference between the treatment groups at Week 24 as measured by fasting glucose level, HbA1c level, C peptide level, or the proportion of patients shifting from normal to abnormal (high or impaired) fasting glucose level at Week 24. Increases (relative to baseline) within the normal range in mean fasting glucose and HbA1c were seen in all groups (statistically significant for quetiapine and risperidone). The results for fasting insulin, $AUC_{0\ 2h}$ for insulin values, index of insulin sensitivity, and the homeostasis model assessment showed less change at Week 24 in the quetiapine group in comparison with the olanzapine and risperidone groups.
Severity and nature of risk	DM is a serious medical condition that is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Although rare, the acute health risks associated with untreated DM include DKA and hyperosmolar coma. The long-term sequelae of diabetes mellitus can include damage to various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (American Diabetes Association 2007). [Relevant laboratory parameters include the following: **Fasting** glucose ≥7.0 mmol/L (≥126 mg/dL), **random** glucose ≥11.1 mmol/L (≥200 mg/dL) in subjects who met the following criteria at baseline: fasting glucose <126 mg/dL or nonfasting glucose <200 mg/dL; HbA1C <6.1; and no history of diabetes]. There were a total of 16 (7.11%) MedDRA PTs that were considered serious events in the all-study data. Of the 225 TEAEs in the all-trial data, 125 were considered mild; 81 moderate and 18 severe, by the investigators.
Background incidence/ prevalence	An American Diabetes Association consensus development report (American Diabetes Association 2004) noted that the prevalence of DM among individuals with schizophrenia and affective disorders is approximately 1.5 to 2.0 times higher than in the general population. Although it is generally recognized that the prevalence of hyperglycemia and DM is higher in patients with schizophrenia and major psychiatric illnesses, it is important to consider confounding factors such as access to health care, specialty of physician seen, and other biases that may affect the number of patients actively screened in studies reporting the occurrence of these conditions (Gupta et al 2003). **Schizophrenia:** The association of hyperglycemia and type 2 DM with schizophrenia was first noted prior to the introduction of antipsychotic medications. Because glucoregulatory abnormalities and increased adiposity have been recognized to be associated with antipsychotic use, it is difficult to discern rates of occurrence of these effects in the population with schizophrenia not exposed to this class of drug. Investigators (Mukherjee et al 1996) found a prevalence of diabetes of 15.8% in a cohort of patients with schizophrenia admitted to a long-term care facility in Italy. Lifetime prevalence of diabetes was reported to

Table II-49 Important identified risks - Hyperglycemia and diabetes mellitus (included per MRP outcome)

Identified risk	Hyperglycemia and DM (included per MRP outcome)

be 15% for people being treated for schizophrenia using a large database compiled by the Schizophrenia Patient Outcomes Research Team (Dixon et al 2000). The prevalence of diabetes and impaired glucose tolerance rose from 8.6% to 19.4% after prospective blood glucose testing was conducted in patients with schizophrenia at the Maudsley Hospital, London (Bushe and Holt 2004, Taylor et al 2003). In a series of 200 patients with schizophrenia in the Netherlands, the prevalence of type 2 DM was 14.5%, of which 8% was previously known and 6.5% was newly diagnosed (Cohen et al 2006). In a cohort of first-episode schizophrenia never having been exposed to neuroleptics (mean age 33.6 years), more than 15% of the individuals were found to have impaired fasting glucose tolerance (Ryan et al 2003). A chart review found the prevalence of known type 2 DM to be 5% among 607 schizophrenic residents of a long-term care ward in Singapore who were naïve to atypical antipsychotics. Following screening, the prevalence of type 2 DM and impaired glucose tolerance prevalence rose to approximately 21% and 31%, respectively. In those aged <60 years, the prevalence rate was double that of the general Singapore population, but in those aged 60 years and above, it was lower than the general population (Subramaniam et al 2003). Rates of type 2 DM in patients with schizophrenia from the CATIE Schizophrenia Trial were significantly higher than those of similar age-, race-, and gender drawn from NHANES III (13% vs 3%) (Goff et al 2005). In the CLAMORS study investigators (Bobes et al 2007) found 14.2% of Spanish patients with schizophrenia seen in mental health centers had hyperglycemia meeting the ATP III metabolic syndrome criterion for high fasting glucose or antidiabetic medication use; hyperglycemia was observed in 13.3% (95% CI: 11.1, 15.6) of males and 15.3% (95% CI: 12.3, 18.3) of females.

Bipolar disorder: A medical-record review of 243 inpatients (50 to 74 years) with bipolar disorder revealed a significantly higher rate of type 2 DM of 26% compared with the national norm of 13% ($p<0.05$) (Regenold et al 2003). In another study of 345 hospitalized patients (20 to 74 years) with bipolar disorder, the prevalence of type 2 DM was 9.9%, significantly greater than expected from national norms (3.4%) (Cassidy et al 1999). A Canadian registry review examined bipolar patients (15 to 82 years) and found a prevalence of DM of 11.7% (McIntyre et al 2005b). Other studies have not found increased prevalence of type 2 DM in bipolar patients. Of 171 patients with bipolar disorder participating in a research diagnostic interview using the Structured Clinical Interview, 8% met the NCEP ATP III metabolic syndrome criterion for high fasting glucose or antidiabetic medication use (Grundy et al 2004, Fagiolini et al 2005). In one cross-sectional study of patients at a large outpatient psychiatric clinic, 4.3% of 1379 patients with bipolar disorder also had type 2 DM (Beyer et al 2005).

MDD: In a case registry study of 29035 patients discharged from hospital with depression, there was no increased risk of readmission for diabetes in patients with depression as compared with patients with osteoarthritis (Kessing et al 2004). Other studies have demonstrated that depression and its associated symptoms constitute a major risk factor for the development of type 2 DM and may accelerate the onset of diabetes complications (Musselman et al 2003). A systematic review and meta-analysis of prospective studies of depression and type 2 DM published between 1950 and 2007, which excluded prevalent cases of diabetes (n=13 studies) found an increased risk for developing type 2 DM in those with baseline depression (relative risk, 1.60; 95% CI: 1.37, 1.88) (Mezuk et al 2008).

GAD: A large 10-year prospective study in Norway found that those with baseline composite anxiety/depression had an increased risk for type 2 DM (OR=1.5, 1; 95% CI: 1.27, 1.81), in both men and women, but not type 1 diabetes (OR=1.17; 95% CI: 0.70, 1.95) (Engum 2007). In a cross-sectional survey of 3032 adults representative of the US population, GAD was not significantly associated with the presence of type 2 DM (Barger

Table II-49 Important identified risks - Hyperglycemia and diabetes mellitus (included per MRP outcome)

Identified risk	Hyperglycemia and DM (included per MRP outcome)
	and Sydeman 2005). However, in another survey of 1817 adults in New York, rates of type 2 DM were significantly higher in individuals with GAD (14%) and MDD (16%), compared with individuals without either diagnosis (7%) (Gwynn et al 2008). **Pediatric patients:** Epidemiologic data on type 2 DM in children is sparse, in part because type 2 DM has only recently been recognized in the young, and differential diagnosis can be difficult (Alberti et al 2004). A recent US, nationally representative study of youth <20 years of age estimated the incidence rate of diabetes mellitus (type 1 and type 2) to be 24.3 per 100,000 person years (SEARCH Study Group 2007). The WHO Multinational Project for Childhood Diabetes estimated the age-adjusted incidence rate of type 1 diabetes among youth ≤14 years of age to range from 4.1 per 100,000 person years in Poland to 43.6 per 100,000 person years in Italy (Karvonen et al 2000). Research has shown that the occurrence of type 2 DM in Europe continues to lag behind the high prevalence of type 2 DM found among US children and adolescents (Soltesz 2006). Epidemiologic and clinical trial data suggest an association between psychiatric disorders and diabetes among children and adolescents, with a potentially increased incidence of anxiety and depression after the onset of diabetes (Dantzer et al 2003). Case reports and spontaneous AE reports have documented diabetes and hyperglycemia among adolescents treated with atypical antipsychotics (Stigler et al 2004, Cohen and Huinink 2007). However, an epidemiologic study conducted among 126 children and adolescents treated in inpatient and outpatient psychiatric settings in Madrid found no association between fasting glucose level and type of atypical antipsychotic medication (Laita et al 2007).
Risk groups or risk factors	The Schizophrenia Patient Outcomes Research Team determined that increasing age, being female, and being of African-American or 'other' non-white racial origin increased the likelihood of having diabetes (Dixon et al 2000). The National Diabetes Information Clearinghouse states that patients with a history of elevated blood glucose or obesity are at risk for developing DM and are advised to have appropriate clinical monitoring. Similarly, patients with existing DM should be monitored for possible exacerbation. Risk factors associated with type 2 DM includes obesity, apple-shaped habitus, increasing age, sedentary lifestyle, family history, ethnicity, high blood pressure, high cholesterol/high fat diet, and history of CVD (NDIC 2006). Genetic factors appear to have a role in the association between schizophrenia and diabetes, since it has been reported that up to 50% of individuals with schizophrenia have a family history of type 2 DM, compared with just 4.6% of healthy adult controls (Cheta et al 1990, Dynes 1969). In a Norwegian population-based study, symptoms of depression and anxiety were identified as significant risk factors for the onset of type 2 DM independent of established diabetes risk factors; these symptoms were not, however, associated with non-fasting blood glucose levels (Engum 2007). Conflicting results are observed from various studies formally testing the association between quetiapine and other antipsychotic with either conventional antipsychotics or no antipsychotics to the development of type 2 DM. This may be related to serious methodological limitations inherent to data sources used in these studies, exposure and outcome characterization, or to other biases impacting subject selection or study design selection and implementation.

Table II-49 Important identified risks - Hyperglycemia and diabetes mellitus (included per MRP outcome)

Identified risk	Hyperglycemia and DM (included per MRP outcome)
Potential mechanisms	Reasons for an increased prevalence of diabetes among patients with these psychiatric disorders remain speculative. The potential mechanisms behind the associations between these conditions and diabetes are likely to be multifactorial and to include environmental, genetic, and neuroendocrine factors. The exact mechanism of atypical antipsychotic-associated hyperglycemia and type 2 DM is not known and remains speculative. These include reduced sensitivity to insulin, amplified insulin resistance, drug-induced weight gain and adiposity, antagonism of serotonin receptors, elevation of serum leptin, dyslipidemia-mediated pancreatic β-cell damage and hepatocyte transcription factor dysregulation (Lean and Pajonk 2003, Buchholz et al 2008). In addition, several psychiatric disorders appear to have relatively high prevalence of abnormal glucose metabolism.
Preventability	Common medical practice would be to recommend weight reduction, blood pressure control, lipid control, diet, and exercise for patients at risk for development of diabetes. Section 4.4, Special Warnings and Precautions for Use, of the MR-SmPC states: **Hyperglycemia:** Hyperglycemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilized antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.
Potential public health impact of Safety Concern/ Impact on individual patient	Hyperglycemia and DM are a serious Safety Concern with known public health impact. The long-term sequelae of DM can include damage to various organs, especially the eyes, kidneys, nerves, heart, and blood vessels, resulting in serious complications such as blindness, kidney damage, and lower-limb amputations (American Diabetes Association 2007). Diabetes was the 6th leading cause of death in the US in 2006 (Centers for Disease Control 2008).
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.
MedDRA terms	Type 2 DM, Insulin-requiring Type 2 DM, Type 2 diabetes mellitus, Anti-insulin antibody increased, Anti-insulin antibody positive, Blood glucose abnormal, Blood glucose fluctuation, Blood glucose increased, Blood insulin abnormal, Blood insulin decreased, Blood insulin increased, Blood proinsulin abnormal, Blood proinsulin decreased, Blood proinsulin increased, Dawn phenomenon, Diabetes complicating pregnancy, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes with hyperosmolarity, Diabetic coma, Diabetic complication, Diabetic hyperglycaemic coma, Diabetic hyperosmolar coma, Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Gestational diabetes, Glucose tolerance decreased, Glucose tolerance impaired, Glucose tolerance impaired in pregnancy, Glucose tolerance test abnormal, Glucose urine present, Glycosuria , Glycosuria during pregnancy, Glycosylated haemoglobin increased, Hyperglycaemia, Hyperglycaemic hyperosmolar nonketotic syndrome, Hyperinsulinaemia, Hyperinsulinism, Impaired fasting glucose, Impaired insulin secretion, Increased insulin requirement, Insulin C-peptide abnormal, Insulin C-peptide decreased, Insulin C-peptide increased, Insulin resistance, Insulin resistance syndrome, Insulin resistant diabetes, Insulin-requiring type 2 diabetes mellitus , Insulin tolerance test abnormal, Polyuria, Somogyi phenomenon

AE Adverse event; AUC_{0-2h} area under the curve from 0 to 2 hours; CATIE Clinical Antipsychotic Trials of Intervention Effectiveness; CI Confidence interval; CVD Cardiovascular disease; DM Diabetes mellitus; GAD Generalised anxiety disorder; MDD Major depressive disorder; MEB Medicines Evaluation Board; MedDRA Medical Dictionary for Regulatory Activities; MRP Mutual recognition procedure; NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III; NHANES National Health and Nutrition Examination Survey; OLE Open-label extension; OR Odds ratio; PLA Placebo; PT Preferred term; QTP Quetiapine; TEAE Treatment-emergent adverse event; US United States; WHO World Health Organization.

Table II-50 Important identified risks - Metabolic risk factors (included per MRP outcome)

Identified risk	Metabolic risk factors (included per MRP outcome)
Frequency/ Seriousness/ Outcomes	**AE reports (MedDRA PTs)** **Placebo-controlled trials** No reports **All studies (including OLEs) QTP exposure** 5 (0.02%) had TEAEs. 0 events were considered serious by the investigators 5 patients Not recovered (100%) **Long-term (≥6 months) QTP exposure** 3 (1.07%) had TEAEs 0 events were considered serious by the investigators 3 patients Not recovered (100%)

Table II-50 Important identified risks - Metabolic risk factors (included per MRP outcome)

Identified risk	Metabolic risk factors (included per MRP outcome)
	Adult patients: Shift from <3 risk factors at baseline to ≥3 factors at end of treatment: **Placebo-controlled trials** 332 (11.1%) quetiapine and 136 (8.8%) placebo patients had TEAEs; MH relative risk: QTP vs PLA (95% CI) 1.30 (1.05, 1.59) **All studies (including OLEs) QTP exposure** 989 (12.8%) **Long-term (≥6 months) QTP exposure** 234(17.1%) **Pediatric patients: Shift from <3 risk factors at baseline to ≥3 factors at end of treatment:** **Placebo-controlled trials** 25 (10.0%) quetiapine and 5 (3.6%) placebo patients had TEAEs MH relative risk: QTP vs PLA (95% CI) 2.99 (1.11, 8.09) **All studies (including OLEs) QTP exposure** 43 (11.9%) had TEAEs. **Long-term (≥6 months) QTP exposure** Not applicable **Adults with ≥ 3 shifts at end of treatment** **Placebo-controlled trials** Risk factors at baseline: 0 (12 QTP, 1 PLA); 1 (92 QTP and 29 PLA); 2 (228 QTP, 106 PLA) **All studies (including OLEs) QTP exposure** Risk factors at baseline: 0 (47 QTP); 1 (273 QTP); 2 (669 QTP) **Long-term (≥6 months) QTP exposure** Risk factors at baseline: 0 (18 QTP); 1 (68 QTP); 2 (148 QTP) **Pediatric patients with ≥ 3 shifts at end of treatment** **Placebo-controlled trials** Risk factors at baseline: 0 (1 QTP, 0PLA); 1 (4 QTP and 0 PLA); 2 (20 QTP, 5 PLA) **All studies (including OLEs) QTP exposure** Risk factors at baseline: 0 (2 QTP); 1 (15 QTP); 2 (26 QTP) **Long-term (≥6 months) QTP exposure** Not applicable For additional details of metabolic shifts see Annex 12.

Table II-50 Important identified risks - Metabolic risk factors (included per MRP outcome)

Identified risk	Metabolic risk factors (included per MRP outcome)
Severity and nature of risk	The co-occurrence of selected metabolic risk factors (increased abdominal or visceral adiposity, low serum HDL cholesterol, elevated fasting triglycerides, hypertension, and impaired fasting glucose or overt diabetes mellitus) has been referred to as metabolic syndrome). As applied in clinical practice and research, identifying individuals at risk for diabetes and cardiovascular disease was a key objective for formulating the definition of metabolic syndrome, which required individuals to meet 3 or more of the noted risk factors (NCEP Expert Panel 2002, NCEP Expert Panel 2001). It has been reported that insulin resistance (or the impairment of insulin effects on target organs, such as liver, muscle, and adipose tissue) is central to the numerous anomalies that have been described in association with this complex of metabolic risk factors (Reaven 1995). However, there are disagreements regarding the potential utility of this concept as a diagnosis of metabolic syndrome may not confer greater predictive value in assessing risk of diabetes or CVD than established risk prediction methods (ie, Diabetes Prediction Model, Framingham Risk Score) (Stern et al 2004). Relevant laboratory parameters include the following: **Adult population:** The co-occurrence of any 3 of the following 5 criteria met at end of treatment in patients with <3 risk factors at baseline: BMI ≥30; supine blood pressure ≥130/85 mmHg; fasting triglycerides ≥150 mg/dL; glucose ≥100 mg/dL if fasting or ≥140 mg/dL if nonfasting; or HDL <40 mg/dL (male)/<50 mg/dL (female). **Pediatric population:** The co-occurrence of any 3 of the following 5 criteria met at end of treatment in patients with <3 risk factors at baseline: BMI percentile ≥85%; blood pressure value ≥90th percentile; fasting triglycerides ≥110 mg/dL; fasting glucose ≥100 mg/dL; or HDL ≤40 mg/dL.
Background incidence/ prevalence	**General:** In the NHANES surveys (2003-2006), both the crude and age-adjusted estimates from a US population indicate that approximately 34% of the population ≥20 years old met the criteria for metabolic syndrome (Ervin 2009). While about 20% of males and 16% of females <40 years old met the criteria for metabolic syndrome, 41% of males and 37% of females 40 to 59 years of age and 52% of males and 54% of females ≥60 years old met the criteria. The age-standardized prevalence of metabolic syndrome in nondiabetic European men and women (aged 30 to 89, median age 57 years) was estimated at 15.7% and 14.2%, respectively, using a modified WHO definition of metabolic syndrome (ie, hyperinsulinemia plus two additional risk factors) (Hu et al 2004). **Schizophrenia:** Data from the CATIE Schizophrenia Trial and other cohort studies have found an increased prevalence of metabolic syndrome in patients with schizophrenia, compared to the general population (Meyer et al 2008, Saari et al 2005, Srisurapanont et al 2007). In addition, cross-sectional studies have also shown a 2-fold increase prevalence of metabolic syndrome in the patient population with schizophrenia (Bushe and Holt 2004, Cohn et al 2004, McEvoy et al 2005, De Hert et al 2006, Bobes et al 2007). In the CLAMORS study (a retrospective study of Spanish outpatients with schizophrenia, schizophreniform or schizoaffective disorder aged 18 to 74 who were taking selected oral antipsychotics for at least 12 weeks), 23.6% of males and 27.2% of females met criteria for metabolic syndrome (Bobes et al 2007). **Bipolar disorder:** Data on the prevalence of metabolic syndrome in bipolar disorder are scant. A meta-analysis of studies from 1996-2005 revealed that insulin resistance and impaired glucose tolerance occur more frequently in people with bipolar disorder than in the

Table II-50 Important identified risks - Metabolic risk factors (included per MRP outcome)

Identified risk	Metabolic risk factors (included per MRP outcome)
	general population (Taylor and MacQueen 2006). Metabolic syndrome was observed in 30% of 171 patients from a bipolar disorder center in Pennsylvania (USA) based on standard NCEP ATP III criteria, and this level increased to 40% prevalence in an expanded sample of 441 subjects based upon modified NCEP ATP III criteria (Fagiolini et al 2008, Fagiolini et al 2005). Approximately one-quarter (24.7%) of 178 subjects with bipolar disorder identified in a claims database from an health maintenance organization in Barcelona, Spain, met the definition for metabolic syndrome based upon the 2002 modification of NCEP ATP-III definition (which included substitution of BMI >28.8 kg/m^2 for central adiposity). All bipolar patients were receiving treatment with at least one drug. This represented a significantly higher prevalence (age-adjusted OR=1.65; 95% CI: 1.11, 2.44) using all other HMO subscribers without bipolar disorder as reference (Sicras et al 2008). **MDD/GAD:** A cross-sectional analysis of the NHANES Survey found the prevalence of metabolic syndrome in a US population (NCEP ATP III criteria) to be 11.7% and 12.3% in depressed men and women, respectively. There was a two-fold increased likelihood that women (but not men) reporting a history of major depressive episode had metabolic syndrome (Kinder et al 2004). Caution in interpretation of such studies is required since one possible interpretation is that psychological attributes are a consequence of metabolic syndrome, and not an antecedent factor. A prospective study of middle-aged women over a 7.4-year follow-up found that high scores for depression (based on Beck Depression Inventory), anger (Speilberger Trait), and tension (Framingham) at baseline and/or increases over the course of the study were associated with an increased risk of developing metabolic syndrome (Räikkönen et al 2002). The limitations associated with this study were due to its reliance on psychological tests and measures and not definitive diagnoses of affective disorders. A small study of outpatients from Sweden who had a diagnosis of depression over a 6-year period were found to have a higher prevalence of metabolic syndrome (Heiskanen et al 2006). GAD, but not MDD, was associated with metabolic syndrome in a cross sectional study of 4256 men participating in the Vietnam Experience Study (Carroll et al 2009). **Pediatric patients:** Prior to the consensus definition provided by the IDF (Zimmet et al 2007), there were many difficulties associated with defining metabolic syndrome in children and adolescents and comparing estimates of metabolic syndrome across studies. The methodologic problems included the use of adult cut points or a single set of cut points for all ages throughout childhood, the fact that disturbances seen in the metabolic indicators in most children were quantitatively moderate, the lack of a normal range for insulin concentration across childhood, the physiological insulin resistance of puberty, the lack of central obesity (ie, waist circumference) cut points linked to obesity morbidity or metabolic syndrome for children, as well as differences in baseline lipid levels among various races (Steinberger et al 2009). Using definitions similar to those ultimately adopted for use by the IDF Investigators, Cook et al determined the prevalence of the metabolic syndrome among adolescents aged 12 to 19 years to be 6.1% in males and 2.1% in females (Cook et al 2003). Metabolic syndrome was present in 28.7% of overweight adolescents with a BMI >95th percentile compared with 6.8% of adolescents whose BMI fell between the 85th to <95th percentile and only 0.1% of those with a BMI below the 85th percentile.
Risk groups or risk factors	According to the NHANES survey in a US population, males had a higher age-adjusted prevalence of metabolic syndrome than females (35.1% vs 32.6%). Males and females 40 to 59 years of age were about 3 times as likely as those 20 to 39 years to meet the criteria for metabolic syndrome. Males and females aged 60 and over were 4 times and 6 times as likely as those 20 to 39 years to meet the criterion for metabolic syndrome, respectively

Table II-50 Important identified risks - Metabolic risk factors (included per MRP outcome)

Identified risk	Metabolic risk factors (included per MRP outcome)
	(Ervin 2009). The age-adjusted patterns of metabolic syndrome for race and ethnicity vary by sex. Non-Hispanic black and Mexican-American females had a higher prevalence of metabolic syndrome (38.8% and 40.6%, respectively) than non-Hispanic white females (31.5%) (Ervin 2009). The (US) NHANES surveys determined that overweight (BMI 25-29.9) males were more than 6 times as likely as underweight and normal-weight males to meet the criteria for metabolic syndrome, OR=6.17 (95% CI: 3.96, 9.62), and overweight females were nearly 5.5 times as likely as underweight and normal-weight females to meet the criteria for metabolic syndrome, OR=5.48 (95% CI: 3.75, 8.02) (Ervin 2009). Obese (BMI >30) males were nearly 32 times as likely to meet the criteria for metabolic syndrome, OR=31.92 (95% CI: 20.06, 50.78), and obese females were more than 17 times as likely to meet this criteria, OR=17.14 (95% CI: 12.54, 23.44) (Ervin 2009). Metabolic syndrome and bipolar disorder share common risk factors including endocrine disturbances, dysregulation of the sympathetic nervous system, and behavior patterns, such as physical inactivity and overeating (Fagiolini et al 2008). Commonly used pharmacologic treatments for serious mental illnesses and affective disorders may intensify the propensity for development of metabolic syndrome due to the confluence of clinical parameters such as dosage and length of treatment, age, gender, smoking, BMI, appetite alternation, deviation from normal weight prior to treatment, environmental factors, drug-induced weight gain, and metabolic disturbances, including alterations in lipid and glucose metabolism. Data from several sources on the use of atypical antipsychotics indicate that some drugs in this class pose a risk for adversely affecting several of the component metabolic risk factors, eg, central adiposity and disordered lipid and glucose metabolism (Newcomer and Haupt 2006). Regarding risk factors in children, the Bogalusa Heart study demonstrated that being overweight in childhood had consequences related to the development of adverse metabolic syndrome risk factors (BMI, lipids, insulin, DM, and blood pressure) in adulthood. Of the overweight children in the Bogalusa Heart study with BMI >95th percentile, 77% remained obese in adulthood (Freedman et al 2001). Investigators (Weiss et al 2004) found that as the degree of obesity increases, the prevalence of metabolic syndrome increases in children and adolescents, with metabolic syndrome occurring in 38.7% of moderately obese (mean BMI 33.4 kg/m2) and 49.7% of severely obese (mean BMI 40.6 kg/m2) children and adolescents. The presence of maternal gestational diabetes, low birth weight, infant feeding practices, early adiposity rebound, and genetic factors may all contribute to a child's future level of risk (Steinberger et al 2009).
Potential mechanisms	Potential mechanisms are likely to be multifactorial and to include environmental, behavioral, genetic, and other metabolic and endocrine factors. The occurrence of metabolic syndrome has been ascribed to excess adiposity and decreased insulin sensitivity; however, the mechanisms are not well described. It is likely that expression of each metabolic risk factor falls partially under its own genetic control, which influences response to different environmental exposures.
Preventability	Common medical practice recommends weight reduction, blood pressure control, lipid control, diet, and exercise for patients at risk for development of metabolic syndrome. Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: **Metabolic Risk:** Given the observed risk for worsening of their metabolic profile, including

Table II-50 Important identified risks - Metabolic risk factors (included per MRP outcome)

Identified risk	Metabolic risk factors (included per MRP outcome)
	changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also section 4.8). **Hyperglycemia:** Hyperglycemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilized antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly. **Lipids:** Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid changes should be managed as clinically appropriate.
Potential public health impact of Safety Concern/ Impact on individual patient	A diagnosis of metabolic syndrome may not confer greater predictive value in assessing risk of diabetes or cardiovascular disease than established risk prediction methods (ie, Diabetes Prediction Model, Framingham Risk Score) (Stern et al 2004). However, given the long-term impact of untreated metabolic risk factors on cardiovascular mortality, especially in populations with a substantially higher risk death due to cardiovascular disease, and the potential reduced access to medical care among these patients, there is a need to recognize the importance of coordination of primary and secondary prevention efforts to avoid a greater burden on morbidity and mortality in this population.
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.
MedDRA terms	Metabolic syndrome

AE Adverse event; BMI Body mass index; CATIE Clinical Antipsychotic Trials of Intervention Effectiveness; CI Confidence interval; CVD Cardiovascular disease; DM Diabetes mellitus; GAD Generalised anxiety disorder; HDL High-density lipoprotein; IDF International Diabetes Foundation; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; MRP Mutual recognition procedure; NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III; NHANES National Health and Nutrition Examination Survey; OLE Open-label extension; OR Odds ratio; PLA Placebo; PT Preferred term; QTP Quetiapine; TEAE Treatment-emergent adverse event; US United States.

Psychiatric disorder

Table II-51 Important identified risk - Suicide and suicidality (per RMS[MEB] imposition)

Potential risk	Suicide and suicidality
Frequency/ Seriousness/ Outcomes	**Placebo-controlled trials** 76 (0.80%) quetiapine and 38 (0.76%) PLA patients had TEAEs; MH relative risk: QTP vs PLA (95% CI) 0.91 (0.61, 1.37). 38 events were considered serious by the investigators. Recovered 67 patients (88.16%); Not recovered 9 patients (11.84%).

Table II-51 Important identified risk - Suicide and suicidality (per RMS[MEB] imposition)

Potential risk	Suicide and suicidality
	All studies (including OLEs) QTP exposure 297 (1.04%). 164 events were considered serious by the investigators. Recovered 245 patients (82.49%); not recovered 35 (11.78%); Unknown 6 (2.02%); **Long-term (≥6 months) QTP exposure** 44 (1.06%) 30 events were considered serious by the investigators. Recovered 32 patients (72.73%); not recovered 7 (15.91%); Unknown 2 (4.55%)
Severity and nature of risk	Suicide and suicidality include a range of behaviors that includes self-harm, suicidal ideation, and suicidal actuation. There were 164 serious events in the all trial data. Of the 297 TEAEs of suicide and suicidality in the all trial data, 81 were considered mild, 81 were considered moderate, and 135 were considered severe, according to the investigators.
Background incidence/ prevalence	**Schizophrenia**: The schizophrenic population has a significantly higher rate of completed suicides and suicide attempts than the general population. It is estimated that suicide claims the lives of 9% to 13% of people with schizophrenia with an annual rate ranging from 0.4% to 0.8% in developed countries (Meltzer 1999, Axelsson and Langerkvist-Briggs 1992, Newman and Bland 1991). A similar range in mortality rates was recognized prior to the introduction of typical antipsychotics, and similar rates have been reported by those treated with typical antipsychotics (Axelsson and Langerkvist-Briggs 1992). Between 40% and 60% will make a suicide attempt during their lifetime; retrospective studies have demonstrated Standardized Mortality Ratios as much as 20 times greater than in the general population (Newman and Bland 1991). Calling attention to the oversimplification of methods that assume a constant rate of suicide over a lifetime, Palmer et al 2005 developed a methodology for extrapolating lifetime suicide prevalence estimates, using studies where the observational period was from first admission or illness, and determined that the lifetime prevalence of suicide in schizophrenia was 5.6% (95% CI: 3.7%, 8.55%). On the basis of a review of clinical trial data submitted to FDA (obtained under the Freedom of Information Act) over a 6-year period for 4 antipsychotic medications (clozapine, olanzapine, risperidone, and quetiapine), the overall incidence of suicide and attempted suicide was 752/100,000 per year and 5,048/100,000 per year, respectively (Palmer et al 2005). Annualized rates of attempted suicide (including completed suicides) were 3.3% during placebo treatment, 5.7% during treatment with an established antipsychotic agent, and 5.0% during atypical antipsychotic drug treatment (not including clozapine). Despite the statistical power provided by the large sample size, the rates for suicide attempts (including completed suicides) among these 3 schizophrenic treatment groups (not preselected for suicidality) were not significantly different from each other. **Bipolar disorder**: The lifetime prevalence of nonfatal suicidal behavior (attempted suicide or self-harm) in those with bipolar disorder is approximately 30% (Chen and Dilsaver 1996,Tondo et al 2003) and may be as high as 50% in secondary care samples (Valtonen et al 2005). In the Epidemiologic Catchment Area study, bipolar patients (n=168) had a lifetime rate of suicide attempts of 29.3% (Chen and Dilsaver 1996). Among 648 bipolar patients in clinical studies, 34% reported a history of a serious suicide attempt (Leverich et al 2003). In a population-based study in the Netherlands, 59.3% of bipolar I patients reported suicidal ideation, and 19.8% reported a suicide attempt (39.0% and 9.8%, respectively, in bipolar NOS patients [ten Have et al 2002]). In just 18 months of follow-up, 20% (35/176) of bipolar patients attempted suicide in the Jorvi Bipolar Study (JoBS). In 220 bipolar patients observed for 22 years, 11% committed suicide, which was 12 times the

Table II-51 Important identified risk - Suicide and suicidality (per RMS[MEB] imposition)

Potential risk	Suicide and suicidality
	expected rate based on the general Swiss population, adjusted for age, sex, and observation period (Angst et al 2002). Other studies found much lower rates of suicidality. Among 1556 patients in the Systematic Treatment Enhancement Program for Bipolar Disorder, 57 (3.66%) patients attempted or completed suicide. Those with a history of suicide attempts were over 4 times as likely to attempt or complete suicide; risk was also increased with increasing percent days depressed in the past year (Marangell et al 2006). Overall, the risk of suicidal behavior (both fatal and nonfatal) is substantially higher in patients with bipolar disorder than in the general population, and this risk is high early in the course of illness, and during depressive phases. **MDD**: The mortality rate from suicide in patients with depression ranges from 3.4% in community outpatients to 15% in inpatient populations (Guze and Robins 1970, Morrison 1982, Blair-West et al 1999,Angst et al 2002). In a study in a large major health plan of 35546 patients over age 18 years treated for depression during a 3-year period, the overall suicide rate was 4.2%, or 59/100,000 patient-years. The rates were 224/100,000 patient-years for inpatients, 64/100,000 patient-years for outpatients, 43/100,000 patient-years for outpatients treated with antidepressants in primary care, and 0 for patients treated in primary care without antidepressants (Simon and VonKorff 1998). Among 4956 duloxetine-treated MDD patients in clinical studies, the suicide rate was 283/100,000 person-years of treatment, and the rate of nonfatal suicide attempts was 1469/100,000 person-years (Acharya et al 2006). Among 2996 patients in placebo-controlled duloxetine studies, the suicide rate was 203/100,000 person years for duloxetine-treated patients and 370/100,000 person years for placebo (Acharya et al 2006). According to analysis of FDA data, rates of suicide and attempted suicide associated with treatment of depression did not differ among placebo- and drug-treated groups. In depression clinical studies reported to the FDA, the rate of suicides was 594/100,000 person years for SSRIs, 757/100,000 person-years for other antidepressants, and 446/100,000 person-years for placebo (Khan et al 2003). The rate of nonfatal suicide attempts was 2087/100,000 person-years for SSRIs and other antidepressants and 2698/100,000 person-years for placebo (Khan et al 2003). Two systematic reviews of randomized controlled trial data (obtained from published data from the MHRA) showed weak evidence for increased risk of self-harm (1.57, 0.99–2.55) (Gunnell et al 2005), or suicidal attempts (2.28, 1.14–4.55) (Fergusson et al 2005) related to SSRI use. **GAD**: An analysis of FDA clinical study data for anxiety disorders showed a 10-fold increased risk for suicide in patients with an anxiety disorder compared with the general population (Khan et al 2002). A longitudinal population-based study in the Netherlands showed increased odds ratios for suicidal ideation and suicide attempts in patients with anxiety disorders, including GAD, as well as increased risk of suicide attempts in patients with any anxiety disorder and comorbid mood disorder (Sareen et al 2005).

Table II-51 Important identified risk - Suicide and suicidality (per RMS[MEB] imposition)

Potential risk	Suicide and suicidality
Risk groups or risk factors	The most robust predictor of a future suicide attempt is having made a previous suicide attempt. The following additional factors have been associated with increased risk of suicide risk in patients with schizophrenia or schizoaffective disorder: male gender, a younger age, unemployment, presence of depressive symptoms, a positive family history for suicide attempts, comorbid substance abuse, a longer duration of untreated psychosis, the use of typical antipsychotics, and the induction of extrapyramidal side effects (Altamura et al 2007). Some psychotropic medications have been associated with an increased risk in suicide in select populations. In addition, the field of psychiatry has been challenged by a lack of conceptual clarity about suicidal behavior and a corresponding lack of well-defined terminology. Historically, no systematic or standardized language exists to define suicidal behavior in clinical studies or in other arenas. In October of 2003, the FDA issued a Public Health Advisory that reported risks of suicidality (suicidal ideation and suicide attempts) in children being treated with certain antidepressants for major depressive disorder. In March 2004, the FDA required manufacturers of 10 antidepressants to issue stronger warning labels regarding risks and potential suicidal tendencies in children and adolescents associated with these medications (Hammad 2004). European regulatory agencies simultaneously issued similar warnings. These warnings prompted a series of systematic investigations to address this concern (Gibbons et al 2006,Hammad et al 2006, Perlis et al 2007). A recent re-analysis of 103,491 adult participants in 406 clinical trials of 12 marketed antidepressant products (proprietary data of the US FDA) found the risk of suicidality associated with use of antidepressants to be strongly age dependent. An increased risk for suicidality and suicidal behavior among adults under 25 was described as “approaching that seen in children and adolescents.” There was no demonstrable effect of antidepressant use on suicidal behavior in adults (described as “possibly protective for suicidal ideation in adults aged 25 to 64”) and, in addition, a reduced risk of both suicidality and suicidal behavior was found for adults age ≥65 (Stone et al 2009). In MDD, the rate of completed suicide has been reported to be higher in men than women (7% vs 1%), and 10 times higher in male vs female youths under age 25 (Blair-West et al 1999). Studies have shown that in patients with bipolar disorder, a wider range of factors are associated with attempted suicide than suicide itself, possibly because the former is a more common outcome. These factors include being single, a positive family history of suicide, mixed states, rapid cycling, alcohol and substance misuse, comorbid anxiety, and, possibly, early abuse or a bipolar-II diagnosis (Hawton et al 2005). Aggression and impulsivity may also be associated with suicide attempts (Oquendo et al 2000). In addition, the following factors have been associated with suicide and serious suicide attempts in persons with bipolar disorder across a range of studies: early sexual abuse, lack of a confidant prior to the onset of the illness, Cluster B personality disorder comorbidity, the presence of suicidal thoughts during depressive episodes, a history of numerous prior psychiatric hospitalizations, early onset of bipolar illness, history of recurrent severe depressive episodes, mixed or depressive manias, low self-esteem, prior history of suicide attempts, hopelessness, interpersonal conflicts with spouse/partner, occupational problems, recent psychosocial stress, severity of anxiety or depression, cigarette smoking, family history of substance abuse and suicide attempts, an increased incidence of early physical or sexual abuse (as well as physical abuse in adulthood), a pattern of increasing severity of mania over the course of their illness, more prior hospitalizations for depression, and more suicidal thoughts when manic and when depressed, younger age at intake, and depressive phase at index episode (Leverich et al 2003,Marangell et al 2006, Valtonen et al 2006).

Table II-51 Important identified risk - Suicide and suicidality (per RMS[MEB] imposition)

Potential risk	Suicide and suicidality
Potential mechanisms	In an evaluation of cultural determinants of suicide in the InterSePT study, investigators (Altamura et al 2007) determined that co-occurrence of alcohol or substance abuse and suicide attempts is relatively consistent worldwide, suggesting that this association is less influenced by social or cultural factors, but probably more by biological or genetic factors. The hypothesis that substance abuse and nicotine abuse may characterize a more severe clinical and biological sub-type of schizophrenia was substantiated in this most recent analysis of InterSePT. Thus, the reports of completed suicide, suicide attempt, suicidal ideation, and other suicide-related events for patient receiving SEROQUEL therapy, may reflect the background incidence of these events in the schizophrenic and bipolar (mania) population.
Preventability	Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: **Suicide/suicidal thoughts or clinical worsening:** Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated. Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders. Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo in patients less than 25 years old. A population-based retrospective study of quetiapine for the treatment of patients with major depressive disorder showed an increased risk of self-harm and suicide in patients aged 25 to 64 years without a history of self-harm during use of quetiapine with other antidepressants. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present. In a post hoc analysis of a population-based retrospective study of quetiapine for the treatment of patients with major depressive disorder an association was observed between non-lethal self-harm in patients under 65 years of age and prior use of quetiapine and

Table II-51 Important identified risk - Suicide and suicidality (per RMS[MEB] imposition)

Potential risk	Suicide and suicidality
	antidepressants.
Potential public health impact of Safety Concern/ Impact on individual patient	Suicide risk peaks in periods immediately after hospital admission and discharge. The risk is particularly high in persons with co-morbid affective disorders and in persons with short hospital treatment (Qin and Nordentoft 2005). Many suicide attempts occur during an acute crisis, such as a personal loss or the exacerbation of an underlying psychiatric disorder. This acute crisis is usually time limited and may be resolvable or treatable. Most suicidal patients are usually ambivalent about dying (Colucciello 2006).
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.
MedDRA terms	Completed suicide, intentional self-injury, self-injurious behaviour, self-injurious ideation, suicidal behaviour, suicidal ideation, suicide attempt

II: 7.3.2 Important potential risks that have been observed with other members of the antipsychotic class

The following safety concerns, categorized by MedDRA (Version 15.0) SOC, are important potential risks:

Nervous system disorders

- Cerebrovascular AEs in the elderly, as identified in Table II-52.
- Cerebrovascular AEs in non-elderly patients, as identified in Table II-53.

Cardiac disorders

- Ischemic heart disease, as identified in Table II-54.
- Torsades de Pointes, as identified in Table II-55

Injury, poisoning, procedural complications

- Abuse and misuse, as identified in Table II-56.

Nervous system disorders

Table II-52 Important potential risks - Cerebrovascular AEs in elderly patients (patients >65 years old)

Potential risk	Cerebrovascular AEs in elderly patients (patients >65 years old)
Frequency/ Seriousness/ Outcomes	**Placebo-controlled trials** 5 (0.66%) quetiapine and 5 (0.80%) placebo patients had TEAEs; MH relative risk: QTP vs PLA (95% CI) 0.66 (0.19, 2.38) 3 events were considered serious by the investigators. Recovered 3 patients (60%); Death 2 patients (40%) **All studies (including OLEs) QTP exposure** 30 (2.05%) 17 events were considered serious by the investigators. Recovered 20 patients (66.67%); not recovered 6 (20.00%); **Long-term (≥6 months) QTP exposure** Not applicable
Severity and nature of risk	Cerebrovascular events are serious events that are often life threatening, can be debilitating, and often require major medical interventions. There were 17 serious events in the all trial data. Of the 30 TEAEs of cerebrovascular events in patients >65 years old in the all-trial data, 7 were considered mild, 9 were considered moderate, and 13 were considered severe, according to the investigators.
Background incidence/ prevalence	**Schizophrenia:** A literature review did not reveal any information on the incidence or prevalence of cerebrovascular AEs in an elderly population with schizophrenia. Population-based data on occurrence of stroke and transient cerebral ischemic events among residents of the Canadian province of Saskatchewan with schizophrenia is provided in Table II-53. **Bipolar disorder:** In the Taiwan National Health Insurance Research Database, 3.0% of patients hospitalized with bipolar disorder in 1998 had utilized emergency medical services for the management of any type of stroke between 1998 and 2003, which was statistically greater than the 1.50% of patients undergoing an appendectomy, even after adjustment (Lin et al 2007). A cross-sectional survey of community adults in Germany in 1997 found that 3.3% of those with a history of bipolar I disorder reported a history of stroke, which was a statistically significant increase compared to 0.7% in those with no history of a psychiatric disorder (Baune et al 2006). A study using the GPRD found an increased rate of stroke mortality among bipolar patients compared to patients with no serious mental illness, which was statistically significant in the age group of 50 to 75 years (Osborn et al 2007). **MDD:** In a randomly sampled Korean population aged ≥65 years (n=714), the age- and education-standardized prevalence of cerebrovascular disorder (stroke or transient ischemic attack) was significantly higher in individuals with MDD (13.0%) than without MDD (6.8%) [p=0.034] (Han et al 2009). **GAD:** A literature review did not reveal any information on the incidence or prevalence of cerebrovascular AEs in the elderly GAD population. **Other/general:** The 10-year probability per 100 of incurring a stroke according to successive 5-year age intervals for elderly men and women, respectively, as derived from the Framingham study were as follows: age 60 to 64, 7.8 and 4.7; age 65 to 69, 11.0 and 7.2; age 70 to 74, 13.7 and 10.9; age 75 to 79, 18.0 and 15.0; and age 80 to 84, 22.3 and 23.9 (Wolf et al 1991). The crude incidence of stroke among elderly subjects (age 65+) not exposed to antipsychotics from a general practice database in Italy (Health Search Database 2000-2003) was 12 cases per 1000. Clinical studies with risperidone and olanzapine showed an increased risk of cerebrovascular events in elderly patients (Wooltorton 2002, Wooltorton 2004). Atypical antipsychotic use was not associated with increased risk of cerebrovascular events

Table II-52 Important potential risks - Cerebrovascular AEs in elderly patients (patients >65 years old)

Potential risk	Cerebrovascular AEs in elderly patients (patients >65 years old)
	in 2 studies of antipsychotic-naïve people over age 65 using linked databases in Canada; incidence was not different for those treated with typical antipsychotics (5.7/1000 person-years), risperidone (7.8/1000 person-years), and olanzapine (5.7/1000 person-years) (Hermann et al 2004), or for those who received atypical antipsychotics (25.5 admissions to hospital for ischemic stroke per 1000 person-years) versus those receiving typicals (22.3/1000 person-years). Among the elderly with dementia, chronic use of atypicals did not increase risk of ischemic stroke compared to chronic use of typical antipsychotics, suggesting no dose effect (Gill et al 2005).
Risk groups or risk factors	The Framingham stroke risk model includes the following: age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, prior cardiovascular disease (including coronary heart disease, cardiac failure, or intermittent claudication), atrial fibrillation, and left ventricular hypertrophy by EKG (Wolf et al 1991). Hypertension is the most important risk factor for stroke with stroke incidence proportional to blood pressure. A higher rate of stroke was found in those subgroups with established risk for stroke such as atrial fibrillation and prior stroke compared to those without risk factors (Gill et al 2005). An increased risk cannot be excluded for other antipsychotics or other patient populations. As with other antipsychotics, SEROQUEL/SEROQUEL XR should be used with caution in the elderly, especially during the initial dosing period. SEROQUEL/SEROQUEL XR should be used with caution in patients with risk factors for stroke. **Bipolar disorder:** A cross-sectional survey of elderly bipolar disorder patients in the UK found that patients with late-onset bipolar disorder (occurring at age ≥60 years) were at higher cerebrovascular risk—assessed using the Framingham stroke risk score—than patients with early onset disease (age <60 years) (Subramaniam et al 2007). **MDD:** The third Rotterdam Study survey recruited elderly men and women (median age 71.2 and 72.5 years, respectively) and showed that participants with depressive symptoms had a non-significantly higher risk of all strokes (HR 1.20) and ischemic stroke (HR 1.43). Men who met DSM-IV criteria for depressive disorder (comprising MDD, dysthymia or minor depression) were at increased risk of all strokes and ischemic strokes (HR 1.75 and 2.52, respectively), although this was not statistically significant. In women, there was no association between depressive disorder and stroke (Bos et al 2008). Follow-up of an elderly Dutch population (aged ≥55 years) showed that pre-existent cardiac disease moderates the association between depression and stroke; a significant association between depressive symptoms and stroke was observed in individuals with cardiac disease, but not in those without cardiac disease (Wouts et al 2008). Cerebrovascular disease risk factors are associated with deficits in neuropsychological functioning in patients with MDD (Smith et al 2007). **Elderly:** In the Health Search Database, the risk of first-time stroke among elderly patients prescribed different classes of antipsychotic medications using nonusers as reference were reported to be elevated: 5.8 times for phenothiazines, 3.6 times for butyrophenones, and 2.5 times for atypicals (Sacchetti et al 2008).
Potential mechanisms	A potential mechanism for cerebrovascular adverse events in elderly patients treated with SEROQUEL/SEROQUEL XR has not been established.
Preventability	Section 4.2 Posology and method of administration states: **Elderly:** As with other antipsychotics, SEROQUEL should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the

Table II-52 Important potential risks - Cerebrovascular AEs in elderly patients (patients >65 years old)

Potential risk	Cerebrovascular AEs in elderly patients (patients >65 years old)
	clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30 50% in elderly subjects when compared to younger patients. Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder. Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: **Elderly patients with dementia-related psychosis** Quetiapine is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomized, placebo-controlled studies in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. SEROQUEL/SEROQUEL XR should be used with caution in patients with risk factors for stroke.
Potential public health impact of Safety Concern/ Impact on individual patient	Stroke is the third leading cause of death in the US, killing 167,000 Americans each year. According to the American Heart Association report (American Heart Association 2003), about 700,000 people have a new or recurrent stroke (500,000 new and 200,000 recurrent). Stroke is the leading cause of disability in adults. Four million Americans are living with the effects of stroke. Fifty percent to 70% of stroke survivors regain functional independence, but 15% to 30% are permanently disabled. Recurrent stroke is a major contributor to stroke disability and death, with the risk of severe disability or death from stroke increasing with each stroke recurrence. About 3% of stroke patients will have another stroke within 30 days of their first stroke and one-third of recurrent strokes take place within 2 years of the first stroke.
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.

Table II-52 Important potential risks - Cerebrovascular AEs in elderly patients (patients >65 years old)

Potential risk	Cerebrovascular AEs in elderly patients (patients >65 years old)
MedDRA terms	Amaurosis fugax, Angiogram cerebral abnormal, Aphasia, Basal ganglia haemorrhage, Basal ganglia infarction, Basal ganglia stroke, Basilar artery occlusion, Basilar artery stenosis, Basilar artery thrombosis, Brachiocephalic artery occlusion, Brain herniation, Brain scan abnormal, Brain stem haemorrhage, Brain stem infarction, Brain stem ischaemia, Brain stem microhaemorrhage, Brain stem stroke, Brain stem thrombosis, Capsular warning syndrome, Carotid aneurysm rupture, Carotid angioplasty, Carotid arterial embolus, Carotid arteriosclerosis, Carotid artery bypass, Carotid artery disease, Carotid artery insufficiency, Carotid artery occlusion, Carotid artery stenosis, Carotid artery stent insertion, Carotid artery stent removal, Carotid artery thrombosis, Carotid endarterectomy, Cerebellar artery occlusion, Cerebellar artery thrombosis, Cerebellar embolism, Cerebellar haematoma, Cerebellar haemorrhage, Cerebellar infarction, Cerebellar ischaemia, Cerebellar microhaemorrhage, Cerebral arteriosclerosis, Cerebral arteriovenous malformation haemorrhagic, Cerebral artery embolism, Cerebral artery occlusion, Cerebral artery stenosis, Cerebral artery thrombosis, Cerebral circulatory failure, Cerebral gas embolism, Cerebral haematoma, Cerebral haemorrhage, Cerebral haemorrhage foetal, Cerebral haemorrhage neonatal, Cerebral hypoperfusion, Cerebral infarction, Cerebral infarction foetal, Cerebral ischaemia, Cerebral microhaemorrhage, Cerebral revascularisation, Cerebral revascularisation synangiosis, Cerebral septic infarct, Cerebral small vessel ischaemic disease, Cerebral thrombosis, Cerebral vasoconstriction, Cerebral ventriculogram abnormal, Cerebralthrombosis, Cerebrospinal thrombotic tamponade, Cerebrovascular accident, Cerebrovascular disorder, Cerebrovascular insufficiency, Cerebrovascular spasm, Cerebrovascular stenosis, Dysphasia, Embolic cerebral infarction, Embolic stroke, Foetal cerebrovascular disorder, Haemorrhage intracranial, Haemorrhagic cerebral infarction, Haemorrhagic stroke, Haemorrhagic transformation stroke, Hemiparesis, Hemiplegia, Hypoxic encephalopathy, Intracerebral haematoma evacuation, Intracranial haematoma, Intracranial tumour haemorrhage, Intraoperative cerebral artery occlusion, Intraventricular haemorrhage, Intraventricular haemorrhage neonatal, Ischaemic cerebral infarction, Ischaemic stroke, Lacunar infarction, Lateral medullary syndrome, Meningorrhagia, Millard-Gubler syndrome, Nuclear Magnetic Resonance Imaging brain abnormal, Perinatal brain damage, Pituitary haemorrhage, Pituitary infarction, Post procedural stroke, Precerebral artery occlusion, Putamen haemorrhage, Reversible ischaemic neurological deficit, Ruptured cerebral aneurysm, Sneddon's Syndrome, Stroke in evolution, Subarachnoid haemorrhage, Subarachnoid haemorrhage neonatal, Subdural haematoma, Subdural haemorrhage, Subdural haemorrhage neonatal, Thalamic infarction, Thalamus haemorrhage, Thrombotic cerebral infarction, Thrombotic stroke, Transient Ischaemic Attack, Vascular encephalopathy, Vertebral artery occlusion, Vertebral artery stenosis, Vertebral artery thrombosis, Vertebrobasilar insufficiency, Wallenberg Syndrome

AE Adverse event; CI Confidence interval; DSM-IV Diagnostic and Statistical Manual of Mental Disorders IV; EKG Electrocardiogram; GAD Generalised anxiety disorder; GPRD General Practice Research Database; HR Hazard ratio; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; OLE Open-label extension; PLA Placebo; QTP Quetiapine; TEAE Treatment-emergent adverse event; UK United Kingdom; US United States; XR Extended release.

Table II-53 Important potential risks - Cerebrovascular AEs in non-elderly patients

Potential risk	Cerebrovascular AEs in non-elderly patients
Frequency/ Seriousness/ outcomes	**Placebo-controlled trials** 7 (0.08%) quetiapine and 5 (0.11%) placebo patients had TEAEs; MH relative risk: QTP vs PLA (95% CI) 0.56 (0.17, 1.86) 0 events were considered serious by the investigators. Recovered 3 patients (42.86%); Not recovered 4 patients (57.14%); **All studies (including OLEs) QTP exposure** 37 (0.14%) 14 events were considered serious by the investigators. Recovered 23 patients (62.16%); not recovered 9 (24.32%); Unknown 1 (2.70%) **Long-term (≥6 months) QTP exposure** 7 (0.18%) 5 events were considered serious by the investigators. Recovered 2 patients (28.57%); not recovered 2 (28.57%); Unknown 1 (14.29%)
Severity and nature of risk	Cerebrovascular events are serious events that are often life threatening, can be debilitating, and often require major medical interventions. There were 14 serious events in the all trial data. Of the 36 TEAEs of cerebrovascular events in non-elderly patients in the all trial data, 12 were considered mild, 10 were considered moderate, and 14 were considered severe, according to the investigators.
Background incidence/ prevalence	Among patients aged 18 to 49, as reported in an electronic medical record database in the UK, 0.02% with severe mental illness died from stroke compared to 0.01% of patients in the same age group without severe mental illness, a nonstatistically significant difference (Osborn et al 2007). Similar null findings were reported separately for patients with schizophrenia, bipolar affective disorder, and other severe mental illnesses. **Schizophrenia:** The prevalence of stroke in a population-based retrospective study (1994-1995) of Saskatchewan residents diagnosed with schizophrenia as compared to an age- and gender- matched randomly selected general population comparison group (4 per case) was 27.5 per 1000 and 14.6 per 1000, respectively, for an adjusted OR = 2.1 (95% CI: 1.6 – 2.7). The estimated OR was adjusted for the following medical risk factors including: hypertension, hyperlipidemia, diabetes, and an interaction term for hypertension and hyperlipidemia. The incidence of stroke during the period January 1996 to March 1999 in Saskatchewan residents with schizophrenia and in the matched comparison group was 7.5 per 1000 and 5.6 per 1000, respectively for an adjusted RR of 1.5 (95% CI: 1.2 –2.0). The RR estimate was adjusted for the following medical risk factors: hypertension, hyperlipidemia, diabetes, cardiovascular disease, and presence of more than 1 of these diseases. The prevalence of transient cerebral ischemia in Saskatchewan residents with schizophrenia as compared to the matched comparison group was 14.6 per 1000 and 6.4 per 1000, respectively; which yielded an adjusted OR = 2.6 (95% CI: 1.7 – 3.7). The OR estimate was adjusted for the following medical risk factors: hypertension, hyperlipidemia, diabetes, and serious pulmonary disease. The incidence of transient cerebral ischemia in Saskatchewan residents with schizophrenia and in the matched comparison group was 3.5 per 1000 and 4.1 per 1000, respectively, for an adjusted RR of 1.0 (95% CI: 0.6 –1.5). The RR estimate was adjusted for the following medical risk factors: hypertension, hyperlipidemia, diabetes, cardiovascular disease, and presence of more than 1 of these diseases.

Table II-53 Important potential risks - Cerebrovascular AEs in non-elderly patients

Potential risk	Cerebrovascular AEs in non-elderly patients
	Bipolar disorder: In the Taiwan National Health Insurance Research Database, 3.0% of patients hospitalized with bipolar disorder in 1998 had utilized emergency medical services for the management of any type of stroke between 1998 and 2003, which was statistically greater than the 1.50% of patients undergoing an appendectomy, even after adjustment (Lin et al 2007). A cross-sectional survey of community adults in Germany in 1997 found that 3.3% of those with a history of bipolar I disorder reported a history of stroke, which was a statistically significant increase compared to 0.7% in those with no history of a psychiatric disorder (Baune et al 2006). A study using the GPRD found an increased rate of stroke mortality among bipolar patients compared to patients with no serious mental illness, which was statistically significant in the age group of 50 to 75 years (Osborn et al 2007). **MDD:** Among depressed individuals under age 65 in the Framingham Heart Study, 1.7% (37 of 2221) had an incident stroke or transient ischemic attack, 4 times the proportion of those without depressive symptoms (Salaycik et al 2007). **GAD:** A literature review did not reveal any information on the incidence or prevalence of cerebrovascular AEs in the non-elderly GAD population.
Risk groups or risk factors	Stroke risk factors included in a predictive model based upon the Framingham study include the following: age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, prior cardiovascular disease (including coronary heart disease, cardiac failure, or intermittent claudication), atrial fibrillation, and left ventricular hypertrophy by EKG (Wolf et al 1991). A higher rate of stroke was found in those subgroups with established risk for stroke, including atrial fibrillation and prior stroke, compared to those without risk factors (Gill et al 2005).
Potential mechanisms	A potential mechanism for cerebrovascular adverse events in non-elderly patients treated with SEROQUEL/SEROQUEL XR has not been established.
Preventability	Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: **Orthostatic hypotension :** Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease. **Elderly patients with dementia-related psychosis** An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.
Potential public health impact of Safety Concern/ Impact on individual patient	See Table II-52.
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.
MedDRA terms	See Table II-52 for a list of the cerebrovascular AE search terms

AE Adverse event; CI Confidence interval; EKG Electrocardiogram; GAD Generalised anxiety disorder; GPRD General Practice Research Database; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; OLE Open-label extension; OR Odds ratio; PLA Placebo; QTP Quetiapine; RR Risk ratio; TEAE Treatment-emergent adverse event; UK United Kingdom; XR Extended release.

Cardiac disorders

Table II-54 Important potential risks - Ischemic heart disease

Potential risk	Ischemic heart disease
Frequency/ Seriousness/ outcomes	**Placebo-controlled trials** 12 (0.13%) quetiapine and 13 (0.27%) placebo patients had TEAEs; MH relative risk: QTP vs PLA (95% CI) 0.45 (0.20, 1.01) 4 events were considered serious by the investigators. Recovered 9 patients (75%); Not recovered 1 patients (8.33%); Death 2 patients (16.67%) **All studies (including OLEs) QTP exposure** 77 (0.27%) 22 events were considered serious by the investigators. Recovered 57 patients (74.03%); not recovered 13 (16.88%); Unknown 2 (2.60%); Death 5 (6.49%). **Long-term (≥6 months) QTP exposure** 13 (0.31%) 3 events were considered serious by the investigators. Recovered 7 patients (53.85%) ; not recovered 3 (23.08%) ; Death 2 (15.38%) A cumulative review of cardiac events in 2010 did not suggest that there is an increased risk of ischemic heart disease associated with the use of quetiapine.
Severity and nature of risk	Ischemic heart disease is characterized by damaged or dysfunctional cardiac tissue secondary to decreased blood supply and is most commonly due to atherosclerosis. It is typically, although not always, associated with ECG and laboratory evidence of cardiac insult. There were 22 serious events in the all trial data. Of the 77 TEAEs of ischemic heart disease in the all trial data, 32 were considered mild, 23 were considered moderate, and 22 were considered severe, according to the investigators.
Background incidence/ prevalence	There is evidence that individuals with schizophrenia and other serious mental and affective disorders have a higher prevalence of Coronary heart disease (CHD); however, it is unclear what role pathophysiology, patient lifestyle, diet, and habits have. **Schizophrenia:** The prevalence of Ischemia heart disease (IHD) in a population-based retrospective study (1994-1995) of Saskatchewan residents diagnosed with schizophrenia (58.6 per 1000) was not significantly different from that in an age- and gender-matched randomly selected general population comparison group (4 per case) (60.6 per 1000), representing an adjusted OR of 1.1 (95% CI: 0.9, 1.3). The estimated OR was adjusted for the following medical risk factors: hypertension, diabetes, hyperlipidemia, and their 2-way interactions and serious pulmonary disease. The prevalence of other cardiovascular comorbidities including arrhythmias, heart failure, stroke, and transient cerebral ischemia were higher in the group with schizophrenia than in the comparison group. The incidence of IHD during the period January 1996-March 1999 in Saskatchewan residents with schizophrenia and in the matched comparison group was 17.4 per 1000 and 15.8 per 1000, respectively, for an adjusted RR of 1.1 (95% CI: 0.9, 1.4). The RR estimate was adjusted for the following medical risk factors: hypertension, diabetes, hyperlipidemia, cardiovascular disease, and presence of more than 1 chronic target disease. The incidence of other cardiovascular comorbidities including ventricular arrhythmia, heart failure, and stroke

Table II-54 Important potential risks - Ischemic heart disease

Potential risk	Ischemic heart disease
	were higher in the group with schizophrenia than in the comparison group. An increased risk of cardiovascular mortality was observed in the Saskatchewan residents with schizophrenia. This finding was consistent with a 2-fold excess CHD mortality for patients with schizophrenia vs the general population reported by other investigators (Brown et al 2000). Myocardial infarction rates were elevated nearly 5-fold (RR=4.81, 95% CI: 2.44, 9.46) among managed-care enrollees treated with antipsychotics for schizophrenia over controls matched by age, sex, and date using data from a large managed care organization (Enger et al 2004). An observational study of the GPRD estimated that the hazard ratios for death due to CHD among people with severe mental illnesses compared to controls to be 3.22 (95% CI: 1.99, 5.21) for those 18 to 49 years, 1.86 (95% CI: 1.63, 212) for those 60 to 75 years, and 1.05 (95% CI: 0.92, 1.19) for those greater than 75 years (Osborn et al 2007). The 10-year Framingham CHD risk function of subjects providing fasting blood samples at baseline in the CATIE schizophrenia trial were significantly elevated, compared to age-, race-, and gender matched controls drawn from the NHANES III survey (9.4% vs 7% in males; 6.3% vs 4.2% in females) (Goff et al 2005). **Bipolar disorder:** Adults with bipolar disorder 1 were found to have an increased age-, race-, and sex-adjusted prevalence of physician-diagnosed Cardiovascular disease (CVD) (OR=4.95, 95%CI: 4.27, 5.75) and hypertension (2.38, 95% CI: 2.16, 2.62) versus controls in a representative sample of the US National Epidemiologic Survey on Alcohol and Related Conditions (Goldstein et al 2009). The prevalence of CVD was significantly greater among subjects with bipolar disorder 1 as compared to subjects with MDD, which was in turn significantly greater as compared to controls (10.1% versus 8.0% versus 4.9%, respectively; p<0.0001). In a cross-sectional study of bipolar patients from 13 centers in Spain, both 10-year Framingham and Coronary Risk Evaluation (SCORE) function scores determined the 10-year risk of a CHD event as 7.6% and 10-year cardiovascular mortality risk of 1.8% (Garcia-Portilla et al 2009). **MDD:** Meta-analyses have confirmed the long held view that depression appears to have both an etiological role (ie, depression preceding the development of CHD) as well as prognostic role (ie, depression altering the course of established disease) in CHD (Frasure-Smith and Lesperance 2006). Two different meta-analyses of studies completed prior to the end of the year 2000 found identical point estimates for the relative risk of depression leading to CHD of 1.64 (with different 95% CIs: 1.41, 1.90 and 1.29, 2.08) (Wulsin and Singal 2003, Rugulies 2002). In a recent meta-analysis investigators, Van der Koy et al 2007 found the risk of depression for the onset of myocardial infarction to be significant but somewhat heterogeneous (OR=1.6, 95%CI: 1.34, 1.92). Depressive symptomatology at baseline was associated with a higher incidence of fatal and nonfatal CHD events (HR=1.66, 95%CI: 1.06, 2.6) in a prospective-community based cohort study of Italians 65 years and older from 8 municipalities in Italy followed for 4 years (Marzari et al 2005). **GAD:** On the basis of questionnaire assessments, anxiety disorders have been hypothesized to be was associated with elevated CHD risk. The Northwick Park Heart Study followed 1457 initially healthy men for a period of 10 years and found that men with the highest levels of phobic anxiety had a relative risk of fatal CHD of 3.77 (95% CI: 1.64, 8.64) compared with men reporting no anxiety (Haines et al 1987). Using data from the Health Professionals Follow-up Study, an ongoing cohort of 33999 US men aged 42 to 72 years, investigators (Kawachi et al 1994a) found the relative risk of fatal CHD among men with the highest levels of anxiety to be 2.45 (95% CI: 1.00, 5.96) compared with men reporting no symptoms of anxiety. In a nested case-control using data from the Normative Aging Study, men reporting 2 or more anxiety symptoms had elevated risks of fatal CHD (age-adjusted OR=3.20; 95% CI: 1.27, 8.09), and sudden death (age-adjusted OR=5.73; 95% CI: 1.26, 26.1) compared to controls reporting no symptoms (Kawachi et al 1994b).

Table II-54 Important potential risks - Ischemic heart disease

Potential risk	Ischemic heart disease
Risk groups or risk factors	Several studies have reported increased cardiovascular co-morbidity in patients with schizophrenia (eg, Enger et al 2004, Goff et al 2005). Hypertension, diabetes mellitus, cigarette smoking, obesity, which are well established CHD risk factors are more common among patients with schizophrenia than in the general population (Hennekens et al 2005). Myocardial infarction was more common in schizophrenic patients with pre-exis~~i~~ting risk factors, such as diabetes in the previously described study of medical claims from a large managed care organization (Enger et al 2004). However, the European Prospective Investigation Into Cancer-Norfolk found that the increased risk of ischemic heart disease mortality in the population with major depression was independent of established risk factors and remained undiminished several years after the original assessment (Surtees et al 2008). In the US, African Americans have the highest overall CHD mortality rates and the highest out-of-hospital coronary death rates of any ethnic group, particularly at younger ages. The previously described CHD risk factors all occur more frequently in African-Americans than in whites. The predictive value of most conventional risk factors for development of CHD appears to be similar for African Americans and whites. However, the risk of death attributable to some risk factors (ie, hypertension, diabetes) is disproportionately greater for African Americans (NCEP Expert Panel 2002). In patients with established CHD, depression is associated with an increased risk of mortality and excess cardiac events beyond the impact of cardiac disease severity. Use of antipsychotic drugs may increase patients' cardiovascular risk to some extent, either directly through actions on the heart or vasculature, or indirectly, via metabolic effects (Drici and Priori 2007). Although it is possible for patients to accumulate "traditional" risk factors for the development of CVD, several factors including use of psychotropic drugs may influence or increase risk in these vulnerable populations (Mackin 2008).
Potential mechanisms	Various behavioural and biological mechanisms have been suggested to explain the links between serious mental illness and affective disorders and CHD. Shared genetic determinants, inflammation, blood clotting, and vascular mechanisms have been suggested as plausible explanatory mechanisms. The autonomic nervous system is dysregulated in CHD patients with depression (Carney et al 2005). Decreased parasympathetic or increased sympathetic activity may promote myocardial ischemia, among other effects upon the cardiovascular system.
Preventability	General medical practice for anyone at risk for ischemic heart disease would be to promote life style modification, reduction in tobacco exposure, access to heathy diets, and establishment of healthy environments that are safe and conducive to physical activity. Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: **Orthostatic hypotension** Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if ~~this~~ orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease. Section 4.9, Overdose, of the SEROQUEL/SEROQUEL XR MR-SmPC states: Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

Table II-54 Important potential risks - Ischemic heart disease

Potential risk	Ischemic heart disease
Potential public health impact of Safety Concern/ Impact on individual patient	CHD is the leading cause of mortality in the US and Europe accounting for >1 in 3 total deaths in developed countries (Hennekens et al 2005, Rayner et al 2009). In Europe, it claims approximately 2 million lives every year. There is limited data regarding the relationship between major risk factors and the subsequent hazard of morbidity and mortality associated with CHD in populations with serious mental diseases and affective disorders. The co-occurrence of multiple risk factors has an additive effect on the occurrence of CHD. For these and other reasons, little attention is given to the high frequency of CHD in patients with schizophrenia by generalists, specialists in other fields, or cardiovascular specialists (Hennekens et al 2005). Meta-analyses reveal that patients with schizophrenia are twice as likely to die from CHD as the general population. When patients with major mental disorders such as schizophrenia develop CHD, they are also less likely to receive the standard of care received by the general population (Druss et al 2000). The patient and provider factors that contribute to this difference and its implications for quality and long-term outcomes of care are relatively unknown.
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.
MedDRA terms	Acute coronary syndrome, acute myocardial infarction, coronary artery embolism, coronary artery occlusion, coronary artery thrombosis, Kounis syndrome, myocardial infarction, papillary muscle infarction, post procedural myocardial infarction, postinfarction angina, silent myocardial infarction, blood creatine phosphokinase MB abnormal, blood creatine phosphokinase MB increased, cardiac enzymes increased, coronary artery reocclusion, coronary bypass thrombosis, electrocardiogram Q wave abnormal, electrocardiogram ST segment abnormal, electrocardiogram ST segment elevation, electrocardiogram ST-T segment elevation, infarction, myocardial reperfusion injury, scan myocardial perfusion abnormal, troponin I increased, troponin T increased, and troponin increased. **The following terms are added in Version 11 of the EU RMP**: angina pectoris, angina unstable, arteriosclerosis coronary artery, arteriospasm coronary, coronary angioplasty, coronary arterial stent insertion, coronary artery bypass, coronary artery disease, coronary artery dissection, coronary artery insufficiency, coronary artery restenosis, coronary artery stenosis, coronary endarterectomy, coronary no-reflow phenomenon, coronary ostial stenosis, coronary revascularisation, dissecting coronary artery aneurysm, ECG signs of myocardial ischaemia, haemorrhage coronary artery, in-stent coronary artery restenosis, ischaemic cardiomyopathy, microvascular angina, myocardial ischaemia, percutaneous coronary intervention, Prinzmetal angina, subclavian coronary steal syndrome, subendocardial ischaemia, and vascular graft occlusion.

CATIE Clinical Antipsychotic Trials of Intervention Effectiveness; CHD Coronary heart disease; CI Confidence interval; CVD Cardiovascular disease; ECG Electrocardiogram; GAD Generalised anxiety disorder; GPRD General Practice Research Database; HR Hazard ratio; IHC Ischemic heart disease; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; NHANES National Health and Nutrition Examination Survey; OLE Open-label extension; OR Odds ratio; PLA Placebo; QTP Quetiapine; RR Risk ratio; TEAE Treatment-emergent adverse event; US United States.

Table II-55 Important potential risks – Torsades de pointes

Identified risk	Torsades de pointes
Frequency/ Seriousness/ Outcomes	**Placebo-controlled trials** No patient had torsades de pointes. 6 (0.06%) quetiapine and 2 (0.04%) placebo patients had TEAEs QT prolongation; MH relative risk: QTP vs PLA (95% CI) 1.90 (0.38, 9.62) 0 events were considered serious by the investigators. Recovered 3 patients (50%); not recovered 3 (50%). **All studies (including OLEs) QTP exposure** No patient had torsades de pointes across all studies. 30 (0.11%) QTP patients and 2 (0.03%) placebo patients had QT prolongation. 2 events in QTP patients were considered serious by the investigators. Recovered 18 patients (60%); not recovered 11 (36.67%); unknown 1 (3.33%) **Long-term (≥6 months) QTP exposure** No patient had torsades de pointes. 7 (0.17%) patients had QT prolongation. No events were considered serious by the investigators. Recovered 4 patients (57.4%); not recovered 3 (42.86%)
Severity and nature of risk	Torsades de pointes is a malignant ventricular arrhythmia that is associated with syncope and sudden death. It is characterized by a long QT interval and a short-long-short sequence in the beat preceding its onset. QT prolongation is the lengthening of the QT interval in electrocardiographic measurements, and is a surrogate marker for the risk of developing the potentially fatal arrhythmia Torsades de Pointes Of the 32 TEAEs of QT prolongation in the all trial data, 2 events were considered serious by the investigators. No patients developed torsades de pointes.
Background incidence/ prevalence	**General:** The exact incidence of drug induced torsades de pointes in the general population is largely unknown. The annual number of drug induced torsades de pointes submitted to WHO from 1983 to 1999 ranged from 1 to 166 (Darpo 2001). The degree of under-reporting of ADRs varies widely and is particularly high when physicians and pharmacists regard the adverse reaction as "expected" in relation to the underlying disease of the patient. The DRAMA pilot study (Darpo 2001) collected a total of 68 episodes of ventricular arrhythmias and of these 14 were regarded as "medium or high confidence torsades de pointes" by the expert group. This corresponded to an incidence in this population of 3.3 cases per million for 28 days, which equalled an annual incidence of 4/100,000. **Schizophrenia / Bipolar Disorder/ MDD/GAD:** Torsades de pointes or surrogates are reported with a frequency of about 1 in 10000 atypical antipsychotic users (Titier et al 2005). Although assessment of QTc is a convention for new drug development, no information on prevalence of torsades de Pointes was found in patients with GAD or MDD.
Risk groups or risk factors	Risk factors that may predispose the patients to occurrence of torsades de pointes include diabetes, long QT syndrome, drug-induced QT prolongation, and hypokalaemia (Titier et al 2005). The mean corrected QT interval of drug-naïve psychiatric emergency patients was reported to be prolonged and significantly longer than psychiatric outpatients who were under treatment (Hatta et al 2000). The elderly patient, patients with congenital long QT syndrome, congestive heart failure,

Table II-55 Important potential risks – Torsades de pointes

Identified risk	Torsades de pointes
	heart hypertrophy, hypokalaemia, or hypomagnesaemia may be at increased risk. In the setting of an overdose, patients are at risk. Patients with cardiovascular disease or family history of QT prolongation, and patients on medicines known to increase QTc interval, may be at risk. The aforementioned risk factors may also predispose patients to antipsychotic-use induced prolongation of QT interval and torsades de pointes. A study of 24 patients with first episode treatment-naïve psychosis found that patients had a significantly increased QT variability index compared with healthy controls (Jindal et al 2009); the data suggest that these differences may be independent of medication effects in these patients.
Potential mechanisms	Many antipsychotics and antidepressants can modulate the cardiac action potential by blocking different cardiac ion channels present in ventricular myocytes (ie, inward sodium current I_{Na}, the inward slow Ca^{2+} current I_{Ca}, and one or more outward potassium currents, I_K) (Sala et al 2006). These channels are involved in depolarization and repolarization phases of the action potential. The overall duration of the QRS complex, contributing to prolongation of the QT interval, is affected by some tricyclic antidepressants due to blocking of sodium channels. In addition, there is a direct antidepressant-mediated effect on depolarization, affecting I_{Kr} which in turn is linked to a greater risk of early-after depolarizations and torsades de pointes (Sala et al 2006). Observations of schizophrenia patients suggest that a putative increase in sympathetic function during an acute psychotic episode might lead to QT variability in a susceptible individual with schizophrenia and making the myocardium vulnerable to arrhythmias (Axelsson and Langerkvist-Briggs 1992, Bär et al 2007). Not all psychotropic drugs that inhibit cardiac ion channels at the cellular level are associated with a similar potential and degree of prolongation of the QT interval; the potential for prolongation of the QT interval is not strictly correlated with the risk of torsades de pointes and sudden death (Goodnick et al 2002, Sala et al 2006).
Preventability	Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: QT Prolongation: As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia, or hypomagnesaemia (see section 4.5). Section 4.5, of the SEROQUEL/SEROQUEL XR MR-SmPC states Interactions with Other Medicinal Products and Other Forms of Interactions, states: Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval. Section 4.8, of the SEROQUEL/SEROQUEL XR MR-SmPC states: Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects.

Table II-55 Important potential risks – Torsades de pointes

Identified risk	Torsades de pointes
Potential public health impact of Safety Concern/ Impact on individual patient	Cardiovascular morbidity and mortality are higher in psychiatric patients than in the general population. In schizophrenic patients without cardiovascular history, long QT interval is a major risk factor for torsades de pointe and for sudden death (Girardin and Gaspoz 2007). An estimated 1 in 10000 individuals is a carrier of the long QT interval gene, and long QT interval may result in 3000 to 4000 cases of sudden death per year in the US (Kao and Furbee 2005). Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest, and torsades de pointes have been reported very rarely with the use of neuroleptics and are considered class effects.
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.
MedDRA terms	Torsades de pointes.

CI Confidence interval; GAD Generalised anxiety disorder; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; OLE Open-label extension; PLA Placebo; QTP Quetiapine; TEAE Treatment-emergent adverse event; UK United Kingdom; US United States; XR Extended release.

Injury, poisoning, procedural complications

Table II-56 Important potential risks - Abuse and misuse

Potential risk	Abuse and misuse
Frequency/ Seriousness/ Outcomes	**Placebo-controlled trials** 7 (0.08%) quetiapine and 1 (0.02%) placebo patients had TEAEs; MH relative risk: QTP vs PLA (95% CI) 4.51 (0.46, 44.10) No events were considered serious by the investigators. Recovered 6 patient (88.71%); Not recovered 1 patients (14.29%); **All studies (including OLEs) QTP exposure** 20 (0.07%) 4 events were considered serious by the investigators. Recovered 18 patients (90.00%); not recovered 2 (10.00%); **Long-term (≥6 months) QTP exposure** 5 QTP patients (0.12%). No events were considered serious by the investigators. Recovered 5 patients (100.00%)
Severity and nature of risk	Substance abuse, according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition), is a disorder characterized by the use of a mood or behavior-altering substance in a maladaptive pattern resulting in significant impairment or distress, such as failure to fulfill social or occupational obligations or recurrent use in situations where it is physically dangerous to do so or which end in legal problems (APA 2000).). There were 4 serious events in the all trial data. Of the 20 TEAEs of abuse and misuse in the all trial data, 5 were considered mild, 9 were considered moderate, and 6 were considered severe, according to the investigators.
Background incidence/ prevalence	**General:** Data from the NIMH's ECA study (n=20291) suggest that the lifetime prevalences of alcohol dependence-abuse and other drug dependence-abuse in the general population are 13.5% and 6.1%, respectively (Regier et al 1990). **Schizophrenia:** Comorbid alcohol and drug abuse is common in patients with schizophrenia and occurs at rates exceeding that found in the general community; a substantial portion of these patients (15% to 60%) abuse psychoactive drugs (Dixon et al 1991). Data from the ECA study suggest that the lifetime prevalence of any substance abuse or dependence is 47% in patients with schizophrenia (Regier et al 1990). A retrospective study of 232 first-episode patients estimated the lifetime prevalence rate of 23.7% for alcohol abuse in patients with schizophrenia, compared with 12.3% in the control group (Bühler et al 2002, Hambrecht and Häfner 1996). Prevalence rates for drug abuse in patients with schizophrenia and the control group were 14.2% and 7%, respectively. **Bipolar disorder:** A review of comorbid conditions prevalent among individuals with bipolar disorder revealed that approximately 50% of this population reported a lifetime history of a substance abuse disorder; 56% of those with bipolar disorder had a history of substance use disorder and 49% of those with bipolar disorder had a history of alcohol abuse (Krishnan 2005). Data from the ECA study suggest that the lifetime prevalence of any substance abuse or dependence is 60.7% in patients with bipolar I disorder and 48.1% in patients with bipolar II disorder (Regier et al 1990). A review of data from the NESARC, which gathered information from 43093 adult American citizens, reported that of the respondents with bipolar I disorder (n=1546), 22.1% reported self-medicating with alcohol only, 18.9% with drugs (illicit or prescription), and 41.0% reported any self-medication (Bolton et al 2009). In individuals with bipolar II disorder (n=538), 23.9% reported self-medicating with alcohol only, 10.8% with drugs, and 34.7% reported any self-medication (Bolton et al 2009).

Table II-56 Important potential risks - Abuse and misuse

Potential risk	Abuse and misuse
	MDD: Analysis of data from NESARC showed that of the patients with MDD (n=7822), 15.4% reported self-medicating with alcohol only, 7.8% with drugs, and 23.2% reported any self-medication (Bolton et al 2009). Data from the ECA study suggest that the lifetime prevalence of any substance abuse or dependence is 27.2% in patients with MDD (Regier et al 1990). **GAD**: A review of epidemiologic studies conducted in Australia and the US estimated the 12-month prevalence of substance misuse among adults with GAD to range from 13.3% to 23% (Gale and Davidson 2007). A German population-based study of adults with GAD concluded that 6.4% met the criteria for alcohol abuse/dependence and 1.4% met the criteria for drug abuse/dependence (Carter et al 2001). From a statistical standpoint, these prevalence estimates were not significantly different from the prevalence estimates of alcohol or drug abuse/dependence among the non-GAD comparison group. Analysis of data from NESARC showed that substance abuse or misuse was associated with an increased lifetime risk of GAD (Bolton et al 2009). Male individuals had significantly higher odds of developing GAD if they self-medicated with alcohol only (odds ratio [OR]: 1.46, 95% CI: 1.05, 2.03) or with drugs (OR: 2.16, 95% CI: 1.36, 3.44). Female individuals also had significantly higher odds of developing GAD if they self-medicated with alcohol only (OR: 1.58, 95% CI: 1.18, 2.11) or with drugs (OR: 2.70, 95% CI: 1.84, 3.95). **Quetiapine:** To date, no epidemiologic data exist regarding quetiapine abuse and misuse. A literature search revealed several case reports of intranasal and intravenous quetiapine abuse and misuse either alone or in combination with other legal and illegal drugs (Waters and Joshi 2007, Hussain et al 2005, Pierre et al 2004). The majority of these cases have involved individuals with a history of substance abuse in a correctional setting (Hanley and Kenna 2008).
Risk groups or risk factors	The presence of a severe mental illness is associated with a significant increase in the risk of substance abuse. Social, environmental, biological, and psychological factors play a role in the development of substance disorder in patients with psychiatric disorders (Cuffel 1996).
Potential mechanisms	It appears that dependence to psychostimulants and opioids is highly inheritable and directly related to addiction liability. CNS pathways that mediate reward, stress response, and compulsivity, among others, are most likely involved in this genetic association. Genes that may have a role in these mechanisms have begun to be identified in knockout mouse strains (Samet 2007).
Preventability	. Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: Misuse and abuse Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse."
Potential public health impact of Safety Concern/ Impact on individual patient	A minority of people who have ever experimented with an illicit drug progress to a clinical drug abuse diagnosis. What makes a person progress from illicit drug use to clinical drug abuse is not fully understood. Genetic susceptibility, the social context of the drug, and comorbid psychiatric conditions may be factors that affect this progression (Samet 2007). Consequences of comorbid substance abuse in patients with schizophrenia include more positive symptoms, relapse of psychosis, increased risk of suicide and violence, lower rates of employment, more medical comorbidities, increased likelihood of legal complications and greater propensity to antipsychotic-related side effects (Buckley et al 2009, Bühler et al 2002).
Evidence source	Clinical studies integrated safety database (Version 27) and literature sources.

Table II-56 Important potential risks - Abuse and misuse

Potential risk	Abuse and misuse
MedDRA terms	Intentional drug misuse, drug abuser, incorrect route of drug administration, substance abuse, drug diversion, off label use, drug dependence, and drug abuse

CI Confidence interval; CNS Central nervous system; DSM IV Diagnostic and Statistical Manual of Mental Disorders IV; ECA Epidemiologic Catchment Area; GAD Generalised anxiety disorder; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; NESARC National Epidemiologic Survey on Alcohol and Related Conditions; NIMH National Institute of Mental Health; OLE Open-label extension; OR Odds ratio; PLA Placebo; QTP Quetiapine; TEAE Treatment-emergent adverse event; US United States.

II: 7.3.3 Other potential risks that require further evaluation

General disorders

- Potential for off-label use and misdosing, as identified in Table II-57.

General disorders

Table II-57 Important potential risks - Potential for off-label use and misdosing

Potential risk	Potential for off-label use and misdosing
Frequency/ Seriousness/ Outcomes	Not applicable
Severity and nature of risk	SEROQUEL is approved for schizophrenia and bipolar disorder, including moderate to severe manic episodes in bipolar disorder, major depressive episodes in bipolar disorder, and prevention of recurrence in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment. SEROQUEL XR is approved for schizophrenia, including preventing relapse in stable schizophrenic patients who have been maintained on SEROQUEL XR, and bipolar disorder, including moderate to severe manic episodes in bipolar disorder, major depressive episodes in bipolar disorder, and prevention of recurrence in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment. SEROQUEL XR is also approved as add-on treatment for major depressive episodes in patients with MDD who have had sub-optimal response to antidepressant monotherapy (preventability is provided below). Even with robust labeling, the potential for off-label use or misdosing exists for all medicines including SEROQUEL and SEROQUEL XR. In particular, there is the potential for healthcare professionals to (a) prescribe SEROQUEL or SEROQUEL XR for other types of depression and other psychiatric conditions or (b) prescribe treatment at the wrong dose in light of (1) the recent approval of quetiapine in bipolar depression and (2) physician awareness of the clinical development programs in MDD and GAD. For example, in bipolar depression, the recommended daily dose is 300 mg. The label also notes that in clinical trials, no additional benefit was seen in the 600 mg group compared to the 300-mg group, but that individual patients may benefit from a 600-mg dose. In contrast, for treatment of manic episodes associated with bipolar disorder, the usual effective dose is in the range of 400 to 800 mg/day. Additionally, the label notes that the dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg/day. There is also the potential for healthcare professionals to prescribe treatment for pediatric

Table II-57 Important potential risks - Potential for off-label use and misdosing

Potential risk	Potential for off-label use and misdosing
	patients as the diseases that SEROQUEL/SEROQUEL XR are approved for in adult patients are also found in pediatric patients. Additionally, there is physician awareness of the SEROQUEL clinical development program in the pediatric population, which provides evidence-based information on the use of SEROQUEL in pediatric and adolescent patients. While safety information from these studies is included in this RMP, SEROQUEL and SEROQUEL XR are currently not approved for use in the pediatric population (preventability is provided below). As with other drugs, there is also the potential for physicians to prescribe SEROQUEL/SEROQUEL XR to take advantage of known side effects (eg, sedation) to treat conditions in non-psychiatric populations. AstraZeneca does not support or endorse off-label use of their products.
Background incidence/ prevalence	Not applicable
Risk groups or risk factors	Even with robust labeling, the potential for off-label use or misdosing exists for all medicines including SEROQUEL and SEROQUEL XR. In particular, there is the potential for healthcare professionals to (a) prescribe SEROQUEL or SEROQUEL XR for other types of depression and other psychiatric conditions or (b) prescribe treatment at the wrong dose or (c) for an unapproved population, such as pediatric patients.
Potential mechanisms	Not applicable
Preventability	Activities adopted to minimize the potential for misdosing, particularly in treating bipolar depression, include indication-specific educational pieces and activities. There is specific language in the SmPC describing dose titration by indication and formulation. Although the SmPC language is specific regarding off-label use and misdosing, the risk remains.
Potential public health impact of Safety Concern/ Impact on individual patient	Severity and nature of the risk is provided above.
Evidence source	Literature sources
MedDRA terms	Not applicable

GAD Generalised anxiety disorder; MDD Major depressive disorder; MedDRA Medical Dictionary for Regulatory Activities; RMP Risk Management Plan; SmPC Summary of Product Characteristics.

II: 7.4 Identified and potential interactions

II: 7.4.1 Overview of potential for interactions

Biotransformation and elimination

Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is significantly affected by a high fat meal but not by a light meal. Quetiapine is approximately 83% bound to plasma proteins. Steady-state peak molar

concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. The PK of quetiapine and norquetiapine are linear across the approved dosing range.

Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 (CYP) mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

The PK of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine do not differ between men and women.

Cytochrome P450 inhibition and induction

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human CYP 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of CYP-mediated metabolism of the other drug. From in vivo studies in mice and rats, it appears that quetiapine can induce CYP enzymes. In drug interaction studies in psychotic patients, multiple dosing of quetiapine at doses up to 750 mg/day had little effect on the PK of lorazepam, divalproex, lithium, and antipyrine.

II: 7.4.2 Important identified and potential interactions

Important identified interactions

CYP 3A4 is the enzyme that is primarily responsible for the CYP-mediated metabolism of quetiapine. Consuming grapefruit juice while on quetiapine therapy is not recommended, per the SmPC.

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

Table II-58 Drug-drug interactions with strong CYP3A4 inhibitors

Interacting substances	**Ketoconazole (and other CYP3A4 inhibitors such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone.)**
Effect of interaction	In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated.
Evidence source	Clinical Studies
Possible mechanisms	Inhibition of the CYP3A4 enzyme by ketoconazole results in an increased plasma concentration of quetiapine. CYP3A4 is the enzyme that is primarily responsible for the CYP-mediated metabolism of quetiapine.
Potential health risk	Drug-drug interactions between quetiapine and the aforementioned medications may lead to an increased frequency of AEs, and may exhibit signs and symptoms consistent with an exaggeration of quetiapine's known pharmacological effects, ie, drowsiness and sedation, tachycardia, and hypotension.
Discussion	Based on the 5- to 8- fold increase of quetiapine seen with concomitant administration of ketoconazole, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. These identified interactions are described in the SmPC and are monitored as part of routine surveillance activities.

AE Adverse event; AUC Area under the curve; CYP Cytochrome P450; HIV Human immunodeficiency virus; SmPC Summary of Product Characteristics.

Table II-59 Drug-drug interactions with strong CYP3A4 inducers

Interacting substances	**Carbamazepine and phenytoin (and other strong CYP3A4 enzyme inducers)**
Effect of interaction	In a multiple-dose study in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known CYP3A4 enzyme inducer), coadministration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 450%.
Evidence source	Clinical Studies
Possible mechanisms	Induction of the CYP3A4 enzyme by carbamazepine, phenytoin, or other inducers may enhance the clearance of quetiapine from the systemic circulation.
Potential health risk	As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy.

Table II-59 Drug-drug interactions with strong CYP3A4 inducers

Interacting substances	Carbamazepine and phenytoin (and other strong CYP3A4 enzyme inducers)
Discussion	Sections 4.4 and 4.5 of the SmPC describe these interactions: Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate). In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy. Co-administration of quetiapine and phenytoin (another CYP3A4 enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate). These identified interactions are monitored as part of routine surveillance activities.

AUC Area under the curve; CYP Cytochrome P450; SmPC Summary of Product Characteristics.

Table II-60 Drug-drug interactions with Thioridazine

Interacting substance	Thioridazine
Effect of interaction	Concomitant use with thioridazine resulted in an increased clearance of quetiapine of approximately 70%.
Evidence source	Clinical studies
Possible mechanisms	Unknown
Potential health risk	QT prolongation and Torsades has occurred with thioridazine alone (a discussion is provided below). Also, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy.

Table II-60 Drug-drug interactions with Thioridazine

Interacting substance	Thioridazine
Discussion	There is compelling evidence that the antipsychotic thioridazine causes prolongation of the QT interval as well as blocks the I_{kr} channels and is related to causing numerous torsades and sudden deaths. The mechanism by which drugs prolong repolarization by blockage of the I_{kr} channels leading to torsades and sudden death is complex. Per Section 4.4 *Special warnings and precautions for use*: In clinical trials and use in accordance with the SmPC, quetiapine was not associated with a persistent increase in absolute QT intervals. In post-marketing, QT prolongation was reported with quetiapine at the therapeutic doses and in overdose. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with CVD or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia. Events related to QT prolongation and/or Torsades have enhanced surveillance.

CVD Cardiovascular disease; SmPC Summary of Product Characteristics.

Formal interaction studies with commonly used cardiovascular medicinal products have not been performed. However, the SmPC does have a caution concerning the use of quetiapine with other medicines known to increase QT interval or with concomitant neuroleptics (as noted in Table II-60). Furthermore, in Section 4.5 *Interactions with other medicinal products and other forms of interaction*, the SmPC states: Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval. Finally, QT prolongation is contained in Section 4.8 *Undesirable effects* and Section 4.9 *Overdose*, of the SmPC.

Table II-61 Drug interactions with CNS depressants

Interacting substances	CNS depressants and alcohol
Effect of interaction	Alcohol and quetiapine coadministration resulted in negative effects in relation to the effects of alcohol alone. Therefore, statistically significant alcohol-quetiapine interactions noted in pharmacodynamic test results from subjects with selected psychotic disorders were not clinically relevant.
Evidence source	**Study 5077IL/0024** part A and part B
Possible mechanisms	Unknown
Potential health risk	The coadministration produced no significant potentiation of quetiapine- or alcohol-related effects. Coadministration of a moderate, single, oral dose of alcohol during repeated dosing with quetiapine (250 mg TID) was well tolerated.
Discussion	In clinical pharmacology studies conducted by AstraZeneca no evidence of a clinically significant interaction between quetiapine and alcohol was seen.

AE Adverse event; CNS Central nervous system.

Other medications that may be used in quetiapine's target populations have been studied. The SmPC states that the PK of quetiapine either were not altered or were not significantly altered by co-administration of the following individual medications: imipramine, fluoxetine, risperidone, haloperidol, cimetidine, and lithium. The PK of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

Table II-62 Drug interactions with Food

Interacting substance	**Food**
Effect of interaction	Increased quetiapine blood concentrations with the use of SEROQUEL XR and high-fat meals.
Evidence source	Clinical studies
Possible mechanisms	Unknown
Potential health risk	This interaction may lead to an increased frequency of AEs including signs and symptoms consistent with an exaggeration of quetiapine's known pharmacological effects, ie, drowsiness and sedation, tachycardia, and hypotension.
Discussion	Per the SmPC for SEROQUEL XR: In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the SEROQUEL XR C_{max} and AUC of approximately 50% and 20%, respectively. It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that SEROQUEL XR is taken once daily without food. (SEROQUEL may be administered with or without food).

AE Adverse event; AUC Area under the curve; Cmax Maximum plasma concentration; SmPC Summary of Product Characteristics; XR Extended release.

II: 7.5 Pharmacological class effects

II: 7.5.1 Pharmacological class risks already included as important identified or potential risks

The following identified risks have been observed with other members of the antipsychotic class:

- EPS
- Weight gain
- Lipid changes (Increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs)
- Hyperglycemia and DM

The following potential risks have been observed with other members of the antipsychotic class:

- Cerebrovascular AEs in the elderly. as identified in the elderly
- Cerebrovascular AEs in non-elderly patients
- Ischemic heart disease
- Torsades de pointes
- Abuse and misuse

Table II-63 Pharmacological class risks already included as important identified or potential risks

Class risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (SMPCs)	Comment
Identified risks			
EPS	Adults and paediatric population: EPS very common (>1/10)	**Amisulpride, Aripiprazole, Asenapine, Clozapine, Olanzapine, Risperidone:** Very common (≥1/10): tremor, rigidity hypokinesia, hypersalivation, akatheisia, and dyskinesia **Sertindole:** Incidence of EPS was equal to that seen in placebo controls.	EPS is found in the SmPC for SEROQUEL and SEROQUEL XR in Sections: 4.4 Special warnings and precautions for use; 4 6 Fertility, pregnancy and lactation; 4.8 Undesirable effects and Section 5.1 (Clinical safety) Pharmacodynamic properties

Table II-63 Pharmacological class risks already included as important identified or potential risks

Class risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (SMPCs)	Comment
Weight gain	Weight gain very common (>1/10) In short term, fixed dose (50mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg for the placebo treated patients. The percentage of quetiapine treated patients who gained ≥7% of body weight ranged from 5.3% for the 50 mg daily dose to 15.5% for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7% for placebo treated patients. Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomized to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomized period the mean weight gain was 0.89 kg, compared to open label baseline	**Amisulpride:** Uncommon (≥1/1000, <1/100) **Aripiprazole:** **Adults** Unknown **Adolescents**: Common (≥1/100, <1/10) **Asenapine,:** Common (≥1/100, <1/10) **Clozapine:** Common (≥1/100, <1/10) **Olanzapine:** Very common (≥1/10) **Risperidone:** Common (≥1/100, <1/10) **Sertindole:** Common (≥1/100, <1/10)	Weight gain is addressed in Section 4.4 Special warnings and precautions for use; Section 4.8 Undesirable effects and Section 5.1 Pharmacodynamic properties (Clinical Safety)

Table II-63 Pharmacological class risks already included as important identified or potential risks

Class risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (SMPCs)	Comment
Lipid changes	Elevations in serum triglyceride levels; Elevations in total cholesterol (predominantly LDL cholesterol); Decreases in HDL cholesterol very common (>1/10)	**Olanzapine:** Very common (≥1/10) Clozapine Hypertriglyceridemia **Very rare (<1/10,000)** **Aripiprazole**: No changes in lipid parameters when compared with placebo group **Amisulpride, Asenapine, risperidone, sertindole**: Lipid change is not listed as an AE.	Changes in serum lipid levels are described in the SEROQUEL IR and SEROQUEL XR SmPC in sections 4.4 Special Precautions and Warnings for Use and Section 4.8 Undesirable effects.
Hyperglycaemia and DM	Blood glucose increased to hyperglycaemic levels Common (≥1/100, <1/10). DM Uncommon (≥1/1000, <1/100)	**Aripiprazole:** Hyperglycemia and DM: Unknown **Asenapine:** Hyperglycemia Uncommon (≥1/1000, <1/100) DM "occasional" AE **Clozapine:** DM Rare (≥1/10,000, <1/1000) Severe hyperglycemia Rare (<1/10,000) **Olanzapine:** DM Uncommon (≥1/1000, <1/100) Elevated glucose levels Common (≥1/100, <1/10) **Risperidone:** DM and hyperglycemia Very rare (<1/10,000) **Sertindole:** DM is not listed as an AE. Hyperglycemia Uncommon (≥1/1000, <1/100) **Amisulpride:** Hyperglycemia and DM are not listed as AEs.	Hyperglycemia and DM are found in the SEROQUEL IR and SEROQUEL XR SmPC in sections 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects.
Potential risks			
Cerebrovascular AEs in the elderly	In placebo-controlled trials there were 5 QTP and 5 PLA patients with events. MH relative risk QTP vs PLA (95% CI) 0.6 (0.19,2.38). There are no longer-term trials (≥ 6 months) in this population.	**aripiprazole** In three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, cerebrovascular AEs, including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall,	A potential mechanism for cerebrovascular AEs in elderly patients treated with SEROQUEL/SEROQUEL XR has not been established. Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: Elderly patients with dementia-related psychosis: Quetiapine is

Table II-63 Pharmacological class risks already included as important identified or potential risks

Class risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (SMPCs)	Comment
		1.3% of aripiprazole-treated patients reported cerebrovascular AEs compared with 0.6% of placebo-treated patients in these trials. **olanzapine** A 3-fold increase in cerebrovascular AEs in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All olanzapine- and placebo-treated patients who experienced a cerebrovascular AE had pre-existing risk factors (age > 75 years, vascular/mixed typaliperidone Rare: An approximately 3-fold increased risk of cerebrovascular adverse reactions has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole, and olanzapine. **risperidone** In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (about 3-fold increased) of cerebrovascular AEs and transient ischaemic attack in patients treated with risperidone compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies in mainly elderly patients (>65 years of age) with dementia showed that cerebrovascular AEs (serious and nonserious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. **asenapine, clozapine, sertindole** Not in SmPC.	not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular AEs has been seen in randomized, placebo-controlled studies in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. SEROQUEL/SEROQUEL XR should be used with caution in patients with risk factors for stroke. Section 5.1, Pharmacodynamic Properties, states: Clinical efficacy: In placebo-controlled studies in elderly patients with dementia-related psychosis, the incidence of cerebrovascular AEs per 100 patient-years was not higher in quetiapine-treated patients than in placebo-treated patients. A cumulative review in 2011 did not reveal new information about this topic.

Table II-63 Pharmacological class risks already included as important identified or potential risks

Class risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (SMPCs)	Comment
Cerebrovascular AEs in non-elderly patients	In placebo-controlled trials there were 6 QTP and 5 PLA patients with events. MH relative risk QTP vs PLA (95% CI) 0.56 (0.17, 1.86). In longer-term trials there were 7 patients with events (0.18%)	**asenapine** Cerebrovascular events have been reported in patients treated with asenapine but there is no evidence of any excess incidence over what is expected in adults between 18 and 65 years of age. **aripiprazole, clozapine, olanzapine, paliperidone, risperidone, sertindole** Not in SmPC	A potential mechanism for cerebrovascular AEs in non-elderly patients treated with SEROQUEL/SEROQUEL XR has not been established A cumulative review in 2011 did not reveal new information about this topic.
Ischemic heart disease	In placebo-controlled trials there was 12 QTP and 13 PLA patients with events. MH relative risk QTP vs PLA (95% CI) 0.45 (0.20, 1.01). In longer-term trials (≥ 6 months) there were 13 (0.31%)	**asenapine, aripiprazole, clozapine, olanzapine, paliperidone, risperidone, sertindole** Not in SmPC	Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states (under Cardiovascular and QT prolongation sections, respectively): Quetiapine should be used with caution in patients with known CVD, cerebrovascular disease, or other conditions predisposing to hypotension. A slower titration regimen could be considered in patients with underlying CVD. Also caution should be exercised when quetiapine is prescribed in patients with CVD. Section 4.9, Overdose, of the SEROQUEL/SEROQUEL XR MR-SmPC states: Patients with pre-existing severe CVD may be at an increased risk of the effects of overdose. (See section 4.4: Cardiovascular)

Table II-63 Pharmacological class risks already included as important identified or potential risks

Class risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (SMPCs)	Comment
Torsades de Pointes	No frequency can be calculated from clinical trial data	**Amisulpride:** Torsades de pointes is very rare (<1/10,000) A**ripiprazole:** Torsades de pointes are listed AEs with no frequency reported. Clinical trial data was equivalent to placebo. **Asenapine:** Torsades de pointes is not a listed AE. **Clozapine:** Torsades de Pointes is not a listed AE. **Olanzapine:** Torsades de Pointes is not a listed AE. **Risperidone:** Torsades de Pointes Very rare (<1/10,000) **Sertindole:** Torsades de Pointes Uncommon (≥1/1000, <1/100)	Torsades de Pointes is found in SEROQUEL IR and SEROQUEL XR SmPC section 4.8 Undesirable effects as a class effect. It is not a listed event.
Abuse and misuse	In placebo-controlled trials there were 7 QTP and 1 PLA patients with events. MH relative risk QTP vs PLA (95% CI) 4.51 (0.46, 44.10). In longer-term trials (≥ 6 months) there were ~~2~~ 5 QTP patients (0.12%) .	**asenapine, aripiprazole, clozapine, olanzapine, paliperidone, risperidol, sertindole** Not in SmPC	The following textwas added to warning and precaution section 4.4 of the SmPC: 'Misuse and abuse Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.' While AstraZeneca maintains that there is insufficient evidence to support a causal relationship between Seroquel and drug abuse and misuse, abuse and misuse will be maintained on this EU RMP as a potential risk.

AE Adverse event; CI Confidence interval; CVD Cardiovascular disease; DM diabetes mellitus; ECG Electrocardiogram; EPS Extrapyramidal symptoms; HDL High-density lipoprotein; LDL Low-density lipoprotein; IR Immediate release; MR Mutual recognition; NA Not applicable;; PLA Placebo; QTP Quetiapine; SmPC Summary of Product Characteristics;; XR Extended release.

II: 7.5.2 Important pharmacological class effects not discussed above

None applicable

EU RMP Part II, Module SVIII

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	01 February 2016

PART II SAFETY SPECIFICATION
MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II: 8.1 Summary of the safety concerns

Table II-64 Summary of safety concerns

Important identified risks[a]	**Nervous system disorders** • Extrapyramidal symptoms (EPS) • Somnolence **Metabolism and nutritional disorders** • Weight gain • Lipid changes (Increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs) • Hyperglycemia and diabetes mellitus (Note: Diabetes mellitus included per MRP outcome) • Metabolic risk factors **Psychiatric disorders** • Suicide and suicidality
Important potential risks that have been observed with other members of the antipsychotic class	**Nervous system disorders**[b] • Cerebrovascular adverse events in the elderly • Cerebrovascular adverse events in non-elderly patients **Cardiac disorders**[b] • Torsades de Pointes • Ischemic heart disease **Injury, poisoning, procedural complications** • Abuse and misuse[b]
Other potential risks that require further evaluation	**General disorders** • Potential for off-label use and misdosing[c]
Missing information	Use in pregnant or breast feeding women Use in patients on concomitant cardiovascular medications Use in patients on concomitant valproic acid

a With the exception of the last item, which is an identified risk in the pediatric patient population, all safety concerns that are considered important identified risks are important events listed in the MR-SmPC.
b Potential risks that have been observed with other members of the antipsychotic class
c Other potential risks that require further evaluation
EPS Extrapyramidal symptoms; HDL High-density lipoprotein; LDL Low-density lipoprotein; MedDRA Medical Dictionary for Regulatory Activities; MRP Mutual recognition procedure; SmPC Summary of product characteristics; XR Extended release.

EU RMP Part III	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	06 December 2016

PART III: PHARMACOVIGILANCE PLAN

III: 1 SAFETY CONCERNS AND OVERVIEW OF PLANNED PHARMACOVIGILANCE ACTIONS

AstraZeneca employs routine pharmacovigilance consistent with the ICH E2E Pharmacovigilance Planning Guideline. AstraZeneca's standard processes and systems for collecting and recording information about all events potentially related to drug / product safety, and for expedited and periodic reporting, are in compliance with current local regulations and defined in globally applied AstraZeneca Standard Operating Procedures.

A comprehensive description of all aspects of the AstraZeneca pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

Additionally, routine pharmacovigilance practices for quetiapine include targeted use of questionnaires for the following specific concerns:

- Cardiac events including Torsades de pointes
- Cerebrovascular disorders
- DM
- Ischaemic heart disease

Additional pharmacovigilance activities that will address the important identified risks, important potential risks, and/or missing information consist of the following:

- As requested by HALMED (Agency for Medicinal Products and Medical Devices of Croatia), marketing authorisation holders (MAHs) of quetiapine in Republic of Croatia (including AstraZeneca) commenced a Croatia PASS study to evaluate the effectiveness of the educational material used as an additional risk minimisation measure concerning important safety information (weight gain, hyperglycemia, other metabolic risks including lipid changes). However, the requirement to conduct this study has been removed by HALMED.

  Planned pharmacovigilance activities for each important safety concern are described in detail below.

III: 1.1 Important identified risks

Nervous system disorders

Table III-1 Extrapyramidal symptoms - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
EPS	**Routine PhV** Signal management, evaluation and review **Additional PhV** **None**	To better characterise the nature of the risk.

PhV Pharmacovigilance.

Table III-2 Somnolence - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Somnolence	**Routine PhV** Signal management, evaluation and review **Additional PhV** **None**	To better characterise the nature of the risk.

PhV Pharmacovigilance

Metabolism and nutritional disorders

Table III-3 Weight gain - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Weight gain	**Routine PhV** Signal management, evaluation and review **Additional PhV** None	To better characterise the nature of the risk.

PhV Pharmacovigilance.

Table III-4 Lipid changes (increased cholesterol [including increased LDLs], increased triglycerides, or decreased HDLs) - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Lipid changes (increased cholesterol [including increased LDLs], increased triglycerides, or decreased HDLs)	**Routine PhV** Signal management, evaluation and review **Additional PhV** None	To better characterise the nature of the risk.

HDL High-density lipoprotein; LDL Low-density lipoprotein;-PhV Pharmacovigilance.

Table III-5 Hyperglycemia and DM - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Hyperglycemia and DM	**Routine PhV** Signal management, evaluation and review Targeted questionnaire for DM. **Additional PhV** **None**	To better characterise the nature of the risk.

DM Diabetes mellitus; PhV Pharmacovigilance.

Table III-6 Metabolic risk factors - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Metabolic risk factors	**Routine PhV** Signal management, evaluation and review **Additional PhV** None	To better characterise the nature of the risk.

PhV Pharmacovigilance.

Psychiatric disorders

Table III-7 Suicide and suicidality- overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Suicide and suicidality	**Routine PhV** Signal management, evaluation and review **Additional PhV** None	To better characterise the nature of the risk.

PhV Pharmacovigilance.

III: 1.1.1 Important potential risks that have been observed with other members of the antipsychotic class

Nervous system disorders

Table III-8 Cerebrovascular adverse events in the elderly - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Cerebrovascular AEs in the elderly	**Routine PhV** Signal management, evaluation and review Targeted questionnaire for topic. **Additional PhV** None	To better characterise the nature of the risk.

AE Adverse event;-PhV Pharmacovigilance; XL/XR Extended release.

Table III-9 Cerebrovascular adverse events in non-elderly patients - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Cerebrovascular AEs in non-elderly patients	**Routine PhV** Signal management, evaluation and review Targeted questionnaire for topic. **Additional PhV~~None~~**	To better characterise the nature of the risk.

PhV Pharmacovigilance.

Cardiac disorders

Table III-10 Ischemic heart disease - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Ischemic heart disease	**Routine PhV** Signal management, evaluation and review Targeted questionnaire for topic. **Additional PhV** ~~**None**~~	To better characterise the nature of the risk.

PhV Pharmacovigilance.

Table III-11 Torsades de pointes - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Torsades de pointes	**Routine PhV** Signal management, evaluation and review Targeted questionnaire for QT prolongation/ torsades de pointes. **Additional PhV** None	To better characterise the nature of the risk.

PhV Pharmacovigilance.

Injury, poisoning, procedural complications

Table III-12 Abuse and misuse - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Abuse and misuse	**Routine PhV** Signal management, evaluation and review **Additional PhV** None	To better characterise the nature of the risk.

PhV Pharmacovigilance.

III: 1.1.2 Other potential risks that require further evaluation

General disorders

Table III-13 Potential for off-label use and misdosing - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Potential for off-label use and misdosing	**Routine PhV** Signal management, evaluation and review **Additional PhV** **None**	To better characterise the nature of the risk.
Use of SEROQUEL in the pediatric population	**Routine PhV** Signal management, evaluation and review **Additional PhV** None	To better characterise the nature of the risk.

PhV Pharmacovigilance

III: 1.1.3 Missing information

Table III-14 Use in pregnant or breast feeding women - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Use in pregnant or breast feeding women	**Routine PhV** Signal management, evaluation and review **Additional PhV** None	To better characterise the nature of risks to the infant and mother associated with use of atypical antipsychotics during pregnancy.

Table III-15 Use in patients on concomitant cardiovascular medications - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Use in patients on concomitant cardiovascular medications	**Routine PhV** Signal management, evaluation and review **Additional PhV** None	To better characterise the nature of the risk

PhV Pharmacovigilance.

Table III-16 Use in patients on concomitant valproic acid - overview of planned pharmacovigilance actions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Use in patients on concomitant valproic acid	**Routine PhV** Signal management, evaluation and review **Additional PhV** None	To better characterise the nature of the risk

PhV Pharmacovigilance.

III: 2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES TO ASSESS EFFECTIVENESS OF RISK MINIMISATION MEASURES

The EU-RMP for SEROQUEL/SEROQUEL XR is a living plan which uses a pharmacoepidemiology program for SEROQUEL/SEROQUEL XR (see Annex 5 for study descriptions).

An internal cross-functional SEROQUEL/SEROQUEL XR Safety Management Team has been established to monitor the safety profile of SEROQUEL/SEROQUEL XR, identify any changes in the benefit:risk profile for SEROQUEL/SEROQUEL XR and initiate any appropriate follow-up, to proactively manage safety strategy including development of the RMP and to ensure consistency of safety strategy across reports to regulatory authorities.

Spontaneous reports of AEs, data from market research, data from the scientific literature, and when available, data from pharmacoepidemiologic studies are used to evaluate the effectiveness of routine risk-minimizing activities. Appropriate actions are undertaken when important signals or AEs are identified, and the RMP for SEROQUEL/SEROQUEL XR is

updated when deemed relevant by the Global Product and Key Brand teams (in consultation with the SEROQUEL Global Clinical Lead and the SEROQUEL/SEROQUEL XR Global Safety Physician). Such measures may include a change in the SmPC, a new intervention, additional clinical investigations, additional pharmacoepidemiologic studies, and additional enhanced risk minimization plans for specific risk topics.

There are no additional pharmacovigilance activities to assess effectiveness of risk minimisation measures.

III: 3 STUDIES AND OTHER ACTIVITIES COMPLETED SINCE LAST UPDATE OF PHARMACOVIGILANCE PLAN

A summary of completed studies is provided. A brief synopsis for each completed study is provided in Annex 9.

Table III-17 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
m-PEM Nested case control studies	
Safety concern(s)/risk minimisation measure investigated	To explore the dose-response relationship between SEROQUEL XL (quetiapine XR) and the occurrence of 1) extrapyramidal symptoms and 2) somnolence /sedation.
Brief summary of results	These studies were conducted in subsets of the patients included in the main m-PEM study, which was summarised in the previous version of this RMP. **Extrapyramidal symptoms** 320 cases of extrapyramidal symptoms were reported. Of these 81 cases were considered to be new, evaluable cases. 577 matched controls were selected. For various reasons including non-return of forms, only 43 cases and 124 matched controls were eligible for analysis. Statistically significant differences were seen between cases and controls for factors of social deprivation, where the most deprived patients had a higher likelihood of developing effects than the least deprived, and proximity of SEROQUEL IR use, where patients who had previously used this drug had a higher likelihood of developing effects than those who did not. The authors concluded that recent dose changes might be an important predictor of risk, but this is based upon a non-significant difference. **Somnolence and sedation** 756 somnolence/sedation cases were reported. Of these, 170 cases were considered suitable for analysis together with 199 controls. Factors that seemed to be predictors of risk were socioeconomic variation, where the least deprived patients had a higher likelihood of symptoms than the most deprived; having an indication of bipolar disorder; and having a previous history of somnolence or sedation. As with EPS, the authors concluded that recent dose changes might be predictive of risk, based on a non-significant difference.

Table III-17 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
Implications	In conclusion, the results in the m-PEM nested case-control studies do not change the benefit-risk profile for SEROQUEL XL, which remains positive.
EU DU	
Safety concern(s)/risk minimisation measure investigated	There was no specific safety concern or risk minimization measure evaluated in the EU Drug Utilisation (EU DU) study. However the study characterized dosing outside label recommendations for patietns with MDD and the use of monotherapy in patients with MDD across the Seroquel PASS (including EU DU study). This study was intended to characterize drug utilization of Seroquel® XL in patients with MDD in five EU countries. The EU DU study was designed to evaluate demographic and medical information, practice setting, patterns of treatment, and drug utilisation from medical records across the EU and specifically to enable comparisons between Sweden and other EU countries. To the extent that MDD patient characteristics and their medical management including SEROQUEL XR were found to be similar, it would follow that the safety findings from the Swedish Record Linkage Study would be considered to be generalisable to the other EU countries.
Brief summary of results	Substantial difficulties were encountered with recruitment both of study sites and of patients within the sites in several of the countries included in the study, and as a result patient numbers were lower than the original estimates. Across the five countries there were similarities in basic demographic characteristics of patients receiving SEROQUEL XR as treatment for MDD with regard to gender and race. One noteworthy difference in patient characteristics was finding the mean age of patients' first treatment with SEROQUEL XR for MDD in Sweden to be on average 8 years younger than patients from the other countries studied. A possible reason for Swedish patients tending to be younger than those from other countries may be the guidance from the National Board for Health and Welfare (Socialstyrelsen 2010), which specifically states 'do not do' for the addition of antipsychotic agents to antidepressants for severe/treatment resistant depression in elderly patients. Many important aspects of patients' psychiatric and medical history were similar across the populations studied and indicated that the majority of the study population had experienced the burden of severe MDD. The majority of the study population were candidates for additional treatment as their physician's rated the therapeutic effect of prior treatment regimens in categories of "minimal or slight improvement" or "unchanged or worse". Where documentation in the medical record was available, patients receiving SEROQUEL XR had a history of three or more lifetime depressive episodes among the majority of patients (57.9% of patients from Spain, 70.3% of patients from Romania, 70.7% of patients from Germany, 78.8% of patients from Italy, and 83.3% from Sweden).

Table III-17 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
	Differences in patients' psychiatric history were in evidence as well. For example, a higher proportion of patients with a past history of hospitalization for MDD was observed among patients in Germany (89.3%) and Romania (76.2%) compared to Sweden (33.3%), Italy (44.2%), and Spain (8.3%) On average, patients initiated SEROQUEL XR treatment 4.7 years following the confirmation of MDD diagnosis with an average initial dose of 160.5 mg. The mean initial dose of SEROQUEL XR that was prescribed in Sweden fell within the range defined by Spain, on the low end, and Romania on the high end; however it was recognized that these exceeded the recommendation for the start dose for the MDD indication in the SmPC. Both the mean (193.1 mg) and median (200 mg) for the most frequently prescribed (modal) dose in Sweden approximated the measures for all countries combined and were within the SmPC-recommended range. A total of 127 patients (15.7%) used SEROQUEL XR treatment as monotherapy at initiation and 102 patients (12.6%) remained on SEROQUEL XR as monotherapy over the course of the study observation period. More patients received SEROQUEL XR as monotherapy in Sweden and Italy than in the other three countries. The vast majority of patients (n=684, 84.3%) received SEROQUEL XR as an add-on at initiation to regimens that included other antidepressants. Among the patients who initiated SEROQUEL XR as add-on therapy, concomitant MDD treatment across the study period included: selective serotonin reuptake inhibitors [SSRIs] (49.3%), anxiolytics (47.1%), serotonin-norepinephrine reuptake inhibitors [SNRIs] (42.4%), other atypical antidepressants (30.1%), mood stabilizers (18.1%), sedatives/hypnotics (16.4%), atypical antipsychotic drugs (12.9%), tricyclics (8.2%), conventional antipsychotics (5.3%), antidepressants in combination with psycholeptics (0.9%), and MAO A inhibitors (0.4%).
Implications	From a pragmatic perspective the information from the EU DU study together with the data from the other PASS indicates that SEROQUEL XR is being prescribed for MDD at doses that are similar in patients across Europe. Some differences in treatment patterns were seen between Sweden and other countries, such as patient age and use of SEROQUEL XR as monotherapy. Provided that these differences are taken into account, results from the SE RLS safety study will be generalizable across countries.
Quiétude – French PASS	
Safety concern(s)/risk minimisation measure investigated	To describe the demographic and clinical characteristics of the patients as well as the prescription conditions of XEROQUEL LP in actual practice in patients receiving the treatment for the first time, irrespective of the indication.

Table III-17 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
	To assess the representativeness of the patients treated with XEROQUEL LP among all patients with schizophrenia or acute-phase bipolar disorder and to identify the existence of potential channelling bias. To assess the patients' health status and the use of medical resources up to one year post initiation of XEROQUEL LP for the treatment of schizophrenia or acute-phase bipolar disorder.
Brief summary of results	Overall, the study demonstrated appropriate use in the context of the indications and forms of usage in the SmPC, both in terms of posology as well as dosage and usage indication. The patients receiving treatment were close to the reference population from a sociodemographic standpoint. However, the study revealed certain usage characteristics from a clinical point of view, with XEROQUEL LP being most frequently prescribed for moderately to severely ill patients with schizophrenia presenting schizoaffective disorders or for moderately to severely ill patients with bipolar disorders during depressive episodes. This appears to correspond to the positioning of the product more than one year after its release in France. There did not appear to be significant evidence of any channelling bias. Around one third of all patients had a change in XEROQUEL LP dose, usually an increase and usually during the first 3 months after initiation. Approximately half of patients received doses lower than recommended in the SmPC. XEROQUEL LP was prescribed in combination with on average 2 concomitant psychiatric treatments. Other antipsychotic agents were prescribed in 15% of patients with bipolar disorder and 33% with schizophrenia. The adverse events reported were consistent with the known safety profile of SEROQUEL XR. Reductions in disease severity were seen in both patients with schizophrenia (up to 1.6 points on the CGI-S score) and bipolar disorder (up to 2 points on the CGI-S score). Up to 18% of patients with schizophrenia and 17% of patients with bipolar disorder experienced a relapse. Permanent treatment discontinuation was noted in 11% of patients with schizophrenia and 15% of patients with bipolar disorder. Healthcare utilisation was overall high, as would be expected in this group of moderately to severely ill patients. 78% of patients with schizophrenia and 80% of patients with bipolar disorder had psychiatric outpatient visits (mean 8.3 and 8.6 visits respectively during the 1 year follow up period) and 13% of patients with schizophrenia and 11% of patients with bipolar disorder required psychiatric inpatient treatment.
Implications	The results from this study do not add any further information that requires alteration of the SmPCs for SEROQUEL or XEROQUEL LP and SEROQUEL XR.
127/128 studies	

Table III-17 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
Safety concern(s)/risk minimisation measure investigated	To assess the effectiveness of risk minimisation (via educational materials distributed to prescribers) using a physician survey (Study 127) and analysis of electronic records from physician practices (Study 128).
Brief summary of results	The number of physicians who recalled receiving the educational materials in Study 127 (a range of 16% to 69% of physicians responded that they recalled receipt of the materials in the 8 countries surveyed) was lower than expected and likely attributable to the length of time between receipt of the materials and completion of the survey (mean: approximately 17 months [range approximately 8 to 20 months]). Overall, physicians reported that 64.5% of their patients were monitored by the physician, someone else in the physician's practice, or by another healthcare provider. These data suggest that healthcare provider awareness of metabolic monitoring was present to a significant extent. In addition, while not conclusive, monitoring behaviours among physicians who reported receiving educational materials were observed to be generally higher than physicians who did not recall or were unsure about receiving the materials, with margins of improvement of 10% or greater. The distribution of educational materials may have contributed to these results. The observed rates of metabolic monitoring documented in real-world practice settings (Study 128) were lower than expected and were likely limited by a lack of access to comprehensive electronic medical records (EMRs) that tracked documented monitoring of patients in different care settings (ie, as patient care moves between specialists and GPs), the short duration of the study observation period, and potential barriers in this population for accessing care for the complete ascertainment of the specific metabolic risk factors. Across all 8 countries, 70% of physicians (58% to 87% of physicians in each country) reported performing at least 3 of 4 key metabolic monitoring activities (ie, monitoring weight, hyperlipidaemia, hyperglycaemia, and monitoring patients with diabetes mellitus [DM] or patients at risk for DM for worsening of glucose control) in patients receiving SEROQUEL or SEROQUEL XL. Applying either country-specific or an alternative fixed level of acceptability (70% to 80%), most metabolic monitoring behaviours were reported at acceptable levels.
Implications	These studies demonstrated substantial awareness of metabolic monitoring among the prescribers. In addition, these studies demonstrated physician-reported levels of monitoring behaviour considered acceptable on the basis of locally defined and fixed-level criteria. Therefore, AstraZeneca concludes that additional risk minimisation activities are not warranted in response to the results of Study 127 and Study 128.

SE-RLS

Part III, Safety evaluation study

Table III-17 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
Safety concern(s)/risk minimisation measure investigated	To evaluate the safety of quetiapine treating MDD patients in Sweden from 2011-2014 with regard to the following outcomes: death from all causes, acute myocardial infarction, stroke, suicide and self-harm, diabetes mellitus, extrapyramidal disorders, and somnolence.
Brief summary of results	Death from all causes: In the treatment change cohort, a significantly higher risk of death from all causes was identified among current users of combination therapy with quetiapine, adjusted OR 1.31 (1.12-1.54). Using both monotherapy and combination therapy with quetiapine as index medication was also associated with a higher risk of death, with adjusted ORs of 1.69 (1.18-2.42) and 1.25 (1.05-1.48), respectively. A high Charlson comorbidity score and a high number of previous somatic hospitalizations were factors strongly associated with death. Prescribing of the antidepressant from a somatic clinic, a history of alcohol or substance abuse, and the number of previous hospitalizations for MDD also increased the risk of death. A sensitivity analyses restricted to those prescribed Seroquel XR did not find a statistically significant elevated adjusted OR for deaths from all causes. In a post hoc analysis of this study an association was observed between deaths from all causes and prior use of quetiapine in patients aged >65 years. This association was no longer present when patients with Parkinson's disease (PD) were removed from the analysis. Caution should be exercised if quetiapine is prescribed to elderly patients with PD. Acute myocardial infarction: No significant associations between categories of quetiapine use and acute myocardial infarction were identified. A history of alcohol abuse, IHD other than MI, diabetes, hypertension, a high Charlson comorbidity score and a high number of somatic hospitalisations were factors associated with a higher risk of acute myocardial infarction. A sensitivity analyses restricted to those prescribed Seroquel XR did not find a statistically significant elevated adjusted OR for acute myocardial infarction. Stroke: No significant associations between categories of quetiapine use and stroke were identified. In the analysis, risk factors for stroke were found largely similar to those mentioned for acute myocardial infarction. A sensitivity analyses restricted to those prescribed Seroquel XR did not find a statistically significant elevated adjusted OR for stroke. Diabetes: Analyses did not demonstrate significant associations between quetiapine monotherapy or quetiapine combination therapy and a diabetes diagnosis. A history of cerebrovascular disease, myocardial infarction, peripheral arterial disease, renal disease and obesity, a high Charlson comorbidity score and frequent somatic hospitalization was associated with a higher risk of a subsequent diabetes diagnosis or medication. A sensitivity analyses restricted to those prescribed Seroquel XR did not find a statistically significant elevated adjusted OR for diabetes.

Table III-17 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
	Self-harm and suicide: . In analyses that included patients with prior history of self-harm in the treatment change cohort, a higher risk of self-harm and suicide was identified among current users of a combination therapy with quetiapine, adjusted OR 1.53 (1.31-1.79). In the analysis of incident cases, excluding those with recorded self-harm prior to the index date, the adjusted OR of current treatment with quetiapine combination therapy was 1.52 (1.26-1.84). In the analysis with index medication as exposure, monotherapy with quetiapine was associated with a higher risk of self-harm, adjusted OR 1.61 (1.03-2.54), while there was no significantly increased risk for combination therapy with quetiapine. In the analysis of all cases, a history of previous self-harm was found to be a strong risk factor for self-harm and suicide, crude OR 6.83 (6.32-7.37). A history of three or more hospitalizations for MDD, alcohol and substance use disorders, disorders of adult personality and behavior, and anxiety disorders were also associated with a higher risk of self-harm and suicide. A sensitivity analyses restricted to those prescribed Seroquel XR did find a statistically significant elevated adjusted OR for self-harm and suicide. Additional post hoc analysis: In an analysis that included patients with a history of recorded self-harm prior to the index date, the risk of non-lethal self-harm was significantly associated with the use of combinations with quetiapine in all age groups except those ≥65 years (<25 years, adjusted odds ratio (OR) 1.57, 95% confidence interval (CI) 1.18-2.10; 25-39 years, adjusted OR 1.74, 95% CI 1.28-2.38; 40-64 years, adjusted OR 1.53, 95% CI 1.13-2.06; ≥65 years, adjusted OR 1.51, 95% CI 0.76-2.99). In contrast for the risk of lethal self-harm; there was no significant association with the use of combinations with quetiapine in any age group (<25 years, adjusted OR 0.39, 95% CI 0.04-3.51; 25-39 years, adjusted OR 1.05, 95% CI 0.26-4.27; 40-64 years, adjusted OR 1.60, 95% CI 0.75- 3.42; ≥65 years, adjusted OR 1.37, 95% CI 0.46-4.08). Results for analyses that included patients with no recorded history of self-harm were slightly different and the risk of non-lethal self-harm was significantly associated with use of combinations with quetiapine in the 25-39 and 40-64 age groups (<25 years, adjusted OR 1.29, 95% CI 0.90-1.84; 25-39 years, adjusted OR 1.78, 95% CI 1.23-2.58; 40-64 years, adjusted OR 1.91, 95% CI 1.31- 2.79; ≥65 years, adjusted OR 0.63, 95% CI 0.31-1.28). There was no significant association of risk of lethal self-harm (i.e., completed suicide) with use of combinations with quetiapine at any age (<25 years, adjusted OR 0.04, 95% CI 0.00-0.90; 25-39 years, adjusted OR 1.33, 95% CI 0.20-8.84; 40-64 years, adjusted OR 1.13, 95% CI 0.51- 2.51; ≥65 years, adjusted OR 2.00, 95% CI 0.47-8.47).

Table III-17 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
	Extrapyramidal disorders: A significantly higher risk of extrapyramidal disorder was identified among current users of monotherapy with quetiapine, adjusted OR 13.51 (4.98- 36.65) and a combination therapy with quetiapine, adjusted OR 6.15 (3.57-10.58). Current use of other antipsychotics than quetiapine was associated with an even higher risk, adjusted OR 19.94 (13.77-28.88). A sensitivity analyses restricted to those prescribed Seroquel XR found a statistically significant elevated adjusted OR 2.8 (1.31-6.02) Somnolence: Associations both with index medication (adjusted OR 2.41 (1.42-4.11) and current quetiapine monotherapy and combination therapy (categories collapsed) were seen, adjusted OR 2.90 (1.78-4.72). Dispensing of anxiolytics and hypnotics between the index date and the event date was also associated with the outcome, adjusted OR 1.95 (1.54-2.46). A sensitivity analyses restricted to those prescribed Seroquel XR did find a statistically significant elevated adjusted OR 2.42 (1.12-5.23)

Table III-17 Studies and other activities completed since last update of Pharmacovigilance Plan

Study/activity title	
Implications	The study found associations between use of quetiapine and death from all causes, and an increased risk of self-harm and suicide, when compared to the use of combinations of other antidepressants. The finding of an increased risk of death from all causes may be explained by several limitations including a bias due to an important confounder, prior diagnosis or treatment for Parkinson's disease, which, when considered, resulted in finding no increased risk of death from all causes that could be ascribed to treatment with quetiapine. If it had been known in advance that patients with Parkinson's disease would be treated with quetiapine, these patients would have been excluded from the study and no increase in risk from death from all causes would have been observed. In this study, as observed in all of the other PASS, there was evidence of selective prescribing of these treatments to patients at high risk for the outcomes in question (confounding by indication/severity). With respect to the finding of self-harm and suicidality it was recognized that quetiapine was prescribed to individuals with a higher burden of psychiatric comorbidity, including a history of previous self-harm and more frequent admissions for MDD. As quetiapine and combinations of antidepressants are second-line therapy, the populations receiving these treatments would be expected to have more severe or more difficult to treat depression, and thus be at higher risk for self-harm and suicide. Post-hoc analyses that considered non-lethal self-harm separate from suicide found no association of treatment with quetiapine with other antidepressants for completed suicide and an increased risk of non-lethal-self harm for individuals aged 25-64. The composite outcome including both self-harm and suicide has been an identified risk known in younger aged individuals (under 25). AstraZeneca considers that the substantial amount of non-age-specific information relating to suicide and suicidal behaviour already included in the SmPC adequately addresses these results, in terms of the type and intensity of patient monitoring that is necessary. It is noteworthy that this study also found significant associations between quetiapine use, extrapyramidal disorders, somnolence, and stroke, but no significant associations between quetiapine and AMI or diabetes.

m-PEM Modified prescription-event monitoring;.

III: 4 DETAILS OF OUTSTANDING ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no outstanding additional pharmacovigilance activities.

III: 4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

Not applicable.

III: 4.2 Mandatory additional pharmacovigilance activity (being a specific obligation)

Not applicable.

III: 4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

Not applicable.

III: 4.4 Stated additional pharmacovigilance activities

Not applicable.

III: 5 SUMMARY OF THE PHARMACOVIGILANCE PLAN

III: 5.1 On-going and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan

Not applicable.

III: 5.2 Completed studies/activities from the Pharmacovigilance Plan

The following studies have been completed since the last version of the RMP:

Table III-18 Table of completed studies/activities from the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (completed)	Date of submission of final study report
D1444C00006 (GPRD) Non-interventional cohort study Epidemiological study to assess the safety of a new slow-release form of SEROQUEL (quetiapine) in the post-marketing phase in the UK, which is run within the GPRD Category 1	• To characterize new users of SEROQUEL XR as compared to new users of other study drugs (comparison group) with regard to indication, comorbidities, drug utilization patterns, discontinuations, and prior use of study drugs. • To study the association between the use of SEROQUEL XR and the occurrence of specific outcomes of interest and compare with the corresponding occurrence after use of comparison drugs. The outcomes of interest are overall death, suicide/suicide attempt/suicide ideation, AMI, Stroke, DM, Hypothyroidism, EPS associated with new use of parasympatholytic drugs, NMS, cataracts, fractures, syncope, and acute symptomatic seizure (excluding seizures due to known causes).	Death from all causes; EPS; Syncope and orthostatic hypotension; Seizure; DM; Hypothyroidism ; NMS; Stroke; Sudden death; AMI; Cataract;; Suicide and suicidality; Fractures; Potential for off-label use and misdosing; Use in elderly patients	Final study report completed 23 Sep 2013	Final study report submitted 26 Sep 2013

Table III-18 Table of completed studies/activities from the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (completed)	Date of submission of final study report
D1444C00011 (HEM) Non-interventional cohort study HEM study. A cohort study to monitor the safety and use of prolonged release quetiapine (SEROQUEL XL) in the mental health trust setting. Category 1	To monitor the short-term (up to 12 weeks) use and safety of SEROQUEL/SEROQUEL XR prescribed to patients with a clinical diagnosis of schizophrenia or with manic episodes associated with bipolar disorder by psychiatrists under normal conditions of use, specifically: • To compile a cohort of all eligible psychiatrists • To recruit cohorts of patients newly initiated on quetiapine (either formulation) • To examine the safety and use in such patients with particular interest in the following: - drug utilization characteristics - comparing rates of events reported by psychiatrists for patients taking high-dose (>600 mg) SEROQUEL XR vs high-dose (>600 mg) SEROQUEL - comparing event rates between patients receiving low-dose (≤600 mg) SEROQUEL XR vs high-dose (>600 mg) SEROQUEL XR - further quantifying and exploring the pattern of selected events reported by psychiatrists for patients taking quetiapine over time	Seizure; Sudden death; Suicide and suicidality; Accidental injury	Final study report completed 18 Sep 2013.	Final study report submitted 26 Sep 2013

Table III-18 Table of completed studies/activities from the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (completed)	Date of submission of final study report
D1443C00127 Non-interventional cohort study, Physician survey on assessment of effectiveness of metabolic educational materials Category 3	A physician survey conducted in 8 EU countries will document the receipt of educational materials and assess the behaviour of physicians around key metabolic monitoring messages communicated through educational materials	Effectiveness of metabolic education addressed	Final study report completed 10 Dec 2013	Final study report submitted 18 Dec 2013
D144C00128 Non-interventional cohort study Electronic Medical Record data to assess monitoring of patients treated with quetiapine; Category 3	Electronic Medical Record data available for 2 of 8 EU countries will be used to evaluate physician activities and monitoring of patients in relation to metabolic monitoring recommendations communicated through educational materials	Effectiveness of metabolic education addressed	Final study report completed 11 Dec 2013.	Final study report submitted 18 Dec 2013
Pharmo Seroquel Safety Study (cohort study) Category 1	The study was conducted in 2 Parts. Part I involved the comparison of users of quetiapine vs. users of other antipsychotics in terms of indications for SEROQUEL use, comorbidities, drug utilization, treatment switches and discontinuations, to assess feasibility of evaluating outcomes Part II: Evaluation of patient characteristics, drug utilization and the incidence of safety outcomes (all-cause mortality, acute MI, stroke, suicide, EPS, diabetes, hypothyroidism) in patients treated with quetiapine compared with those treated with olanzapine and risperidone.	Outcomes for (all-cause mortality, acute MI, stroke, suicide, EPS, diabetes, hypo-thyroidism)	Final study report completed 20 May 2010.	Final study report submitted 31 May 2010

Table III-18 Table of completed studies/activities from the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (completed)	Date of submission of final study report
D144AC00004 Non-interventional cohort study m-PEM on extended-release quetiapine (SEROQUEL XR) Category 1	To examine the safety and prescribing patterns in early users of SEROQUEL XL in England, with EPS and somnolence/sedation (drowsiness) being of special interest in the approved bipolar depression indication, specifically: • To quantify the incidence of frequently and rarely reported events • To identify previously unrecognized ADRs • To quantify drug utilization characteristics • To quantify incidence of both new onset and exacerbation of pre-existing hyperglycemia, type II DM, and EPS, and to explore the patterns of these events over time • To determine dose dependent characteristics of EPS and somnolence/sedation (drowsiness) as well as to evaluate these events as reasons for stopping treatment To quantify, follow-up, and causally assess reports of neutropenia, agranulocytosis, and metabolic syndrome	EPS; TD; Somnolence; Seizure; Neutropenia; Agranulocytosis ; Hyperglycemia and DM; Metabolic risk factors; Hypothyroidism ; NMS; Sudden death; Increased mortality in elderly patients with dementia; Suicide and suicidality; Potential for off-label use and misdosing; Use in elderly patients with bipolar disorder and MDD	Completed	Final study report submitted 18 Dec 2013 CSR for Nested case control study – Somnolence Dec 2014 CSR for Nested case control study –EPS 13 Oct 2014 Nested case control studies' report submitted: 1Q2016

Table III-18 Table of completed studies/activities from the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (completed)	Date of submission of final study report
D1443C00056 SE-RLS Non-Interventional cohort study SRLS-three register-based studies, Pilot (Methodology); Drug Utilization; Safety evaluation. Pilot study Category 1	**Pilot:** The outcomes of interest for the pilot evaluation include: death from all causes, AMI, stroke, suicide, DM, EPS, and somnolence. • Evaluation of the methodology to deliver the data of interest by testing of algorithm to define SEROQUEL/SEROQUEL XR as add-on treatment and comparator group, evaluation of the best way to identify dose and exposure period, and evaluation of the method to identify indication • Description of the use of SEROQUEL/SEROQUEL XR by number of patients (by indication), combinations of use together with SEROQUEL/SEROQUEL XR and comparator drugs, co-morbidity and co-medication use (confounders) • Estimation of crude incidence rates for the outcomes of interest in users of SEROQUEL/SEROQUEL XR and in users of other drugs for the treatment of	EPS; Somnolence; Hyperglycemia and DM; Cerebrovascular AEs in elderly patients; Cerebrovascular AEs in the non-elderly; Sudden death; Ischemic heart disease; Increased mortality in elderly patients with dementia; Suicide and suicidality	Part I Pilot study report: Dec 2012	Part I Pilot study report: Dec 2012

Table III-18 Table of completed studies/activities from the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (completed)	Date of submission of final study report
SE-RLS Non-Interventional cohort study SE-RLS-three register-based studies. Drug Utilization study Category 1	**Part II Drug Utilization study** (non-interventional cohort: • Characterization of patients dispensed SEROQUEL XR for the treatment of MDD, in add-on therapy, in monotherapy (if any), in comparison with patients treated for MDD with other antidepressants either as add-on therapy or in monotherapy • Characterization of valuation of doses, durations of treatments, treatments changes in patients dispensed SEROQUEL XR or other antidepressant treatments for MDD, as well as the trend in usage over time, and specialty of prescriber	Potential for off-label use and misdosing	Part II Drug Utilisation interim report: May 2013	Part II Drug Utilisation final report: May 2014
SE-RLS Non-Interventional cohort study SE-RLS-three register-based studies. Safety evaluation study Category 1	**Part III Safety evaluation study** (non-interventional cohort) The outcomes of interest are the same as in the pilot study Evaluation of the incidence rates of specific outcomes of interest, contrasting MDD patients treated with SEROQUEL XR as add-on to those treated with other antidepressive treatments	Death from all causes, Acute myocardial infarction, Stroke, Suicide and self-harm, Diabetes mellitus, Extrapyramidal disorders, Somnolence	Part III Safety evaluation study: Completed July 2016	Part III Safety evaluation study: December 2016
D1443C00057 EU DUS Non-interventional cohort study A Multinational, Multicenter, Retrospective, Observational Drug Utilisation Study of SEROQUEL XR Prescribed by Psychiatrists as Treatment for MDD in Selected Countries in the EU Category 1	• Documentation of characteristics of patients under specialists (psychiatric care) who are prescribed SEROQUEL XR as treatment for MDD in each of the selected countries over a 9-month period, starting 3 months following the launch of the product for its approved indication Description of differences between countries concerning treatment practices involving use of SEROQUEL XR for treatment of MDD	NA	Completed	1st Study Report June 2013 2nd Study Report May 2014 Final study report: May 2015

Table III-18 Table of completed studies/activities from the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (completed)	Date of submission of final study report
D1443L00091 French PASS study non-interventional cohort study An observational study of the use of quetiapine XR in real-life practice in France Category 1	• To describe patient characteristics (demographic and clinical) and the patterns of use of Quetiapine XR in patients receiving the drug for the first time in real-life practice regardless of the final diagnosis • To assess patient's health and healthcare utilization up to 1 year after receiving Quetiapine XR for the first time in real-life practice for the treatment of schizophrenia or acute bipolar disorder • To evaluate the representativeness of Quetiapine XR treated patients in the context of all schizophrenia or acute bipolar disease patients and to identify the potential level of channelling bias	Safety concerns are provided in the objectives.	Completed	Final Report: December 2015 Regulatory submission: 1Q2016

EU RMP Part IV	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	12 June 2014

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV: 1 APPLICABILITY OF EFFICACY TO ALL PATIENTS IN THE TARGET POPULATION

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to dopamine D_2 receptors which is believed to contribute to the clinical antipsychotic properties and low EPS liability of SEROQUEL compared to typical antipsychotics. Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin $5HT_1A$ receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at $5HT_1A$ sites by norquetiapine may contribute to SEROQUEL's therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine have high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha-2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptor subtypes.

Approximately 28576 subjects have been exposed to SEROQUEL or SEROQUEL XR in clinical studies. In adult patients, the safety and efficacy of quetiapine has been demonstrated in comprehensive clinical development programs in schizophrenia, bipolar mania, bipolar depression, recurrence prevention in bipolar disorder, and MDD, which have lead to approval for these indications in many countries worldwide. In addition, safety data from the GAD clinical program has been included in the overall assessment of the safety of quetiapine. Whilst GAD is not an approved indication in the EU and US, it has been approved in 9 countries globally.

SEROQUEL XR is a modified release formulation of SEROQUEL. SEROQUEL XR is registered in most European countries and in the US for treatment of schizophrenia, moderate to severe manic episodes in the framework of bipolar disorder and major depressive episodes in bipolar disorder, and recurrence prevention in bipolar disorder. Applications have recently been approved in the US and in some European countries for add-on treatment in patients with MDD.

Efficacy

Schizophrenia

The efficacy and safety studies included more than 2400 patients with schizophrenia, more than 1500 of whom were treated with SEROQUEL XR. Four pharmacodynamic studies provided safety and tolerability data supporting the selection of 300 mg/day as the appropriate starting dose for SEROQUEL XR (Studies 5077IL/0087 and 5077IL/0098) as well as the schedules for dose escalation (Studies 5077IL/0109 and 5077IL/0145) in patients with schizophrenia, schizoaffective disorder, or bipolar disorder. Two clinical pharmacology studies with SEROQUEL XR (Studies D1448C00008 and D1448C00013) provided data in healthy volunteers.

Five Phase III studies have been conducted to evaluate the efficacy and safety of SEROQUEL XR in patients with schizophrenia. These studies have addressed a spectrum of clinically relevant settings: treatment of acute exacerbation of schizophrenia (3 studies), relapse prevention in clinically stable patients (1 study), and switching from SEROQUEL to SEROQUEL XR in clinically stable patients (1 study).

The efficacy of SEROQUEL XR in treatment of acute exacerbation of schizophrenia was evaluated in Studies 5077IL/0041, D1444C00132, and D1444C00133. The efficacy of SEROQUEL XR was demonstrated in the Study D1444C00132. The other 2 studies provided supportive data. In relapse prevention Study D1444C00004, SEROQUEL XR significantly prolonged time to first schizophrenic relapse in clinically stable patients treated for up to 9 months. The results of Study D1444C00146 provided support for the maintenance of efficacy when clinically stable patients treated with twice-daily SEROQUEL are switched to the same total daily dose of once-daily SEROQUEL XR.

Data from clinical trials demonstrate that SEROQUEL is effective in the dose range of 150 to 750 mg/day. The dose at which SEROQUEL has maximum clinical effect is generally 300 mg/day; this dose may be adjusted based on clinical response and tolerability within the range of 150 to 750 mg/day

Data from clinical trials support the effectiveness of SEROQUEL XR across the dose range of 400 to 800 mg/day. In patients with acute schizophrenia, treatment effects were, on average, larger for fixed doses of 600 mg/day and 800 mg/day than for 400 mg/day. SEROQUEL XR, flexibly dosed in the range of 400 to 800 mg/day, significantly prolonged time to first schizophrenic relapse in clinically stable patients treated for up to approximately 9 months. Patients with schizophrenia whose clinical condition was stable when treated with twice-daily SEROQUEL at a total daily dose of 400 mg, 600 mg, or 800 mg had maintained efficacy overall when treatment was switched to the same once-daily dose of SEROQUEL XR

Bipolar disorder

Bipolar mania

The efficacy of SEROQUEL was evaluated in 4 studies (Studies 5077IL/0104, 5077IL/0105, 5077IL/0099, and 5077IL/0100) ranging from 3 to 12 weeks in patients with acute bipolar mania. With the exception of the Study 5077IL/0100, the result of other 3 studies demonstrated the efficacy of SEROQUEL. In the 3-week Study D144CC00004, the efficacy of SEROQUEL XR in reducing manic symptoms in patients with bipolar mania or mixed episode was demonstrated. The SEROQUEL XR doses of 400 to 800 mg once daily were chosen for Study D144CC00004 because the SEROQUEL effective and approved dose in bipolar mania is in the range of 400 to 800 mg/day. Patients in Study D144CC00004 were flexibly dosed between 400 mg and 800 mg once daily depending on the clinical effect and tolerability. The efficacy results of this study demonstrated that SEROQUEL XR in the dose range of 400 to 800 mg/day was effective in bipolar mania and has been proposed in the SEROQUEL XR SmPC. The flexible dosing regimen, rather than fixed doses, offers a better management of manic symptoms in patients with bipolar disorder.

Bipolar depression

In all of the 8-week studies with SEROQUEL (D1447C00135, 5077US/0049, D1447C00001, and D1447C00134), the efficacy in the acute treatment of bipolar depression was demonstrated. The efficacy against placebo was marked and consistent across all studies. In the 8-week Study D144CC00002, the efficacy of SEROQUEL XR was shown to be superior to placebo at Week 8; the treatment effect was considered to be clinically meaningful. The onset of effect was rapid, with significant differentiation from placebo as early as Week 1. In the SEROQUEL studies in bipolar depression, SEROQUEL was titrated up to 600 mg by Day 8. In the SEROQUEL 8-week studies, there were no obvious differences in efficacy on a group level between the 300 and 600 mg doses given once daily, although the advantage of the 600 mg dose became apparent in recurrence prevention. In SEROQUEL XR Study D144CC00002, which included SEROQUEL XR 300 mg only, this dose was shown to be well-tolerated and effective. Based on the similar efficacy with SEROQUEL XR and SEROQUEL in bipolar depression, 600 mg SEROQUEL XR can be expected to produce outcomes similar to those with 600 mg SEROQUEL once daily.

Recurrence prevention in patients with bipolar disorder

Monotherapy study

In the double-blind, placebo-controlled Study D1447C00144 , the efficacy of SEROQUEL and lithium (active comparator) was evaluated for up to 104 weeks of recurrence prevention treatment in adult patients with bipolar I disorder who had been stabilised on SEROQUEL for at least 4 weeks. SEROQUEL used as monotherapy significantly increased the time to recurrence of a mood event. SEROQUEL also significantly increased the time to recurrence of manic and depressive events compared to placebo. Maintenance of the effect was shown in patients who continued SEROQUEL treatment for up to 52 weeks in Studies D1447C00001 and D1447C00134.

Adjunct therapy studies

In maintenance effect Studies D1447C00126 and D177C00127, SEROQUEL used in combination with lithium or valproate was superior to placebo (in combination with lithium or valproate) in increasing time to recurrence of a mood episode in patients with bipolar I disorder for up to 104 weeks. AstraZeneca believes that the results of these studies support the result of the earlier study (5077IL/0099), where the efficacy of combined treatment with SEROQUEL and mood stabiliser was demonstrated versus mood stabiliser alone, at 3 weeks.

Dosing

In the recurrence prevention studies, the individual median SEROQUEL dose was distributed across the entire dose range of 300 to 800 mg/day. The most commonly used daily dose during randomized treatment was 600 mg/day (Study D1447C00144). In the majority of patients, efficacy was maintained on the same dose they had stabilised on at the end of the acute treatment. Therefore, it could be recommended that patients should stay on the same

dose during recurrence prevention treatment as they responded to in acute treatment, and that the dose should be adjusted within the range of 300 to 800 mg/day depending on clinical response and tolerance of the individual patient.

Major Depressive Disorder (as adjunctive treatment)

The clinical program for the development of SEROQUEL XR for the treatment of patients with MDD comprised 8 studies: 4 double-blind, placebo-controlled, monotherapy studies in non-elderly adults (D1448C00001, D1448C00002, D1448C00003, and D1448C00004), 1 similarly designed study in elderly patients (D1448C00014), 2 double blind, placebo-controlled, adjunct therapy studies (D1448C00006 and D1448C00007), and 1 longer-term randomized withdrawal study (D1448C00005). The program included 3796 patients with MDD treated with SEROQUEL XR in the MDD program. Both sexes, as well as the adult age range, including elderly patients, were well represented.

Data from these studies found SEROQUEL XR to be efficacious at 150 mg to 300 mg. Approval for SEROQUEL XR is for treatment of MDD when used in an adjunct setting (ie, patients have not responded to an adequate trial of first line anti-depressant agents, such as selective serotonine reuptake inhibitors, etc).

Many clinical trials are controlled to try to improve signal to noise ratio in determining both benefit and risk. For that reason, clinical trials do not always represent the real world population. For example, many patients who suffer from these mental illnesses have either used various treatments in the past, and or are currently using polypharmacy. Clinical trial participants in this regard may not represent the actual population as confounding medications that may affect signal detection are generally excluded prior to entry. Another difference between patients enrolled in studies compared with actual patients may be severity of the disease in patients in trials. There are some inclusion criteria around severity of illness when entering a trial. Severity of illness at baseline (Hamilton Depression Rating Scale, Clinical Global Impression, etc) depending on the indication, may not have a place in actual practice settings; thus, a mix of patients with ~~both~~ low, moderate or high baseline severity may be the actual treated population. However, none of these are likely to change the overall benefit and risk profile of SEROQUEL or create significant knowledge gaps on the use of SEROQUEL.

Given the broad range of trials conducted to date, even with these known limitations, the SEROQUEL risk and benefit profile has been studied across a broad range of indications and patients, and are felt to be generalizable to the actual patient population.

In summary, SEROQUEL and SEROQUEL XR have shown to be efficacious when tested in numerous pivotal clinical trials including schizophrenia, bipolar disorder (mania and depression) and MDD (in the adjunct setting).

IV: 2 TABLES OF POST-AUTHORISATION EFFICACY STUDIES

There were no post-authorisation efficacy studies during this period.

IV: 3 SUMMARY OF POST AUTHORISATION EFFICACY DEVELOPMENT PLAN

There were no ongoing or planned post-authorisation efficacy studies during this period.

IV: 4 SUMMARY OF COMPLETED POST AUTHORISATION EFFICACY STUDIES

There were no completed post-authorisation efficacy studies during this period.

EU RMP Part V	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	14.1
Data lock point for this module	06 December 2016

PART V: RISK MINIMISATION MEASURES

V: 1 RISK MINIMISATION MEASURES BY SAFETY CONCERN

AstraZeneca believes that the most appropriate risk minimization activities consist of high quality SmPCs and PILs for both SEROQUEL and SEROQUEL XR, which communicate information about benefits and risks; robust, ongoing patient-risk assessments; and routine and enhanced pharmacovigilance. Thus, for most risks across indications, no additional risk minimization activities, beyond robust SmPC language, are proposed at this time.

Additional risk minimization meaures (RMM) are in place for EPS, somnolence, metabolic and nutritional disorders (weight gain, lipid changes, hyperglycemia, diabetes mellitus, metabolic risk factors), off-label use and misdosing. Combined safety messages for all safety concerns requiring additional RMM are included in one core document found in 'Details of proposed additional risk minimization measures' (Annex 10). The core elements outlined in Annex 10 include information on Seroquel XR use in add-on treatment for Major Depressive Disorder, drug administration in patients with bipolar depression and on monitoring of metabolic parameters to reduce the risk of metabolic adverse events. The core document also includes safety messages regarding EPS and somnolence, in order to optimize the benefit-risk profile of patients taking SEROQUEL and Seroquel XR. Local materials suitable for distribution to prescribing physicians can be derived from the core elements for approval nationally by national health authorities.

The results of the SE RLS and the SEROQUEL PASS programme as a whole underscore the need to continue the already existing additional risk minimisation measures for the important identified risks of EPS and somnolence as outlined in the approved risk management plan. AstraZeneca also proposes that the educational materials remain in place for metabolic parameters. Such actions continue to be important in ensuring the benefit-risk profile for SEROQUEL XR use in the treatment of MDD remains positive.

Because of different legal environments and healthcare systems in EU member states, local AstraZeneca subsidiaries will implement activities according to local regulations while still maintaining the core principles of the risk minimization plan. This includes the details of the distribution plan for educational materials, which shall be agreed upon with the National Competent Authorities in each CMS where the product is marketed. Educational materials for bipolar depression, EPS and somnolence have been delivered as per defined content and timelines in all countries.The delivery of the educational materials related to core messages for metabolic parameters commenced in all countries. In Croatia, materials were delivered in December 2013.

V: 1.1 Important identified risks

Table V-1 Risk minimisation measures – EPS

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	The SEROQUEL/SEROQUEL XR MR-SmPC contains an extensive description of the risk of EPS during use of quetiapine. Section 4.2, Posology and method of administration, states: For the treatment of major depressive episodes in bipolar disorder (adults): SEROQUEL/SEROQUEL XR should be administered at bedtime. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600-mg group compared to the 300-mg group. Individual patients may benefit from a 600-mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder. The safety and efficacy of SEROQUEL/SEROQUEL XR have not been evaluated in children and adolescents. Section 4.8, Undesirable Effects, lists EPS as a Very Common (frequency is ≥1/10) ADR event for all patients including children and adolescents (10 to 17 years of age). **EPS in the adult population:** Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states: **Extrapyramidal symptoms:** In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder and major depressive disorder (see sections 4.8 and 5.1). The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental. **Section 5.1 Pharmacodynamic properties** **Mechanism of Action**: Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin (5-HT_2) and dopamine D1- and D2-receptors. It is this combination of receptor antagonism with a higher selectivity for 5-HT_2 relative to D2-receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of SEROQUEL compared to typical antipsychotics. **Pharmacodynamic effects:** In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy

Table V-1 Risk minimisation measures – EPS

at effective dopamine D2-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. (See Section 4.8)

Clinical efficacy:

Seroquel

Schizophrenia

In three placebo-controlled clinical trials, in patients with schizophrenia, using variable doses of quetiapine, there were no differences between the Seroquel and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics. A placebo-controlled trial evaluating fixed doses of quetiapine across the range of 75 to 750 mg/day showed no evidence of an increase in EPS or the use of concomitant anticholinergics.

Bipolar Disorder

In four placebo-controlled clinical trials, evaluating doses of Seroquel up to 800 mg/day for the treatment of moderate to severe manic episodes, two each in monotherapy and as combination therapy to lithium or divalproex, there were no differences between the Seroquel and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics.

Clinical efficacy:

Seroquel XR

Schizophrenia:

There were no additional safety findings associated with treatment with Seroquel XR for up to 9 months (median 7 months). In particular, reports of adverse events related to EPS did not increase with longer-term treatment with Seroquel XR.

Bipolar disorder

EPS in the paediatric population:

Section 4.4, Special Warnings and Precautions for Use, of the SEROQUEL/SEROQUEL XR MR-SmPC states:

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania, and bipolar depression (see section 4.8).

Section 5.1 Pharmacodynamic properties

Clinical safety

In the short-term pediatric trials with quetiapine described above, the rates of EPS in the active arm vs. placebo were 12.9% vs. 5.3% in the schizophrenia trial, 3.6% vs. 1.1% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial

Section 4.6, Fertility, pregnancy and lactation, of the SEROQUEL/SEROQUEL XR MR-SmPCs state:

Third trimester

Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Table V-1 Risk minimisation measures – EPS

	The PIL is a primary tool for communicating the benefits and risks to patients. The PIL advises patients of the possibility of abnormal muscle movements (affecting 1 in 10 patients).
Additional risk minimisation measure(s)	For the bipolar depression indication, recommended educational pieces (a laminated easy-to-read card, brochure, or similar form) on benefit:risk and messages targeted for physicians were delivered by the sales representatives to 100% of physicians on their visit lists. In conjunction with this, sales representatives proactively described the warning language related to EPS, and were prepared to answer questions on these topics. The format of the educational piece may have differed between countries but included the content and messages agreed with the Regulatory Authority (MEB). Educational materials have been delivered as per defined content and timelines in each country. The suggested educational piece (recommended for use by local AstraZeneca marketing companies) presented the recommended dosing and titration schedule for both SEROQUEL and SEROQUEL XR in bipolar depression, along with information on time of drug administration. Other content recommendations included language to advise physicians that indication-specific warnings were added to the labeling for EPS and that they should refer to local prescribing information for details. Combined core messages for all safety concerns requiring additional risk minimization measures are included in one core document found in 'Details of proposed additional risk minimization measures' (Annex 10). The above mentioned content for EPS are included in this core piece. The key aim of educational activities for physicians and other HCPs is to give guidance, based on the SmPC, to ensure the safe and appropriate use of SEROQUEL/SEROQUEL XR. To ensure such use in patients with bipolar depression, educational materials contain messages introducing physicians to the indication, the recommended dosing regimen, and the benefit:risk profile.
Effectiveness of minimisation measures	
How effectiveness of risk minimisation measures for the Safety Concern will be measured	To measure the retention of the benefit:risk message in physicians, physician recall for dosing and titration was conducted using web-based applications, a face-to-face questionnaire, and phone-based surveys (completed), in all countries that have launched SEROQUEL/SEROQUEL XR in bipolar depression.
Criteria for judging the success of the proposed risk minimisation measures	The effectiveness was assessed at the national level.
Planned dates for assessment	Complete
Results of effectiveness measurement	No change to the SmPC based on ongoing pharmacovigilance.
Impact of risk minimisation	Increased knowledge of the benefits and risks associated with quetiapine via the SmPC.
Comment	NA

5-HT2 5-hydroxytryptophan type 2; ADR Adverse drug reaction; EPS Extrapyramidal symptoms; HCP Healthcare provider; MDD Major depressive disorder; MEB Medicines Evaluation Board; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; XR Extended release.

Table V-2 Risk minimisation measures – Somnolence

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	The SEROQUEL/SEROQUEL XR MR-SmPC contains an extensive description of the risk of somnolence during use of quetiapine. Section 4.2, Posology and method of administration states: For the treatment of depressive episodes in bipolar disorder (adults): SEROQUEL/SEROQUEL XR should be administered at bedtime. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600-mg group compared to the 300-mg group. Individual patients may benefit from a 600-mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder. The safety and efficacy of SEROQUEL/SEROQUEL XR have not been evaluated in children and adolescents. For the treatment of MDD/GAD (adults): SEROQUEL/SEROQUEL XR should be administered once daily in the evening. Initial dosing should begin at 50 mg on Day 1 and 2, increased to 150 mg on Day 3 and 4. Further adjustments can be made upwards or downwards within the recommended dose range of 50 mg to 300 mg depending upon the clinical response and tolerability of the patient. For maintenance therapy in major depressive disorder or generalized anxiety disorder, the effective dose during initial treatment should be continued. The dose can be adjusted within the recommended dose range depending upon the clinical response and tolerability of the patient. Section 4.4, Special Warnings and Precautions for Use-states: Somnolence and dizziness Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8). In clinical trials for treatment of patients with bipolar depression, and major depressive disorder (XR only) onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity.-Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve, and treatment discontinuation may need to be considered. **Section 4.5** Interaction with other medicinal products and other forms of interaction In a 6-week, randomised, study of lithium and SEROQUEL XR versus placebo and SEROQUEL XR in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group (see section 5.1). Section 4.6, Fertility, pregnancy and lactation, states: Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal

Table V-2 Risk minimisation measures – Somnolence

	symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Section 4.7, Effect on Ability to Drive and Use Machines, states: Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known. Section 4.8, Undesirable Effects, states: The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine are somnolence, … Section 4.8, Undesirable Effects, lists somnolence as a very common (frequency is ≥10%) ADR. The footnotes associated with this event indicate the following: [1] somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine [2] somnolence may lead to falls. Section 4.9, Overdose, states: In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. In healthy subjects, SEROQUEL XR was associated with a lower intensity of self-reported sedation vs SEROQUEL during dose initiation; potential evening or next-day sedation with SEROQUEL XR may be managed by administration a few hours before bedtime (Datto et al 2009). The PIL is a primary tool for communicating the benefits and risks to patients. The PIL is updated to instruct patients to report feelings of severe sleepiness to their physicians, because it could increase the risk of accidental injury (fall) in elderly patients, and to follow physician advice on when to take their medication. (ie, at bedtime). It cautions re: alcohol use since the combined effect of Seroquel/Seroquel XR and alcohol can induce sleepiness. It warns against driving or using tools until the effect of the tablets is known. Feeling sleepy may go away over time. Newborn babies may have sleepiness as a withdrawal symptom if their mothers have used Seroquel during the third trimester.
Additional risk minimisation measure(s)	For the bipolar depression indication, recommended educational pieces (a laminated easy-to-read card, brochure, or similar form) on benefit:risk and messages targeted for physicians were delivered by the sales representatives to 100% of physicians on their visit lists. In conjunction with this, sales representatives proactively described the warning language related to somnolence, and were prepared to answer questions on these topics. The format of the educational piece may have differed between countries but included the content and messages agreed with the Regulatory Authority (MEB) and outlined in Annex 10. Educational materials have been deliverd as per defined content and timelines required in each country Educational materials have been delivered as per defined content and timelines in each country The suggested educational piece (recommended for use by local AstraZeneca marketing companies) presented the recommended dosing and titration schedule for both SEROQUEL and SEROQUEL XR in bipolar depression, along with information on time of drug administration. Combined core messages for all safety concerns requiring additional risk minimization

Table V-2 Risk minimisation measures – Somnolence

	are included in one core document found in 'Details of proposed additional risk minimization measures' (Annex 10). The above mentioned content for somnolence and bipolar depression is included in this core piece.
Effectiveness of minimisation measures	
How effectiveness of risk minimisation measures for the Safety Concern will be measured	To measure the retention of the benefit:risk message in physicians, physician recall for dosing and titration was conducted using web-based applications, a face-to-face questionnaire, and phone-based surveys, in all countries that have launched SEROQUEL/SEROQUEL XR in bipolar depression. In France, this was conducted during the period 26 MAR 2014 through 08 APR 2014. In Croatia, The Agency for Medicinal Products and Medical Devices' (HALMED) did not require the distribution of the "titration card" to HCPs upon Croatian accession to EU, since dosing cards were already in place at the time of approval of new indications for Seroquel and several years have passed since addition of these indications to the SmPC. To date, a need to repeat this message has not been identified.
Criteria for judging the success of the proposed risk minimisation measures	The effectiveness was assessed at the national level.
Planned dates for assessment	Complete
Results of effectiveness measurement	No change to the SmPC based on ongoing pharmacovigilance.
Impact of risk minimisation	Increased knowledge of the benefits and risks associated with quetiapine via the SmPC.
Comment	NA

ADR Adverse drug reaction; EPS Extrapyramidal symptoms; GAD Generalised anxiety disorder; MDD Major Depressive Disorder; MEB Medicines Evaluation Board; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; XR Extended release.

Table V-3 Risk minimisation measures – Weight gain

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	The SEROQUEL/SEROQUEL XR MR-SmPC contains an extensive description of the risk of weight gain during use of quetiapine. **Use in adults:** Section 4.4, Special Warnings and Precautions for Use, states: Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilized antipsychotic guidelines (see Sections 4.8 and 5.1). Metabolic Risk Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also section 4.8). Section 4.8, Undesirable Effects, lists weight gain as a very common (frequency is ≥10%) ADR, with the following footnotes: [1] Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults. [2] In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (See Section 4.4). Section 4.8, Undesirable Effects, lists increased appetite as a common (frequency is ≥1% to <10%) ADR. Section 5.1, Pharmacodynamic Properties, Clinical Safety, states: In short-term, fixed-dose (50 mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50-mg daily dose to 1.4 kg for the 600-mg daily dose (with lower gain for the 800-mg daily dose), compared to 0.2 kg for the placebo-treated patients. The percentage of quetiapine-treated patients who gained ≥7% of body weight ranged from 5.3% for the 50-mg daily dose to 15.5% for the 400-mg daily dose (with lower gain for the 600- and 800-mg daily doses), compared to 3.7% for placebo-treated patients. Longer-term relapse prevention trials had an open-label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open-label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open-label baseline. For patients who were randomized to placebo, the mean weight gain during the open-label period was 2.39 kg, and by week 48 of the randomized period, the mean weight gain was 0.89 kg, compared to open-label baseline. **Paediatric population:** Section 4.4 (SEROQUEL SmPC only), Special Warnings and Precautions for Use states:

Table V-3 Risk minimisation measures – Weight gain

	Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents. Section 4.8, Undesirable Effects, lists increased appetite as very common (frequency of ≥10%) ADR. Section 5.1, Pharmacodynamic Properties states: In short-term clinical trials with SEROQUEL in pediatric patients (10 to 17 years of age), the rates of weight gain ≥ 7% of baseline body weight in the active arm vs. placebo were 17% vs. 2.5% in the schizophrenia and bipolar mania trials, and 12.5% vs. 6% in the bipolar depression trial. When adjusting for normal growth over longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion. The PIL is a primary tool for communicating the benefits and risks to patients and includes recommendations of checking weight regularly.
Additional risk minimisation measure(s)	The SmPC was updated to include labeling with regards to metabolic parameters, including weight gain. An educational programme describing labeling regarding metabolic parameters was developed for prescribing physicians. The content of the metabolic educational materials on metabolic parameters was developed in conjunction with the RMS (MEB) and the method of distribution was agreed upon with national authorities. Delivery of the educational materials on metabolic parameters commenced in all countries in 2012, except Croatia, where these materials were distributed in 2013. Redistribution of education materials commenced in 2015. The strategic details of the distribution plan of the educational materials is negotiated with the National Competent Authorities in each CMS where the product is marketed. AZ follows the distribution plan in term of content and timelines as agreed upon with the National Competent Authorities in each CMS where the product is marketed. Combined core messages for all safety concerns requiring additional risk minimization are included in one core document found in 'Details of proposed additional risk minimization measures' (Annex 10). The above mentioned content for metabolic parameters, including weight gain are included in this core piece. The key aim of educational activities for physicians and other HCPs is to give guidance, based on the SmPC, to ensure the safe and appropriate use of SEROQUEL/SEROQUEL XR.

Table V-3 Risk minimisation measures – Weight gain

Effectiveness of minimisation measures	
How effectiveness of risk minimisation measures for the Safety Concern will be measured	AstraZeneca performed a physician survey in eight EU countries which included questions on the performance of specific metabolic monitoring activities (i.e., monitoring of weight at initiation of treatment and during the course of treatment) on patients receiving quetiapine. This study was designed as a companion study of an evaluation of electronic medical records to determine the frequency of recording of weight at physician visits using the IMS Disease Analyzer database in two countries. Following the distribution of educational materials the physician survey was administered to specialist physicians drawn from the same list used for distribution, asking about specific metabolic monitoring activities performed on their patients, and whether they recalled receiving the materials.
Criteria for judging the success of the proposed risk minimisation measures	Process measure: Across the physicians surveyed in 8 countries, the proportion having recalled receiving the educational materials and reading them served as process measure. In addition, the level of awareness (an additional proxy process measure) was considered as the physician's report of the proportion of patients receiving quetiapine being monitored within their practice or by others. Outcome measure: The proportion performing monitoring activities was compared against a locally determined, country-specific criterion and a fixed criterion applied across all countries based upon an expected activity level of 70-80%, (derived from the experience of GPs in the UK where physicians receive financial incentives to perform monitoring).
Planned dates for assessment	Varied by country during 2013. Completed.
Results of effectiveness measurement	Across all physicians surveyed within the eight countries, the proportion of physician practices reporting monitoring for weight was 67 % (95% CI [63.6, 70.3]). In the EMR study monitoring of weight was recorded by 39% of GPs in the UK and 0.3-0.4% of specialist physicians in Germany during a 7- month period following initiation of treatment with Seroquel XR. Additional findings related to process/outcome measures for metabolic risk issues are presented in Table V-6.
Impact of risk minimisation	Increased knowledge of the benefits and risks associated with quetiapine via the SmPC and educational materials on metabolic parameters.
Comment	In response to the Assessment received in the FVAR on these PASS, AstraZeneca agree to retain the current educational materials, as per our previous commitment with the RMS. The safety messages specifically related to metabolic parameters, including weight gain are included in the core material found in Annex 10. The method for dissemination of these educational materials to new prescribers is to be agreed at the national level. .

ADR Adverse drug reaction; EMR Electronic medical record; EU European Union; HCP Healthcare provider; MEB Medicines Evaluation Board; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; RMS Reference member state; SmPC Summary of Product Characteristics; XR Extended release.

Table V-4 Risk minimisation measures – Lipid changes (Increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs)

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Detailed wording in the SEROQUEL/SEROQUEL XR MR-SmPC provides clear information to prescribing physicians regarding the appropriate use of quetiapine, as shown below: Section 4.4, Special Warnings and Precautions for Use Metabolic Risk Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also section 4.8). Lipids: Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid changes should be managed as clinically appropriate. Section 4.8, Undesirable Effects, lists elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), and decreases in HDL cholesterol as very common (frequency ≥10%) ADRs, with the following footnotes: [1] Triglycerides ≥200 mg/dL (≥2.258 mmol/L) [P] (patients ≥18 years of age) or ≥150 mg/dL (patients <18 years of age) on at least one occasion. [2] Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L). [3] HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time [4] Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment. [5] In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (See Section 4.4).
Additional risk minimisation measure(s)	The SmPC was updated to include labeling with regards to metabolic parameters, including lipid changes. An educational programme describing labeling regarding metabolic parameters was developed for prescribing physicians using an approach similar to that described above for the bipolar depression indication. The content of the metabolic educational materials on metabolic parameters was developed in conjunction with the RMS (MEB) and the method of distribution was agreed upon with national authorities. Delivery of the educational materials on metabolic parameters commenced in all countries by 2012. Redistribution of education materials was commenced in 2015. The strategic details of the distribution plan of the educational materials is negotiated with the National Competent Authorities in each CMS where the product is marketed. AZ follows the distribution plan as agreed upon with the National Competent Authorities in each CMS where the product is marketed.

Table V-4 Risk minimisation measures – Lipid changes (Increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs)

	The key aim of educational material for physicians and other HCPs is to give guidance, based on the SmPC, to ensure the safe and appropriate use of SEROQUEL/SEROQUEL XR. To ensure such use in patients with bipolar depression, educational material contains messages introducing physicians to the indication, the recommended dosing regimen, and the benefit:risk profile. Combined core messages for all safety concerns requiring additional risk minimization are included in one core document found in 'Details of proposed additional risk minimization measures' (Annex 10). The above mentioned content for lipid changes and bipolar depression are included in this core piece.
Effectiveness of minimisation measures	
How effectiveness of risk minimisation measures for the Safety Concern will be measured	A physician survey on monitoring activities related to metabolic parameters was performed in 8 EU countries and a companion study to provide an objective assessment of monitoring based upon EMRs evaluated the distribution of educational materials (involving updated label information about metabolic parameters) to physicians. See Table V-6.
Criteria for judging the success of the proposed risk minimisation measures	See Table V-6.
Planned dates for assessment	Completed See Table V-6.
Results of effectiveness measurement	Across all physicians surveyed within the eight countries, the proportion of physician practices reporting monitoring for weight was 67 % (95% CI [63.6, 70.3]). In the EMR study, monitoring of weight was recorded by 39% of GPs in the UK and 0.3-0.4% of specialist physicians in Germany during a 7-month period following initiation of treatment with Seroquel XR. Additional findings related to process/outcome measures for metabolic risk issues are presented in Table VI-11.
Impact of risk minimisation	Increased knowledge of the benefits and risks associated with quetiapine via the SmPC and HCP guidance.
Comment	NA

ADR Adverse drug reaction; EMR Electronic medical record; EU European Union; HCP Healthcare provider; HDL High-density lipoprotein; LDL Low-density lipoprotein; MEB Medicines Evaluation Board; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; RMS Reference member state; SmPC Summary of Product Characteristics; XR Extended release.

Table V-5 Risk minimisation measures – Hyperglycemia and diabetes mellitus

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Detailed wording in the SEROQUEL/SEROQUEL XR MR-SmPC provides clear information to prescribing physicians regarding the appropriate use of quetiapine, as shown below: Section 4.4, Special Warnings and Precautions for Use Hyperglycemia: Hyperglycemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilized antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly. Section 4.8, Undesirable Effects, lists blood glucose increased to hyperglycemic levels as a common (frequency is ≥1% - <10%) ADR with the following footnotes: [1] Fasting blood glucose ≥126 mg/dL (≥7.0 mmol/L) or a non-fasting blood glucose ≥200 mg/dL (≥11.1 mmol/L) on at least one occasion. [2] In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (See Section 4.4). Section 4.8, Undesirable Effects, lists Exacerbation of pre-existing diabetes as very rare (frequency <1/10,000); DM as uncommon (frequency ≥0.1% to <1%) with the following footnotes: [1] See section 4.4. [2] Calculations of frequency for these ADRs have been taken from postmarketing data with the immediate release formulation of quetiapine. The PIL is updated to include recommendations of checking weight regularly.
Additional risk minimisation measure(s)	An educational programme describing labeling regarding metabolic parameters was developed for and distributed to prescribing physicians using an approach similar to that described above for the bipolar depression indication. The content of the metabolic educational materials on metabolic parameters was developed in conjunction with the RMS (MEB) and the method of distribution was agreed upon with national authorities. Delivery of the educational materials on metabolic parameters commenced in all countries by 2012. Redistribution of education materials was commenced in 2015. The strategic details of the distribution plan of the educational materials is negotiated with the National Competent Authorities in each CMS where the product is marketed. AZ follows the distribution plan as agreed upon with the National Competent Authorities in each CMS where the product is marketed.

Table V-5 Risk minimisation measures – Hyperglycemia and diabetes mellitus

	The key aim of educational material for physicians and other HCPs is to give guidance, based on the SmPC, to ensure the safe and appropriate use of SEROQUEL/SEROQUEL XR. To ensure such use in patients with bipolar depression, educational material contains messages introducing physicians to the indication, the recommended dosing regimen, and the benefit:risk profile. Combined core messages for all safety concerns requiring additional risk minimization are included in one core document found in 'Details of proposed additional risk minimization measures' (Annex 10). The above mentioned content for hyperglycemia/diabetes mellitus and bipolar depression are included in this core piece.
Effectiveness of minimisation measures	
How effectiveness of risk minimisation measures for the Safety Concern will be measured	A physician survey on monitoring activities related to metabolic parameters was performed in 8 EU countries and a companion study to provide an objective assessment of monitoring based upon EMRs evaluated the distribution of educational materials (involving updated label information about metabolic parameters) to physicians. See Table V-6.
Criteria for judging the success of the proposed risk minimisation measures	See Table V-6.
Planned dates for assessment	Completed See Table V-6.
Results of effectiveness measurement	Across all physicians surveyed within the eight countries, the proportion of physician practices reporting monitoring for signs and symptoms of hyperglycemia and worsening of glycemic control among patients with diabetes mellitus was 71 % (95% CI [68, 74.4]) and 77% (95% CI [74.1, 80]), respectively. In the EMR study, monitoring for signs and symptoms of hyperglycemia and worsening of glycemic control among patients with diabetes mellitus was 31.9% and 34.4%, respectively as recorded by GPs in the UK. 0.1%-0.7% of specialists physicians in Germany monitoring for signs and symptoms of hyperglycemia and 0.7%-6.9% monitored for worsening of glycemic control among patients with diabetes mellitus during an 7 month period following initiation of treatment with Seroquel XR. Additional findings related to process/outcome measures for metabolic risk issues are presented in Table V-6.
Impact of risk minimisation	Increased knowledge of the benefits and risks associated with quetiapine via the SmPC and HCP guidance.
Comment	NA

ADR Adverse drug reaction; DM Diabetes mellitus; EMR Electronic medical record; EU European Union; HCP Healthcare provider; MEB Medicines Evaluation Board; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; RMS Reference member state; SmPC Summary of Product Characteristics; XR Extended release.

Table V-6 Risk minimisation measures – Metabolic risk factors

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Section 4.4, Special Warnings and Precautions for Use, states: Metabolic Risk: Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia), and lipids seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening of these parameters should be managed as clinically appropriate (see also section 4.8). Wording in Section 4.4 of the SEROQUEL/SEROQUEL XR MR-SmPC (see lipid changes [Table V-4] and hyperglycemia and DM [Table V-5]). Section 4.8, Undesirable Effects, lists metabolic syndrome as a rare (frequency is ≥0.01% to <0.1%) ADR, with the following footnote: [1] Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine
Additional risk minimisation measure(s)	An educational programme describing labeling regarding metabolic parameters was developed for and distributed to prescribing physicians using an approach similar to that described above for the bipolar depression indication. The content of the metabolic educational materials on metabolic parameters was developed in conjunction with the RMS (MEB) and the method of distribution was agreed upon with national authorities. Delivery of the educational materials to physicians in EU countries on metabolic parameters commenced in all countries by 2012, except Croatia, where it was completed in 2012. Redistribution of education materials commenced in 2015. The strategic details of the distribution plan of the educational materials is negotiated with the National Competent Authorities in each CMS where the product is marketed. AZ follows the distribution plan as agreed upon with the National Competent Authorities in each CMS where the product is marketed. The key aim of educational materials for physicians and other HCPs is to give guidance, based on the SmPC, to ensure the safe and appropriate use of SEROQUEL/SEROQUEL XR. To ensure such use in patients with bipolar depression, educational material contains messages introducing physicians to the indication, the recommended dosing regimen, and the benefit:risk profile. Combined core messages for all safety concerns requiring additional risk minimization are included in one core document found in 'Details of proposed additional risk minimization measures' (Annex 10). The above mentioned content for metabolic risk factors are included in this core piece.

Table V-6 Risk minimisation measures – Metabolic risk factors

Effectiveness of minimisation measures	
How effectiveness of risk minimisation measures for the Safety Concern will be measured	AstraZeneca performed a physician survey in eight EU countries which included questions on the performance of specific metabolic monitoring activities (i.e., monitoring of weight at initiation of treatment and during the course of therapy, monitoring of lipids, monitoring of signs and symptoms of hyperglycemia and monitoring of blood glucose among patients with diabetes mellitus) performed on patients receiving quetiapine. This study was designed as a companion study of an evaluation of electronic medical records to determine the frequency of recording of weight at physician visits using the IMS Disease Analyzer database in two countries. Following the distribution of educational materials a physician survey was administered to specialist physicians drawn from the same list used for distribution, asking about specific metabolic monitoring activities performed on their patients, and whether they recalled receiving the materials.
Criteria for judging the success of the proposed risk minimisation measures	Criteria were based on the reported/observed monitoring levels.
Planned dates for assessment	Complete
Results of effectiveness measurement	A high level of awareness (proxy measure of process) was seen, with physicians reporting that 64.5% of patients receiving quetiapine were monitored within their practice or by others. In the physician survey, monitoring of signs and symptoms of hyperglycemia was reported to be measured by 71% (95% CI: 68, 74.4). Monitoring of other metabolic parameters was reported to range between 67% and 77%. In the EMR study metabolic monitoring was recorded by 27.7% - 39% of GPs in the UK and 0.1% - 6.9% of specialist physicians in Germany during a 7-month period following initiation of treatment with Seroquel XR. Outcome measures (defined by reported monitoring behaviours) were generally higher (≥10%) among physicians who reported receiving the educational materials than those who did not.
Impact of risk minimisation	Increased knowledge of the benefits and risks associated with quetiapine via the SmPC and HCP guidance educational materials on metabolic parameters.
Comment	NA

ADR Adverse drug reaction; DM Diabetes mellitus; EMR Electronic medical record; EU European Union; HCP Healthcare provider; MEB Medicines Evaluation Board; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; RMS Reference member state; SmPC Summary of Product Characteristics; XR Extended release.

Table V-7 Risk minimisation measures – Suicide and suicidality

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Detailed wording in the SEROQUEL/SEROQUEL XR MR-SmPC provides clear information to prescribing physicians regarding the appropriate use of quetiapine, as shown below: Section 4.4, Special Warnings and Precautions for Use Suicide/suicidal thoughts or clinical worsening: Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated. Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders. Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo in patients less than 25 years old. A population-based retrospective study of quetiapine for the treatment of patients with major depressive disorder showed an increased risk of self-harm and suicide in patients aged 25 to 64 years without a history of self-harm during use of quetiapine with other antidepressants. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present. In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adults patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo. Section 4.8, Undesirable effects, Table 1 ADRs associated with quetiapine therapy: Suicidal ideation and suicidal behavior are included with a frequency of common. Section 5.1, Pharmacodynamic Properties Suicide/suicidal thoughts or clinical worsening: In short-term placebo-controlled clinical trials with SEROQUEL in pediatric patients

Table V-7 Risk minimisation measures – Suicide and suicidality

	with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebo-controlled trials with SEROQUEL in pediatric patients with bipolar mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.
Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

MDD Major depressive disorder; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; XR Extended release.

V: 1.2 Important potential risks

V: 1.2.1 Important potential risks that have been observed with other members of the antipsychotic class

Table V-8 Risk minimisation measures – Cerebrovascular adverse events in the elderly (>65 years old)

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Detailed wording in the SEROQUEL/SEROQUEL XR MR-SmPC provides clear information to prescribing physicians regarding the appropriate use of quetiapine, as shown below: Section 4.4, Special Warnings and Precautions for Use: Orthostatic hypotension: **Orthostatic hypotension:** Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease. Elderly patients with dementia-related psychosis: Quetiapine is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomized, placebo-controlled studies in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. SEROQUEL/SEROQUEL XR should be used with caution in patients with risk factors for stroke. Section 5.1, Pharmacodynamic Effects, Clinical Efficacy: In placebo-controlled studies in elderly patients with dementia-related psychosis, the incidence of cerebrovascular adverse events per 100 patient-years was not higher in quetiapine-treated patients than in placebo-treated patients.

Table V-8 Risk minimisation measures – Cerebrovascular adverse events in the elderly (>65 years old)

Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

AE Adverse event; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; XR Extended release.

Table V-9 Risk minimisation measures – Cerebrovascular adverse events in non-elderly patients

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Wording in Section 4.4 of the SEROQUEL/SEROQUEL XR MR-SmPC (see Cerebrovascular AEs in the elderly (>65 years old).
Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

AE Adverse event; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; XR Extended release.

Table V-10 Risk minimisation measures – Torsades de pointes

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Wording of QT prolongation / Torsades de pointes in Sections 4.4, 4.5, 4.8, and 4.9 of the SEROQUEL/SEROQUEL XR MR-SmPC.
Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; XR Extended release.

Table V-11 Risk minimisation measures – Ischemic heart disease

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Detailed wording in the SEROQUEL/SEROQUEL XR MR-SmPC provides clear information to prescribing physicians regarding the appropriate use of quetiapine, as shown below: Section 4.4, Special Warnings and Precautions for Use, states: **Orthostatic hypotension** Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease. Section 4.9, Overdose, states: Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4: Orthostatic hypotension.
Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; XR Extended release.

Table V-12 Risk minimisation measures – Abuse and misuse

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Detailed wording in the SEROQUEL/SEROQUEL XR MR-SmPC provides clear information to prescribing physicians regarding the appropriate use of quetiapine, as shown below: Section 4.4, Special Warnings and Precautions for Use, states: Misuse and abuse, Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse
Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

NA Not applicable; SmPC Summary of Product Characteristics.

Table V-13 Risk minimisation measures – Suicide and suicidality

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Detailed wording in the SEROQUEL/SEROQUEL XR MR-SmPC provides clear information to prescribing physicians regarding the appropriate use of quetiapine, as shown below: Section 4.4, Special Warnings and Precautions for Use Suicide/suicidal thoughts or clinical worsening: Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated. Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders. Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present. In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adults patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo. In a post hoc analysis of a population-based retrospective study of quetiapine for the treatment

Table V-13 Risk minimisation measures – Suicide and suicidality

	of patients with major depressive disorder an association was observed between non-lethal self-harm in patients under 65 years of age and prior use of quetiapine and antidepressants. Section 4.8, Undesirable effects, Table 1 ADRs associated with quetiapine therapy: Suicidal ideation and suicidal behavior are included with a frequency of common. Section 5.1, Pharmacodynamic Properties Suicide/suicidal thoughts or clinical worsening: In short-term placebo-controlled clinical trials with SEROQUEL in pediatric patients with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebo-controlled trials with SEROQUEL in pediatric patients with bipolar mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.
Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

MDD Major depressive disorder; MR Mutual recognition; NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; XR Extended release.

V: 1.2.2 Other potential risks that require further evaluation

Table V-13 Risk minimisation measures – Potential for off-label use and misdosing

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Detailed wording in the SEROQUEL/SEROQUEL XR MR-SmPC provides clear information to prescribing physicians regarding the appropriate use of quetiapine, as shown below: Section 4.1, Therapeutic indications SEROQUEL and SEROQUEL XR are indicated for: Treatment of Schizophrenia Treatment of bipolar disorder: For the treatment of moderate to severe manic episodes in bipolar disorder For the treatment of major depressive episodes in bipolar disorder For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment. SEROQUEL XR only: Add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy (see Section 5.1). Prior to initiating treatment, clinicians should consider the safety profile of SEROQUEL XR (see Section 4.4). Section 4.2, Posology and Method of Administration Paediatric population: SEROQUEL XR is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials with SEROQUEL is presented in sections 4.4, 4.8, 5.1 and 5.2.
Additional risk minimisation measure(s)	Activities adopted to minimize the potential for misdosing, particularly in treating bipolar depression include indication-specific educational pieces and activities based on core messages related to the potential for off-label use found in Annex 10. Core guidance document to ensure consistent capture of indication from spontaneous postmarking reports has been developed and in use. The suggested educational piece (recommended for use by local AstraZeneca marketing companies) presents the recommended dosing and titration schedule for both SEROQUEL and SEROQUEL XR in bipolar depression, along with information on time of drug administration. The key aim of educational material for physicians and other HCPs is to give guidance, based on the SmPC, to ensure the safe and appropriate use of SEROQUEL/SEROQUEL XR. To ensure such use in patients with bipolar depression, educational material contains messages introducing physicians to the recommended dosing regimen. Combined core messages for all safety concerns requiring additional risk minimization are included in one core document found in 'Details of proposed additional risk minimization measures' (Annex 10). The above mentioned content for the potential for off-label use and bipolar depression are included in this core piece.

Table V-13 Risk minimisation measures – Potential for off-label use and misdosing

Effectiveness of minimisation measures	
How effectiveness of risk minimisation measures for the Safety Concern will be measured	To measure the retention of the benefit:risk message in physicians, physician recall for dosing and titration was conducted using web-based applications, a face-to-face questionnaire, and phone-based surveys, in all applicable countries that have launched SEROQUEL/SEROQUEL XR in bipolar depression. In France, this was conducted during the period 26 MAR 2014 through 08 APR 2014. In Croatia, The Agency for Medicinal Products and Medical Devices' (HALMED) did not require the distribution of the "titration card" to HCPs upon Croatian accession to EU, since dosing cards were already in place at the time of approval of new indications for Seroquel and several years have passed since addition of these indications to the SmPC. To date, there has been no identified need to repeat the message.
Criteria for judging the success of the proposed risk minimisation measures	NA
Planned dates for assessment	NA
Results of effectiveness measurement	NA
Impact of risk minimisation	NA
Comment	NA

V: 1.3 Missing information

Table V-14 Risk minimisation measures – Use in pregnant or breast feeding women

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Section 4.6, Fertility, Pregnancy and lactation, states: First trimester The moderate amount of published data from exposed pregnancies (i.e. between 300-1000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks. Third trimester Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Breast feeding Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue Seroquel XR therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman Fertility The effects of quetiapine on human fertility have not been assessed. Effects related to elevated prolactin levels were seen in rats, although these are not directly relevant to humans (See section 5.3 preclinical data).
Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics.

Table V-15 Risk minimisation measures – Use in patients on concomitant cardiovascular medications

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Section 4.4, Special warnings and precautions for use, states: QT prolongation In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose (See section 4.9 Overdose). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e., the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesemia (See section 4.5 Interaction with other medicinal products and other forms of interaction). Section 4.5, Interactions with other medicinal products and other forms of interactions, states: Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval.
Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics.

Table V-16 Risk minimisation measures – Use in patients on concomitant valproic acid

Objective(s) of the risk minimisation measures	The SmPC and PIL are the primary tools to communicate information about the benefits and risks associated with the use of quetiapine, and these documents provide information to the prescriber and to the patient about the identified safety concerns and how these should be managed in certain circumstances.
Routine risk minimisation measures	Section 4.5, Interactions with other medicinal products and other forms of interactions, states: The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups. In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy. Co administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see section 4.4). Section 5.1, Pharmacodynamic properties, Clinical efficacy, states: In two recurrence prevention studies evaluating quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.
Additional risk minimisation measure(s)	None
Effectiveness of minimisation measures	NA

DSM-IV Diagnostic and Statistical Manual of Mental Disorders IV; NA Not applicable; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics.

NA Not applicable; SmPC Summary of Product Characteristics.

V: 2 RISK MINIMISATION MEASURE FAILURE (IF APPLICABLE)

Not applicable.

V: 2.1 Analysis of risk minimisation measure(s) failure

Not applicable

V: 2.2 Revised proposal for risk minimisation

Not applicable

V: 3 SUMMARY TABLE OF RISK MINIMISATION MEASURES

Table V-17 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks: Nervous system disorders		
EPS	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Clear guidance on the method of administration of SEROQUEL/SEROQUEL XR provided in Section 4.2, Posology and Method of Administration EPS data, including data pertaining to all patients described in Sections 4.8. Caution advised, including use in the Paediatric population in Section 4.4, Special Warnings and Precautions for Use EPS in neonates exposed to quetiapine described in Section 4.6, Fertility, Pregnancy and Lactation EPS data, including data pertaining to the Paediatric population, described in Sections 4.8, Undesirable Effects and 5.1, Pharmacodynamic Properties Updated wording in the PIL to advise patients on the possibility of abnormal muscle movements	Educational material on benefit:risk for physicians based on core messages. Distribution plan as agreed upon with National Authorities
Somnolence	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Clear guidance on the method of administration of SEROQUEL/SEROQUEL XR provided in Section 4.2, Posology and Method of Administration Caution advised in Section 4.4, Special Warnings and Precautions for Use Somnolence in neonates exposed to quetiapine described in Section 4.6, Fertility, Pregnancy and Lactation Advise to patients not to drive or operate machinery provided in Section 4.7, Effect on Ability to Drive and Use Machines Somnolence data described in Sections 4.8, Undesirable Effects and 4.9, Overdose Wording in the PIL to instruct patients to report feelings of severe sleepiness to their physicians, and to follow physician advice on when to take their medication	Educational material on benefit:risk for physicians based on core safety messages (Annex 10). Distribution plan as agreed upon with National Authorities.

Table V-17 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks: Metabolism and nutritional disorders		
Weight gain	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Increased appetite and weight gain observed with use in all patients described in Sections 4.4 Special Warnings and Precautions for Use, 4.8, Undesirable Effects and 5.1, Pharmacodynamic Properties, respectively Caution advised, including use in the Paediatric population~~)~~, in Section 4.4, Special Warnings and Precautions for Use Increased appetite and weight gain observed with use in children and adolescents (10 to 17 years of age) described in Sections 4.8, Undesirable Effects and 5.1, Pharmacodynamic Properties, respectively Wording in the PIL to include recommendations of checking weight regularly	Educational Material on benefit: risk for physicians based on core safety messages (Annex 10). Distribution plan as agreed upon by National Authorities.
Lipid changes (Increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs)	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution advised in Section 4.4, Special Warnings and Precautions for Use Description about lipid changes (increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs) provided in Section 4.8, Undesirable Effects Wording in the PIL to include recommendations of checking lipids. PIL informs that "changes in certain fats (triglycerides and total cholesterol)" are among the side effects that can be seen.	Educational material on metabolic parameters for physicians based on core safety messages (Annex 10). Distribution plan as agreed upon by National Authorities
Hyperglycemia and DM	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution advised, including use in patients with DM or with risk factors for DM, in Section 4.4, Special Warnings and Precautions for Use DM and blood glucose increased to hyperglycemic levels and exacerbation of pre-existing diabetes as described in Section 4.8, Undesirable Effects Wording in the PIL indicates that increases in level of sugar in blood can be a common side effect. Also indicates that doctors may check patients' blood sugar levels while taking SEROQUEL if they have diabetes or are at a risk for getting diabetes.	Educational Material on metabolic parameters for physicians based on core messages (Annex 10). Distribution plan as agreed upon by National Authorities.

Table V-17 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Metabolic risk factors	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution advised (including lipid changes and hyperglycemia and DM) in Section 4.4, Special Warnings and Precautions for Use Description about metabolic syndrome provided in Section 4.8, Undesirable Effects Wording in the PIL to include recommendations of checking weight regularly	Educational material on metabolic parameters for physicians based on core safety messages (Annex 10). Distribution plan as agreed upon by National Authorities
Important Identified Risks: Psychiatric disorder		
Suicide and suicidality	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution advised and instructions regarding close supervision of patients at high risk of suicide provided in Section 4.4, Special Warnings and Precautions for Use Inclusion in Section 4.8, Undesirable effects, Table 1 ADRs associated with quetiapine therapy of Suicidal ideation and suicidal behavior with a frequency of common. Description about suicide/suicidal thoughts provided in Sections 5.1, Pharmacodynamic Properties	None
Important potential risks that have been observed with other members of the antipsychotic class: Nervous system disorders		
Cerebrovascular adverse events in the elderly (>65 years old)	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with known CVD, cerebrovascular disease, or other conditions predisposing to hypotension, and patients with risk factors for stroke, advised in Section 4.4, Special Warnings and Precautions for Use Statement that quetiapine is not approved for the treatment of dementia-related psychosis provided in Section 4.4, Special Warnings and Precautions for Use Description of cerebrovascular AEs in elderly patients with dementia-related psychosis provided in Sections 4.8, Undesirable Effects and 5.1, Pharmacodynamic Properties	None

Table V-17 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Cerebrovascular adverse events in non-elderly patients	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with known CVD, cerebrovascular disease, or other conditions predisposing to hypotension, and patients with risk factors for stroke, advised in Section 4.4, Special Warnings and Precautions for Use. Description of effects of overdose, including cerebrovascular AEs, in patients with pre-existing severe CVD provided in Section 4.9, Overdose.	None
Important potential risks that have been observed with other members of the antipsychotic class: Cardiac disorders		
Torsades de pointes	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with CVD or family history of QT prolongation advised in Section 4.4, Special Warnings and Precautions for Use Caution with concomitant use of drugs known to cause electrolyte imbalance or to increase QT interval, especially in the elderly, in patients with congenital long QT syndrome, CHF, heart hypertrophy, hypokalaemia, or hypomagnesaemia advised in Section 4.5, Interactions with Other Medicinal Products and Other Forms of Interactions Description about QT prolongation (including torsades de pointes) provided in Sections 4.8, Undesirable Effects and 4.9, Overdose	None
Ischemic heart disease	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with CVD or family history of QT prolongation advised in Section 4.4, Special Warnings and Precautions for Use Description of effects of overdose, including ischemic heart disease, in patients with pre-existing severe CVD provided in Section 4.9, Overdose	None
Important potential risks that have been observed with other members of the antipsychotic class: Injury, poisoning, procedural complications		
Abuse and misuse	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patient with a history of alcohol or drug abuse advised in Section 4.4, Special Warnings and Precautions for Use.	None

Table V-17 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Other potential risks that require further evaluation: General disorders		
Potential for off-label use and misdosing	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Clear guidance on the use of SEROQUEL/SEROQUEL XR provided in Sections 4.1, Therapeutic Indications and 4.2, Posology and Method of Administration	Educational Material on potential for off-label use for physicians based on core safety messages (Annex 10). Distribution plan as agreed upon by National Authorities.
Missing information		
Use in pregnant or breast feeding women	Section 4.6, Fertility, Pregnancy and Lactation provides information on the use of SEROQUEL/SEROQUEL XR in the first and third trimesters.	None
Use in patients on concomitant cardiovascular medications	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with CVD or family history of QT prolongation advised in Section 4.4, Special Warnings and Precautions for Use Caution with concomitant use of drugs known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, CHF, heart hypertrophy, hypokalaemia, or hypomagnesaemia advised in Section 4.4, Special Warnings and Precautions for Use Caution with concomitant use of drugs known to cause electrolyte imbalance or to increase QT interval advised in Section 4.5, Interactions with Other Medicinal Products and Other Forms of Interactions	None
Use in patients on concomitant valproic acid	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with concomitant use of sodium valproate advised in Section 4.5, Interactions with Other Medicinal Products and Other Forms of Interactions Use in patients on concomitant valproic acid described in Section 5.1, Pharmacodynamic properties	None

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; CHF Congestive heart failure; CVD Cardiovascular disease; CYP Cytochrome P450; DM Diabetes mellitus; EPS Extrapyramidal symptoms; GAD Generalised anxiety disorder; GGT Gamma-glutamyltransferase; HDL High-density lipoprotein; LDL Low-density lipoprotein; MDD Major depressive disorder; MR Mutual recognition; NA Not applicable; NMS Neuroleptic malignant syndrome; PIL Patient Information Leaflet; SmPC Summary of Product Characteristics; XR Extended release.

EU RMP Part VI	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	14.1
Data lock point for this module	06 December 2016

PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

VI: 1 ELEMENTS FOR SUMMARY TABLES IN THE EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

VI: 1.1 Summary table of safety concerns

Table VI-1 Summary of safety concerns

Important identified risks[a]	**Nervous system disorders** • Extrapyramidal symptoms (EPS) • Somnolence **Metabolism and nutritional disorders** • Weight gain • Lipid changes (Increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs) • Hyperglycemia and diabetes mellitus (Note: Diabetes mellitus included per MRP outcome) • Metabolic risk factors
Important potential risks that have been observed with other members of the antipsychotic class	**Nervous system disorders**[b] • Cerebrovascular adverse events in the elderly • Cerebrovascular adverse events in non-elderly patients **Cardiac disorders**[b] • Torsades de Pointes • Ischemic heart disease **Injury, poisoning, procedural complications/ Psychiatric disorders** • Abuse and misuse[b] • Suicide and Suicidality
Other potential risks that require further evaluation	**General disorders** • Potential for off-label use and misdosing[c]
Missing information	Use in pregnant or breast feeding women Use in patients on concomitant cardiovascular medications Use in patients on concomitant valproic acid

a With the exception of the last item, which is an identified risk in the pediatric patient population, all safety concerns that are considered important identified risks are important events listed in the MR-SmPC.
b Potential risks that have been observed with other members of the antipsychotic class
c Other potential risks that require further evaluation.
EPS Extrapyramidal symptoms; HDL High-density lipoprotein; LDL Low-density lipoprotein; MedDRA Medical Dictionary for Regulatory Activities;; MRP Mutual recognition procedure; SmPC Summary of product characteristicsXR Extended release.

VI: 1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

There are no on-going and planned additional PhV studies/activities in the pharmacovigilance plan.

VI: 1.3 Summary of post authorisation efficacy development plan

There were no ongoing or planned post-authorisation efficacy studies during this period.

VI: 1.4 Summary table of Risk Minimisation Measures

Table VI-2 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks: Nervous system disorders		
EPS	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Clear guidance on the method of administration of SEROQUEL/SEROQUEL XR provided in Section 4.2, Posology and Method of Administration Caution advised, including use in children and adolescents (10 to 17 years of age), in Section 4.4, Special Warnings and Precautions for Use EPS in neonates exposed to quetiapine described in Section 4.6, Fertility, Pregnancy and Lactation EPS data, including data pertaining to use in children and adolescents (10 to 17 years of age), described in Sections 4.8, Undesirable Effects and 5.1, Pharmacodynamic Properties	Updated wording in the PIL to advise patients on the possibility of abnormal muscle movements Educational program on benefit:risk for physicians (ie, treatment path guidance)
Somnolence	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Clear guidance on the method of administration of SEROQUEL/SEROQUEL XR provided in Section 4.2, Posology and Method of Administration Caution advised in Section 4.4, Special Warnings and Precautions for Use Somnolence in neonates exposed to quetiapine described in Section 4.6, Fertility, Pregnancy and Lactation Advise to patients not to drive or operate machinery provided in Section 4.7, Effect on Ability to Drive and Use Machines Somnolence data described in Sections 4.8, Undesirable Effects and 4.9, Overdose	Wording in the PIL to instruct patients to report feelings of severe sleepiness to their physicians, and to follow physician advice on when to take their medication Educational program on benefit:risk for physicians (ie, treatment path guidance)

Table VI-2 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks: Metabolism and nutritional disorders		
Weight gain	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution advised, including use in children and adolescents (10 to 17 years of age), in Section 4.4, Special Warnings and Precautions for Use Increased appetite and weight gain observed with use in children and adolescents (10 to 17 years of age) described in Sections 4.8, Undesirable Effects and 5.1, Pharmacodynamic Properties, respectively	Wording in the PIL to include recommendations of checking weight regularly Educational program on metabolic parameters for physicians
Lipid changes (Increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs)	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution advised in Section 4.4, Special Warnings and Precautions for Use Description about lipid changes (increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs) provided in Section 4.8, Undesirable Effects	Wording in the PIL to include recommendations of checking lipids. PIL informs that "changes in certain fats (triglycerides and total cholesterol)" are among the side effects that can be seen. Educational program on metabolic parameters for physicians

Table VI-2 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Hyperglycemia and DM	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution advised, including use in patients with DM or with risk factors for DM, in Section 4.4, Special Warnings and Precautions for Use DM and blood glucose increased to hyperglycemic levels described in Section 4.8, Undesirable Effects	Wording in the PIL indicates that increases in level of sugar in blood can be a common side effect. Also indicates that doctors may check patients' blood sugar levels while taking SEROQUEL /SEROQUEL XR if they have diabetes or are at a risk for getting diabetes. Educational program on metabolic parameters for physicians
Metabolic risk factors	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution advised (including lipid changes and hyperglycemia and DM) in Section 4.4, Special Warnings and Precautions for Use Description about metabolic syndrome provided in Section 4.8, Undesirable Effects	Wording in the PIL to include recommendations of checking weight regularly Educational program on metabolic parameters for physicians

Table VI-2 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk: Psychiatric disorder		
Suicide and suicidality	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution advised and instructions regarding close supervision of patients at high risk of suicide provided in Section 4.4, Special Warnings and Precautions for Use Inclusion in Section 4.8, Undesirable effects, Table 1 ADRs associated with quetiapine therapy of Suicidal ideation and suicidal behavior with a frequency of common. Description about suicide/suicidal thoughts provided in Sections 5.1, Pharmacodynamic Properties	None
Important potential risks that have been observed with other members of the antipsychotic class: Nervous system disorders		
Cerebrovascular adverse events in the elderly (>65 years old)	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with known CVD, cerebrovascular disease, or other conditions predisposing to hypotension, and patients with risk factors for stroke, advised in Section 4.4, Special Warnings and Precautions for Use Statement that quetiapine is not approved for the treatment of dementia-related psychosis provided in Section 4.4, Special Warnings and Precautions for Use Description of cerebrovascular AEs in elderly patients with dementia-related psychosis provided in Sections 4.8, Undesirable Effects and 5.1, Pharmacodynamic Properties	None
Cerebrovascular adverse events in non-elderly patients	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with known CVD, cerebrovascular disease, or other conditions predisposing to hypotension, and patients with risk factors for stroke, advised in Section 4.4, Special Warnings and Precautions for Use. Description of effects of overdose, including cerebrovascular AEs, in patients with pre-existing severe CVD provided in Section 4.9, Overdose.	None

Table VI-2 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risks that have been observed with other members of the antipsychotic class: Cardiac disorders		
Torsades de pointes	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with CVD or family history of QT prolongation advised in Section 4.4, Special Warnings and Precautions for Use Caution with concomitant use of drugs known to cause electrolyte imbalance or to increase QT interval, especially in the elderly, in patients with congenital long QT syndrome, CHF, heart hypertrophy, hypokalaemia, or hypomagnesaemia advised in Section 4.5, Interactions with Other Medicinal Products and Other Forms of Interactions Description about QT prolongation (including torsades de pointes) provided in Sections 4.8, Undesirable Effects and 4.9, Overdose	None
Ischemic heart disease	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with CVD or family history of QT prolongation advised in Section 4.4, Special Warnings and Precautions for Use Description of effects of overdose, including ischemic heart disease, in patients with pre-existing severe CVD provided in Section 4.9, Overdose	None
Important potential risks that have been observed with other members of the antipsychotic class: Injury, poisoning, procedural complications		
Abuse and misuse	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patient with a history of alcohol or drug abuse advised in Section 4.4, Special Warnings and Precautions for Use.	None

Table VI-2 Summary table of risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Other potential risks that require further evaluation: General disorders		
Potential for off-label use and misdosing	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Clear guidance on the use of SEROQUEL/SEROQUEL XR provided in Sections 4.1, Therapeutic Indications and 4.2, Posology and Method of Administration	Educational program for physicians: Indication-specific educational pieces and activities Core guidance document
Potential risk in the bipolar depression patient population		
Missing Information		
Use in pregnant or breast feeding women	Statement that the safety and efficacy of quetiapine during human pregnancy have not been established provided in Section 4.6, Fertility, Pregnancy and Lactation	None
Use in patients on concomitant cardiovascular medications	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with use in patients with CVD or family history of QT prolongation advised in Section 4.4, Special Warnings and Precautions for Use Caution with concomitant use of drugs known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, CHF, heart hypertrophy, hypokalaemia, or hypomagnesaemia advised in Section 4.4, Special Warnings and Precautions for Use Caution with concomitant use of drugs known to cause electrolyte imbalance or to increase QT interval advised in Section 4.5, Interactions with Other Medicinal Products and Other Forms of Interactions	None
Use in patients on concomitant valproic acid	Appropriate wording in the SEROQUEL/SEROQUEL XR MR-SmPC: Caution with concomitant use of hepatic enzyme inducers or potent CYP3A4 inhibitors advised in Section 4.4, Special Warnings and Precautions for Use Caution with concomitant use of sodium valproate advised in Section 4.5, Interactions with Other Medicinal Products and Other Forms of Interactions Use in patients on concomitant valproic acid described in Section 5.1, Pharmacodynamic properties	None

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; CHF Congestive heart failure; CVD Cardiovascular disease; CYP Cytochrome P450; DM Diabetes mellitus; EPS Extrapyramidal symptoms; GAD Generalised anxiety disorder; GGT Gamma-glutamyltransferase; HDL High-density lipoprotein; LDL Low-density lipoprotein; MDD Major depressive disorder; MR Mutual recognition; NA Not applicable; NMS Neuroleptic malignant syndrome; PIL Patient Information Leaflet; SIADH Syndrome of inappropriate antidiuretic hormone; SJS Stevens

Johnson syndrome; SmPC Summary of Product Characteristics; TD Tardive dyskinesia; VTE Venous thromboembolism; XR Extended release.

VI: 2 ELEMENTS FOR A PUBLIC SUMMARY

Quetiapine is a type of medication known as an antipsychotic medicine. The medicine is available in two forms: SEROQUEL and SEROQUEL XR/XL (a slow-releasing form), hereafter SEROQUEL/SEROQUEL XR. SEROQUEL/SEROQUEL XR works by correcting imbalances of chemical substances which act on the brain and nervous system. SEROQUEL/SEROQUEL XR is used to treat schizophrenia, bipolar disorder, and Major Depressive Disorder.

Inclusion of information relating to a potential risk should not be taken to imply that causal association with the use of SEROQUEL/SEROQUEL XR has been established.

VI: 2.1 Overview of disease epidemiology

VI: 2.1.1 Schizophrenia

Schizophrenia is a serious mental health condition that causes disordered ideas, beliefs and experiences. Symptoms include hearing, seeing, or sensing things that are not real, having mistaken beliefs, and feeling unusually suspicious. The incidence of schizophrenia is variable across countries, but tends to be higher in more developed countries. In men, the highest risk of developing schizophrenia is between 18 and 25 years of age; women aged between 26 and 45 years, and between 55 to 64 years have a higher risk of developing schizophrenia. People who have other family members with schizophrenia have a higher risk of developing the condition, and schizophrenia tends to be more common in people with lower family incomes. If untreated, people with schizophrenia have a higher risk of death.

Schizophrenia may be treated with antipsychotics medicines, as well as non-drug treatments such as behavioural therapy and counselling.

VI: 2.1.2 Bipolar disorder

Bipolar disorder is a life-long illness that causes periods of depression (lows) and periods of mania (highs), affecting mood, energy, and ability to function. Bipolar I patients have intense mania, while Bipolar II patients have less severe mania (known as hypomania). All bipolar patients spend more time depressed than manic or hypomanic.

People aged around 20 years old have the highest risk of developing bipolar disorder; risk reduces with increasing age. Bipolar I occurs in men and women equally: Bipolar II is more common in women. The chances of developing bipolar disorder are unrelated to race or family income. If untreated, bipolar patients have a higher risk of other mental health and medical conditions, and a higher risk of death, especially suicide.

Bipolar patients may be treated with various medications or combinations of medications including antipsychotics, antidepressants, mood stabilisers such as lithium, anti-epileptic medicines and non-drug treatments such as behavioural therapy and counselling.

VI: 2.1.3 Major Depressive Disorder

Major depression is a medical illness that causes a continual feeling of sadness and loss of interest, usually requiring long-term treatment. The incidence of major depression is variable across European countries. People aged between 18 and 30 have the highest risk of developing major depression: it is also more common in women than in men, and in people with other long-term diseases such as Parkinson's disease, chronic pain, stroke, heart disease, AIDS, lung diseases, thyroid diseases and cancer. Having other mental health problems such as anxiety or personality disorders, or abusing drugs or alcohol, may also increase the risk of developing major depression. If untreated, major depression can increase the risk of death.

Major depression may be treated with antidepressants (sometimes in combination with other medicines, including antipsychotics). Electric shock treatment is an option for patients who do not respond to standard drug treatments.

VI: 2.2 Summary of treatment benefits

SEROQUEL/SEROQUEL XR is a type of medication known as an antipsychotic medicine which works by correcting imbalances of chemical substances which act on the brain and nervous system. Because SEROQUEL/SEROQUEL XR only acts specifically with certain chemicals in the brain, patients taking SEROQUEL/SEROQUEL XR may experience a lower level of certain side effects, such as muscle spasms, restlessness, shaking or rigidity.

Over 28,000 adult patients have received SEROQUEL or SEROQUEL XR in clinical studies. SEROQUEL XR releases medicine more slowly than SEROQUEL.

There have been five clinical studies in schizophrenia which showed that SEROQUEL XR treatment significantly increased the time to a schizophrenic episode in clinically stable patients treated for up to 9 months. Data from clinical studies demonstrate that SEROQUEL is effective in the dose range of 150 to 750 mg daily (400 to 800 mg daily for SEROQUEL XR).

There have been eleven clinical studies of SEROQUEL and SEROQUEL XR in the treatment of bipolar disorder which showed that SEROQUEL and SEROQUEL XR are effective in the treatment of both depressive and manic episodes and that continued treatment, either alone or in combination with other mood stabilisers such as lithium or valproate, increased the time to an episode of depression or mania taking place. A study on long term treatment showed that benefits were maintained for up to one year. Data showed that a range of 300 to 800 mg daily was effective.

There have been eight clinical studies in major depression which showed that giving SEROQUEL XR at a dose of 150 to 300 mg daily was effective in patients who had not responded to initial treatment with standard antidepressants.

VI: 2.3 Unknowns relating to treatment benefits

Most clinical studies excluded seriously ill patients (heart, liver or kidney failure; uncontrolled diabetes), pregnant women and patients with recent suicide attempts. Reduced doses are recommended in patients with liver damage and standard doses in patients with kidney damage. Babies of women using SEROQUEL/SEROQUEL XR during pregnancy may experience withdrawal effects.

VI: 2.4 Summary of safety concerns

This section presents a summary of important identified risks, important potential risks and missing information; these are defined as follows:

- An important identified risk is an important side effect that is known to be related to the medicine of interest.
- An important potential risk is an important side effect that is suspected to be related to the medicine of interest but a connection has not been confirmed. It is not known whether the potential risks described in this summary are due to the use of SEROQUEL/SEROQUEL XR.
- Missing information is information about the safety of a medicine that is not available when the medicine was approved for sale. This may be unknown information about the safety of the medicine for conditions for which it is not approved for use.

Inclusion of information relating to a potential risk should not be taken to imply that causal association with the use of SEROQUEL/SEROQUEL XR has been established.

For SEROQUEL/SEROQUEL XR, important identified risks, important potential risks and missing information are provided in Table VI-3, Table VI-4, and Table VI-5, respectively.

Table VI-3 Important identified risks

Risk	What is known	Preventability
Abnormal muscle movements such as muscle spasms, restlessness, shaking, rigidity, muscle stiffness without pain.	Approximately 1 in 10 of all patients in SEROQUEL/SEROQUEL XR clinical studies experienced uncontrollable muscle movements resulting from drug treatment. Patients with bipolar disorder appeared to be more likely to experience these effects compared with patients with schizophrenia	Doctors and patients are made aware of the increased risk of abnormal muscle movements in the SEROQUEL/SEROQUEL XR product information. Medication adjustments may be necessary.

Table VI-3 Important identified risks

Risk	What is known	Preventability
Feeling sleepy	Approximately 42 in 100 of all patients in SEROQUEL/SEROQUEL XR clinical studies reported feeling sleepy after starting treatment with SEROQUEL/SEROQUEL XR.	Patients should be aware of the risk of feeling more sleepy when starting SEROQUEL/SEROQUEL XR treatment. The effect of feeling sleepy may be reduced by using a lower dose. The effects may also reduce with time, if SEROQUEL/SEROQUEL XR is continued. Patients should not drive or use any tools or machines until they know how the tablets affect them.
Weight gain	Approximately 1 in 5 of all patients in SEROQUEL/ SEROQUELXR clinical studies had weight gain of 7% or more compared with baseline.	A healthy diet and exercise are recommended for patients at risk for weight gain.
Changes in cholesterol levels	The following changes in cholesterol levels were seen in patients in SEROQUEL/ SEROQUEL XR clinical studies: increases in total cholesterol (approximately 1 in 10 patients), triglycerides (approximately 1 in 5 patients), and LDL (bad) cholesterol (approximately 7 in 100 patients), with decreases in HDL (good) cholesterol (approximately 15 in 100 patients).	A healthy diet and exercise are recommended for patients at risk for increased cholesterol. For some patients, a cholesterol lowering medication may be required.
High blood sugar levels and diabetes	Approximately 3 in 100 patients in SEROQUEL SEROQUELXR / clinical studies developed high blood sugar levels after starting treatment with SEROQUEL/ SEROQUELXR.	Weight reduction, blood pressure control, cholesterol control, diet, and exercise are recommended in patients at risk for development of diabetes.
Metabolic syndrome risk factors (metabolic syndrome describes a combination factors that, when occurring together, increase the risk of developing heart disease and diabetes)	Approximately 1 in 10 patients in SEROQUEL/ SEROQUELXR clinical studies shifted their risk score for metabolic syndrome from less than 3 (low risk) to 3 or more (high risk) after starting treatment with SEROQUEL/SEROQUELXR.	Weight reduction, blood pressure control, cholesterol control, diet, and exercise are recommended in patients at risk for development of metabolic syndrome.

Table VI-3 Important identified risks

Risk	What is known	Preventability
Changes in electrical activity of the heart	Approximately 1 in 1,000 patients in the SEROQUEL/SEROQUEL XR clinical studies had changes in electrical activity of the heart after starting treatment with SEROQUEL/SEROQUEL XR.	SEROQUEL/SEROQUEL XR should be used with care in patients with heart disease or a family history of changes in the electrical activity of the heart. Caution should also be taken when SEROQUEL/SEROQUEL XR is given at the same time as other medicines known to affect the electrical activity of the heart, including other antipsychotic medicines. This is especially true for patients with heart electrical activity abnormalities or a family history of such abnormalities, elderly patients, patients with low levels of sodium or magnesium in the blood, and patients with heart failure or an increased heart size. Patients who have taken an overdose of SEROQUEL/SEROQUEL XR should be observed for any changes in the electrical activity of the heart.

XR extended release.

Table VI-4 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Stroke	In clinical studies, stroke was seen in approximately 1 in 50 elderly patients (more than 65-years-old) after starting treatment with SEROQUEL/SEROQUEL XR. In non-elderly patients, the frequency of patients experiencing stroke was approximately 1 in 1,000.
Reduced blood supply to the heart (ischemic heart disease)	Reduced blood supply to the heart (ischemic heart disease) is considered an effect which is observed with other antipsychotic medicines of the same type as SEROQUEL/SEROQUEL XR. In the SEROQUEL/SEROQUEL XR clinical studies, approximately 1 in 375 patients had ischemic heart disease.
Abuse and misuse	Abuse/misuse is considered an effect which is observed with other antipsychotic medicines of the same type as SEROQUEL/SEROQUEL XR. In the SEROQUEL/SEROQUEL XR clinical studies, approximately 7 in 10,000 patients had an event of abuse or misuse.
Suicide and suicidality	Patients with schizophrenia, bipolar disorder and major depression have a higher risk for suicide than patients who do not have these diseases. Approximately 1 in 100 patients in the SEROQUEL/SEROQUEL XR clinical studies had an event associated with suicide or suicidal behaviour

Table VI-4 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Potential for off-label use and misdosing	Antipsychotic medicines like SEROQUEL/SEROQUEL XR are often used in situations that have not been tested in clinical studies, and therefore to treat patients or diseases, or to use doses, that they are not specifically approved for. Although AstraZeneca does not support the use of its products for off-label or unapproved uses, there is a potential that SEROQUEL/SEROQUEL XR will be used in such situations.

Table VI-5 Missing information

Risk	What is known
Use in pregnant or breast feeding women	Women were not allowed to take part in the SEROQUEL/SEROQUEL XR clinical studies if they were pregnant. However, some women became pregnant during clinical studies. Following pregnancies in which SEROQUEL/SEROQUEL XR was used, some babies displayed withdrawal symptoms. If you are pregnant or breast feeding, think you may be pregnant or planning to have a baby ask your doctor for advice before taking Seroquel XR. You should not take Seroquel XR during pregnancy unless this has been discussed with your doctor. Seroquel XR should not be taken if you are breast-feeding.
Use in patients taking medications for heart conditions	The effects of SEROQUEL/SEROQUEL XR when given at the same time as other medicines which affect the heart have not been formally studied. Because some patients in the SEROQUEL/SEROQUEL XR clinical studies had changes in electrical activity of the heart after starting treatment, SEROQUEL/SEROQUEL XR should be used with care in patients with heart disease or a family history of changes in the electrical activity of the heart. Caution should also be taken when SEROQUEL/SEROQUEL XR is given at the same time as other commonly used medicines taken for heart conditions, or other medicines known to affect the electrical activity of the heart, including other antipsychotic medicines. This is especially true for patients with heart electrical activity abnormalities or a family history of such abnormalities, elderly patients, patients with low levels of sodium or magnesium in the blood and patients with heart failure or an increased heart size.
Use in patients taking the anti-epileptic medicine valproic acid (valproate)	A small study of SEROQUEL and valproate taken at the same time found that the combination of the two products was generally safe and well tolerated.

VI: 2.5 Summary of additional risk minimisation measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC), which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for reducing them. An easier-to-read summary of

this information is provided in the form of the patient information leaflet (PIL). The information in these documents is known as routine risk minimisation (reduction) measures.

SEROQUEL/SEROQUEL XR has special conditions and restrictions for its safe and effective use (additional risk reduction measures). The way in which these special conditions are put into practice across the European Union may be different for different countries.

These additional risk reduction measures are for the risks described in Table VI-6 to Table VI-11.

Table VI-6 Abnormal muscle movements

Risk minimisation measure(s): Healthcare Professional education
Objective and rationale
To reduce the known risk that SEROQUEL/SEROQUEL XR can cause abnormal muscle movement, clear guidelines are needed for physicians to enable early detection of any abnormal muscle movement and to ensure the appropriate actions are taken to treat any changes that do occur.
Main additional risk minimisation measures
• Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on abnormal muscle movement with a reference to the local prescribing information for details • Educational programmes on the risks and benefits of SEROQUEL/SEROQUEL XR, delivered by company sales representatives

Table VI-7 Sleepiness

Risk minimisation measure(s): Healthcare Professional education
Objective and rationale
To reduce the known risk that SEROQUEL/SEROQUEL XR can cause sleepiness, clear guidelines are needed for physicians to enable early detection of any problems with patients' sleep patterns and to ensure the appropriate actions are taken to treat any changes that do occur
Main additional risk minimisation measures
• Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on sleep patterns with a reference to the local prescribing information for details • Educational programmes on the risks and benefits of SEROQUEL/SEROQUEL XR, delivered by company sales representatives

Table VI-8 Weight gain

Risk minimisation measure(s): Healthcare Professional education

Objective and rationale

To reduce the known risk that SEROQUEL/SEROQUEL XR can cause weight gain, clear guidelines are needed for physicians to enable early detection of any problems with patients' weight and to ensure the appropriate actions are taken to treat any changes that do occur

Main additional risk minimisation measures

- Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on patients' weight
- Educational programme describing the effects of SEROQUEL/SEROQUEL XR treatment on the metabolism, including weight gain

Table VI-9 High blood sugar levels and diabetes

Risk minimisation measure(s): Healthcare Professional education

Objective and rationale

To reduce the known risk that SEROQUEL/SEROQUEL XR can cause increases in blood sugar and diabetes, clear guidelines are needed for physicians to enable early detection of any problems with patients' blood sugar levels and to ensure the appropriate actions are taken to treat any changes that do occur

Main additional risk minimisation measures

- Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on patients' blood sugar levels
- Educational programme describing the effects of SEROQUEL/SEROQUEL XR treatment on the metabolism, including high blood sugar levels and diabetes

Table VI-10 Changes in blood cholesterol levels

Risk minimisation measure(s): Healthcare Professional education

Objective and rationale

To reduce the known risk that SEROQUEL/SEROQUEL XR can cause changes in blood cholesterol levels, clear guidelines are needed for physicians to enable early detection of any problems with patients' cholesterol levels and to ensure the appropriate actions are taken to treat any changes that do occur

Main additional risk minimisation measures

Educational activities and materials

- Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on patients' cholesterol levels
- Educational programme describing the effects of SEROQUEL/SEROQUEL XR treatment on the metabolism, including cholesterol levels

Table VI-11 Metabolic syndrome risk factors

Risk minimisation measure(s): Healthcare Professional education
Objective and rationale
To reduce the known risk that SEROQUEL/SEROQUEL XR can cause increase the risk factor for metabolic syndrome (a combination of factors that, when occurring together, increase the risk of developing heart disease and diabetes), clear guidelines are needed for physicians to enable early detection of any problems with patients' cholesterol levels and to ensure the appropriate actions are taken to treat any changes that do occur.
Main additional risk minimisation measures
Educational activities and materials • Provide additional printed information (eg, a laminated card, brochure, or similar document) to remind physicians of the risks that SEROQUEL/SEROQUEL XR treatment may increase a patient's risk of developing metabolic syndrome • Educational programme describing the effects of SEROQUEL/SEROQUEL XR treatment on the metabolism, including the possibility of an increased risk factor for metabolic syndrome

Table VI-12 Potential for off-label use and misdosing

Risk minimisation measure(s): Healthcare Professional education
Objective and rationale
To provide clear guidance on the safe and appropriate use of SEROQUEL/SEROQUEL XR.
Main additional risk minimisation measures
Educational activities and materials • Core guidance document ensuring consistent capture of indication from spontaneous postmarking reports • The key aim of educational activities for health care professionals is to give guidance, based on the product information, to ensure the safe and correct use of SEROQUEL/SEROQUEL XR. To ensure such use in patients with bipolar depression, AstraZeneca developed informational material to introduce physicians to the recommended dosing schedule.

VI: 2.6 Planned post authorisation development plan

There are no studies in the post authorisation development plan.

Studies which are a condition of the marketing authorisation

All studies that were conditions of the marketing authorisations for SEROQUEL and/or SEROQUEL XR have been completed.

VI: 2.7 Summary of changes to the Risk Management Plan over time

Table VI-13 Summary of changes to the Risk Management Plan over time

RMP Version number	Date of authorisation of the RMP	Formulation	Summary of changes
15		SEROQUEL and SEROQUEL XR	PASS information has been updated to reflect the finalization of SE-SLS part III study report and applicable information has been included for each outcome. Routine risk minimization activities have been updated with changes to SmPCs section 4.4 for misuse and abuse. The 2 preganancy registries were incorrectly classified as PASS. They have been removed from the applicable tables and are correctly classified under routine pharmacovigilance (edition 2).Any reference to the pregnancy registries has been removed completely as per the regulators request (edition 3). The pregnancy Additionally, the requirement for PASS-NI-001-CRO (Croatia PASS Study) was removed by HALMED (Agency for Medicinal Products and Medical Devices of Croatia). This is an administrative update. . Annex 2, 5, 6 and 9 have been updated accordingly. Suicide and Suicidality has ben added to the RMP as an important identified risk at the request of the RMS (MEB).This was previously classified as an important potential identified risk and removed from version 14 per the MEBs request.
14.1 (dated |02 Dec 2016)		SEROQUEL and SEROQUEL XR	Part V has been updated to remove any reference to additional risk minimization measures being completed. Clarity has been provided throughout Part V that additional risk minimization meaures are in place for EPS, somnolence, metabolic and nutritional disorders (weight gain, lipid changes, hyperglycemia, diabetes mellitus, metabolic risk factors), off-label use and misdosing. Annex 10 (Details of proposed additional risk minimization measures) has been newly added which includes the core elements to be included in any educational materials created nationally.
14 (dated February 2016		SEROQUEL and SEROQUEL XR	The following important identified risk was deleted as a result of the preliminary assessment report of procedure number NL/H/xxxx/WS/118: QT prolongation PASS information has been updated to reflect the current status of these studies. Risk minimization measure has been added to misuse and abuse: The SEROQUEL/SEROQUEL XR MR-SmPC does not list any information about misuse and abuse at this time. However, MEB has imposed the following amendments to the Product Information in section 4.4 of the SmPC: “Misuse and abuse, Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.”

Table VI-13 Summary of changes to the Risk Management Plan over time

RMP Version number	Date of authorisation of the RMP	Formulation	Summary of changes
13 (dated 28 August 2015	21 October 2015	SEROQUEL and SEROQUEL XR	The following identified or potential risks or information considered missing, were deleted per procedure number NL/H/0156/001-012/IB/110 final variation assessment report: dysarthria, rhabdomyolysis, serotonin syndrome, sudden death, myocarditis, cataract, risk in patients with hepatic impairment for all SEROQUEL formulations, us in patients with renal disease, use in patients with different ethnic or racial origin, treatment emergent mania in patients with bipolar depression and use in patients with longer exposure. The following important identified or potential risks were deleted as a result of the preliminary assessment report of procedure number NL/H/xxxx/WS/118: TD, syncope and orthostatic hypotension, seizure, neutropenia, agranulocytosis, SIADH and hyponatremia, hypothyroidism, hyperprolactinemia, anaphylactic reaction, Stevens-Johnson syndrome and other serious skin reactions, neuroleptic malignant syndrome, withdrawal (discontinuation) symptoms and neonatal withdrawal, dysphagia, pancreatitis, intestinal obstruction/ileus, venous thromboembolism, increased blood pressure in the pediatric population, increased mortality in elderly demented patients, aggression/agitation, accidental injury, aspiration pneumonia, use of SEROQUEL/SEROQUEL XR in elderly patients The three risks that comprised Liver Disorder (Hepatitis, Jaundice and elevated liver enzymes have been combined into one risk, Hepatitis with or without jaundice. SEROQUEL/SEROQUEL XR clinical safety database was updated and clinical tables reflect the changes from version 26 to version 27. Experience of SEROQUEL marketed products information was updated. For the risks that contain post-marketing information, the numbers of patients experiencing adverse events was updated through 12 June 2014. PASS information has been updated to reflect the current status of these studies. Risk minimization activities have been updated. Changes to the SmPCs as a result of the harmonization process are reflected in this EU-RMP.
12	31Jan 2014	SEROQUEL and SEROQUEL XR	Blockage of bowel and withdrawal effects in babies have been added as identified risks. Risk tables have been provided in a new format. Experience of SEROQUEL marketed products information has been updated. Risk minimisation activities have been updated and Asian patients are no longer considered missing information.

Table VI-13 Summary of changes to the Risk Management Plan over time

RMP Version number	Date of authorisation of the RMP	Formulation	Summary of changes
11	13 Aug 2012	SEROQUEL and SEROQUEL XR	The following potential risks were changed to identified risks: severe reductions in a type of white blood cell called neutrophils, metabolic syndrome risk factors, muscle wasting, inflammation of the pancreas, changes in electrical activity of the heart, low blood sodium levels and harmful effects on a hormone that controls urine volume, and blood clots in the vein. Experience of SEROQUEL marketed products information was updated and risk minimisation activities were updated.
10	22 Sep 2012	SEROQUEL and SEROQUEL XR	Risk minimisation activities were updated and enhanced. The number of patients who have used SEROQUEL was updated. Information on the numbers of patients experiencing adverse events was updated, as were measures of monitoring the safety of patients using SEROQUEL, including the additional real-life clinical studies.
9	07 Dec 2009	SEROQUEL and SEROQUEL XR	Added new and newly characterised risks. Updated information from published literature. Added final results of cataract and sedation studies, and updated and enhanced risk minimisation activities.
8	19 Dec 2008	SEROQUEL and SEROQUEL XR	Bipolar depression was added to the uses of SEROQUEL (with update risk minimisation activities).
7	02 Sep 2008	SEROQUEL and SEROQUEL XR	Information was added on studies in generalised anxiety disorder and use in children.
6	21 Apr 2008	SEROQUEL XR	Severe depression added to the uses of SEROQUEL XR.
5	11 Apr 2008	SEROQUEL and SEROQUEL XR	Prevention of recurrence in bipolar disorder added to the uses of SEROQUEL.
4	15 Jan 2008	SEROQUEL and SEROQUEL XR	Update on information on bipolar depression and mania, and update on long term treatment in schizophrenia.
2	13 Jul 2007	SEROQUEL XR	Update on information on schizophrenia. Underactive thyroid was added as a potential risk and food-drug interactions were added as an identified risk (food-drug interactions were later deleted as risk, as this was no longer considered a risk). The name of the slow-releasing formulation was changed from SEROQUEL SR to SEROQUEL XR.

Table VI-13 Summary of changes to the Risk Management Plan over time

RMP Version number	Date of authorisation of the RMP	Formulation	Summary of changes
Unnumbered	18 Sep 2006	SEROQUEL SR	Schizophrenia was added to the uses of SEROQUEL SR.
Unnumbered	24 May 2006	SEROQUEL	Bipolar depression was added to the uses of SEROQUEL.

RMP Risk management plan. SR Sustained release; XR Extended release.

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EU RMP Part VII Annex 1	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	12
Data lock point for this module	12 June 2013

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® and SEROQUEL XR®)

Part VII ANNEX 1 - EUDRAVIGILANCE INTERFACE – NOT APPLICABLE

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL/SEROQUEL XR
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

EU RMP Part VII Annex 2

Drug Substance	Quetiapine fumarate
Version number of RMP when last updated	14
Data lock point for this module	06 December 2016

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® and SEROQUEL XR®)

Part VII ANNEX 2 - SMPC & PACKAGE LEAFLET

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL/SEROQUEL XR
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

1. SMPC & PACKAGE LEAFLET

Summary of product characteristics, Labelling, and Package Leaflet	**Date**
SEROQUEL™ (quetiapine fumarate) Doc ID-003198801)	09 August 2016
SEROQUEL™ XR (quetiapine fumarate) Doc ID-003198825)	09 August 2016

See Module 1.3.1 for the SmPC document(s), and Package Leaflet(s).

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 25 mg film-coated tablets
Seroquel 100 mg film-coated tablets
Seroquel 150 mg film-coated tablets
Seroquel 200 mg film-coated tablets
Seroquel 300 mg film-coated tablets
Seroquel 3-Day Starterpack (Combined pack)
Seroquel 4-Day Starterpack

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Seroquel 25 mg contains 25 mg quetiapine (as quetiapine fumarate)
Seroquel 100 mg contains 100 mg quetiapine (as quetiapine fumarate)
Seroquel 150 mg contains 150 mg quetiapine (as quetiapine fumarate)
Seroquel 200 mg contains 200 mg quetiapine (as quetiapine fumarate)
Seroquel 300 mg contains 300 mg quetiapine (as quetiapine fumarate)
Seroquel 3-Day Starterpack (Combined pack) contains 6 tablets Seroquel 25 mg and 2 tablets Seroquel 100 mg
Seroquel 4-Day Starterpack contains 6 tablets Seroquel 25 mg, 3 tablets Seroquel 100 mg and 1 tablet Seroquel 200 mg

Excipients with known effect:

Seroquel 25 mg contains 18 mg lactose (anhydrous) per tablet
Seroquel 100 mg contains 20 mg lactose (anhydrous) per tablet
Seroquel 150 mg contains 29 mg lactose (anhydrous) per tablet
Seroquel 200 mg contains 39 mg lactose (anhydrous) per tablet
Seroquel 300 mg contains 59 mg lactose (anhydrous) per tablet
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Seroquel 25 mg tablets are peach coloured, round biconvex and engraved with SEROQUEL 25 on one side
Seroquel 100 mg tablets are yellow, round biconvex and engraved with SEROQUEL 100 on one side
Seroquel 150 mg tablets are pale yellow, round biconvex and engraved with SEROQUEL 150 on one side
Seroquel 200 mg tablets are white, round biconvex and engraved with SEROQUEL 200 on one side
Seroquel 300 mg tablets are white, capsule-shaped and engraved with SEROQUEL on one side and 300 on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Seroquel is indicated for:

- treatment of schizophrenia.
- treatment of bipolar disorder:
    - For the treatment of moderate to severe manic episodes in bipolar disorder

- For the treatment of major depressive episodes in bipolar disorder

- For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.

4.2 Posology and method of administration

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition.

Seroquel can be administered with or without food.

Adults
For the treatment of schizophrenia
For the treatment of schizophrenia, Seroquel should be administered twice a day. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). From Day 4 onwards, the dose should be titrated to the usual effective dose of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

For the treatment of moderate to severe manic episodes in bipolar disorder
For the treatment of manic episodes associated with bipolar disorder, Seroquel should be administered twice a day. The total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.

The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg/day. The usual effective dose is in the range of 400 to 800 mg/day.

For the treatment of major depressive episodes in bipolar disorder
Seroquel should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

For preventing recurrence in bipolar disorder
For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.

Elderly
As with other antipsychotics, Seroquel should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30-50% in elderly subjects when compared to younger patients.

Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Paediatric population

Seroquel is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

Renal impairment
Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment
Quetiapine is extensively metabolised by the liver. Therefore, Seroquel should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25-50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

As Seroquel has several indications, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

Paediatric population
Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with quetiapine have shown that in addition to the known safety profile identified in adults (see section 4.8), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment with quetiapine on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania, and bipolar depression (see section 4.8).

Suicide/suicidal thoughts or clinical worsening
Depression in bipolar disorder is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive

episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).

Metabolic risk

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patients' metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also section 4.8).

Extrapyramidal symptoms

In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see section 4.8 and 5.1).

The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Tardive dyskinesia

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8).

Somnolence and dizziness

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8). In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Orthostatic hypotension

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see section 4.8) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.

Sleep apnoea syndrome
Sleep apnoea syndrome has been reported in patients using quetiapine. In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnoea, such as those who are overweight/obese or are male, quetiapine should be used with caution.

Seizures
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8).

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Severe neutropenia and agranulocytosis
Severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) has been reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9$/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5×10^9/L) (see section 5.1).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g. fever, weakness, lethargy, or sore throat) at any time during Seroquel therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

Anti-cholinergic (muscarinic) effects
Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anti-cholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see section 4.5, 4.8, 5.1 and 4.9).

Interactions
See section 4.5.
Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic

enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

Weight
Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilized antipsychotic guidelines (see sections 4.8 and 5.1).

Hyperglycaemia
Hyperglycaemia and/ or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid changes should be managed as clinically appropriate.

QT prolongation
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. In post-marketing, QT prolongation was reported with quetiapine at the therapeutic doses (see section 4.8) and in overdose (see section 4.9). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see section 4.5).

Cardiomyopathy and myocarditis
Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, however, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Withdrawal
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see section 4.8).

Elderly patients with dementia-related psychosis
Quetiapine is not approved for the treatment of dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.

In a meta-analysis of atypical antipsychotics, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. In two 10-week placebo-controlled quetiapine studies in the same patient population (n=710); mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the

placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population.

Dysphagia
Dysphagia (see section 4.8) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction
Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see section 4.8). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Venous thromboembolism (VTE)
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Pancreatitis
Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see section 4.4), gallstones, and alcohol consumption.

Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). The data showed an additive effect at week 3.

Lactose
Seroquel tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Misuse and abuse
Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, quetiapine should be used with caution in combination with other centrally acting medicinal products and alcohol.

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see section 4.4).

Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see section 4.4).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antipsychotics risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused an increased clearance of quetiapine with approx. 70%.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine.

The pharmacokinetics of lithium were not altered when co-administered with quetiapine.

In a 6-week, randomised, study of lithium and Seroquel XR versus placebo and Seroquel XR in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group (see section 5.1).

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.

Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

First trimester

The moderate amount of published data from exposed pregnancies (i.e. between 300-1000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

Third trimester
Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding
Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue Seroquel therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
The effects of quetiapine on human fertility have not been assessed. Effects related to elevated prolactin levels were seen in rats, although these are not directly relevant to humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine (≥10%) are somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

The incidences of ADRs associated with quetiapine therapy, are tabulated below (Table 1) according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

Table 1 ADRs associated with quetiapine therapy

The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100, rare (≥1/10,000, <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Blood and lymphatic system disorders	Decreased haemoglobin[22]	Leucopenia[1, 28], decreased neutrophil count, eosinophils increased[27]	Neutropenia[1], Thrombocytopenia, Anaemia, platelet count decreased[13]	Agranulocytosis[26]		
Immune system disorders			Hypersensitivity (including allergic skin reactions)		Anaphylactic reaction[5]	
Endocrine disorders		Hyperprolactinaemia [15], decreases in total T_4 [24], decreases in free T_4 [24], decreases in total T_3 [24], increases in TSH[24]	Decreases in free T_3 [24], Hypothyroidism[21]		Inappropriate antidiuretic hormone secretion	

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Metabolism and nutritional disorders	Elevations in serum triglyceride levels[10,30] Elevations in total cholesterol (predominantly LDL cholesterol)[11,30] Decreases in HDL cholesterol[17,30], Weight gain[8,30]	Increased appetite, blood glucose increased to hyperglycaemic levels[6, 30]	Hyponatraemia[19], Diabetes Mellitus [1,5] Exacerbation of pre-existing diabetes	Metabolic syndrome[29]		
Psychiatric disorders		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour[20]		Somnambulism and related reactions such as sleep talking and sleep related eating disorder		
Nervous system disorders	Dizziness[4, 16], somnolence[2,16], headache, Extrapyramidal symptoms[1, 21]	Dysarthria	Seizure[1], Restless legs syndrome, Tardive dyskinesia[1, 5], Syncope[4,16]			
Cardiac disorders		Tachycardia[4], Palpitations[23]	QT prolongation[1,12, 18] Bradycardia[32]			
Eye disorders		Vision blurred				
Vascular disorders		Orthostatic hypotension[4,16]		Venous thromboembolism [1]		
Respiratory, thoracic and mediastinal disorder		Dyspnoea[23]	Rhinitis			
Gastrointestinal disorders	Dry mouth	Constipation, dyspepsia, vomiting[25]	Dysphagia[7]	Pancreatitis[1], Intestinal obstruction/ Ileus		
Hepato-biliary disorders		Elevations in serum alanine aminotransferase (ALT)[3], Elevations in gamma-GT levels[3]	Elevations in serum aspartate aminotransferase (AST)[3]	Jaundice[5], Hepatitis		
Skin and subcutaneous tissue disorders					Angioedema[5], Stevens-Johnson syndrome[5]	Toxic Epidermal Necrolysis, Erythema Multiforme
Musculoskeletal and connective tissue disorders					Rhabdomyolysis	
Renal and urinary disorders			Urinary retention			

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Pregnancy, puerperium and perinatal conditions						Drug withdrawal syndrome neonatal[31]
Reproductive system and breast disorders			Sexual dysfunction	Priapism, galactorrhoea, breast swelling, menstrual disorder		
General disorders and administration site conditions	Withdrawal (discontinuation) symptoms[1,9]	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome[1], hypothermia		
Investigations				Elevations in blood creatine phosphokinase[14]		

1. See section 4.4.
2. Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
3. Asymptomatic elevations (shift from normal to > 3X ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
4. As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (see section 4.4).
5. Calculation of Frequency for these ADR's have been taken from postmarketing data only.
6. Fasting blood glucose ≥126 mg/dL (≥7.0 mmol/L) or a non-fasting blood glucose ≥200 mg/dL (≥11.1 mmol/L) on at least one occasion.
7. An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
8. Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
9. The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
10. Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion.
11. Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).
12. See text below
13. Platelets ≤100 x 10^9/L on at least one occasion
14. Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome
15. Prolactin levels (patients >18 years of age): >20 μg/L (>869.56 pmol/L) males; >30 μg/L (>1304.34 pmol/L) females at any time
16. May lead to falls
17. HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
18. Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
19. Shift from >132 mmol/L to ≤132 mmol/L on at least one occasion.
20. Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see section 4.4 and 5.1).

21. See section 5.1
22. Decreased haemoglobin to ≤13 g/dL (8.07 mmol/L) males, ≤12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in hemoglobin at any time was -1.50 g/dL.
23. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
24. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.8 x LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.
25. Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
26. Based on shift in neutrophils from >=1.5 x 10^9/L at baseline to <0.5 x 10^9/L at any time during treatment and based on patients with severe neutropenia (<0.5 x 10^9/L) and infection during all quetiapine clinical trials (see section 4.4).
27. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as >1x 10^9 cells/L at any time.
28. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as ≤3 x 10^9 cells/L at any time.
29. Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.
30. In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (see section 4.4).
31. See section 4.6.
32. May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects.

Paediatric population

The same ADRs described above for adults should be considered for children and adolescents. The following table summarises ADRs that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

Table 2 ADRs in children and adolescents associated with quetiapine therapy that occur in a higher frequency than adults, or not identified in the adult population

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

SOC	Very Common	Common
Endocrine disorders	Elevations in prolactin[1]	
Metabolism and nutritional disorders	Increased appetite	
Nervous system disorders	Extrapyramidal symptoms[3, 4]	Syncope
Vascular disorders	Increases in blood pressure[2]	
Respiratory, thoracic and mediastinal disorders		Rhinitis
Gastrointestinal disorders	Vomiting	
General disorders and administration site conditions		Irritability[3]

1. Prolactin levels (patients <18 years of age): >20 µg/L (>869.56 pmol/L) males; >26 µg/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 µg/L.
2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.
3. Note: The frequency is consistent to that observed in adults, but might be associated with different clinical implications in children and adolescents as compared to adults.
4 See section 5.1.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects, i.e. drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects. Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see section 4.4, Orthostatic hypotension).

Management of overdose
There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

Based on public literature, patients with delerium and agitation and a clear anti-cholinergic syndrome may be treated with physostigmine, 1-2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

Close medical supervision and monitoring should be continued until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics, ATC code: N05A H04

Mechanism of action

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antispychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic) effects. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to Seroquel's therapeutic efficacy as an antidepressant.

Pharmacodynamic effects

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2-receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration (see section 4.8).

Clinical efficacy

Schizophrenia

In three placebo-controlled clinical trials, in patients with schizophrenia, using variable doses of quetiapine, there were no differences between the Seroquel and placebo treatment groups in the incidence of EPS or concomitant use of anti-cholinergics. A placebo-controlled trial evaluating fixed doses of quetiapine across the range of 75 to 750 mg/day showed no evidence of an increase in EPS or the use of concomitant anti-cholinergics. The long-term efficacy of Seroquel IR in prevention of schizophrenic relapses has not been verified in blinded clinical trials. In open label trials, in patients with schizophrenia, quetiapine was effective in maintaining the clinical improvement during continuation therapy in patients who showed an initial treatment response, suggesting some long-term efficacy.

Bipolar disorder

In four placebo-controlled clinical trials, evaluating doses of Seroquel up to 800 mg/day for the treatment of moderate to severe manic episodes, two each in monotherapy and as combination therapy to lithium or divalproex, there were no differences between the Seroquel and placebo treatment groups in the incidence of EPS or concomitant use of anti-cholinergics.

In the treatment of moderate to severe manic episodes, Seroquel demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. There are no data from long-term studies to demonstrate Seroquel's effectiveness in preventing subsequent manic or depressive episodes. Seroquel data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.

The mean last week median dose of Seroquel in responders was approximately 600 mg/day and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.

In 4 clinical trials with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, Seroquel IR 300 mg and 600 mg was significantly superior to placebo treated patients for the relevant outcome measures: mean improvement on the MADRS and for response defined as at least a 50% improvement in MADRS total score from baseline. There was no difference in

magnitude of effect between the patients who received 300 mg Seroquel IR and those who received 600 mg dose.

In the continuation phase in two of these studies, it was demonstrated that long-term treatment, of patients who responded on Seroquel IR 300 or 600 mg, was efficacious compared to placebo treatment with respect to depressive symptoms, but not with regard to manic symptoms.

In two recurrence prevention studies evaluating Seroquel in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with Seroquel was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Seroquel was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In a 6-week, randomised, study of lithium and Seroquel XR versus placebo and Seroquel XR in adult patients with acute mania, the difference in YMRS mean improvement between the lithium add-on group and the placebo add-on group was 2.8 points and the difference in % responders (defined as 50% improvement from baseline on the YMRS) was 11% (79% in the lithium add-on group vs. 68% in the placebo add-on group).

In one long-term study (up to 2 years treatment) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event.

Clinical trials have demonstrated that Seroquel is effective in schizophrenia and mania when given twice a day, although quetiapine has a pharmacokinetic half-life of approximately 7 hours. This is further supported by the data from a positron emission tomography (PET) study, which identified that for quetiapine, $5HT_2$- and D_2-receptor occupancy are maintained for up to 12 hours. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

Clinical safety

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for Seroquel XR and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for Seroquel XR and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (e.g, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

In short-term, fixed-dose (50mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg for the placebo treated patients. The percentage of quetiapine treated patients who gained ≥7% of body weight ranged from 5.3% for the 50 mg daily dose to 15.5% for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7% for placebo treated patients.

A 6-week, randomised, study of lithium and Seroquel XR versus placebo and Seroquel XR in adult patients with acute mania indicated that the combination of Seroquel XR with lithium leads to more adverse events (63% versus 48% in Seroquel XR in combination with placebo). The safety results showed a higher incidence of extrapyramidal symptoms reported in 16.8% of patients in the lithium add-on group and 6.6% in the placebo add-on group, the majority of which consisted of tremor, reported in 15.6% of the patients in the lithium add-on group and 4.9% in the placebo add-on group. The incidence of somnolence was higher in the Seroquel XR with lithium add-on group (12.7%) compared to the Seroquel XR with the placebo add-on group (5.5%). In addition, a higher percentage of patients treated in the lithium add-on group (8.0%) had weight gain (≥7%) at the end of treatment compared to patients in the placebo add-on group (4.7%).

Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomized to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomized period the mean weight gain was 0.89 kg, compared to open label baseline.

In placebo-controlled studies in elderly patients with dementia-related psychosis, the incidence of cerebrovascular adverse events per 100 patient years was not higher in quetiapine-treated patients than in placebo-treated patients.

In all short-term placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥1.5 x 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 x 10^9/L, was 1.9% in patients treated with quetiapine compared to 1.5% in placebo-treated patients. The incidence of shifts to >0.5-<1.0 x 10^9/L was the same (0.2%) in patients treated with quetiapine as with placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count ≥1.5 x 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 x 10^9/L was 2.9% and to <0.5 x 10^9/L was 0.21% in patients treated with quetiapine.

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. The incidences of shifts in TSH was 3.2 % for quetiapine versus 2.7 % for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T3 or T4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were not associated with clinically symptomatic hypothyroidism.
The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment.

Cataracts/lens opacities
In a clinical trial to evaluate the cataractogenic potential of Seroquel (200-800 mg/day) versus risperidone (2-8 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in Seroquel (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.

Paediatric population

Clinical efficacy
The efficacy and safety of Seroquel was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n=222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Seroquel were excluded. Treatment with Seroquel was initiated at 50 mg/day and on day 2 increased to

100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was –5.21 for Seroquel 400 mg/day and –6.56 for Seroquel 600 mg/day. Responder rates (YMRS improvement ≥50%) were 64% for Seroquel 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was –8.16 for Seroquel 400 mg/day and –9.29 for Seroquel 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as ≥30% reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

In a third short-term placebo-controlled monotherapy trial with Seroquel XR in children and adolescent patients (10-17 years of age) with bipolar depression, efficacy was not demonstrated.

No data are available on maintenance of effect or recurrence prevention in this age group.

Clinical safety
In the short-term paediatric trials with quetiapine described above, the rates of EPS in the active arm vs. placebo were 12.9% vs. 5.3% in the schizophrenia trial, 3.6% vs. 1.1% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. The rates of weight gain ≥7% of baseline body weight in the active arm vs. placebo were 17% vs. 2.5% in the schizophrenia and bipolar mania trials, and 13.7% vs. 6.8% in the bipolar depression trial. The rates of suicide related events in the active arm vs. placebo were 1.4% vs. 1.3% in the schizophrenia trial, 1.0% vs. 0% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. During an extended posttreatment follow-up phase of the bipolar depression trial, there were two additional suicide related events in two patients; one of these patients was on quetiapine at the time of the event.

Long-term safety
A 26-week open-label extension to the acute trials (n=380 patients), with Seroquel flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see section 4.4 and 4.8). With respect to weight gain, when adjusting for normal growth over the longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

5.2 Pharmacokinetic properties

Absorption
Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range.

Distribution
Quetiapine is approximately 83% bound to plasma proteins.

Biotransformation
Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. *In vitro* investigations established that CYP3A4 is the primary enzyme responsible for

cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination
The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations

Gender
The kinetics of quetiapine do not differ between men and women.

Elderly
The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

Renal impairment
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m^2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment
The mean quetiapine plasma clearance decreases with approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2).

Paediatric population
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though C_{max} in children was at the higher end of the range observed in adults. The AUC and C_{max} for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

5.3 Preclinical safety data

There was no evidence of genotoxicity in a series of *in vitro* and *in vivo* genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy**,** a lowering in plasma T_3 levels, decreased haemoglobin concentration and a

decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts. (For cataracts/lens opacities see section 5.1.)

In an embryofetal toxicity study in rabbits the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown.

In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Povidone
Calcium Hydrogen Phosphate Dihydrate
Microcrystalline Cellulose
Sodium Starch Glycolate Type A
Lactose Monohydrate
Magnesium Stearate

Coating
Hypromellose 2910
Macrogol 400
Titanium Dioxide (E171)
Ferric Oxide, Yellow (E172) (25 mg, 100 mg and 150 mg tablets)
Ferric Oxide, Red (E172) (25 mg tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

PVC/aluminium blisters

Pack sizes

Blisters:

Tablet Strength	***Carton (pack) contents***	***Blisters***
25 mg tablets	*6 tablets*	*1 blister of 6 tablets*

Tablet Strength	*Carton (pack) contents*	*Blisters*
	20 tablets	*2 blisters of 10 tablets*
	30 tablets	*3 blisters of 10 tablets*
	50 tablets	*10 blisters of 5 tablets*
	50 tablets	*5 blisters of 10 tablets*
	60 tablets	*6 blisters of 10 tablets*
		12 blisters of 5 tablets
	100 tablets	*10 blisters of 10 tablets*
100 mg, 150 mg, 200 mg and 300 mg tablets	*10 tablets*	*1 blister of 10 tablets*
	20 tablets	*2 blisters of 10 tablets*
	30 tablets	*3 blisters of 10 tablets*
	50 tablets	*10 blisters of 5 tablets*
	50 tablets	*5 blisters of 10 tablets*
	60 tablets	*6 blisters of 10 tablets*
	90 tablets	*9 blisters of 10 tablets*
	100 tablets	*10 blisters of 10 tablets*
	120 tablets	*12 blisters of 10 tablets (150 mg and 300 mg tablets only)*
	180 tablets	*18 blisters of 10 tablets (150 mg and 300 mg tablets only)*
	240 tablets	*24 blisters of 10 tablets (150 mg and 300 mg tablets only)*
3-Day Starterpack (Combined pack)	*8 tablets*	*1 blister containing 6 x 25 mg and 2 x 100 mg tablets*
4-Day Starterpack	*10 tablets*	*1 blister containing 6 x 25mg, 3 x 100mg and 1 x 200mg tablets*

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 April 1998
Date of latest renewal: 23 November 2015

10. DATE OF REVISION OF THE TEXT

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 25 mg film-coated tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 25 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

6 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Seroquel 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 25 mg film-coated tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 100 mg (or 150 mg, or 200 mg or 300 mg) film-coated tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg (or 150 mg, or 200 mg or 300 mg) quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
90 film-coated tablets
100 film-coated tablets
120 film-coated tablets (150 mg and 300 mg tablets only)
180 film-coated tablets (150 mg and 300 mg tablets only)
240 film-coated tablets (150 mg and 300 mg tablets only)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Seroquel 100 mg (or 150 mg, or 200 mg or 300 mg)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 100 mg (or 150 mg, or 200 mg or 300 mg) film-coated tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 3-Day starter pack

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 25 mg and 100 mg film-coated tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 25 mg quetiapine (as fumarate)
Each tablet contains 100 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

8 film-coated tablets

Combined pack

This pack contains:
6 x 25 mg film-coated tablets
2 x 100 mg film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Seroquel 25 mg and 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL 3-Day starter pack

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 25 mg and 100 mg tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. OTHER

Day 1
Day 2
Day 3
morning
evening
25 mg
2x25 mg
100 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 4-Day starter pack

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 25 mg, 100 mg and 200 mg film-coated tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 25 mg quetiapine (as fumarate)
Each tablet contains 100 mg quetiapine (as fumarate)
Each tablet contains 200 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

Combined pack

This pack contains:
6 x 25 mg film-coated tablets
3 x 100 mg film-coated tablets
1 x 200 mg film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Seroquel 25 mg, 100 mg and 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL 4-Day starter pack

1. NAME OF THE MEDICINAL PRODUCT

Seroquel 25 mg, 100 mg and 200 mg tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. OTHER

Day 1
Day 2
Day 3
Day 4
morning
evening
25 mg
2x25 mg
100 mg
200 mg

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Seroquel 25 mg, 100 mg, 150 mg, 200 mg, 300 mg film-coated tablets
Seroquel 3-Day Starterpack (Combined pack)
Seroquel 4-Day Starterpack

quetiapine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Seroquel is and what it is used for

Seroquel contains a substance called quetiapine. This belongs to a group of medicines called anti-psychotics. Seroquel can be used to treat several illnesses, such as:

- Bipolar depression: where you feel sad. You may find that you feel depressed, feel guilty, lack energy, lose your appetite or can't sleep.
- Mania: where you may feel very excited, elated, agitated, enthusiastic or hyperactive or have poor judgment including being aggressive or disruptive.
- Schizophrenia: where you may hear or feel things that are not there, believe things that are not true or feel unusually suspicious, anxious, confused, guilty, tense or depressed.

Your doctor may continue to prescribe Seroquel even when you are feeling better.

2. What you need to know before you take Seroquel

Do not take Seroquel:
- if you are allergic to quetiapine or any of the other ingredients of this medicine (listed in section 6).

- if you are taking any of the following medicines:
    - Some medicines for HIV
    - Azole medicines (for fungal infections)
    - Erythromycin or clarithromycin (for infections)
    - Nefazodone (for depression).

If you are not sure, talk to your doctor or pharmacist before taking Seroquel.

Warnings and Precautions

Talk to your doctor or pharmacist before taking Seroquel:

- if you, or someone in your family, have or have had any heart problems, for example heart rhythm problems, weakening of the heart muscle or inflammation of the heart or if you are taking any medicines that may have an impact on the way your heart beats.
- if you have low blood pressure.
- if you have had a stroke, especially if you are elderly.
- if you have problems with your liver.
- if you have ever had a fit (seizure).
- if you have diabetes or have a risk of getting diabetes. If you do, your doctor may check your blood sugar levels while you are taking Seroquel.
- if you know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines).
- if you are an elderly person with dementia (loss of brain function). If you are, Seroquel should not be taken because the group of medicines that Seroquel belongs to may increase the risk of stroke, or in some cases the risk of death, in elderly people with dementia.
- if you or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.
- if you have or have had a condition where you stop breathing for short periods during your normal nightly sleep (called "sleep apnoea") and are taking medicines that slow down the normal activity of the brain ("depressants").
- if you have or have had a condition where you can't completely empty your bladder (urinary retention), have an enlarged prostate, a blockage in your intestines, or increased pressure inside your eye. These conditions are sometimes caused by medicines (called "anti-cholinergics") that affect the way nerve cells function in order to treat certain medical conditions.
- if you have a history of alcohol or drug abuse.

Tell your doctor immediately if you experience any of the following after taking Seroquel:

- A combination of fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called "neuroleptic malignant syndrome"). Immediate medical treatment may be needed.
- Uncontrollable movements, mainly of your face or tongue.
- Dizziness or a severe sense of feeling sleepy. This could increase the risk of accidental injury (fall) in elderly patients.
- Fits (seizures).
- A long-lasting and painful erection (Priapism).

These conditions can be caused by this type of medicine.

Tell your doctor as soon as possible if you have:

- A fever, flu-like symptoms, sore throat, or any other infection, as this could be a result of a very low white blood cell count, which may require Seroquel to be stopped and/or treatment to be given.
- Constipation along with persistent abdominal pain, or constipation which has not responded to treatment, as this may lead to a more serious blockage of the bowel.
- **Thoughts of suicide and worsening of your depression**
  If you are depressed you may sometimes have thoughts of harming or killing yourself. These may be increased when first starting treatment, since these medicines all take time to work, usually about two weeks but sometimes longer. These thoughts may also be increased if you suddenly stop taking your medication. You may be more likely to think like this if you are a young adult. Information from clinical trials has shown an increased risk of suicidal thoughts and/or suicidal behaviour in young adults aged less than 25 years with depression.

  If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Weight gain
Weight gain has been seen in patients taking Seroquel. You and your doctor should check your weight regularly.

Children and adolescents
Seroquel is not for use in children and adolescents below 18 years of age.

Other medicines and Seroquel
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Do not take Seroquel if you are taking any of the following medicines:
- Some medicines for HIV.
- Azole medicines (for fungal infections).
- Erythromycin or clarithromycin (for infections).
- Nefazodone (for depression).

Tell your doctor if you are taking any of the following medicines:
- Epilepsy medicines (like phenytoin or carbamazepine).
- High blood pressure medicines.
- Barbiturates (for difficulty sleeping).
- Thioridazine or Lithium (other anti-psychotic medicines).
- Medicines that have an impact on the way your heart beats, for example, drugs that can cause an imbalance in electrolytes (low levels of potassium or magnesium) such as diuretics (water pills) or certain antibiotics (drugs to treat infections).
- Medicines that can cause constipation.
- Medicines (called “anti-cholinergics”) that affect the way nerve cells function in order to treat certain medical conditions.

Before you stop taking any of your medicines, please talk to your doctor first.

Seroquel with food, drink and alcohol
- Seroquel can be taken with or without food.
- Be careful how much alcohol you drink. This is because the combined effect of Seroquel and alcohol can make you sleepy.
- Do not drink grapefruit juice while you are taking Seroquel. It can affect the way the medicine works.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby ask your doctor for advice before taking this medicine. You should not take Seroquel during pregnancy unless this has been discussed with your doctor. Seroquel should not be taken if you are breast-feeding.

The following symptoms which can represent withdrawal may occur in newborn babies of mothers that have used Seroquel in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Driving and using machines
Your tablets may make you feel sleepy. Do not drive or use any tools or machines until you know how the tablets affect you.

Seroquel contains lactose
Seroquel contains lactose which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Effect on Urine Drug Screens
If you are having a urine drug screen, taking Seroquel may cause positive results for methadone or certain drugs for depression called tricyclic antidepressants (TCAs) when some test methods are used, even though you may not be taking methadone or TCAs. If this happens, a more specific test can be performed.

3. How to take Seroquel

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will decide on your starting dose. The maintenance dose (daily dose) will depend on your illness and needs but will usually be between 150 mg and 800 mg.

- You will take your tablets once a day, at bedtime or twice a day, depending on your illness.
- Swallow your tablets whole with a drink of water.
- You can take your tablets with or without food.
- Do not drink grapefruit juice while you are taking Seroquel. It can affect the way the medicine works.
- Do not stop taking your tablets even if you feel better, unless your doctor tells you.

Liver problems
If you have liver problems your doctor may change your dose.

Elderly people
If you are elderly your doctor may change your dose.

Use in children and adolescents
Seroquel should not be used by children and adolescents aged under 18 years.

If you take more Seroquel than you should
If you take more Seroquel than prescribed by your doctor, you may feel sleepy, feel dizzy and experience abnormal heart beats. Contact your doctor or nearest hospital straight away. Keep the Seroquel tablets with you.

If you forget to take Seroquel
If you forget to take a dose, take it as soon as you remember. If it is almost time to take the next dose, wait until then. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Seroquel
If you suddenly stop taking Seroquel, you may be unable to sleep (insomnia), or you may feel sick (nausea), or you may experience headache, diarrhoea, being sick (vomiting), dizziness or irritability. Your doctor may suggest you reduce the dose gradually before stopping treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common: may affect more than 1 in 10 people
- Dizziness (may lead to falls), headache, dry mouth.
- Feeling sleepy (this may go away with time, as you keep taking Seroquel) (may lead to falls).

- Discontinuation symptoms (symptoms which occur when you stop taking Seroquel) include not being able to sleep (insomnia), feeling sick (nausea), headache, diarrhoea, being sick (vomiting), dizziness, and irritability. Gradual withdrawal over a period of at least 1 to 2 weeks is advisable.
- Putting on weight.
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Changes in the amount of certain fats (triglycerides and total cholesterol).

Common: may affect up to 1 in 10 people
- Rapid heartbeat.
- Feeling like your heart is pounding, racing or has skipped beats.
- Constipation, upset stomach (indigestion).
- Feeling weak.
- Swelling of arms or legs.
- Low blood pressure when standing up. This may make you feel dizzy or faint (may lead to falls).
- Increased levels of sugar in the blood.
- Blurred vision.
- Abnormal dreams and nightmares.
- Feeling more hungry.
- Feeling irritated.
- Disturbance in speech and language.
- Thoughts of suicide and worsening of your depression.
- Shortness of breath.
- Vomiting (mainly in the elderly).
- Fever.
- Changes in the amount of thyroid hormones in your blood.
- Decreases in the number of certain types of blood cells.
- Increases in the amount of liver enzymes measured in the blood.
- Increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
    - Men and women to have swelling of breasts and unexpectedly produce breast milk.
    - Women to have no monthly period or irregular periods.

Uncommon: may affect up to 1 in 100 people
- Fits or seizures.
- Allergic reactions that may include raised lumps (weals), swelling of the skin and swelling around the mouth.
- Unpleasant sensations in the legs (also called restless legs syndrome).
- Difficulty swallowing.
- Uncontrollable movements, mainly of your face or tongue.
- Sexual dysfunction.
- Diabetes.
- Change in electrical activity of the heart seen on ECG (QT prolongation).
- A slower than normal heart rate which may occur when starting treatment and which may be associated with low blood pressure and fainting.
- Difficulty in passing urine.
- Fainting (may lead to falls).
- Stuffy nose.
- Decrease in the amount of red blood cells.
- Decrease in the amount of sodium in the blood.
- Worsening of pre-existing diabetes.

Rare: may affect up to 1 in 1,000 people
- A combination of high temperature (fever), sweating, stiff muscles, feeling very drowsy or faint (a disorder called “neuroleptic malignant syndrome”).

- Yellowing of the skin and eyes (jaundice).
- Inflammation of the liver (hepatitis).
- A long-lasting and painful erection (priapism).
- Swelling of breasts and unexpected production of breast milk (galactorrhoea).
- Menstrual disorder.
- Blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.
- Walking, talking, eating or other activities while you are asleep.
- Body temperature decreased (hypothermia).
- Inflammation of the pancreas.
- A condition (called "metabolic syndrome") where you may have a combination of 3 or more of the following: an increase in fat around your abdomen, a decrease in "good cholesterol" (HDL-C), an increase in a type of fat in your blood called triglycerides, high blood pressure and an increase in your blood sugar.
- Combination of fever, flu-like symptoms, sore throat, or any other infection with very low white blood cell count, a condition called agranulocytosis.
- Bowel obstruction.
- Increased blood creatine phosphokinase (a substance from the muscles).

Very rare: may affect up to 1 in 10,000 people
- Severe rash, blisters, or red patches on the skin.
- A severe allergic reaction (called anaphylaxis) which may cause difficulty in breathing or shock.
- Rapid swelling of the skin, usually around the eyes, lips and throat (angioedema).
- A serious blistering condition of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome).
- Inappropriate secretion of a hormone that controls urine volume.
- Breakdown of muscle fibers and pain in muscles (rhabdomyolysis).

Not known: frequency cannot be estimated from the available data
- Skin rash with irregular red spots (erythema multiforme).
- Serious, sudden allergic reaction with symptoms such as fever and blisters on the skin and peeling of the skin (toxic epidermal necrolysis).
- Symptoms of withdrawal may occur in newborn babies of mothers that have used Seroquel during their pregnancy.

The class of medicines to which Seroquel belongs can cause heart rhythm problems, which can be serious and in severe cases may be fatal.

Some side effects are only seen when a blood test is taken. These include changes in the amount of certain fats (triglycerides and total cholesterol) or sugar in the blood, changes in the amount of thyroid hormones in your blood, increased liver enzymes, decreases in the number of certain types of blood cells, decrease in the amount of red blood cells, increased blood creatine phosphokinase (a substance in the muscles), decrease in the amount of sodium in the blood and increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
- Men and women to have swelling of breasts and unexpectedly produce breast milk.
- Women to have no monthly period or irregular periods.

Your doctor may ask you to have blood tests from time to time.

Additional side effects in children and adolescents
The same side effects that may occur in adults may also occur in children and adolescents.

The following side effects have been seen more often in children and adolescents or have not been seen in adults:

Very common: may affect more than 1 in 10 people

- Increase in the amount of a hormone called prolactin, in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
    - Boys and girls to have swelling of breasts and unexpectedly produce breast milk.
    - Girls to have no monthly period or irregular periods.
- Increased appetite.
- Vomiting.
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Increase in blood pressure.

Common: may affect up to 1 in 10 people
- Feeling weak, fainting (may lead to falls).
- Stuffy nose.
- Feeling irritated.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Seroquel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Seroquel contains

- The active substance is quetiapine. Seroquel tablets contain 25 mg, 100 mg, 150 mg, 200 mg or 300mg of quetiapine (as quetiapine fumarate).

- The other ingredients are:
  Tablet core: povidone, calcium hydrogen phosphate dihydrate, microcrystalline cellulose, sodium starch glycollate Type A, lactose monohydrate, magnesium stearate
  Tablet coating: hypromellose, macrogol, titanium dioxide (E171). The 25 mg, 100 mg and 150 mg tablet also contain iron oxide yellow (E172) and the 25 mg contain iron oxide red (E172).

What Seroquel looks like and contents of the pack

Seroquel 25 mg film-coated tablets are peach coloured, round biconvex and engraved with SEROQUEL 25 on one side
Seroquel 100 mg film-coated tablets are yellow, round biconvex and engraved with SEROQUEL 100 on one side
Seroquel 150 mg film-coated tablets are pale yellow, round biconvex and engraved with SEROQUEL 150 on one side

Seroquel 200 mg film-coated tablets are white, round biconvex and engraved with SEROQUEL 200 on one side
Seroquel 300 mg film-coated tablets are white, capsule-shaped and engraved with SEROQUEL on one side and 300 on the other side

Pack sizes of 20, 30, 50, 60 and 100 tablets are registered for all strengths. In addition, for 25 mg tablets pack size of 6 tablets is registered. For 100 mg, 150 mg, 200 mg and 300 mg tablets pack sizes of 10, 90 are registered. For 150 mg and 300 mg tablets pack sizes of 120, 180 and 240 tablets are registered. For 3-Day Starterpack pack size of 8 tablets is registered and for 4-Day Starterpack pack size of 10 tablets is registered. Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

COUNTRY	TRADE NAME
Austria	Seroquel
Belgium	Seroquel
Croatia	Seroquel
Cyprus	Seroquel
Denmark	Seroquel
Estonia	Seroquel
Finland	Seroquel
Germany	Seroquel® 25 mg Filmtabletten, Seroquel® 100 mg Filmtabletten, Seroquel® 200 mg Filmtabletten, Seroquel® 300 mg Filmtabletten
Greece	Seroquel
Iceland	Seroquel
Ireland	Seroquel
Italy	Seroquel
Latvia	Seroquel
Lithuania	Seroquel
Luxembourg	Seroquel
Malta	Seroquel
Netherlands	Seroquel
Norway	Seroquel
Portugal	Seroquel
Romania	Seroquel
Slovenia	Seroquel
Spain	Seroquel
Sweden	Seroquel
United Kingdom	Seroquel

This leaflet was last revised in {MM/YYYY}.

<[To be completed nationally]>

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 50 mg prolonged-release tablets
Seroquel XR 150 mg prolonged-release tablets
Seroquel XR 200 mg prolonged-release tablets
Seroquel XR 300 mg prolonged-release tablets
Seroquel XR 400 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Seroquel XR 50 mg contains 50 mg quetiapine (as quetiapine fumarate)
Seroquel XR 150 mg contains 150 mg quetiapine (as quetiapine fumarate)
Seroquel XR 200 mg contains 200 mg quetiapine (as quetiapine fumarate)
Seroquel XR 300 mg contains 300 mg quetiapine (as quetiapine fumarate)
Seroquel XR 400 mg contains 400 mg quetiapine (as quetiapine fumarate)

Excipients with known effect:

Seroquel XR 50 mg contains 119 mg lactose (anhydrous) per tablet
Seroquel XR 150 mg contains 71 mg lactose (anhydrous) per tablet
Seroquel XR 200 mg contains 50 mg lactose (anhydrous) per tablet
Seroquel XR 300 mg contains 47 mg lactose (anhydrous) per tablet
Seroquel XR 400 mg contains 15 mg lactose (anhydrous) per tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet
Seroquel XR 50 mg tablets are peach-coloured and engraved with “XR 50” on one side
Seroquel XR 150 mg tablets are white and engraved with “XR 150” on one side
Seroquel XR 200 mg tablets are yellow and engraved with “XR 200” on one side
Seroquel XR 300 mg tablets are pale yellow and engraved with “XR 300” on one side
Seroquel XR 400 mg tablets are white and engraved with “XR 400” on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Seroquel XR is indicated for:

- treatment of schizophrenia

- treatment of bipolar disorder:
  - For the treatment of moderate to severe manic episodes in bipolar disorder
  - For the treatment of major depressive episodes in bipolar disorder
  - For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.

- add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy (see section 5.1). Prior to initiating treatment, clinicians should consider the safety profile of Seroquel XR (see section 4.4).

4.2 Posology and method of administration

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition.

Seroquel XR should be administered once daily, without food. The tablets should be swallowed whole and not split, chewed or crushed.

Adults
For the treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder
Seroquel XR should be administrated at least one hour before a meal. The daily dose at the start of therapy is 300 mg on Day 1 and 600 mg on Day 2. The recommended daily dose is 600 mg, however if clinically justified the dose may be increased to 800 mg daily. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

For the treatment of major depressive episodes in bipolar disorder
Seroquel XR should be administered at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

For preventing recurrence in bipolar disorder
For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Seroquel XR for acute treatment of bipolar disorder should continue on Seroquel XR at the same dose administered at bedtime. Seroquel XR dose can be adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day. It is important that the lowest effective dose is used for maintenance therapy.

For add-on treatment of major depressive episodes in MDD
Seroquel XR should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine - see section 5.1) and at 50 mg/day in short-term monotherapy trials. There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.

Switching from Seroquel immediate-release tablets
For more convenient dosing, patients who are currently being treated with divided doses of immediate release Seroquel tablets may be switched to Seroquel XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Elderly
As with other antipsychotics and antidepressants, Seroquel XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of Seroquel XR may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients. Elderly patients should be started on 50 mg/day. The dose can be increased in

increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. The lowest effective dose, starting from 50 mg/day should be used. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment.

Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Paediatric population
Seroquel XR is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in section 4.4, 4.8, 5.1 and 5.2.

Renal impairment
Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment
Quetiapine is extensively metabolized by the liver. Therefore, Seroquel XR should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

As Seroquel XR has several indications, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see section 5.1).

Paediatric population
Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with quetiapine have shown that in addition to the known safety profile identified in adults (see section 4.8), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment with quetiapine on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania, and bipolar depression (see section 4.8).

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adults patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo.

Metabolic risk
Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see section 4.8).

Extrapyramidal symptoms
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder and major depressive disorder (see section 4.8 and 5.1).

The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Tardive dyskinesia
If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8).

Somnolence and dizziness
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8). In clinical trials for treatment of patients with bipolar depression and major depressive disorder, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Orthostatic hypotension
Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see section 4.8) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.

Sleep apnoea syndrome
Sleep apnoea syndrome has been reported in patients using quetiapine. In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnoea, such as those who are overweight/obese or are male, quetiapine should be used with caution.

Seizures
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8).

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Severe neutropenia and agranulocytosis
Severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) has been reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times$

10^9/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 x 10^9/L) (see section 5.1).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g. fever, weakness, lethargy, or sore throat) at any time during Seroquel therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

Anti-cholinergic (muscarinic) effects
Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anti-cholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see section 4.5, 4.8, 5.1, and 4.9).

Interactions
See section 4.5.
Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

Weight
Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilized antipsychotic guidelines (see section 4.8 and 5.1).

Hyperglycaemia
Hyperglycaemia and/ or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid changes should be managed as clinically appropriate.

QT prolongation
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. In post marketing, QT prolongation was reported with quetiapine at the therapeutic doses (see section 4.8) and in overdose (see section 4.9). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or

family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see section 4.5).

Cardiomyopathy and myocarditis
Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, however, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Withdrawal
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see section 4.8).

Elderly patients with dementia-related psychosis
Quetiapine is not approved for the treatment of dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.

In a meta-analysis of atypical antipsychotics, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. In two 10-week placebo-controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population.

Dysphagia
Dysphagia (see section 4.8) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction
Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see section 4.8). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Venous thromboembolism (VTE)
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Pancreatitis
Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see section 4.4), gallstones, and alcohol consumption.

Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). The data showed an additive effect at week 3.

Lactose
Seroquel XR tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Misuse and abuse
Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, quetiapine should be used with caution in combination with other centrally acting medicinal products and alcohol.

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see section 4.4).

Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5-to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

In a multiple-dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see section 4.4).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antipsychotics risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused an increased clearance of quetiapine with approx. 70%.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine.

The pharmacokinetics of lithium were not altered when co-administered with quetiapine.

In a 6-week, randomised, study of lithium and Seroquel XR versus placebo and Seroquel XR in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor),

somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group (see section 5.1).

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.

Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
First trimester
The moderate amount of published data from exposed pregnancies (i.e. between 300-1000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

Third trimester
Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding
Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue Seroquel XR therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
The effects of quetiapine on human fertility have not been assessed. Effects related to elevated prolactin levels were seen in rats, although these are not directly relevant to humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine (≥10%) are somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

The incidences of ADRs associated with quetiapine therapy, are tabulated below (Table 1) according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

Table 1 ADRs associated with quetiapine therapy

The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100, rare (≥1/10,000, <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Blood and lymphatic system disorders	Decreased haemoglobin[22]	Leucopenia[1, 28], decreased neutrophil count, eosinophils increased[27]	Neutropenia[1] Thrombocyto-penia, Anaemia, platelet count decreased[13]	Agranulocytosis[26]		
Immune system disorders			Hypersensitivity (including allergic skin reactions)		Anaphylactic reaction[5]	
Endocrine disorders		Hyperprolactinaemia [15], decreases in total T_4 [24], decreases in free T_4 [24], decreases in total T_3 [24], increases in TSH[24]	Decreases in free T_3 [24], Hypothyroidism[2 1]		Inappropriate antidiuretic hormone secretion	
Metabolism and nutritional disorders	Elevations in serum triglyceride levels[10,30] Elevations in total cholesterol (predominantly LDL cholesterol)[11,30] Decreases in HDL cholesterol[17,30], Weight gain[8,30],	Increased appetite, blood glucose increased to hyperglycaemic levels[6, 30]	Hyponatraemia[19] Diabetes Mellitus[1,5] Exacerbation of pre-existing diabetes	Metabolic syndrome[29]		
Psychiatric disorders		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour[20]		Somnambulism and related reactions such as sleep talking and sleep related eating disorder		

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Nervous system disorders	Dizziness[4, 16], somnolence[2,16], headache, Extrapyramidal symptoms[1, 21]	Dysarthria	Seizure[1], Restless legs syndrome, Tardive dyskinesia[1, 5], Syncope[4,16]			
Cardiac disorders		Tachycardia[4], Palpitations[23]	QT prolongation[1,12, 18] Bradycardia[32]			
Eye disorders		Vision blurred				
Vascular disorders		Orthostatic hypotension[4,16]		Venous thromboembolism [1]		
Respiratory, thoracic and mediastinal disorder		Dyspnoea[23]	Rhinitis			
Gastrointestinal disorders	Dry mouth	Constipation, dyspepsia, vomiting[25]	Dysphagia[7]	Pancreatitis[1], Intestinal obstruction/ Ileus		
Hepato-biliary disorders		Elevations in serum alanine aminotransferase (ALT)[3], Elevations in gamma-GT levels[3]	Elevations in serum aspartate aminotransferase (AST)[3]	Jaundice[5] Hepatitis		
Skin and subcutaneous tissue disorders					Angioedema[5], Stevens-Johnson syndrome[5]	Toxic Epidermal Necrolysis, Erythema Multiforme
Musculoskeletal and connective tissue disorders					Rhabdomyolysis	
Renal and urinary disorders			Urinary retention			
Pregnancy, puerperium and perinatal conditions						Drug withdrawal syndrome neonatal[31]
Reproductive system and breast disorders			Sexual dysfunction	Priapism, galactorrhoea, breast swelling, menstrual disorder		
General disorders and administration site conditions	Withdrawal (dis continuation) symptoms[1,9]	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome[1], hypothermia		
Investigations				Elevations in blood creatine phosphokinase[14]		

(1) See section 4.4.

(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.

(3) Asymptomatic elevations (shift from normal to >3 x ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
(4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (see section 4.4).
(5) Calculation of Frequency for these ADR's have only been taken from postmarketing data with the immediate release formulation of quetiapine.
(6) Fasting blood glucose ≥126 mg/dL (≥7.0 mmol/L) or a non-fasting blood glucose ≥200 mg/dL (≥11.1 mmol/L) on at least one occasion.
(7) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
(8) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
(9) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
(10) Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion
(11) Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).
(12) See text below
(13) Platelets ≤100 x 10^9/L on at least one occasion
(14) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome
(15) Prolactin levels (patients >18 years of age): >20 µg/L (>869.56 pmol/L) males; >30 µg/L (>1304.34 pmol/L) females at any time.
(16) May lead to falls.
(17) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
(18) Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
(19) Shift from >132 mmol/L to ≤132 mmol/L on at least one occasion.
(20) Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see section 4.4 and 5.1).
(21) See section 5.1
(22) Decreased haemoglobin to ≤13 g/dL (8.07 mmol/L) males, ≤12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in hemoglobin at any time was -1.50 g/dL.
(23) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
(24) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.8 x LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.
(25) Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
(26) Based on shift in neutrophils from >=1.5 x 10^9/L at baseline to <0.5 x 10^9/L at any time during treatment and based on patients with severe neutropenia (<0.5 x 10^9/L) and infection during all quetiapine clinical trials (see section 4.4).
(27) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as >1 x 10^9 cells/L at any time.
(28) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as ≤ 3 x10^9 cells/L at any time.
(29) Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.
(30) In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (see section 4.4).
(31) See section 4.6.

(32) May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects.

Paediatric population

The same ADRs described above for adults should be considered for children and adolescents. The following table summarises ADRs that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

Table 2 ADRs in children and adolescents associated with quetiapine therapy that occur in a higher frequency than adults, or not identified in the adult population

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

SOC	Very Common	Common
Endocrine disorders	Elevations in prolactin[1]	
Metabolism and nutritional disorders	Increased appetite	
Nervous system disorders	Extrapyramidal symptoms[3, 4]	Syncope
Vascular disorders	Increases in blood pressure[2]	
Respiratory, thoracic and mediastinal disorders		Rhinitis
Gastrointestinal disorders	Vomiting	
General disorders and administration site conditions		Irritability[3]

1. Prolactin levels (patients <18 years of age): >20 µg/L (>869.56 pmol/L) males; >26 µg/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 µg/L.
2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.
3. Note: The frequency is consistent to that observed in adults, but might be associated with different clinical implications in children and adolescents as compared to adults.
4. See section 5.1.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects, i.e. drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects. Overdose could lead to QT-prolongation, seizures, status epilepticus,

rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see section 4.4, Orthostatic hypotension).

Management of overdose
There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

Based on public literature, patients with delirium and agitation and a clear anti-cholinergic syndrome may be treated with physostigmine, 1-2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

Close medical supervision and monitoring should be continued until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines
ATC code: N05A H04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antispychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic) effects. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to Seroquel XR's therapeutic efficacy as an antidepressant.

Pharmacodynamic effects
Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2-receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration (see section 4.8).

Clinical efficacy

Schizophrenia

The efficacy of Seroquel XR in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled Seroquel immediate release-to-Seroquel XR switching study in clinically stable outpatients with schizophrenia.

The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. Seroquel XR 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose.

In the 6-week active-controlled switching study the primary outcome variable was the proportion of patients who showed lack of efficacy, i.e. who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit. In patients stabilised on Seroquel immediate release 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of Seroquel XR given once daily.

In a long-term study in stable schizophrenic patients who had been maintained on Seroquel XR for 16 weeks, Seroquel XR was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the Seroquel XR treatment group compared to 68.2% for placebo. The average dose was 669 mg. There were no additional safety findings associated with treatment with Seroquel XR for up to 9 months (median 7 months). In particular, reports of adverse events related to EPS and weight gain did not increase with longer-term treatment with Seroquel XR.

Bipolar disorder

In the treatment of moderate to severe manic episodes, Seroquel demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. The efficacy of Seroquel XR was further demonstrated with significance versus placebo in an additional 3-week study. Seroquel XR was dosed in the range of 400 to 800 mg/day and the mean dose was approximately 600 mg/day. Seroquel data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.

In a clinical trial, in patients with depressive episodes in bipolar I or bipolar II disorder, 300 mg/day Seroquel XR showed superior efficacy to placebo in reduction of MADRS total score.

In 4 additional clinical trials with quetiapine, with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, Seroquel IR 300 mg and 600 mg was significantly superior to placebo treated patients for the relevant outcome measures: mean improvement on the MADRS and for response defined as at least a 50% improvement in MADRS total score from baseline. There was no difference in magnitude of effect between the patients who received 300 mg Seroquel IR and those who received 600 mg dose.

In the continuation phase in two of these studies, it was demonstrated that long-term treatment, of patients who responded on Seroquel IR 300 or 600 mg, was efficacious compared to placebo treatment with respect to depressive symptoms, but not with regard to manic symptoms.

In two recurrence prevention studies evaluating quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In a 6-week, randomised, study of lithium and Seroquel XR versus placebo and Seroquel XR in adult patients with acute mania, the difference in YMRS mean improvement between the lithium add-on group and the placebo add-on group was 2.8 points and the difference in % responders (defined as 50% improvement from baseline on the YMRS) was 11% (79% in the lithium add-on group vs. 68% in the placebo add-on group).

In one long-term study (up to 2 years treatment) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event.

Major depressive episodes in MDD
Two short-term (6-week) studies enrolled patients who had shown an inadequate response to at least one antidepressant. Seroquel XR 150 mg and 300 mg/day, given as add-on treatment to ongoing antidepressant therapy (amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) demonstrated superiority over antidepressant therapy alone in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs. placebo of 2-3.3 points).

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see below).

The following studies were conducted with Seroquel XR as monotherapy treatment, however Seroquel XR is only indicated for use as add-on therapy:

In three out of four short term (up to 8-weeks) monotherapy studies, in patients with major depressive disorder, Seroquel XR 50 mg, 150 mg and 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score (LS mean change vs. placebo of 2-4 points).

In a monotherapy relapse prevention study, patients with depressive episodes stabilised on open-label Seroquel XR treatment for at least 12 weeks were randomised to either Seroquel XR once daily or placebo for up to 52 weeks. The mean dose of Seroquel XR during the randomised phase was 177 mg/day. The incidence of relapse was 14.2% for Seroquel XR treated patients and 34.4% for placebo-treated patients.

In a short-term (9 week) study non-demented elderly patients (aged 66 to 89 years) with major depressive disorder, Seroquel XR dosed flexibly in the range of 50 mg to 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs placebo -7.54). In this study patients randomised to Seroquel

XR received 50 mg/day on Days 1-3, the dose could be increased to 100 mg/day on Day 4, 150 mg/day on Day 8 and up to 300 mg/day depending on clinical response and tolerability. The mean dose of Seroquel XR was 160 mg/day. Other than the incidence of extrapyramidal symptoms (see section 4.8 and 'Clinical safety' below) the tolerability of Seroquel XR once daily in elderly patients was comparable to that seen in adults (aged 18-65 years). The proportion of randomized patients over 75 years of age was 19%.

Clinical safety

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for Seroquel XR and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for Seroquel XR and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (e.g. akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

In short-term, fixed-dose (50mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg for the placebo treated patients. The percentage of quetiapine treated patients who gained ≥7% of body weight ranged from 5.3% for the 50 mg daily dose to 15.5% for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7% for placebo treated patients.

A 6-week, randomised, study of lithium and Seroquel XR versus placebo and Seroquel XR in adult patients with acute mania indicated that the combination of Seroquel XR with lithium leads to more adverse events (63% versus 48% in Seroquel XR in combination with placebo). The safety results showed a higher incidence of extrapyramidal symptoms reported in 16.8% of patients in the lithium add-on group and 6.6% in the placebo add-on group, the majority of which consisted of tremor, reported in 15.6% of the patients in the lithium add-on group and 4.9% in the placebo add-on group. The incidence of somnolence was higher in the Seroquel XR with lithium add-on group (12.7%) compared to the Seroquel XR with the placebo add-on group (5.5%). In addition, a higher percentage of patients treated in the lithium add-on group (8.0%) had weight gain (≥7%) at the end of treatment compared to patients in the placebo add-on group (4.7%).

Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomized to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomized period the mean weight gain was 0.89 kg, compared to open label baseline.

In placebo-controlled studies in elderly patients with dementia-related psychosis, the incidence of cerebrovascular adverse events per 100 patient years was not higher in quetiapine-treated patients than in placebo-treated patients.

In all short-term placebo-controlled monotherapy trials in patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of a shift to neutrophil count $< 1.5 \times 10^9$/L, was 1.9% in patients treated with quetiapine compared to 1.5% in placebo-treated patients. The incidence of shifts to $> 0.5 - < 1.0 \times 10^9$/L was the same (0.2%) in patients treated with quetiapine as with placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of a shift to neutrophil count $< 1.5 \times 10^9$/L was 2.9% and to $< 0.5 \times 10^9$/L was 0.21% in patients treated with quetiapine.

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. The incidences of shifts in TSH was 3.2 % for quetiapine versus 2.7 % for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T3 or T4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment.

Cataracts/lens opacities
In a clinical trial to evaluate the cataractogenic potential of Seroquel (200-800 mg/ day) versus risperidone (2-8 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in Seroquel (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.

Paediatric population

Clinical efficacy
The efficacy and safety of Seroquel was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n=222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Seroquel were excluded. Treatment with Seroquel was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was -5.21 for Seroquel 400 mg/day and -6.56 for Seroquel 600 mg/day. Responder rates (YMRS improvement ≥50%) were 64% for Seroquel 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was -8.16 for Seroquel 400 mg/day and -9.29 for Seroquel 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as ≥30% reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

In a third short-term placebo-controlled monotherapy trial with Seroquel XR in children and adolescent patients (10-17 years of age) with bipolar depression, efficacy was not demonstrated.

No data are available on maintenance of effect or recurrence prevention in this age group.

Clinical safety
In the short-term paediatric trials with quetiapine described above, the rates of EPS in the active arm vs. placebo were 12.9% vs. 5.3% in the schizophrenia trial, 3.6% vs. 1.1% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. The rates of weight gain ≥7% of baseline body weight in the active arm vs. placebo were 17% vs. 2.5% in the schizophrenia and bipolar mania trials, and 13.7% vs. 6.8% in the bipolar depression trial. The rates of suicide related events in the active arm vs. placebo were 1.4% vs. 1.3% in the schizophrenia trial, 1.0% vs. 0% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. During an extended post-treatment follow-up phase of the bipolar depression trial, there were two additional suicide related events in two patients; one of these patients was on quetiapine at the time of the event.

Long-term safety
A 26-week open-label extension to the acute trials (n=380 patients), with Seroquel flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see section 4.4 and 4.8). With respect to weight gain, when adjusting for normal growth over the longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

5.2 Pharmacokinetic properties

Absorption
Quetiapine is well absorbed following oral administration. Seroquel XR achieves peak quetiapine and norquetiapine plasma concentrations at approximately 6 hours after administration (T_{max}). Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear and dose-proportional for doses up to 800 mg administered once daily. When Seroquel XR administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate (Seroquel immediate release) administered twice daily, the area under the plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (C_{max}) is 13% lower at steady state. When Seroquel XR is compared to Seroquel immediate release, the norquetiapine metabolite AUC is 18% lower.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the Seroquel XR C_{max} and AUC of approximately 50% and 20% respectively. It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that Seroquel XR is taken once daily without food.

Distribution
Quetiapine is approximately 83% bound to plasma proteins.

Biotransformation
Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination
The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73% of a radiolabelled drug was excreted in the urine and 21% in the faeces with less than 5% of the total radioactivity representing unchanged drug-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations

Gender
The pharmacokinetics of quetiapine does not differ between men and women.

Elderly
The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

Renal impairment
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73 m^2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment
The mean quetiapine plasma clearance decreases with approximately 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2).

Paediatric population
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine (Seroquel) twice daily. At steady-state, the dose-normalized plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though C_{max} in children was at the higher end of the range observed in adults. The AUC and C_{max} for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

No information is available for Seroquel XR in children and adolescents.

5.3 Preclinical safety data

There was no evidence of genotoxicity in a series of *in vitro* and *in vivo* genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:
In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T_3 levels, decreased haemoglobin concentration and a

decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts. (For cataracts/lens opacities see section 5.1.)

In an embryofoetal toxicity study in rabbits the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown.

In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Cellulose, microcrystalline
Sodium citrate
Lactose monohydrate
Magnesium stearate
Hypromellose 2208

Coating
Hypromellose 2910
Macrogol 400
Titanium dioxide (E171)
Iron oxide, yellow (E172) (50, 200 and 300 mg tablets)
Iron oxide, red (E172) (50 mg tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polychlorotrifluoroethylene and polyvinylchloride with aluminium blister

Tablet Strength	*Carton (pack) contents*	*Blisters*
50 mg, 150 mg 200 mg, 300 mg and 400 mg tablets	*10 tablets*	*1 blister of 10 tablets*
	30 tablets	*3 blisters of 10 tablets*
	50 tablets	*10 blisters of 5 tablets*
	50 tablets	*5 blisters of 10 tablets*
	60 tablets	*6 blisters of 10 tablets*
	100 tablets	*10 blisters of 10 tablets*
	100 tablets	*100 blisters of 1 tablet*

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 August 2007
Date of latest renewal: 23 November 2015

10. DATE OF REVISION OF THE TEXT

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 50 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-relaease tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Seroquel XR 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 50 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 150 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-relaease tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

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<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Seroquel XR 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 150 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 200 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-relaease tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Seroquel XR 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 200 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 300 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-relaease tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Seroquel XR 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 300 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 400 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-relaease tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Seroquel XR 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 400 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Seroquel XR 50 mg, 150 mg, 200 mg, 300 mg, 400 mg prolonged-release tablets

quetiapine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Seroquel XR is and what it is used for

Seroquel XR contains a substance called quetiapine. This belongs to a group of medicines called anti-psychotics. Seroquel XR can be used to treat several illnesses, such as:

- Bipolar depression and major depressive episodes in major depressive disorder: where you feel sad. You may find that you feel depressed, feel guilty, lack energy, lose your appetite or can't sleep.
- Mania: where you may feel very excited, elated, agitated, enthusiastic or hyperactive or have poor judgment including being aggressive or disruptive.
- Schizophrenia: where you may hear or feel things that are not there, believe things that are not true or feel unusually suspicious, anxious, confused, guilty, tense or depressed.

When Seroquel XR is being taken to treat major depressive episodes in major depressive disorder, it will be taken in addition to another drug being used to treat this illness.

Your doctor may continue to prescribe Seroquel XR even when you feel better.

2. What you need to know before you take Seroquel XR

Do not take Seroquel XR:
- if you are allergic to quetiapine or any of the other ingredients of this medicine (listed in section 6).
- if you are taking any of the following medicines:
  - Some medicines for HIV
  - Azole medicines (for fungal infections)
  - Erythromycin or clarithromycin (for infections)
  - Nefazodone (for depression)

If you are not sure, talk to your doctor or pharmacist before taking Seroquel XR.

Warnings and Precautions

Talk to your doctor or pharmacist before taking Seroquel XR:
- if you, or someone in your family, have or have had any heart problems, for example heart rhythm problems, weakening of the heart muscle or inflammation of the heart or if you are taking any medicines that may have an impact on the way your heart beats.
- if you have low blood pressure.
- if you have had a stroke, especially if you are elderly.
- if you have problems with your liver.
- if you have ever had a fit (seizure).
- if you have diabetes or have a risk of getting diabetes. If you do, your doctor may check your blood sugar levels while you are taking Seroquel XR.
- if you know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines).
- if you are an elderly person with dementia (loss of brain function). If you are, Seroquel XR should not be taken because the group of medicines that Seroquel XR belongs to may increase the risk of stroke, or in some cases the risk of death, in elderly people with dementia.
- if you or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.
- if you have or have had a condition where you stop breathing for short periods during your normal nightly sleep (called "sleep apnea") and are taking medicines that slow down the normal activity of the brain ("depressants").
- if you have or have had a condition where you can't completely empty your bladder (urinary retention), have an enlarged prostate, a blockage in your intestines, or increased pressure inside your eye. These conditions are sometimes caused by medicines (called "anti-cholinergics") that affect the way nerve cells function in order to treat certain medical conditions.
- if you have a history of alcohol or drug abuse.

<u>Tell your doctor immediately if you experience any of the following after taking Seroquel XR:</u>
- A combination of fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called "neuroleptic malignant syndrome"). Immediate medical treatment may be needed.
- Uncontrollable movements, mainly of your face or tongue.
- Dizziness or a severe sense of feeling sleepy. This could increase the risk of accidental injury (fall) in elderly patients.
- Fits (seizures).
- A long-lasting and painful erection (Priapism).

These conditions can be caused by this type of medicine.

<u>Tell your doctor as soon as possible if you have:</u>
- A fever, flu-like symptoms, sore throat, or any other infection, as this could be a result of a very low white blood cell count, which may require Seroquel XR to be stopped and/or treatment to be given.
- Constipation along with persistent abdominal pain, or constipation which has not responded to treatment, as this may lead to a more serious blockage of the bowel.
- **Thoughts of suicide and worsening of your depression**
  If you are depressed you may sometimes have thoughts of harming or killing yourself. These may be increased when first starting treatment, since these medicines all take time to work, usually about two weeks but sometimes longer. These thoughts may also be increased if you suddenly stop taking your medication. You may be more likely to think like this if you are a young adult. Information from clinical trials has shown an increased risk of suicidal thoughts and/or suicidal behaviour in young adults aged less than 25 years with depression.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Weight gain
Weight gain has been seen in patients taking Seroquel XR. You and your doctor should check your weight regularly.

Children and adolescents
Seroquel XR is not for use in children and adolescents below 18 years of age.

Other medicines and Seroquel XR
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Do not take Seroquel XR if you are taking any of the following medicines:
- Some medicines for HIV.
- Azole medicines (for fungal infections).
- Erythromycin or clarithromycin (for infections).
- Nefazodone (for depression).

Tell your doctor if you are taking any of the following medicines:

- Epilepsy medicines (like phenytoin or carbamazepine).
- High blood pressure medicines.
- Barbiturates (for difficulty sleeping).
- Thioridazine or Lithium (other anti-psychotic medicines).
- Medicines that have an impact on the way your heart beats, for example, drugs that can cause an imbalance in electrolytes (low levels of potassium or magnesium) such as diuretics (water pills) or certain antibiotics (drugs to treat infections).
- Medicines that can cause constipation.
- Medicines (called “anti-cholinergics”) that affect the way nerve cells function in order to treat certain medical conditions.

Before you stop taking any of your medicines, please talk to your doctor first.

Seroquel XR with food, drink and alcohol
- Seroquel XR can be affected by food and you should therefore take your tablets at least one hour before a meal or prior to bedtime.
- Be careful how much alcohol you drink. This is because the combined effect of Seroquel XR and alcohol can make you sleepy.
- Do not drink grapefruit juice while you are taking Seroquel XR. It can affect the way the medicine works.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby ask your doctor for advice before taking this medicine. You should not take Seroquel XR during pregnancy unless this has been discussed with your doctor. Seroquel XR should not be taken if you are breast-feeding.

The following symptoms which can represent withdrawal may occur in newborn babies of mothers that have used Seroquel in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Driving and using machines
Your tablets may make you feel sleepy. Do not drive or use any tools or machines until you know how the tablets affect you.

Seroquel XR contains lactose
Seroquel XR contains lactose which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Effect on Urine Drug Screens
If you are having a urine drug screen, taking Seroquel may cause positive results for methadone or certain drugs for depression called tricyclic antidepressants (TCAs) when some test methods are used, even though you may not be taking methadone or TCAs. If this happens, a more specific test can be performed.

3. How to take Seroquel XR

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will decide on your starting dose. The maintenance dose (daily dose) will depend on your illness and needs but will usually be between 150 mg and 800 mg.

- You will take your tablets once a day.
- Do not split, chew or crush the tablets.
- Swallow your tablets whole with a drink of water.
- Take your tablets without food (at least one hour before a meal or at bedtime, your doctor will tell you when.
- Do not drink grapefruit juice while you are taking Seroquel XR. It can affect the way the medicine works.
- Do not stop taking your tablets even if you feel better, unless your doctor tells you.

Liver problems
If you have liver problems your doctor may change your dose.

Elderly people
If you are elderly your doctor may change your dose.

Use in children and adolescents
Seroquel XR should not be used by children and adolescents aged under 18 years.

If you take more Seroquel XR than you should
If you take more Seroquel XR than prescribed by your doctor, you may feel sleepy, feel dizzy and experience abnormal heart beats. Contact your doctor or nearest hospital straight away. Keep the Seroquel XR tablets with you.

If you forget to take Seroquel XR
If you forget to take a dose, take it as soon as you remember. If it is almost time to take the next dose, wait until then. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Seroquel XR
If you suddenly stop taking Seroquel XR, you may be unable to sleep (insomnia), or you may feel sick (nausea), or you may experience headache, diarrhoea, being sick (vomiting), dizziness or irritability. Your doctor may suggest you reduce the dose gradually before stopping treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common: may affect more than 1 in 10 people
- Dizziness (may lead to falls), headache, dry mouth.
- Feeling sleepy (this may go away with time, as you keep taking Seroquel) (may lead to falls).
- Discontinuation symptoms (symptoms which occur when you stop taking Seroquel) include not being able to sleep (insomnia), feeling sick (nausea), headache, diarrhoea, being sick (vomiting), dizziness, and irritability. Gradual withdrawal over a period of at least 1 to 2 weeks is advisable.
- Putting on weight.
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Changes in the amount of certain fats (triglycerides and total cholesterol).

Common: may affect up to 1 in 10 people
- Rapid heartbeat.
- Feeling like your heart is pounding, racing or has skipped beats.
- Constipation, upset stomach (indigestion).
- Feeling weak.
- Swelling of arms or legs.
- Low blood pressure when standing up. This may make you feel dizzy or faint (may lead to falls).
- Increased levels of sugar in the blood.
- Blurred vision.
- Abnormal dreams and nightmares.
- Feeling more hungry.
- Feeling irritated.
- Disturbance in speech and language.
- Thoughts of suicide and worsening of your depression.
- Shortness of breath.
- Vomiting (mainly in the elderly).
- Fever.
- Changes in the amount of thyroid hormones in your blood.
- Decreases in the number of certain types of blood cells.
- Increases in the amount of liver enzymes measured in the blood.
- Increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
    - Men and women to have swelling of breasts and unexpectedly produce breast milk.
    - Women to have no monthly period or irregular periods.

Uncommon: may affect up to 1 in 100 people
- Fits or seizures.
- Allergic reactions that may include raised lumps (weals), swelling of the skin and swelling around the mouth.
- Unpleasant sensations in the legs (also called restless legs syndrome).
- Difficulty swallowing.
- Uncontrollable movements, mainly of your face or tongue.
- Sexual dysfunction.

- Diabetes.
- Change in electrical activity of the heart seen on ECG (QT prolongation).
- A slower than normal heart rate which may occur when starting treatment and which may be associated with low blood pressure and fainting.
- Difficulty in passing urine.
- Fainting (may lead to falls).
- Stuffy nose.
- Decrease in the amount of red blood cells.
- Decrease in the amount of sodium in the blood.
- Worsening of pre-existing diabetes.

Rare: may affect up to 1 in 1,000 people
- A combination of high temperature (fever), sweating, stiff muscles, feeling very drowsy or faint (a disorder called "neuroleptic malignant syndrome").
- Yellowing of the skin and eyes (jaundice).
- Inflammation of the liver (hepatitis).
- A long-lasting and painful erection (priapism).
- Swelling of breasts and unexpected production of breast milk (galactorrhoea).
- Menstrual disorder.
- Blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.
- Walking, talking, eating or other activities while you are asleep.
- Body temperature decreased (hypothermia).
- Inflammation of the pancreas.
- A condition (called "metabolic syndrome") where you may have a combination of 3 or more of the following: an increase in fat around your abdomen, a decrease in "good cholesterol" (HDL-C), an increase in a type of fat in your blood called triglycerides, high blood pressure and an increase in your blood sugar.
- Combination of fever, flu-like symptoms, sore throat, or any other infection with very low white blood cell count, a condition called agranulocytosis.
- Bowel obstruction.
- Increased blood creatine phosphokinase (a substance from the muscles).

Very rare: may affect up to 1 in 10,000 people
- Severe rash, blisters, or red patches on the skin.
- A severe allergic reaction (called anaphylaxis) which may cause difficulty in breathing or shock.
- Rapid swelling of the skin, usually around the eyes, lips and throat (angioedema).
- A serious blistering condition of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome).
- Inappropriate secretion of a hormone that controls urine volume.
- Breakdown of muscle fibers and pain in muscles (rhabdomyolysis).

Not known: frequency cannot be estimated from the available data
- Skin rash with irregular red spots (erythema multiforme).
- Serious, sudden allergic reaction with symptoms such as fever and blisters on the skin and peeling of the skin (toxic epidermal necrolysis).
- Symptoms of withdrawal may occur in newborn babies of mothers that have used Seroquel XR during their pregnancy.

The class of medicines to which Seroquel XR belongs can cause heart rhythm problems, which can be serious and in severe cases may be fatal.

Some side effects are only seen when a blood test is taken. These include changes in the amount of certain fats (triglycerides and total cholesterol) or sugar in the blood, changes in the amount of thyroid hormones in your blood, increased liver enzymes, decreases in the number of certain types of blood cells, decrease in the amount of red blood cells, increased blood creatine phosphokinase (a substance in the muscles), decrease in the amount of sodium in the blood and increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:

- Men and women to have swelling of breasts and unexpectedly produce breast milk.
- Women to have no monthly period or irregular periods.

Your doctor may ask you to have blood tests from time to time.

Additional side effects in children and adolescents
The same side effects that may occur in adults may also occur in children and adolescents.

The following side effects have been seen more often in children and adolescents or have not been seen in adults:

Very common: may affect more than 1 in 10 people

- Increase in the amount of a hormone called prolactin, in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
  - Boys and girls to have swelling of breasts and unexpectedly produce breast milk.
  - Girls to have no monthly period or irregular periods.
- Increased appetite.
- Vomiting.
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Increase in blood pressure.

Common: may affect up to 1 in 10 people

- Feeling weak, fainting (may lead to falls).
- Stuffy nose.
- Feeling irritated.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Seroquel XR

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container after EXP. The expiry date refers to the last day of that month.

Seroquel XR does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Seroquel XR contains

- The active substance is quetiapine. Seroquel XR tablets contain 50 mg, 150 mg, 200 mg, 300 mg or 400 mg of quetiapine (as quetiapine fumarate).
- The other ingredients are:
  Tablet core: microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose.
  Tablet coating: hypromellose, macrogol, titanium dioxide (E171). The 50 mg, 200 mg and 300 mg tablets also contain iron oxide yellow (E172) and the 50 mg tablets contain iron oxide red (E172).

What Seroquel XR looks like and contents of the pack

All prolonged-release tablets are capsule shaped and marked with XR and the strength. 50 mg tablets are peach coloured; 150 mg tablets are white coloured, 200 mg tablets are yellow coloured; 300 mg tablets are pale yellow coloured and 400 mg tablets are white coloured.

Pack sizes of 10, 30, 50, 60 and 100 tablets are registered for all strengths. Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

COUNTRY	TRADE NAME
Austria	Seroquel XR
Belgium	Seroquel XR
Croatia	Seroquel XR
Cyprus	Seroquel XR
Denmark	Seroquel Prolong
Estonia	Seroquel XR
Finland	Seroquel Prolong
France	Xeroquel LP
Germany	Seroquel Prolong® 50 mg Retardtabletten, Seroquel Prolong® 150 mg Retardtabletten, Seroquel Prolong® 200 mg Retardtabletten, Seroquel Prolong® 300 mg Retardtabletten, Seroquel Prolong® 400 mg Retardtabletten
Greece	Seroquel XR
Hungary	Seroquel XR
Iceland	Seroquel Prolong
Ireland	Seroquel XR
Italy	Seroquel compresse a rilascio prolungato
Latvia	Seroquel XR
Lithuania	Seroquel XR
Luxembourg	Seroquel XR

Netherlands	Seroquel XR Quetiapine XR AstraZeneca
Norway	Seroquel Depot
Portugal	Seroquel SR
Romania	Seroquel XR
Slovakia	Seroquel XR
Slovenia	Seroquel SR
Spain	Seroquel Prolong
Sweden	Seroquel Depot
United Kingdom	Seroquel XL

This leaflet was last revised in {MM/YYYY}.

<[To be completed nationally]>

EU RMP Part VII Annex 3

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	12 June 2014

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® and SEROQUEL XR®)

Part VII ANNEX 3 - WORLDWIDE MARKETING AUTHORISATION BY COUNTRY (INCLUDING EEA)

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL/SEROQUEL XR
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

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EU RMP Part VII Annex 4

Drug Substance	Quetiapine fumarate
Version Number	12
Data lock point for this module	12 June 2013

EUROPEAN UNION RISK MANAGEMENT PLAN EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® AND SEROQUEL XR®)

Part VII ANNEX 4 - SYNOPSIS OF ON-GOING AND COMPLETED CLINICAL TRIAL PROGRAMME

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL® and SEROQUEL XR®
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

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1. SYNOPSIS OF ON-GOING AND COMPLETED CLINICAL TRIAL PROGRAMME

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
Main or pivotal studies						
Depression and anxiety disorders						
D1441L00016	A Multi-center, Randomized, Double-blind, parallel-group, Placebo-controlled Study of the Efficacy and Safety of Quetiapine Fumarate Extended-Release (SEROQUEL XR) Compared with Placebo as an Adjunct to Treatment in Patients with Generalized Anxiety Disorder who Demonstrate Partial or No Response to SSRI or SNRI	United States of America	Multi-center, randomized, double-blind, parallel-group, placebo-controlled with single-blind, placebo run-in	600	8 weeks	19-Feb-2009

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1447C00001	An International, Multi-centre, Double-blind, Randomised, Parallel-group, Placebo -controlled, Phase III study of the Efficacy and Safety of Quetiapine Fumarate (Seroquel), single oral 300 mg or 600 mg dose) and Lithium as Monotherapy in Adult Patients with Bipolar Depression for 8 weeks and Quetiapine in Continuation Treatment for 26 up to 52 weeks.	Serbia and Montenegro, Republic of Korea, Ukraine, Taiwan, Poland, Philippines, Norway, Malaysia, Lithuania Latvia, Korea, Indonesia, Germany, Estonia, Croatia, Canada, Turkey, Russian Federation	Multi-center, double-blind, randomized, parallel-group, placebo-controlled, double-dummy	921	52 weeks	16-Oct-2007
D1447C00134	An International, Multi-centre, Double-blind, Randomised, Parallel-group, Placebo-controlled, Phase III study of the Efficacy and Safety of Quetiapine Fumarate (Seroquel, single oral 300 mg or 600 mg dose) and Paroxetine as Monotherapy in Adult Patient with Bipolar Depression for 8 weeks and Quetiapine in Continuation Treatment for 26 up to 52 weeks.	Chile, United Kingdom, United States of America, Turkey, South Africa, EU member states, Australia, Venezuela, Romania, Peru, Mexico, Greece, Great Britain, Costa Rica, Colombia	Multi-center, double-blind, randomized, parallel-group, placebo-controlled, double-dummy	1001	52 weeks	15-Oct-2007

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1447C00135	A Confirmatory Multi-center, Double-blind, Randomized, Placebo-controlled Study of the Use of Quetiapine Fumarate (Seroquel) in the Treatment of Patients with Bipolar Depression.	United States of America	Multi-center, double-blind, randomized, parallel-group, placebo-controlled	788	8 weeks	01-Dec-2005
D1448C00001	A 6-week Multi-centre, Double-blind, Randomised, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate sustained release (Seroquel SR) 50 mg/day, 150/mg/day and 300 mg/day as Monotherapy in the Treatment of Subjects with Major Depressive Disorder	United States of America	Multi-center, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	1075	6 weeks	30-Nov-2007
D1448C00002	An 6-week Multi-centre, Double-blind, Randomised, Parallel-group, Placebo-controlled and Active-Controlled (Duloxetine 60 mg/day) Phase III Study of the Efficacy and Safety of Quetiapine Fumarate sustained release (Seroquel SR) 150 mg/day and 300 mg/day as Monotherapy in the Treatment of Patients with Major Depressive Disorder	United States of America	Multi-center, double-blind, double-dummy, randomized, parallel-group, placebo-controlled, active-controlled	911	6 weeks	12-Dec-2007

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1448C00003	An 8-week multi-centre, double-blind, randomised, parallel group, placebo-controlled Phase III study of the efficacy and safety of Quetiapine fumarate sustained release (Seroquel SR) 150 mg/day and 300 mg/day as monotherapy in the treatment of adult patients with Major Depressive Disorder	United States of America	Multi-center, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	513	10 weeks	15-Oct-2007
D1448C00004	A Multi-centre, Double-Blind, Randomised, Parallel Group, Placebo-Controlled and Active-Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Sustained Release (Seroquel SR) as Monotherapy in the Treatment of Adult Patients with Major Depressive Disorder (AMBER STUDY)	Spain, South Africa, Philippines, Mexico, Malaysia, Korea, Finland, China, Canada	Multi-center, double-blind, double-dummy, randomized, parallel-group, placebo-controlled, active-controlled	661	10 weeks	23-Jan-2008

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1448C00005	A 52-Week, Multi-centre, Double-blind, Randomized Withdrawal, parallel-group, Placebo-controlled, PhaseIII Study of the Efficacy (Time to Event) and Safety of Quetiapine Fumarate Sustained Release (Seroquel SR) 50, 150, 300 mg/day as Monotherapy in the Maintenance Treatment of Patients with Major Depressive Disorder following a 16-week, Open-Label Stabilisation Period	Bulgaria, United Kingdom, South Africa, United States of America, Slovakia, Russian Federation, Romania, Philippines, Great Britain, France, Finland, Germany, Canada, Brazil	Multi-center, double-blind, double-dummy, randomized, parallel-group, placebo-controlled with 4 periods: enrolment, open-label run-in, open-label stabilization, and randomized withdrawal	2882	52 weeks	04-Feb-2008
D1448C00006	A 6-week Multi-centre, Double-blind, Randomised, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate sustained release (Seroquel SR) 150 mg/day and 300 mg/day in combination with an anti-depressant in the Treatment of Patients with Major Depressive Disorder with inadequate response to an antidepressant treatment	United States of America	Multi-center, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	656	6 weeks	19-Dec-2007

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1448C00007	A Multi-centre, Double-Blind, Randomised, Parallel-Group, Placebo-Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Sustained Release (Seroquel SR) in Combination with an Antidepressant in the Acute Treatment of Patients with Major Depressive Disorder with Inadequate Response to an Antidepressant Treatment (ONYX STUDY)	Belgium, South Africa, United States of America, Europe, Australia, Sweden, Romania, Poland, Norway, France, Finland, Germany, Czech Republic, Canada	Multi-center, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	572	6 weeks	16-Oct-2007
D1448C00008	A Double-blind, Randomized, 2-Period Crossover Study to Compare the Tolerance and Safety of Sustained Release Formulation Quetiapine Fumarate (SEROQUEL®) with Placebo in Healthy Volunteers	United States of America	Crossover, Randomized, Double-blind,	92	3 weeks	02-Feb-2006
D1448C00009	An 8-week, Multi-centre, Randomised, Double-blind, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of Quetiapine Fumarate (Seroquel) 50, 150, and 300 mg/day Compared with Placebo in the Treatment of Generalised Anxiety Disorder	United States of America	Multi-center, randomized, double-blind, parallel-group, placebo-controlled; 2 week post-treatment follow-up period	1364	8 weeks	24-Mar-2008

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1448C00010	An 8-week, Multi-centre, Randomized, Double-blind, Parallel-group, Placebo-controlled, Active-controlled (Escitalopram Oxalate 10mg) Study of the Efficacy and Safety of Quetiapine Fumarate (Seroquel) 150 mg/day and 300 mg/day compared with Placebo in the Treatment of Generalised Anxiety Disorder	United States of America	Multi-center, randomized, double-blind, parallel-group, placebo-controlled, active-controlled; 2 week post-treatment follow-up period	1334	8 weeks	27-Mar-2007
D1448C00011	An International, Multi-center, Randomized, Double-blind, Parallel-group, Placebo -controlled, Active-controlled Study of the Efficacy and Safety of Sustained-release Quetiapine Fumarate (Seroquel SR) in the Treatment of Generalized Anxiety Disorder (SILVER Study)	Bulgaria, South Africa, Mexico, Europe, Canada, Argentina, Turkey, Slovakia, Sweden, Romania, Norway, Italy, Greece, France, Finland, Spain, Denmark, Germany, Czech Republic	Multi-center, randomized, double-blind, parallel-group, placebo-controlled, active-controlled; 2 week post-treatment follow-up period	1051	8 weeks	17-Mar-2008

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1448C00012	A Multi-centre, Double-Blind, Randomised-Withdrawal, Parallel-Group, Placebo-Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Sustained Release (Seroquel SR) as Monotherapy in the Maintenance Treatment of Patients with Generalised Anxiety Disorder Following an Open-Label Stabilisation Period (PLATINUM STUDY)	Bulgaria, United Kingdom, Europe, Australia, Asia, South Africa, United States of America, Russian Federation, Romania, Philippines, Republic of Korea, Indonesia, Hungary, Great Britain, Finland, Germany, Canada	Multi-center, double-blind, parallel-group, placebo-controlled, randomized withdrawal with open-label run-in and stabilization periods	1811	78 weeks	18-Apr-2008
D1448C00013	A Double-blind, Randomized, 2-Period Crossover Study to Compare the Safety and Tolerability of a Titration of Sustained Release Formulation Quetiapine Fumarate (SEROQUEL) with Placebo in Healthy Volunteers	United States of America	Crossover, Randomized, Double-blind,	68	3 weeks	02-Aug-2006

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D144CC00002	A Multi-center, Double-blind, Randomized, Parallel-group, Placebo-controlled, Phase III Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL) Sustained-release as Monotherapy in Adult Patients with Acute Bipolar Depression	United States of America	Multi-center, double-blind, randomized, parallel-group, placebo-controlled in patients with bipolar disorder I or bipolar disorder II with acute depressive episode	418	8 weeks	15-Nov-2007
D144CC00005	A Multi-center, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL) Extended Release as Mono-therapy in the Treatment of Patients with Bipolar Depression	China	Multi-center, Double-blind, Randomized, Placebo-controlled	357	8 weeks	May 2013
Healthy patients						
D1441C00081	The Pharmacokinetics of Quetiapine Fumarate (SEROQUEL]) Given Before and During Treatment with Ketoconazole	United States of America	Open-label	12	1 week	10-Feb-1999
D1441C00084	A Bioequivalence Trial of Quetiapine Fumarate (SEROQUEL]) 25 and 150 mg of the Granular Formulation versus 25- and 150-mg Tablets in Healthy Volunteers (5077IL/0084)	Germany	Crossover, Randomized, Open-label	32	4 weeks	18-Dec-2002

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1443C00033	A Double-blind, Double-dummy, Randomized, Crossover Study to Compare the Tolerability of Quetiapine Fumarate Immediate Release with Quetiapine Fumarate Extended Release During Initial Dose Escalation in Healthy Volunteers	United States of America	Crossover, Randomized, Double-bind	63	4 weeks	07-Jul-2009
D1443C00038	An open label, 1-sequence cross-over, Positron Emission Tomography (PET) study with [11C]raclopride to determine central D2 dopamine receptor occupancy of Quetiapine Fumarate Immediate Release (SEROQUEL) with Quetiapine Fumarate Extended Release (SEROQUEL XR) in healthy male volunteers	Sweden	Crossover, Open-label	12	2 weeks	14-Jan-2010
Mania						
5077IL/0099	A Multi-center, Double-Blind, Randomized, Placebo-Controlled Trial of the Safety and Efficacy of SEROQUEL (Quetiapine Fumarate) as Add-on Therapy with Lithium or Divalproex in the Treatment of Acute Mania	United States of America	Double-bind, Randomized, Placebo-controlled, Parallel	270	3 weeks	01-Sep-2002

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
5077IL/0100	An International, Multi-Centre, Double-Blind, Randomised, Placebo-Controlled Study Of The Safety And Efficacy Of Seroquel (Quetiapine Fumerate) As Add-On Therapy With Lithium Or Divalproex In The Treatment Of Acute Mania.	Belgium, Romania, Hungary, Great Britain, United Kingdom, Spain, South Africa, Rumania, India, Germany, Canada, Bulgaria	Double-blind, Randomized, Placebo-controlled, Parallel	250	6 weeks	02-Dec-2002
5077IL/0104	An International, Multi-Centre, Double-Blind, Randomised, Placebo-Controlled Study Of The Safety And Efficacy Of Quetiapine Fumerate And Haloperidol As Monotherapy In Treatment Of Acute Mania.	Argentina, Brazil, Taiwan, Poland, Philippines, Lithuania, Latvia, Indonesia, Estonia, Croatia, China, Chile	Double-blind, Randomized, Placebo-controlled, Parallel	353	12 weeks	06-Dec-2002
5077IL/0105	An International, Multi-Centre, Double-Blind, Randomised, Placebo-Controlled Study Of The Safety And Efficacy Of Seroquel (Quetiapine Fumerate) And Lithium As Monotherapy In The Treatment Of Acute Mania.	Bulgaria, Russian Federation, Turkey, Romania, India, Greece, Croatia, China	Double-blind, Randomized, Placebo-controlled, Parallel	370	12 weeks	20-Dec-2002

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1447C00126	A Multi-center, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400mg to 800mg daily in divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Valproate) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients	Denmark, United Kingdom, Turkey, Sweden, Spain, South Africa, Poland, Norway, Italy, Hungary, Germany, France, Finland, Czech Republic, Bulgaria, Belgium, Australia, United States of America, Russian Federation, Great Britain	Multi-center, double-blind, randomized, parallel-group, placebo-controlled with open-label stabilization run-in phase	1729	104 weeks	19-Jun-2007
D1447C00127	A Multi-center, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400 mg to 800 mg daily in divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Divalproex) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients	United States of America	Multi-center, double-blind, randomized, parallel-group, placebo-controlled with open-label stabilization run-in phase	2588	104 weeks	09-Jul-2007

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1447C00144	Multi-center, Randomized, Parallel-group, Double-blind, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate and Lithium as Monotherapy in up to 104 weeks Maintenance Treatment of Bipolar I Disorder in Adult Patients	Chile, Ukraine, United States of America, Thailand, Taiwan, Romania, Philippines, Peru, Mexico, Malaysia, Lithuania, India, Colombia, Bulgaria, Argentina, Russian Federation, Malaysia, France	Multi-center, randomized, parallel-group, double-blind, double-dummy placebo-controlled with 3 phases: enrolment, open-label stabilization, and randomized treatment	2957	104 weeks	07-Apr-2008

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D144AC00003	A Multi-center, Double-blind, Randomized, Placebo-controlled, Phase IV Study of the Safety and Efficacy of Lithium versus Placebo as an add on to SEROQUEL XR (Quetiapine Fumarate) in Adult Patients with Acute Mania	Belgium, France, South Africa, Ukraine, Russian Federation, Poland, India, Israel, Finland, Germany, Bulgaria	Multi-center, double-blind, randomized, placebo-controlled, Phase IV study of the safety and efficacy of lithium versus placebo as an add on to SEROQUEL XR™ (Quetiapine Fumarate) in adult patients with acute mania	441	6 weeks	06-Oct-2011
D144AL00002	A Multi-center, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind, Phase III Study to Compare the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL) versus Placebo as Adjunct Therapy with Mood Stabilizers (Lithium or Divalproex) for the Treatment of Alcohol Dependence in Patients with Bipolar I Disorder	United States of America	Double-blind, Randomized, Placebo-controlled, Parallel	586	12 weeks	03-Apr-2008

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D144CC00004	A Multi-center, Double-blind, Randomized, Parallel-group, Placebo-controlled, Phase III Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL) Sustained-release as Monotherapy in Adult Patients with Acute Bipolar Mania	United States of America	Multi-center, randomized, parallel-group, double-blind placebo-controlled in patients with bipolar I disorder with an acute manic episode	459	3 weeks	20-Nov-2007
Other						
5077US/0049	A Multi-center, Double-blind, Randomized, Placebo-controlled, Double-dummy Trial of the Use of Quetiapine Fumarate (SEROQUEL) in the Treatment of Patients with Bipolar Depression	United States of America	Multi-center, double-blind, randomized, parallel-group, placebo-controlled, double-dummy	838	8 weeks	10-Mar-2004
D1443C00040	A Phase IV Multi-center Double-Blind Double-Dummy Randomized Parallel-group study to compare the tolerability of quetiapine fumarate immediate release (Seroquel) to quetiapine fumarate extended release (Seroquel XR) during initial dose escalation in patients with bipolar depression	United States of America	Double-blind, Randomized, Parallel	198	1 weeks	25-Mar-2010

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
Psychotic Disorder						
5077IL/0063	The Pharmacokinetics, Tolerability, and Safety of Quetiapine (SEROQUEL) When Coadministered with Fluoxetine or Imipramine in Subjects with Selected Psychotic Disorders	United States of America	Open-label, randomized	36	7 weeks	29-Sep-1997
5077IL/0064	The Tolerability, Safety, and Pharmacokinetics of ICI 204,636 (SEROQUEL) When Coadministered With Haloperidol, Risperidone, or Thioridazine in Subjects With Selected Psychotic Disorders.	United States of America	Open-label, randomized	55	10 weeks	02-Oct-1997
5077IL/0066	Tolerability and Pharmacokinetics of Once-daily Dosing of Quetiapine (SEROQUEL) in Men and Women with Selected Psychotic Disorders.	United States of America	Open-label	16	34 days	09-Mar-1998
5077IL/0070	A Double-blind, Randomised, Pilot Trial to Compare the Tolerability of Dose-escalation Regimens of Seroquel Over a 4-Day Period in Patients with Subchronic or Chronic Schizophrenia (ODESSA)	Russia	Double-blind, randomized	158	4 days	19-Jan-1998
5077IL/0072	A Bioequivalence Trial Comparing Four 25-mg Tablets with One 100-mg Tablet of Quetiapine (SEROQUEL]) in Men with Selected Psychotic Disorders	Canada	Crossover, Randomized, Open-label	25	13 days	15-Dec-1997

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1441C00048	A Multi-center, Open-label Trial Evaluating the Safety and Tolerability of ICI 204,636 (SEROQUEL) in the Treatment of Elderly Patients with Selected Idiopathic and Organic Psychoses	United States of America	Open-label	151	52 weeks	12-Jun-1998
D1441C00061	The Tolerability and Safety of Switching to and Subsequently Withdrawing from ICI 204,636 (SEROQUEL) in Subjects with Selected Psychotic Disorders (5077IL/0061)	United States of America	Double-blind, randomized, placebo-controlled	50	73 days	29-Oct-1997
D1441C00062	A Single-center, Open-label Trial Evaluating the Safety, Tolerability, and Efficacy of SEROQUEL] (quetiapine fumarate) in the Treatment of Psychosis in Subjects with Parkinsonism Who Have Failed Treatment or Are Not Candidates for treatment with Other Antipsychotic Medications.	United States of America	Open-label	31	24 weeks	19-Dec-2000
D1441C00065	The Tolerability and Safety of Either Adding ICI 204,636 SEROQUEL]) to, or Switching to ICI 204,636 from, a Haloperidol Decanoate Regimen in Subjects with Selected Psychotic Disorders (5077IL/0065)	United States of America	Double-blind, randomized, placebo-controlled	39	17 days	04-Dec-2001

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1441C00080	The Effect of Coadministration of Quetiapine Fumarate (SEROQUEL) and Carbamazepine on the Pharmacokinetics of Quetiapine in Subjects with Selected Psychotic Disorders	United States of America	Open-label	18	37 days	07-Oct-1999
D1441C00082	The pharmacokinetics, safety, tolerability and pharmacodynamics of alprazolam given before and during treatment with quetiapine fumarate (SEROQUEL) in men and women with selected psychotic disorders (5077IL/0082)	United States of America	Open-label	15	22 days	28-Sep-1999
D1441C00093	An Open-label, Multiple-dose Clinical Trial to Assess the Effect of Quetiapine Fumarate on the QTc Interval in Psychiatric Subjects (5077IL/0093).	United States of America	Open-label	13	11 days	29-Sep-2000
D1444C00086	Multiple-dose Pharmacokinetics and the Effect of Food on Sustained-release (SR) Quetiapine Fumarate (SEROQUEL)	United States of America	Open-label	16	22 days	25-Jun-1999
Schizophrenia						
204636/0007	A Multi-centre, double-blind, controlled comparison of SEROQUEL and chlorpromazine in the treatment of hospitalised patients with acute exacerbation of subchronic or chronic schizophrenia.	Belgium, United Kingdom, Spain, South Africa, France	Double-blind, randomized, parallel	201	6 weeks	16-May-1995

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
5077IL/0041	A Multi-center, Double-blind, Randomized Comparison of the Efficacy and Safety of Sustained-release Formulation of Quetiapine Fumarate (Seroquel) and Placebo in the Treatment of Patients with Schizophrenia	Canada, United States of America	Multi-center, placebo-controlled, double-blind, double-dummy, randomized, parallel-group study (IR treatment arm included to demonstrate assay sensitivity and provide guidance for XR-IR comparability)	739	6 weeks	02-Mar-2006
5077IL/0057	Open-label trial for quetiapine (SEROQUEL)	United States of America	Open-label	176	108 weeks	02-Oct-2006
5077IL/0089	A Multi-center, Open-Label, Flexible-Dose, Parallel-Group Evaluation of the Cataractogenic Potential of Quetiapine Fumarate and Risperidone in the Long-Term Treatment of Patients with Schizophrenia or Schizoaffective Disorder.	United States of America	Open-label, randomized, parallel	1838	104 weeks	30-Mar-2010

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
5077IL/0107	A Multi-centre, Open-label, Non-Comparative Trial Examining The Clinical Benefit Derived By Patients Receiving Quetiapine.	Austria, South Africa, Portugal, Philippines, Mexico, Italy, Indonesia, Finland, Switzerland, Brazil, Germany, Czech Republic, Belgium	Open-label	306	12 weeks	25-Jun-2003
5077IL/0109	A Pilot Safety Trial To Determine the Appropriate Titration Scheme for Sustained-release Quetiapine Fumarate (SEROQUEL)	United States of America	Double-blind, randomized	28	12 days	30-Aug-2002
5077IL/0116	Single-center, Open-label, Multiple Dose, Steady State, Pharmacokinetic Study of the Sustained Release Formulation of Quetiapine Fumarate (Seroquel) in Adolescents with Schizophrenia	United States of America	Open-label	1	1 week	31-May-2003
5077IL/0118	Steady State, Dose Unit Proportionality, and Food Effect Study Using Commercial Scale Sustained Release (SR) Quetiapine Fumarate (SEROQUEL)	United States of America	Open-label	30	17 days	31-May-2003
5077US/0002	Disposition and Metabolism of Radiolabeled ICI 204,636 in Patients with Schizophrenic Symptomatology (5077US/0002)	United States of America	Open-label	8	20 days	23-Jul-1993

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
5077US/0004	Quetiapine (SEROQUEL) Experience with Safety and Tolerability (QUEST) (5077US/004)	United States of America	Open-label, randomized	751	120 days	09-Mar-1999
5077US/0043	A Multi-center, Double-blind, Randomized comparison of the Efficacy and Safety of Quetiapine Fumerate (SEROQUEL) and Risperidone (RISPERDAL) in the Treatment of Patients with Schizophrenia	United States of America	Double-blind, randomized	861	8 weeks	09-May-2003
D1441C00013	A Multi-center, Double-blind, Placebo-Controlled, Randomized, Multiple Fixed Dose Comparison of SEROQUEL (ICI 204,636) and Haloperidol in the Treatment of Hospitalized Subjects with Acute Exacerbation of Chronic or Subchronic Schizophrenia.	Canada, United States of America	Double-blind, randomized, parallel	402	6 weeks	25-Mar-1996
D1441C00015	A Multi-center, Double-blind, Randomized, Controlled, Multiple Fixed Dose and Dose Regimen Comparison of SEROQUEL (ICI 204,636) and Haloperidol in the Prevention of Psychotic Relapse in Outpatients with Chronic or Subchronic Schizophrenia.	Canada, United States of America	Double-blind, randomized	331	52 weeks	12-Jun-1996

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1441C00031	A Multi-center, Double-Blind, Randomized, Comparison of Quetiapine (SEROQUEL) and Chlorpromazine in the Treatment of Subjects with Treatment-Resistant Schizophrenia	Canada, United States of America	Double-blind, randomized, parallel	328	126 weeks	05-Aug-2005
D1441C00033	A trial to investigate the relationship between plasma levels of ICI 204,636 and brain dopamine D2 and serotonin 5HT2 receptor occupancy after dosing with 750 mg, 450 mg, 300 mg, 150 mg and 0 mg a day of SEROQUEL in chronic schizophrenic subjects (5077IL/0033)	Sweden	Open-label	10	60 weeks	08-Apr-1997
D1441C00050	A Double-blind, randomized, Double-blind, Randomised Trial to Compare the Effects of Quetiapine and Haloperidol Treatment Strategies on Treatment Outcomes	Australia, Spain, Germany, Canada	Double-blind, randomized	418	52 weeks	09-Apr-2001
D1441C00052	A Multi-centre, Double-Blind, Randomised Trial to Compare the Effects of SEROQUEL and haloperidol in Schizophrenic Patients with a History of Partial Response to Traditional Antipsychotic Treatment (5077IL/0052)	Canada, United Kingdom, Spain, South Africa, Portugal, Mexico, Italy, Israel, Hungary, Holland, Greece, Germany, Finland	Double-blind, randomized	395	12 weeks	30-Sep-1998

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1441C00053	A Multi-centre, Double-Blind Randomised Comparison of SEROQUEL and Risperidone in the Treatment of Schizophrenic Patients with Acute Exacerbation (5077IL/0053)	Australia, United Kingdom, Sweden, Spain, South Africa, Portugal, Poland, Norway, New Zealand, Hungary, Holland, Germany, Finland, Denmark, Czech Republic, Canada, Belgium, Austria	Double-blind, randomized, parallel	408	10 weeks	12-Jun-1998
D1441C00054	This was an international, Multi-centre, double-blind, randomised, parallel-group trial to compare the effects of quetiapine and chlorpromazine in patients with treatment-resistant schizophrenia.	France	Double-blind, randomized, parallel	256	10 weeks	13-Nov-2000
D1441C00056	A Multi-centre, Open, Randomised Comparison of ICI 204,636 (SEROQUEL) and Usual Care on Health Outcomes in Subjects With Schizophrenia and Schizoaffective Disorder (5077IL/0056).	United States of America	Open-label, randomized, parallel	508	52 weeks	17-Jun-2005

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1441C00125	A 24-Week, International, Multi-centre, Open-label, Flexible-dose, Randomised, Parallel-Group, Phase IV Study to Compare the Effect on Glucose Metabolism of Quetiapine, Olanzapine and Risperidone in the Treatment of Patients with Schizophrenia.	Denmark, United Kingdom, South Africa, Slovakia, Romania, Norway, Hungary, Germany, Czech Republic, Bulgaria, Great Britain	Open-label, randomized, parallel	574	24 weeks	19-Jun-2006
D1441C00130	A study to characterize the steady-state PK and Safety and tolerability of Seroquel in adults with selected psychotic disorders	United States of America	Open-label	29	12 days	07-Sep-2005
D1444C00001	A Phase I, Randomized, Open-label, 5-Treatment, 5-Period, 4-Sequence Crossover Study to Compare the Pharmacokinetics of 4 Sustained release Formulations and the Immediate release Formulation of Quetiapine Fumarate (SEROQUEL) in Adults with Schizophrenia, Schizoaffective Disorder, or Bipolar Disorder	United States of America	Open-label, crossover, randomized	28	19 days	12-Oct-2005

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1444C00003	A Study to Compare the Pharmacokinetics of 50 mg and 300 mg Quetiapine fumarate SR Tablets Administered following a Light Meal and in the Fasted State in Adult Volunteers and Adults with Schizophrenia, Schizoaffective Disorder or Bipolar Disorder	Germany, Berlin,	Open-label, crossover, randomized	60	6 days	02-Nov-2005
D1444C00004	A 1-year, international, Multi-center, randomized, double-blind, parallel-group, placebo-controlled phase III study to evaluate prevention of relapse in patients in stable condition with chronic schizophrenia receiving either sustained-release quetiapine fumarate (SEROQUEL) or placebo.	Russian Federation, Ukraine, Poland, India, Bulgaria	Multi-center, randomized, double-blind, parallel-group, placebo-controlled with 16-week open label stabilization period	358	52 weeks	03-Oct-2006
D1444C00007	A Randomized, Open-label Trial to Evaluate the Pharmacokinetics of Extended-Release (XR) Quetiapine Fumarate 300 mg, 600 mg and 800 mg in Chinese schizophrenic patients	China	Open-label, randomized	73	1 week	08-Nov-2010

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1444C00008	A 6-Week, Multi-centre, Double-blind, Double-dummy, Chlorpromazine-Controlled Randomised Study to Evaluate the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL) Extended-Release (XR) in the Treatment of Schizophrenic Patients with Acute Episode	China	Double-blind, randomized	464	6 weeks	24-Nov-2010
D1444C00037	Sustained-release (SR) Quetiapine Fumarate (SEROQUEL]) - Determination of Dosage Form Proportionality for SR Formulation C and Determination of Comparative Bioavailability of SR Formulations C and D	United States of America	Open-label	15	18 days	03- Jun-1999
D1444C00087	A Pilot Safety Trial to Determine the highest Tolerable Starting Dose of Sustained Release Quetiapine fumarate (SEROQUEL)	United States of America	Double-blind, randomized	87	1 week	27-Jun-2000
D1444C00097	A Trial to compare the Steady state pharmacokinetics of Quetiapine in Men and Women with selected Psychotic Disorders following the administration of sustained Released (SR) Quetiapine fumarate (SEROQUEL) or Immediate Release (IR) Quetiapine fumarate (SEROQUEL).	United States of America	Open-label, crossover, randomized	28	10 days	21-Dec-2001

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1444C00098	A Pilot Safety Trial to Determine the Tolerable Starting Dose of 400, 600, and 800 mg of Sustained-release Quetiapine Fumarate (SEROQUEL) (5077IL/0098)	United States of America	Double-blind, randomized	22	4 days	25-Jun-2001
D1444C00132	A 6-week, International, Multi-center, Double-blind, Double-dummy, Randomized Comparison of the Efficacy and Safety of Sustained-Release Formulation Quetiapine Fumarate (SEROQUEL) and Placebo in the Treatment of Acutely Ill Patients with Schizophrenia	South Africa, Russia, Romania, Philippines, Indonesia, India, Greece	Multi-center, placebo-controlled, double-blind, double-dummy, randomized, parallel-group study (IR treatment arm included to demonstrate assay sensitivity and provide guidance for XR-IR comparability)	665	6 weeks	10-May-2006

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1444C00133	A 6-week, Multi-center, Double-blind, Double-dummy, Randomized Comparison of the Efficacy and Safety of Sustained-Release Formulation Quetiapine Fumarate (SEROQUEL) and Placebo in the Treatment of Acutely Ill Patients with Schizophrenia.	United States of America	Multi-center, placebo-controlled, double-blind, double-dummy, randomized, parallel-group study (IR treatment arm included to demonstrate assay sensitivity and provide guidance for XR-IR comparability)	762	6 weeks	04-Jun-2006
D1444C00145	A Phase I, Randomized, Double-Blind, Parallel-Group, Multi-Center Study to Compare the Safety and Tolerability of Two Titration Schemes for Sustained-Release Quetiapine Fumarate with a Constant-Dose Scheme of Sustained-Release Quetiapine Fumarate in Schizophrenic and Schizoaffective Patients	United States of America	Double-blind, randomized, parallel	55	1 week	18-May-2005

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1444C00146	A 6-week International, Multi-center, Double-blind Study to Evaluate the Feasibility of Switching from Immediate-release Quetiapine Fumarate to Sustained-release Quetiapine Fumarate (SEROQUEL) in Patients with Schizophrenia.	United States of America, Spain, South Africa, Singapore, Lithuania, Latvia, Italy, Hungary, Germany, Finland, Estonia, Canada, Bulgaria, Australia	Multi-center, double-blind, double-dummy, randomized, parallel-group study to demonstrate continued efficacy/safety after random switch from treatment w/ QTP IR to an equivalent total daily dose of QTP XR or continued treatment w/ QTP IR after 4-week run-in period with QTP IR	630	10 weeks	09-Jun-2006

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1444C00147	A 12-Week International, Multi-center, Non-comparative Study to Evaluate the Feasibility of Switching any Antipsychotic Treatment to Sustained-release Quetiapine Fumarate (SEROQUEL) in Patients with Schizophrenia	Spain, United States of America, South Africa, Malaysia, Latvia, Hungary, Germany, Finland, Estonia, Canada, Bulgaria, Australia, Lithuania, Italy	Open-label	540	12 weeks	06-Feb-2007
DC-990-0165	A Canadian, Multi-center, Double-Blind, Randomized, Parallel-Group Study of the Safety, Tolerability, and Efficacy of Treatment with Higher Doses of Quetiapine Fumarate (Seroquel®) greater than 800 mg/day in Schizophrenic or Schizoaffective Subjects	Canada	Open-label, double-blind, randomized, parallel	199	13 weeks	30-Nov-2006

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
Studies in special populations						
Alzheimer's disease and dementia						
D1446L00002	A Multi-center, double-blind, randomized comparison of the efficacy and safety of quetiapine fumarate (SEROQUEL) and placebo in the treatment of agitation associated with dementia (5077US/0046)	United States of America	Double-blind, randomized, placebo-controlled, parallel	435	10 weeks	20-Sep-2005
Pediatric patients						
5077IL/0038	Tolerability and Pharmacokinetics of Quetiapine (SEROQUEL) in Adolescents with Selected Psychotic Disorders (5077IL/0038).	United States of America	Open-label, rising multiple-dose, pharmacokinetics and tolerability in pediatric patients with selected psychiatric disorders	10	3 weeks	04-Sep-1998

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1441C00028	A Study to characterize the steady-state Pharmacokinetics, Safety and Tolerability of Quetiapine Fumarate (Seroquel) in children and adolescents with selected psychotic disorders	United States of America	Multi-center, open-label in-patient, steady-state pharmacokinetics, safety, and tolerability in pediatric patients with selected psychiatric disorders	28	13 days	28-Jun-2006
D1441C00112	A 6-week, Multi-center, Double-blind, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL) in the Treatment of Adolescents with Schizophrenia.	Serbia and Montenegro, Ukraine, United States of America, South Africa, Serbia, Poland, Philippines., Malaysia, India, Germany, Russian Federation, Philippines, Hungary	Placebo-controlled monotherapy in adolescents (13 to 17 yrs) with schizophrenia	262	6 weeks	18-Feb-2008

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
D1441C00149	A 3-week, Multi-center, Double-blind, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of Quetiapine Fumarate (Seroquel) in the Treatment of Children and Adolescents with Acute Bipolar I Mania	Serbia and Montenegro, United States of America	Placebo-controlled monotherapy in adolescents (10 to 17 yrs) with schizophrenia	389	3 weeks	06-Sep-2007
D144AC00001	An 8-week, Multi-center, Double-blind, Randomized, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL) Extended-release in Children and Adolescent Subjects with Bipolar Depression	Brazil, South Africa, United States of America, Taiwan, Thailand, Serbia, Mexico, Italy, India, France, Spain, Colombia	Multi-center, double-blind, randomized, parallel-group, placebo-controlled efficacy and safety in children and adolescent with bipolar depression	262	8 weeks	14-Jun-2011
D1441C00150	A 26-week, Multi-center, Open-label Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL) in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia.	Serbia and Montenegro, Ukraine, South Africa, Serbia, Poland, Philippines, Malaysia, India, Germany, United States of America, Russian Federation, Hungary	Multi-center, single-arm, flexible-dose open-label extension for Studies 00112 and 00149 (placebo-controlled studies)	377	26 weeks	05-Aug-2008

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
Elderly patients						
D1448C00014	A Multi-Centre, Double-Blind, Randomised, Parallel-Group, Placebo-Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Sustained Release (Seroquel SR) as Monotherapy in the Treatment of Elderly Patients with Major Depressive Disorder (SAPPHIRE STUDY)	Lithuania, United States of America, Ukraine, Finland, Estonia, Argentina, Russian Federation	Multi-center, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	447	9 weeks	28-Apr-2008
D1448C00015	A Multi-center, Double-blind, Randomised, Parallel Group, Placebocontrolled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Sustained Release (Seroquel SR) as Mono-therapy in the Treatment of Elderly Patients with Generalised Anxiety Disorder (CHROMIUM Study)	Czech Republic, United States of America, Ukraine, Poland, Estonia, Russian Federation, Lithuania, Finland	Multi-center, randomized, double-blind, parallel-group, placebo-controlled; 2 week post-treatment follow-up period; elderly patients (>65 years) with GAD	556	9 weeks	29-Aug-2008

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
5077IL/0115	An Exploratory, Multi-centre, Double-blind, Double-dummy, Randomised, Parallel-group, Controlled Phase III Study to Evaluate the Safety and Tolerability of Sustained-Release Formulation Quetiapine Fumarate (SEROQUEL) in Treatment of Elderly Subjects with Alzheimer's Disease with Symptoms of Psychosis and/or Agitation Compared to Seroquel Immediate Release Formulation.	Australia, South Africa, Norway, Canada, Belgium	Exploratory, Multi-center, double-blind, double-dummy, randomized, controlled, parallel group; elderly patients (≥65 yr) with Alzheimer's disease and symptoms of psychosis/agitation	109	43 days	19-Dec-2005
5077IL/0039	A Multi-center, Double-blind Comparison of Efficacy and Safety of SEROQUEL (Quetiapine Fumarate), Haloperidol, and Placebo in the Treatment of Elderly Subjects Residing in Nursing Homes or Assisted Care Facilities and Presenting with Alzheimer's Dementia and Psychoses or Other Selected Psychoses	United States of America	Multi-center, double-blind, randomized, controlled, with screening phase and OLE treatment phase; elderly patients (residents) (>65 yr) with Alzheimer's dementia/psychoses	501	10 weeks	3-Oct-2006

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
Hepatic impairment						
5077IL/0018	The Pharmacokinetics and Safety of a Single Oral 25 mg SEROQUEL (ICI 204,636) Dose in Liver Disease	United States of America	Open-label	16	1 day	06-Oct-1995
Normal and severely impaired renal function						
5077IL/0019	The Pharmacokinetics of ICI 204,636 (Seroquel) in Subjects with Normal and Severely Impaired Renal Function	United States of America	Open-label	16	1 day	11-Sep-1995
Japanese patients						
H-15-21	ICI 204,636 Early Phase II Study in Schizophrenia patients [non-randomised, open study].	Japan	Open-label	54	8 weeks	12-Nov-1995
H-15-22	ICI 204,636 Late Phase II Study in Schizophrenia patients [non-randomised, open study].	Japan	Open-label	165	8 weeks	18-Jun-1995
H-15-31	Phase III Study of ICI 204,636 in Schizophrenia (a double-blind comparison study with haloperidol)	Japan	Multi-center, double-blind comparison study	200	8 weeks	15-Dec-1998
H-15-32	Phase III Study of ICI 204,636 in Schizophrenia (a double-blind comparison study with mosapramine hydrochloride)	Japan	Multi-center, double-blind comparison study	181	8 weeks	08-Dec-1998
H-15-33	Clinical effects of Quetiapine Fumarate against treatment-resistant schizophrenia.	Japan	Multi-center, open-label	32	8 weeks	23-Feb-1999

Table 1 Synopsis of on-going and completed clinical trial programme

Study	Description (Phase, short description of study [1 – 2 sentences including comparator name(s)/placebo])	Countries	Study design	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date[a]
H-15-34	Phase III Study of ICI 204,636 in Schizophrenia (a study of pharmacokinetics between the elderly and non-elderly patients)	Japan	Multi-center, open-label	24	8 weeks	16-Dec-1998
H-15-35	Phase III Study of ICI 204,636 in Schizophrenia (a clinical study to evaluate the safety of ICI 204,636 when administered for a long period of time.)	Japan	Multi-center, open-label	30	24 to 52 weeks	17-Mar-1999
H-15-36	Phase III Study of ICI 204,636 in Schizophrenia (a clinical study to evaluate the safety of ICI 204,636 when administered for a long period of time.)	Japan	Multi-center, open-label	25	24 to 52 weeks	14-Apr-1999
H-15-37	Phase III Study of ICI 204,636 in Schizophrenia (a clinical study to evaluate the safety of ICI 204,636 when administered for a long period of time.)	Japan	Multi-center, open-label	67	24 to 52 weeks	30-Mar-1999
H-15-11	ICI 204,636 phase I study [single oral dose study]	Japan	Placebo-controlled, randomized	17	1 day	28-Nov-1995
H-15-13	ICI 204,636 Phase I Study [Multiple oral dose study]	Japan	Placebo-controlled, randomized	8	4 days	28-Nov-1995

a Date when final study report expected.

5HT2 5-hydroxytryptamine 2; EU European Union; GAD generalized anxiety disorder; IR immediate release; OLE open-label extension; PK pharmacokinetics; SNRI; serotonin-norepinephrine reuptake inhibitor; SR sustained release; SSRI selective serotonin re-uptake inhibitor; QTP quetiapine; XR extended release; yr/yrs year/years.

EU RMP Part VII Annex 5

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	14
Data lock point for this module	02 December 2016

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® and SEROQUEL XR®)

Part VII ANNEX 5 - SYNOPSIS OF ON-GOING AND COMPLETED PHARMACOEPIDEMIOLOGICAL STUDY PROGRAMME

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL/SEROQUEL XR
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

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1. SYNOPSIS OF ON-GOING AND COMPLETED PHARMACOEPIDEMIOLOGICAL STUDY PROGRAMME

Table 1 Synopsis of on-going and completed pharmacoepidemiological study programme

Study	Research question	Study design	Population and study size	Duration of follow up	Milestones and dates	Status
PHARMO: Seroquel Safety Study (cohort study)	The study was conducted in 2 Parts. Part I involved the comparison of users of quetiapine vs. users of other antipsychotics in terms of indications for Seroquel use, comorbidities, drug utilization, treatment switches and discontinuations, to assess feasibility of evaluating outcomes Part II : Evaluation of patient characteristics, drug utilization and the incidence of safety outcomes (all cause mortality, acute MI, stroke, suicide, EPS, diabetes, hypo-thyroidism) in patients treated with quetiapine compared with those treated with olanzapine and risperidone.	This population-based cohort study was planned as a 2-part study: drug utilization and feasibility assessment (Part I) and safety study (Part II). Part II of the study examined the incidence of outcomes of interest and made comparisons of the incidence between patients who were naïve users of SEROQUEL (IR and XR) with the incidence in naïve users of comparison drugs during the observation period	The data source for this study was the PHARMO Record Linkage System a patient-centric database linking patient demographics, drug dispensing hospital morbidity, and GP information on approximately 2 million inhabitants of the Netherlands. Part I of the retrospective cohort study included patients who received antipsychotics. Part II of the study included naive users of quetiapine and atypical antipsychotics specifically olanzapine and risperidone	The duration of Part I of the study included all patients who received antipsychotic medications during the period January 1, 1998 to December 31, 2009. Part II of the study included naive users of quetiapine and atypical antipsychotics (specifically olanzapine and risperidone) treated from January 1, 2000 to November 30, 2009.	Original Protocol: Dec 2008 Part 1 Report: 21 Nov 2009 Part 2 Protocol: 20 May 2010 Part 2 Report: 26 April 2011	Completed

Table 1 Synopsis of on-going and completed pharmacoepidemiological study programme

Study	Research question	Study design	Population and study size	Duration of follow up	Milestones and dates	Status
m-PEM study (exposure only cohort study with nested case control studies)	Examine the safety and use of quetiapine XL prescribed in general practice (as a treatment for schizophrenia, bipolar disorder and as add-on treatment for MDD) in adult patients, using M-PEM methodology. a) Quantify both the incidence of new and worsening of pre existing type II diabetes mellitus, metabolic syndrome and EPS and explore the patterns of these events over time b) Determine the dose dependent characteristics of EPS and somnolence/sedation (including drowsiness) c) Quantify the incidence of rarely and frequently reported events d) Quantify drug utilization characteristics e) Identify previously unrecognized adverse drug reactions f) Quantify, follow-up & causally assess reports of neutropenia (including agranulocytosis), metabolic syndrome & events related to raised blood glucose. The study questionnaire captures the primary indication for starting treatment. To examine the incidence of EPS and somnolence in relation to the prescribed dose.	Physician completed survey characterizing patients treated with quetiapine XL in the general practice setting in England or the treatment of schizophrenia, manic and depressive episodes associated with bipolar disorder, and as add-on therapy for major depressive disorder	>12,000 patients; 500 elderly patients (i.e., age >65 yrs) treated with XL for bipolar disorder and 500 elderly patients treated for major depressive disorder Nested case control study includes cases of EPS and somnolence/sedation (including drowsiness)	12 months following first treatment with quetiapine XL	**Original protocol**: 9 Dec 2009 **Protocol amendment:** 22 June 2010 (revised questionnaire included date of BMI measurement) **Annual Progress Report:**: January 2011 **Interim PEM Report**: 31 Jan 2011 **Expanded case definition to include all cases of bipolar disorder initiated**: Oct 2011 **Protocol amendment**: December 2011 (to include 1000 patients with MDD including 500 elderly) **Annual Progress Report**: February 2011 **Annual Progress Report**: February 2012 **Annual Progress Report**: February 2013 **Main study**: December 2013 Nested case control study report (on somnolence): December 2014 Clinical Study Report (on EPS): 13 October 2014	Completed

Table 1 Synopsis of on-going and completed pharmacoepidemiological study programme

Study	Research question	Study design	Population and study size	Duration of follow up	Milestones and dates	Status
GPRD study (cohort study with nested case-control studies)	1) to characterize new users of quetiapine XL as well as new users of other study drugs (i.e. the comparison group) with regard to the indication for which they receive the study drug, diagnosed comorbidities and drug utilization patterns prior to receiving a study drug, and the duration of treatment prior to iscontinuation, 2) to quantify the risk of developing newly diagnosed outcomes of interest in new users of XRQ and in the comparison group(s), namely • death of all causes • suicide/suicide attempt/ suicide ideation • acute myocardial infarction (AMI) • thrombotic or hemorrhagic stroke • diabetes mellitus • hypothyroidism • neuroleptic malignant syndrome • fractures • syncope • extrapyramidal symptoms associated with new use of parasympaticolytic drugs • seizures • cataract	UK-based computerized database of anonymized longitudinal medical records from primary care, specifically, the General Practice Research Database (GPRD); patients treated with quetiapine XL	Patients treated with quetiapine XL for approved indications- from earliest use of quetiapine XL for schizophrenia in November 2008 through June 2012 6025 patients receiving quetiapine XL through June 2012 (2265 patients were treated with XL exclusive, 3760 have been treated with both formulations of quetiapine) In nested case-control studies controls not experiencing events of interest are matched to cases in a ratio of 8:1	A minimum follow-up period of six months; also to include patients with a minimum follow-up of 12 months)	Original protocol dated: 14 Dec 2007 Annual Progress Report: April 2010 Protocol amendment: 7 October 2010 (to include patients treated with quetiapine XL for MDD) Annual Progress Report: April 2011 Annual Progress Report: May 2012 Annual Progress Report: May 2013 Final report: September 2013	Completed

Table 1 Synopsis of on-going and completed pharmacoepidemiological study programme

Study	Research question	Study design	Population and study size	Duration of follow up	Milestones and dates	Status
HEM/OASIS (exposure only cohort study)	To monitor the short-term (up to 12 weeks) use and safety of quetiapine XL and quetiapine IR prescribed to patients with a clinical diagnosis of schizophrenia, plus manic episodes associated with bipolar disorder by psychiatrists under normal conditions of use a) to compile a cohort of all eligible psychiatrists b) to recruit cohorts of patients newly initiated on quetiapine (immediate release and prolonged release formulations) c) to examine the safety and use in new users of both quetiapine formulations with particular interest in the following: i) drug utilisation characteristics ii) to compare rates of events reported by psychiatrists for patients taking high dose (> 600mg) quetiapine XL to high dose (>600mg) quetiapine IR iii) to compare event rates between patients receiving low dose quetiapine XL (< 600mg) and patients receiving high dose quetiapine XL (> 600 mg). iv) to further quantify and explore the pattern of selected events reported by psychiatrists for patients taking quetiapine over time	Physician completed survey characterizing patients treated with quetiapine XL in the mental health trust setting in the UK	934 patients recruited from the mental health trusts in England. 24 % of 809 evaluable patients (based on interim safety report, January 2013) had been treated with IR. Approximately 5% of those treated with IR had received a dose >600 mg/d. 612/809= 76% had been treated with XL. Approximately 13% of those treated with XL has receved a dose > 600 mg/d.	12 weeks from date of first treatment with quetiapine XL	Protocol date: 31 May 2009 Interim Report: August 2010 Revised protocol: 25 December 2011 (recruitment of add'l junior psychiatrists Interim and Annual Report: Feb 2011 Annual Report: Feb 2012 Annual Report: Mar 2013 Final Report: August 2013	Completed
Swedish Record Linkage	1.To assess the feasibility of using a record linkage approach to studying	Data linkage of the following population-	The study encompassed	The drug utilization study is	Protocol date: 18 June 2010 Protocol	Completed

Table 1 Synopsis of on-going and completed pharmacoepidemiological study programme

Study	Research question	Study design	Population and study size	Duration of follow up	Milestones and dates	Status
study (population-based cohort study with nested case-control studies included)	the use and safety of Seroquel XR through a pilot study prior to approval in the MDD indication. 2a.To characterize patients dispensed Seroquel XR for the treatment of MDD, in add-on therapy, in monotherapy (if any), and compare with patients treated for MDD with other antidepressants (AD) either as add-on therapy or in monotherapy. 2b.To characterize doses, durations of treatments, treatments changes in patients dispensed Seroquel XR or other AD for MDD, as well as trend over time in usage, and specialty of prescriber. 3. To study the incidence rates of specific outcomes of interest and compare MDD patients treated with Seroquel XR as add-on to those treated with other AD. The outcomes of interest: acute MI, Stroke, Suicide, Diabetes mellitus, EPS, Somnolence, and death from all causes.	based data registers in Sweden is to be performed: Prescription Drug Register, including all purchases of prescribed drugs at pharmacies (dispensed drugs), National Patient Register which contains information on hospitalizations, outpatient visits at hospitals, including day surgery carried out by both private and public caregivers Cause of Death Register which contains data on all deaths from 1961. The data collected includes underlying and contributing causes of death, in addition to about 30 other variables (however, there is a lag time of up to 2 years). Population Register contains information on dates of emigration and death for all patients. It is to be used to ascertain time at risk for all patients included in the study.	2 cohorts of users, a treatment change cohort (which was comprised of 7421 quetiapine users and 281303 users of other antidepressants) and a new-user cohort (which was comprised of 819 quetiapine users and 37953 users of other antidepressants); both were followed up to estimate crude event rates of the 7 outcomes of interest. For each outcome, nested case-control analyses were performed. For each occurrence of an outcome, up to 5 controls were selected using incidence density sampling among those who were alive and had not experienced an outcome event.	planned to start three months after launch in Sweden (January 2011) and collect data for the following 2 years. The start date of the observation period for the Safety study coincided with the date of launch in Sweden (January 2011) and continued through December 2014. In the safety evaluation study all patients were censored after 12 months of observation for development of the study outcomes.	amendment: 10 October 2010 Annual Report: July 2011 Annual Report : July 2012 Annual Report : July 2013 Annual Report : July 2014 Annual Report: June 2015 Submission of the Pilot Study Report: November 2012 Submission of safety evaluation report: December 2016.	

Table 1 Synopsis of on-going and completed pharmacoepidemiological study programme

Study	Research question	Study design	Population and study size	Duration of follow up	Milestones and dates	Status
EU Drug Utilisation study (drug utilisation cohort study)	1.Document characteristics of patients under specialist (psychiatric) care who are prescribed Seroquel XR as treatment for MDD in each of the selected countries over a 9 month period, starting 3 months following the launch of the product for its approved indication. 2. Describe differences between countries concerning treatment practices involving use of Seroquel XR through the use of a drug utilisation questionnaire of psychiatrist in 5 European countries	Data is abstracted from the medical records of patients with MDD who were treated with quetiapine XL by psychiatrists from different practice settings in Germany, Spain, Italy, Romania and Sweden. Data abstracted includes characteristics of the participating psychiatrist, patients' medical and psychiatric history, and the drugs utilised in the medical management of MDD.	Up to 25 investigational sites per country for a total of 100-400 patients per country. The target enrolment is 300-400 patients per country.	An inception cohort defined by patients initiating Seroquel XR (as add-on therapy or as monotherapy) during a 9 month period corresponding to 3 to 12 months following the launch of the product in each country for the MDD indication	Protocol: 16 June 2010 Protocol amendment: 14 April 2011 SAB meeting 5 July 2011 Pilot study completed: 13 April 2012 Protocol amendment: 03 May 2012 Annual Report: July 2011 SAB meeting: 9 Mar 2012 Interim report: February 2013 Annual Report: July 2012 Annual Report: July 2013 Annual Report: July 2014 Final report: May 2015 Submission of the DU Study, 1st Report: June 2013 Submission of the DU Study, 2nd Report: May 2014	Completed
D1443C00091 A naturalistic study of	To describe patient characteristics (demographic and clinical) and the patterns of use of Quetiapine XR in	Patients of psychiatrists receiving Quetiapine XR for the first time in	Patients treated with Seroquel among 425 psychiatrists in France	12 months	Protocol date: 19 Dec 2011 Interim report: December	Completed

Table 1 Synopsis of on-going and completed pharmacoepidemiological study programme

Study	Research question	Study design	Population and study size	Duration of follow up	Milestones and dates	Status
quetiapine XR use in France (cohort study)	patients receiving the drug for the first time in real-life practice. Secondary objectives: - to assess the patient's health and healthcare utilization up to one year after receiving Quetiapine XR -to evaluate representativeness of the schizophrenia or acute bipolar disease Quetiapine XR treated patients in the context of all schizophrenia or acute bipolar disease patients and identify the potential level of channelling bias. - the proportion of patients experiencing AEs & SAEs possibly related to Quetiapine XR, including those leading to discontinuation of treatment are presented	the inclusion period with a diagnosis of schizophrenia or bipolar disorder. The prescription of the medicinal product is clearly separated from the decision to include the subject in the study	who are expected to participate in the study		2014 Final report: December 2015	
D1443C00127 Physician survey on monitoring of patients treated with quetiapine	Survey physicians' receipt of educational materials and assess through self-report their activity monitoring patients treated with Seroquel®, Seroquel® XL or quetiapine fumarate. The evaluation of monitoring includes the recording of weight at initiation and during treatment, testing of lipids, evaluation of signs and symptoms of hyperglycemia, testing of plasma glucose of patients with diabetes, and in a similar fashion testing blood glucose for worsening of glycemic control in patients with risk factors for diabetes.	This is a cross sectional survey that will be conducted over the course of 3-4 months	Survey responses from General Practitioners and specialist physicians (i.e., psychiatrists and neurologists) from each of eight selected countries representing the geographic diversity of the EU (UK, Germany, Sweden, Romania, Spain, Hungary, Italy and Austria) 100 physicians in each of eight EU countries	NA	Protocol date: 11 Dec 2012 Final report: December 2013	Completed

Table 1 Synopsis of on-going and completed pharmacoepidemiological study programme

Study	Research question	Study design	Population and study size	Duration of follow up	Milestones and dates	Status
D1443C00128 EMR data to assess monitoring of patients treated with quetiapine	Evaluate electronic medical record data to assess the medical monitoring performed by physicians during encounters with patients diagnosed with schizophrenia, bipolar disorder or major depressive disorder who were being treated with Seroquel®, Seroquel® XL or quetiapine fumarate. Assessment of the monitoring includes: recording of weight at initiation and during treatment, testing of lipids, evaluation of signs and symptoms of hyperglycemia, testing of plasma glucose of patients with diabetes, and in a similar fashion testing for worsening of glycemic control in patients with risk factors for diabetes.	IMS's LifeLink Electronic Medical Record (EMR)-EU comprised of longitudinal patient-level data from physician-practice data systems of office-based physicians in the UK and Germany. The data includes basic demographics, medical diagnoses, linked prescriptions, lab tests and notes (entered in fixed fields) related to patient status as recorded during medical encounters	The levels of measurement will be at the physician practice and at the patient level. Based on the study eligibility criteria, inclusion of approximately 800 patients in each country is anticipated	Patient encounters recorded in IMS Disease Analyzer in Germany during the calendar period 13 February 2012 - 31 August 2012 and for patient encounters with in the UK during 11 January 2012 - 31 July 2012	Protocol date: 19 Dec 2012 Final report: December 2013	Completed

AD antidepressants; AE adverse event; AMI acute myocardial infarction; BMI body mass index; EMR electronic medical record; EPS extrapyramidal symptoms; EU European Union; GPRD General Practice Research Database; HEM hospital-event monitoring; IR immediate release; MDD major depressive disorder; m-PEM modified prescription-event monitoring; NA not applicable; PEM prescription-event monitoring; SAE serious adverse event; UK United Kingdom; XL prolonged release; XR extended release.

EU RMP Part VII Annex 6

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	06 December 2016

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR SEROQUEL/SEROQUEL XR

Part VII ANNEX 6 - PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN CATEGORIES 1-3 OF THE SECTION "SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES" IN RMP PART III

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL® and SEROQUEL XR®
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

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1. PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN CATEGORIES 1-3 OF THE SECTION "SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES" IN RMP PART III

There are no applicable studies.

EU RMP Part VII Annex 7

Drug Substance	Quetiapine fumarate
Version Number of RMP /PRMP when last updated	13
Data lock point for this module	12 June 2014

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® AND SEROQUEL XR®)

Part VII ANNEX 7 - SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL® and SEROQUEL XR®
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

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1. SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Routine pharmacovigilance practices for quetiapine include targeted use of questionnaires for the following specific concerns; the questionnaires are presented in the order presented below.

- Cardiac events including QT prolongation, Sudden death, Torsades de pointes
- Cataract
- Cerebrovascular disorders
- Diabetes-related data
- Ischaemic heart disease
- Liver injury
- Cardiomyopathy and Myocarditis
- Pancreatitis
- Muscle data collection (including Rhabdomyolysis)
- Serotonin syndrome
- Suicide-related events
- Toxic skin reactions

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SERIOUS CARDIAC EVENTS DATA COLLECTION FORM

Date Received by AstraZeneca (dd/mm/yyyy):_____

Clintrace/AZ reference #: _____

AstraZeneca drug: _____

AstraZeneca study number (if applicable): _____

Instructions for : ☐ Investigator ☐ Clintrace Data Entry Site ☐ Marketing companies
This questionnaire should be completed for the following events (PTs)
Please provide verbatim term as report by reporter/investigator

Patient details

Initials:	**Age (years):**

Weight:	**Height:**	**Ethnic Origin:**
☐ lbs. ☐ kgs.	☐ ins. ☐ cms.	

Gender:

☐ F ☐ M

Reporter details

Reporter Name:	**Date of this report (dd/mm/yyyy):**
(Optional) Reporter Address:	**Reporter's Signature:**
Telephone Number:	

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QT related events

Reported events

(If available and appropriate, the total duration of event should be reported [sec/min/hr]; also note if event was repetitive [for example 2 episodes of 20 second TdP])

Adverse event	Start date (dd/mm/yyyy)	Stop date (dd/mm/yyyy)	Outcome	
			☐ Recovered ☐ Ongoing ☐ Improved	☐ Recovered with sequelae ☐ Death ☐ Worsened
			☐ Recovered ☐ Ongoing ☐ Improved	☐ Recovered with sequelae ☐ Death ☐ Worsened
			☐ Recovered ☐ Ongoing ☐ Improved	☐ Recovered with sequelae ☐ Death ☐ Worsened

If patient recovered but with sequelae please describe here:

Please include cause of death and a description of events:

If patient died was an autopsy performed? ☐ Yes ☐ No *(If yes, please provide relevant results)*

Associated signs and symptoms

		Start date (mm/dd/yyyy)	Stop date (mm/dd/yyyy)	Additional information
Palpitations	☐ Yes ☐ No			
Dizziness	☐ Yes ☐ No			
Pre-syncope	☐ Yes ☐ No			
Syncope	☐ Yes ☐ No			
Chest pain	☐ Yes ☐ No			
Cardiac arrest	☐ Yes ☐ No			
Other	☐ Yes ☐ No			

ECG information data

	Baseline exam Date (mm/dd/yyyy) ____/____/_____	Follow-up ECGs Date (mm/dd/yyyy) ____/____/_____	Follow-up ECGs Date (mm/dd/yyyy) ____/____/_____
Source	☐ 12 Lead ☐ 1 or 2 lead telemetry ☐ Holter ☐ Implanted device ☐ Other _____	☐ 12 Lead ☐ 1 or 2 lead telemetry ☐ Holter ☐ Implanted device ☐ Other _____	☐ 12 Lead ☐ 1 or 2 lead telemetry ☐ Holter ☐ Implanted device ☐ Other _____
ECG interpreted by:	☐ Central lab ☐ Physician ☐ Other	☐ Central lab ☐ Physician ☐ Other	☐ Central lab ☐ Physician ☐ Other
Timing of ECG:	☐ Prior to first dose ☐ During dosing ☐ After last dose	☐ Prior to first dose ☐ During dosing ☐ After last dose	☐ Prior to first dose ☐ During dosing ☐ After last dose
Recording situation	☐ Pt at rest 10 mins before ECG ☐ ECG taken as emergency ☐ Other (describe) _____	☐ Pt at rest 10 mins before ECG ☐ ECG taken as emergency ☐ Other (describe) _____	☐ Pt at rest 10 mins before ECG ☐ ECG taken as emergency ☐ Other (describe) _____
Overall quality of ECG			

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	Baseline exam Date (mm/dd/yyyy) ____/____/______	**Follow-up ECGs Date (mm/dd/yyyy)** ____/____/______	**Follow-up ECGs Date (mm/dd/yyyy)** ____/____/______
Describe how ECG was read (if known): (For example: What lead was used for measurements? Was the QT calculated as an average of 3 beats or more?)			
Heart rate	__________beats/minute	__________beats/minute	__________beats/minute
Rhythm			
PR interval (ms) (normal 120-200 msec)			
QRS interval (msec) (normal <100 ms)			
QTc (sec) Normal (≤0.44 sec) *please specify correction method*			
QRS axis (degrees)			
U wave amplitude (mm) (normal ≤0.1 mm) Polarity (normal=same as T)			
T-wave alternans	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Notched or biphid T-wave in 3 leads	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Torsade de pointes	☐ Yes ☐ No (if yes, answer questions below) How many beats? _________ Rate: _________ Duration: _________ Polymorphic ☐ Yes ☐ No Isolated or repetitive episodes? (circle one) Other episodes of monomorphic VT? ☐ Yes ☐ No	☐ Yes ☐ No (if yes, answer questions below) How many beats? _________ Rate: _________ Duration: _________ Polymorphic ☐ Yes ☐ No Isolated or repetitive episodes? (circle one) Other episodes of monomorphic VT? ☐ Yes ☐ No	☐ Yes ☐ No (if yes, answer questions below) How many beats? _________ Rate: _________ Duration: _________ Polymorphic ☐ Yes ☐ No Isolated or repetitive episodes? (circle one) Other episodes of monomorphic VT? ☐ Yes ☐ No

	Baseline exam Date (mm/dd/yyyy) ____/____/_____	Follow-up ECGs Date (mm/dd/yyyy) ____/____/_____	Follow-up ECGs Date (mm/dd/yyyy) ____/____/_____
Other information:			

Suspect drug(s): *(Please only include drugs considered to be causally related to the adverse event(s) and not concomitant medications)*

Suspect Drug Name *Provide formulation if applicable*	Indication	Daily Dose	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Was this medication withdrawn or dose altered?
					☐ Yes, prior to event ☐ Yes, after event ☐ No
					☐ Yes, prior to event ☐ Yes, after event ☐ No
					☐ Yes, prior to even ☐ Yes, after event ☐ No

If any of the above drug(s) were withdrawn, what was the reason? ☐ Yes ☐ No ☐ n/a
If applicable, please provide name of drug(s)withdrawn

If any of the above drug(s) were withdrawn, did the event(s) improve after stopping? ☐ Yes ☐ No ☐ n/a
If applicable, please provide name of drug(s)withdrawn

Was the drug(s) re-introduced? ☐ Yes ☐ No
If yes, please provide each date drug was re-introduced

Did the event(s) reoccur/worsen after reintroduction? ☐ Yes ☐ No ☐ n/a
If yes, please provide date that event recurred.

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Medical history or risk factors relevant for the event

Disorder or risk factors			Onset date (dd/mm/yyyy)	If yes, please provide details
Atrial arrhythmia	☐ Yes ☐ No	☐ Current ☐ Past		
Ventricular arrhythmia	☐ Yes ☐ No	☐ Current ☐ Past		
Other arrhythmia	☐ Yes ☐ No	☐ Current ☐ Past		
Coronary artery disease	☐ Yes ☐ No	☐ Current ☐ Past		
Acute coronary syndrome	☐ Yes ☐ No	☐ Current ☐ Past		
Congestive hear failure	☐ Yes ☐ No	☐ Current ☐ Past		
Cardiomyopathy	☐ Yes ☐ No	☐ Current ☐ Past		
Prolonged QTc interval	☐ Yes ☐ No	☐ Current ☐ Past		
Hypertension	☐ Yes ☐ No	☐ Current ☐ Past		
Ventricular hypertrophy	☐ Yes ☐ No	☐ Current ☐ Past		
Cardiac pacemaker or device	☐ Yes ☐ No	☐ Current ☐ Past		
Hypokalemia	☐ Yes ☐ No	☐ Current ☐ Past		
Recent cerebral event (including brain metastases)	☐ Yes ☐ No	☐ Current ☐ Past		
Malignant condition	☐ Yes ☐ No	☐ Current ☐ Past		
Perioperative condition (specify type of surgery and body location)				
Family history of unexplained sudden cardiac death	☐ Yes ☐ No	☐ Current ☐ Past		

Family history of prolonged QTc	☐ Yes ☐ No	☐ Current ☐ Past		
Family history of congenital deafness	☐ Yes ☐ No	☐ Current ☐ Past		
Other relevant concomitant medical conditions (*If any please specify*) ☐ Yes ☐ No				
Nutritional problems (*If any please specify*) ☐ Yes ☐ No				

Concomitant medication(s): (*Include all prescription, OTC drugs, herbal/dietary supplements. Exclude suspect drugs listed above*)

Drug(s): Exclude drugs used to treat the event	**Indication for use**	**Daily Dose**	**Start Date (dd/mm/yyyy)**	**Stop Date (dd/mm/yyyy)**	**Was this medication withdrawn?**
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a

Laboratory values

Laboratory parameter	Baseline Date (dd/mm/yyyy) ____/____/_____		Follow-up Date (dd/mm/yyyy) ____/____/_____		Follow-up Date (dd/mm/yyyy) ____/____/_____		Follow-up Date (dd/mm/yyyy) ____/____/_____		Follow-up Date (dd/mm/yyyy) ____/____/_____	
Serum potassium		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum magnesium		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum calcium (total)		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum calcium (ionized)		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum sodium		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum creatinine		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L

Please provide any other relevant information:

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QT PROLONGATION DATA COLLECTION FORM

Date Received by AstraZeneca (dd/mm/yyyy):_____

Clintrace/AZ reference #: _____

AstraZeneca drug: _____

AstraZeneca study number (if applicable): _____

Instructions for :	☐ Investigator ☐ Clintrace Data Entry Site ☐ Marketing companies
This questionnaire should be completed for the following events (PTs)	
Please provide verbatim term as report by reporter/investigator	

Patient details

Initials:	**Age (years):**

Weight:	**Height:**	**Ethnic Origin:**
☐ lbs. ☐ kgs.	☐ ins. ☐ cms.	

Gender:

☐ F ☐ M

Reporter details

Reporter Name:	**Date of this report (dd/mm/yyyy):**
(Optional) Reporter Address:	**Reporter's Signature:**
Telephone Number:	

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QT related events

Reported events

(If available and appropriate, the total duration of event should be reported [sec/min/hr]; also note if event was repetitive [for example 2 episodes of 20 second TdP])

Adverse event	Start date (dd/mm/yyyy)	Stop date (dd/mm/yyyy)	Outcome	
			☐ Recovered ☐ Ongoing ☐ Improved	☐ Recovered with sequelae ☐ Death ☐ Worsened
			☐ Recovered ☐ Ongoing ☐ Improved	☐ Recovered with sequelae ☐ Death ☐ Worsened
			☐ Recovered ☐ Ongoing ☐ Improved	☐ Recovered with sequelae ☐ Death ☐ Worsened

If patient recovered but with sequelae please describe here:

Please include cause of death and a description of events:

If patient died was an autopsy performed? ☐ Yes ☐ No *(If yes, please provide relevant results)*

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Associated signs and symptoms

		Start date (mm/dd/yyyy)	Stop date (mm/dd/yyyy)	Additional information
Palpitations	☐ Yes ☐ No			
Dizziness	☐ Yes ☐ No			
Pre-syncope	☐ Yes ☐ No			
Syncope	☐ Yes ☐ No			
Chest pain	☐ Yes ☐ No			
Cardiac arrest	☐ Yes ☐ No			
Other	☐ Yes ☐ No			

ECG information data

	Baseline exam Date (mm/dd/yyyy) ____/____/_____	Follow-up ECGs Date (mm/dd/yyyy) ____/____/_____	Follow-up ECGs Date (mm/dd/yyyy) ____/____/_____
Source	☐ 12 Lead ☐ 1 or 2 lead telemetry ☐ Holter ☐ Implanted device ☐ Other _____	☐ 12 Lead ☐ 1 or 2 lead telemetry ☐ Holter ☐ Implanted device ☐ Other _____	☐ 12 Lead ☐ 1 or 2 lead telemetry ☐ Holter ☐ Implanted device ☐ Other _____
ECG interpreted by:	☐ Central lab ☐ Physician ☐ Other	☐ Central lab ☐ Physician ☐ Other	☐ Central lab ☐ Physician ☐ Other
Timing of ECG:	☐ Prior to first dose ☐ During dosing ☐ After last dose	☐ Prior to first dose ☐ During dosing ☐ After last dose	☐ Prior to first dose ☐ During dosing ☐ After last dose
Recording situation	☐ Pt at rest 10 mins before ECG ☐ ECG taken as emergency ☐ Other (describe) _____	☐ Pt at rest 10 mins before ECG ☐ ECG taken as emergency ☐ Other (describe) _____	☐ Pt at rest 10 mins before ECG ☐ ECG taken as emergency ☐ Other (describe) _____
Overall quality of ECG			

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	Baseline exam Date (mm/dd/yyyy) ____/____/______	Follow-up ECGs Date (mm/dd/yyyy) ____/____/______	Follow-up ECGs Date (mm/dd/yyyy) ____/____/______
Describe how ECG was read (if known): (For example: What lead was used for measurements? Was the QT calculated as an average of 3 beats or more?)			
Heart rate	__________beats/minute	__________beats/minute	__________beats/minute
Rhythm			
PR interval (ms) (normal 120-200 msec)			
QRS interval (msec) (normal <100 ms)			
QTc (sec) Normal (≤0.44 sec) *please specify correction method*			
QRS axis (degrees)			
U wave amplitude (mm) (normal ≤0.1 mm) Polarity (normal=same as T)			
T-wave alternans	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Notched or biphid T-wave in 3 leads	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Torsade de pointes	☐ Yes ☐ No (if yes, answer questions below) How many beats? __________ Rate: __________ Duration: __________ Polymorphic ☐ Yes ☐ No Isolated or repetitive episodes? (circle one) Other episodes of monomorphic VT? ☐ Yes ☐ No	☐ Yes ☐ No (if yes, answer questions below) How many beats? __________ Rate: __________ Duration: __________ Polymorphic ☐ Yes ☐ No Isolated or repetitive episodes? (circle one) Other episodes of monomorphic VT? ☐ Yes ☐ No	☐ Yes ☐ No (if yes, answer questions below) How many beats? __________ Rate: __________ Duration: __________ Polymorphic ☐ Yes ☐ No Isolated or repetitive episodes? (circle one) Other episodes of monomorphic VT? ☐ Yes ☐ No

	Baseline exam Date (mm/dd/yyyy) ____/____/_____	Follow-up ECGs Date (mm/dd/yyyy) ____/____/_____	Follow-up ECGs Date (mm/dd/yyyy) ____/____/_____
Other information:			

Suspect drug(s): *(Please only include drugs considered to be causally related to the adverse event(s) and not concomitant medications)*

Suspect Drug Name *Provide formulation if applicable*	Indication	Daily Dose	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Was this medication withdrawn or dose altered?
					☐ Yes, prior to event ☐ Yes, after event ☐ No
					☐ Yes, prior to event ☐ Yes, after event ☐ No
					☐ Yes, prior to even ☐ Yes, after event ☐ No

If any of the above drug(s) were withdrawn, what was the reason? ☐ Yes ☐ No ☐ n/a
If applicable, please provide name of drug(s)withdrawn

If any of the above drug(s) were withdrawn, did the event(s) improve after stopping? ☐ Yes ☐ No ☐ n/a
If applicable, please provide name of drug(s)withdrawn

Was the drug(s) re-introduced? ☐ Yes ☐ No
If yes, please provide each date drug was re-introduced

Did the event(s) reoccur/worsen after reintroduction? ☐ Yes ☐ No ☐ n/a
If yes, please provide date that event recurred.

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Medical history or risk factors relevant for the event

Disorder or risk factors			Onset date (dd/mm/yyyy)	If yes, please provide details
Atrial arrhythmia	☐ Yes ☐ No	☐ Current ☐ Past		
Ventricular arrhythmia	☐ Yes ☐ No	☐ Current ☐ Past		
Other arrhythmia	☐ Yes ☐ No	☐ Current ☐ Past		
Coronary artery disease	☐ Yes ☐ No	☐ Current ☐ Past		
Acute coronary syndrome	☐ Yes ☐ No	☐ Current ☐ Past		
Congestive hear failure	☐ Yes ☐ No	☐ Current ☐ Past		
Cardiomyopathy	☐ Yes ☐ No	☐ Current ☐ Past		
Prolonged QTc interval	☐ Yes ☐ No	☐ Current ☐ Past		
Hypertension	☐ Yes ☐ No	☐ Current ☐ Past		
Ventricular hypertrophy	☐ Yes ☐ No	☐ Current ☐ Past		
Cardiac pacemaker or device	☐ Yes ☐ No	☐ Current ☐ Past		
Hypokalemia	☐ Yes ☐ No	☐ Current ☐ Past		
Recent cerebral event (including brain metastases)	☐ Yes ☐ No	☐ Current ☐ Past		
Malignant condition	☐ Yes ☐ No	☐ Current ☐ Past		
Perioperative condition (specify type of surgery and body location)				
Family history of unexplained sudden cardiac death	☐ Yes ☐ No	☐ Current ☐ Past		

Family history of prolonged QTc	☐ Yes ☐ No	☐ Current ☐ Past		
Family history of congenital deafness	☐ Yes ☐ No	☐ Current ☐ Past		
Other relevant concomitant medical conditions (*If any please specify*) ☐ Yes ☐ No				
Nutritional problems (*If any please specify*) ☐ Yes ☐ No				

Concomitant medication(s): (*Include all prescription, OTC drugs, herbal/dietary supplements. Exclude suspect drugs listed above*)

Drug(s): Exclude drugs used to treat the event	**Indication for use**	**Daily Dose**	**Start Date (dd/mm/yyyy)**	**Stop Date (dd/mm/yyyy)**	**Was this medication withdrawn?**
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a

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Laboratory values

Laboratory parameter	Baseline Date (dd/mm/yyyy) ____/____/_____		Follow-up Date (dd/mm/yyyy) ____/____/_____		Follow-up Date (dd/mm/yyyy) ____/____/_____		Follow-up Date (dd/mm/yyyy) ____/____/_____		Follow-up Date (dd/mm/yyyy) ____/____/_____	
Serum potassium		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum magnesium		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum calcium (total)		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum calcium (ionized)		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum sodium		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L
Serum creatinine		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L		☐ mg/dL ☐ mmol/L

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Please provide any other relevant information:

Adverse Event Report – additional information

Cataract Checklist Case Number:_____

Reporter's name:	**Reporter's address:**	**Telephone no:**
Date:		**Fax no:**
Patient Initials:	**Sex:** ☐ **M** ☐ **F**	**Date of Birth/Age:** /
Patient's Occupational History:	**Patient's eye color:**	**Patient's race:**

Relevant Medical History

1. Family history of cataract:	☐ Yes	☐ No	*Specify* ……....
2. Patient history of eye disease	☐ Yes	☐ No	*Specify* ……....
3. Patient history of congenital eye disease/anomaly:	☐ Yes	☐ No	*Specify* ……....
4. Patient history of trauma to the eye:	☐ Yes	☐ No	*Specify* ……....
5. Patient history of eye surgery:	☐ Yes	☐ No	*Specify* ……....
6. History of smoking:	☐ Smoker	☐ Previous smoker	☐ Non-smoker
	Please specify how much and how long (pack/day)		
7. Patient history of substance abuse: drug abuse	☐ Yes	☐ No	*Specify* ……....
alcohol abuse	☐ Yes	☐ No	
8. Concomitant medical conditions:	☐ Yes	☐ No	
If any, please specify			
9. Nutritional problems:	☐ Yes	☐ No	
If yes, please specify			

Drug Therapy

10. Suspected Medication(s) :	**Indication For Use:**	**Daily Dosage:**	**Start Date:**	**Stop Date:**	**Action Taken**
			___/___/___	___/___/___	
			___/___/___	___/___/___	

11. Other Current Medication(s):	**Indication For Use:**	**Daily Dosage:**	**Start Date:**	**Stop Date:**
			___/___/___	___/___/___
			___/___/___	___/___/___
			___/___/___	___/___/___
			___/___/___	___/___/___
			___/___/___	___/___/___

Please list additional concomitant medication data on the back of this page

12. Previous or current corticosteroid or antipsychotic medications:

a) Corticosteroids: ☐ Yes *Please check appropriate category* __ *systemic* __ *inhalant* __ *topical* ☐ No

b) Antipsychotics: ☐ Yes ☐ No

Please specify below for past medications. If current please specify in the Suspected or Current Medications tables above as appropriate.

13. Past Medication(s):	**Indication For Use:**	**Daily Dosage:**	**Start Date:**	**Stop Date:**
			___/___/___	___/___/___
			___/___/___	___/___/___
			___/___/___	___/___/___
			___/___/___	___/___/___

Please forward the forms to AstraZeneca Drug Safety
Fax: (302)886-4114 or (302)886-5886
Thank you.

Adverse Event Report – additional information

Cataract Checklist Case Number:_____

Details of Adverse Event(s)

14. Description of cataract:

a) Where was the cataract? ☐ Right eye ☐ Left eye ☐ Both eyes (bilateral) ☐ Unknown

b) Was visual acuity affected? ☐ Yes ☐ No ☐ Unknown
If known, please specify visual acuity in the table below.

c) Was cataract surgery performed? ☐ Yes ☐ No ☐ Unknown
If yes, please specify right eye and/or left eye……..

d) Cataract location:

Right eye	**Left eye**
☐ Anterior Subcapsular	☐ Anterior Subcapsular
☐ Cortical	☐ Cortical
☐ Nuclear	☐ Nuclear
☐ Posterior Subcapsular	☐ Posterior Subcapsular
☐ Other *(specify)*	☐ Other *(specify)*
☐ Don't know	☐ Don't know

Eye Examination	**Baseline Exam & Dates of Exam**	**Followup Exam & Dates of Exam**
Was a baseline eye examination performed? *yes/no* **Was a follow-up eye examination done?** *yes/no*		
Visual acuity in the right eye (OD)		
Visual acuity in the left eye (OS)		
Was a slit lamp or ophthalmoscope used? *(please specify which)*		
Was/were the pupil(s) dilated with mydriatic drops?		
Was there anything abnormal detected? *(Please describe any abnormalities)*		
Who performed the eye examination?		
(1) Ophthalmologist		
(2) Optometrist		
(3) Other *(please specify specialty)*		

Did the same examiner perform the baseline and followup eye exams? ☐ Yes ☐ No

Please provide the examiner name: _____

Address: _____

Telephone number: _____

15. Does the examiner feel this is a drug-induced cataract? ☐ Yes ☐ No

Please explain why and indicate suspect drug(s) (see item #10 above)

16. Do you feel this is a drug-induced cataract? ☐ Yes ☐ No

Please explain why and indicate suspect drug(s) (see item #10 above)

Please forward the forms to AstraZeneca Drug Safety
Fax: (302)886-4114 or (302)886-5886
Thank you.

AstraZeneca SEROQUEL® CEREBROVASCULAR DISORDERS QUESTIONNAIRE
(Page 1)

Please **check the appropriate Adverse Event/ Serious Adverse Event Box**:

☐ *Ischemic stroke* ☐ *Transient ischemic attack* ☐ *Hemorrhagic stroke*
☐ *Stroke type unspecified*

Date:	Reporter's Name: Reporter's Specialty:
AE Number:	Reporter's Address: Phone Number:
1. Patient's age:	2. Patient's Gender/ Height/ Weight:
3. **SEROQUEL®** Formulation (*please circle*): IR/ XR/ UNK	4. INDICATION for use of **SEROQUEL®** ?
5. **SEROQUEL®** Start Date? **SEROQUEL®** Stop Date?	6. **SEROQUEL®** Dosage?

7. Was the patient receiving any other medications at the time of the event in addition to on SEROQUEL®? If Yes, please provide drug, dates of use and indication for use

Drug	**Indication**	**Dates of Use**

8. Please **circle** the signs and symptoms observed: **Motor-related symptoms**

- Arm or leg weakness (circle)
- Facial weakness
- Impaired gait
- Ataxia or incoordination
- Diplopia or other abnl eye movements (circle)
- Dysarthria or Dysphagia (circle)

Sensory-type symptoms

- Dizziness/vertigo (circle)
- Impaired vision or visual field defect (circle)
- Sensory deficit in face, arm or leg (circle)

Cognitive or other symptoms

- Sensory neglect
- Amnesia or impaired memory (circle)
- Seizures
- Aphasia
- Impaired consciousness or coma (circle)
- Vegetative state

OTHER: Please specify:

Deleted:

Deleted: .

AstraZeneca SEROQUEL® CEREBROVASCULAR DISORDERS QUESTIONNAIRE

9. Has the patient had or presently have any of the following **risk factors** and/ or **concomitant diseases**? If Yes, please **CIRCLE**

- Prior Transient ischemic attack (TIA)/ Cerebrovascular accident (CVA)/ Myocardial infarction (MI)
- Coronary artery disease (CAD)
- Hypertension (HTN)
- Atrial fibrillation
- Heart valvue malformation
- Mitral valve stenosis
- Diabetes
- Antiphospholipid antibodies
- Obesity
- Hyperlipidemia
- Alcohol/ drug abuse
- Smoker
- Sickle cell disease
- Vascular stenosis
- Hypercoagulable state
- Cardiomyopathy/heart failure
- Other relevant past medical history?
- Any contributory family medical history? Please specify

10. Were any of the following tests used to diagnose the event? **Please Circle or Check the applicable box.**

- Brain Scan: **Yes/ No**. If Yes, then ☐ Magnetic resonance imaging (MRI) ☐ Computed tomography(CT)
- Echocardiogram: **Yes/ No**
- Angiogram: **Yes/ No**. If Yes, then☐ Magnetic resonance imaging (MRI) ☐ Contrast dye
- Abnormal Labs

Please provide any relevant diagnostic results

10. Did the patient *receive any treatment? If Yes,* please specify.

- Tissue plasminogen activator(tPA)
- Aspirin
- Plavix (clopidogrel)

Other: Please specify

Did the patient Improve?

10. Did the symptoms resolve or improve while continuing SEROQUEL® ?

11. Was SEROQUEL stopped? Did the symptoms improve?

12. Did the patient die? If Yes, please provide date of death, cause of death and autopsy as well as toxicology results if done.

Diabetes-Related Adverse Event Report Questionnaire

Date: _____ Reporter's Name: _____

Manufacturer's Case Number: _____
Reporter's Address: _____

Patient Demographic Information

Initials: ___ ___ ___ (Circle One)
Date of Birth (mm/dd/yy): ___/___/___ Weight_____ lbs/kg
Sex: __ male __ female Height_____ inches/cm
BMI (if available)____ Hip Circumference _____ inches/cm
BMI (baseline)_____ Waist Circumference ____ inches/cm

Primary Suspect Drug Information

Indication for therapy: _____ Dose/Frequency_____
Date started: (mm/dd/yy): ___/___/___
Date stopped (mm/dd/yy): ___/___/___
Was the drug discontinued (dechallenge)? ___yes ___ no
Outcome of dechallenge:_____
Was the drug reintroduced? ___yes ___no
If yes: Date drug was reintroduced (mm/dd/yy): ___/___/___
Dose/frequency upon reintroduction: _____
Outcome of rechallenge:_____

Other Medications: Please indicate **S for suspect or C for concomitant**.
Please include all medications one year prior to event.

Medication	S or C	Indication:	Daily Dosage:	Start Date:	Stop Date:	Action Taken
				___/___/___	___/___/___	
				___/___/__	___/___/___	
				___/___/____	__/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/____	__/___/___	
				___/___/____	__/___/___	
				___/___/___	___/___/___	
				___/___/____	__/___/___	
				___/___/____	__/___/___	
				___/___/____	__/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	

Medical History /Concurrent Illness

Condition	Ongoing (Y/N)	Onset Date (mm/dd/yy)	Additional Information
ETOH Use			
Fatty liver			
Family history of diabetes			
FBS ≥ 126 mg/dL			
Gestational Diabetes			
Random Glucose ≥ 200			
Hypertension			
Hyperthyroidism			
Hyperlipidemia			
Metabolic Syndrome (insulin resistance, Syndrome X)*			
Obesity			
Pancreatitis			
Weight Gain		Dates Approx:	Total Wt. Gain:
Smoking			
* Constellation of symptoms including insulin resistance, dyslipidemia characterized by hypertriglyceridemia and low serum HDL, and hypertension.			
Concomitant medical conditions: *If any, please specify*	☐ Yes		
Medications	**Y/N**	**Provide dates (only if not in above Medication table)**	**Indication (only if not in above Medication table)**
Beta-agonists e.g. albuterol			
Glucocorticosteroids			
Diazoxide			
Thiazide diuretics			
Thyroid hormone			
Phenytoin			
Oral contraceptives			

Are there any other lifestyle, nutritional or medical issues that could have contributed to the diagnosis of hyperglycemia and/or diabetes?

Has the patient ever been pregnant? If yes, were there any complications of pregnancy?

Birth weights (if available)

If the patient developed Diabetes: **Associated Signs/Symptoms**

Sign/Symptom	Present (Yes/No)	Start Date	Stop Date
Polyuria			
Polydipsia			
Polyphagia			
Other (e.g.fatigue, weakness, dizziness, blurred vision, wt. loss)			

Have there been any acute complications of diabetes? Yes__ No___
(e.g. diabetic ketoacidosis, hyperosmolar coma, renal, other)

Was there a medical condition preceding the complication?
(e.g. infection)
Yes___ No____Unknown____

Has the patient been hospitalized for any events associated with the diagnosis of diabetes? Yes_____ No_____
(Please explain and/or attach hospital discharge summary)

Has the patient received medication for diabetes? **Insulin/Oral Diabetic**	**Daily Dosage:**	**Start Date:**	**Stop Date:**
		___/___/___	___/___/___
		___/___/___	___/___/___
		___/___/___	___/___/___

Laboratory Values /You may attach results if desired.

Laboratory Findings	Baseline yes/no/unk	Baseline results	Date (mm/dd/yy)	Additional Results	Date(s) (mm/dd/yy)	Ref. Range
HgbA1c						
FBS						
Random Bld Glucose						
Glucose Tolerance Test (GTT)						
Urine glucose dipstick						


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ISCHEMIC HEART DISEASE DATA COLLECTION FORM

Adverse Event Report Received by AstraZeneca (dd/mm/yyyy):_____

AZ reference #: _____

AZ Drug: _____

AZ Study # (if applicable): _____ **Subject # (Eno):**_____

The questionnaire should be completed for the following events (PTs)

Please fill in the verbatim term as reported by the reporter/investigator to be able to identify the correct SAE/PMS report

Patient details

Initials:	**Age (years):**

Weight:	**Height:**	**Ethnic Origin:**
☐ lbs. ☐ kgs.	☐ ins. ☐ cms.	

Gender:

☐ F ☐ M

Reporter Name:	**Date of this report (dd/mm/yyyy):**
(Optional) Reporter Address:	**Reporter's Signature:**
Telephone Number:	

ISCHEMIC HEART DISEASE

Table 1 Reported event(s)

Coronary Adverse Event	Start date	Stop date	Intensity (optional column)	Outcome
			☐ Mild ☐ Mod. ☐ Sev	☐ Recovered ☐ Recovered with sequaele# ☐ Ongoing ☐ Death* ☐ Improved ☐ Worsened
			☐ Mild ☐ Mod. ☐ Sev	☐ Recovered ☐ Recovered with sequaele# ☐ Ongoing ☐ Death* ☐ Improved ☐ Worsened
			☐ Mild ☐ Mod. ☐ Sev	☐ Recovered ☐ Recovered with sequaele# ☐ Ongoing ☐ Death* ☐ Improved ☐ Worsened
			☐ Mild ☐ Mod. ☐ Sev	☐ Recovered ☐ Recovered with sequaele# ☐ Ongoing ☐ Death* ☐ Improved ☐ Worsened

** If died, please provide cause and date of death:*

** If died, was an autopsy performed?* ☐ Yes ☐ No

** If applicable, please provide relevant results:*

 # If resolved with sequelae, please provide sequelae:

Suspect drug(s)

Please only include drugs you consider to have a causal relationship to the adverse event(s) and not concomitant medications medications (include any herbal or over-the-counter drugs).

Suspect Drug Name *Provide formulation if applicable*	**Suspect Drug Name (Generic)**	**Indication**	**Daily Dosage**	**Start Date**	**Stop Date**	**Was this suspect medication withdrawn / dose altered?**
						☐ Yes, prior to event ☐ Yes, after event ☐ No
						☐ Yes, prior to event ☐ Yes, after event ☐ No
						☐ Yes, prior to event ☐ Yes, after event ☐ No
						☐ Yes, prior to event ☐ Yes, after event ☐ No
						☐ Yes, prior to event ☐ Yes, after event ☐ No

						☐ Yes, prior to event ☐ Yes, after event ☐ No
						☐ Yes, prior to event ☐ Yes, after event ☐ No
						☐ Yes, prior to event ☐ Yes, after event ☐ No
						☐ Yes, prior to event ☐ Yes, after event ☐ No

If any of the above drug(s) were withdrawn, did the event(s) improve after stopping? ☐ Yes ☐ No ☐ n/a

If applicable, please provide name of drug(s) withdrawn	
Was the drug(s) re-introduced? ☐ Yes ☐ No	
If yes, please provide each date drug was re-introduced:	
Did the event(s) re-occur after reintroduction? ☐ Yes ☐ No ☐ n/a	
If yes, please provide the date the event(s) re-occured:	

Table 2 Current and Past History relevant for the event

Disorder or risk factor			Start year	If yes, please provide details
Previously known ischemic heart disease	☐ Yes ☐ No	☐ Current ☐ Past		
Family history of premature IHD*	☐ Yes ☐ No	☐ Mother ☐ Father ☐ Sibling		
Hypertension	☐ Yes ☐ No	☐ Current ☐ Past		
Dyslipidemia	☐ Yes ☐ No	☐ Current ☐ Past		
Diabetes	☐ Yes ☐ No	☐ Current ☐ Past		

Smoking	☐ Yes ☐ No	☐ Current ☐ Past		
Heart failure	☐ Yes ☐ No	☐ Current ☐ Past		
Congenital heart disease	☐ Yes ☐ No	☐ Current ☐ Past		
Valvular heart disease	☐ Yes ☐ No	☐ Current ☐ Past		
Pericardial disease	☐ Yes ☐ No	☐ Current ☐ Past		
Cardiac arrhythmia	☐ Yes ☐ No	☐ Current ☐ Past		
Cardiomyopathy	☐ Yes ☐ No	☐ Current ☐ Past		
Alcohol consumption	☐ Yes ☐ No	☐ Current ☐ Past		
Drug abuse	☐ Yes ☐ No	☐ Current ☐ Past		
Previous drug reactions	☐ Yes ☐ No	☐ Current ☐ Past		
Other	☐ Yes ☐ No	☐ Current ☐ Past		

*** Female <65 years and/or male <55 years**

Symptoms of ischemic heart disease

Description of symptom(s)*:	**Yes No**	**Start date (dd/mm/yyyy)**	**Stop date (dd/mm/yyyy)**	**Further details/ Specify**
Chest pain on exercise	☐ Yes ☐ No			
Chest pain at rest	☐ Yes ☐ No			
Fatigue	☐ Yes ☐ No			

Breathlessness	☐ Yes ☐ No			
Cardiac arrest	☐ Yes ☐ No			
Other	☐ Yes ☐ No			

Diagnostic evaluation

Description of evaluation(s)*:	**Results**	**Specify abnormality (if possible)**
Electrocardio-graphy (ECG)	☐ Normal ☐ Abnormal ☐ Not done	
Exercise testing	☐ Normal ☐ Abnormal ☐ Not done	
Exercise testing *with imaging* *(e.g., thallium-201 or technetium-99m)*	☐ Normal ☐ Abnormal ☐ Not done	Test:
Echocardiography	☐ Normal ☐ Abnormal ☐ Not done	LVEF=……%
Coronary angiography	☐ Normal ☐ Abnormal ☐ Not done	
Cardiac enzymes *CK*	☐ Normal ☐ Abnormal ☐ Not done	Test: Value=…… (ULN =……)
Cardiac enzymes *Troponin T*	☐ Normal ☐ Abnormal ☐ Not done	Test: Value=…… (ULN =……)
Cardiac enzymes *Troponin N*	☐ Normal ☐ Abnormal ☐ Not done	Test: Value=…… (ULN =……)
Haemoglobin	☐ Normal ☐ Abnormal ☐ Not done	Value=……
Other	☐ Normal ☐ Abnormal ☐ Not done	

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Response to treatment directed towards ischemic heart disease

Did the symptoms and/or signs of ischemic heart disease improve after withdrawal of suspected drug? ☐ **Yes** ☐ **No**

Did the symptoms and/or signs of ischemic heart disease improve after specific treatment? ☐ **Yes*** ☐ **No**

***If yes specify initiated treatment**

IHD treatment	**Yes No**	**Start date (dd/mm/yyyy)**	**Stop date (dd/mm/yyyy)**	**Further details*/ Specify drug and dose**
Beta-adrenoceptor antagonist	☐ Yes ☐ No			
Calcium antagonist	☐ Yes ☐ No			
Nitrate	☐ Yes ☐ No			
Statin	☐ Yes ☐ No			
ACE inhibitor	☐ Yes ☐ No			
Platelet inhibitor	☐ Yes ☐ No			
Anticoagulant	☐ Yes ☐ No			
Thrombolytic	☐ Yes ☐ No			
Other drug(s)	☐ Yes ☐ No			
Revascularisation	☐ Yes ☐ No			☐ PCI ☐ CABG ☐ Unknown

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Consultation

Has a specialist (e.g cardiologist) been consulted? ☐ Yes ☐ No

If yes, please summarize or send a copy of the report in English:

Concomitant medication(s).

Include all prescription and over the counter drugs, herbal and dietary supplements given 1 month prior to liver injury. Suspect drugs excluded (entered on page 2)

Drug(s): Exclude drugs used to treat the event	**Indication**	**Daily Dosage**	**Start Date (dd/mm/yyyy)**	**Stop Date (dd/mm/yyyy)**	**Was this concomitant medication withdrawn?**
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a

Additional information:

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Thank You!

AZ Date of Receipt: _____

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LIVER INJURY DATA COLLECTION FORM

AZ ref: _____

1. Patient Details

Initials:

Sex: ☐ Male ☐ Female

Weight: ☐ lbs. ☐ kgs

Height: ☐ ins. ☐ cms.

Date of Birth or Age:

Ethnic Origin:

2. Hepatic Adverse Event(s):	Start Date	Stop Date	Intensity	Outcome
			☐ Mild ☐ Mod. ☐ Severe	☐ Recovered ☐ Recovered with sequelae# ☐ Event ongoing ☐ Patient Died*
			☐ Mild ☐ Mod. ☐ Severe	☐ Recovered ☐ Recovered with sequelae# ☐ Event ongoing ☐ Patient Died*
			☐ Mild ☐ Mod. ☐ Severe	☐ Recovered ☐ Recovered with sequelae# ☐ Event ongoing ☐ Patient Died*

** If died, Please provide cause and date of death:*

** Please also provide autopsy report if applicable.*

 # If resolved with sequelae, please provide sequelae:

Clinical diagnosis of the event(s):

Was the patient hospitalized for the event(s)? ☐ Yes ☐ No

Did the patient experience any of the following symptoms:

Asthenia	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Fever	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Arthralgia	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Abdominal pain	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Vomiting	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Pruritis	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Purpura	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Skin Rash*	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
* If Yes please specify rash type:								
Jaundice	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Hepatomegaly	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Elevated LFTs#	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Splenomegaly	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
Lymphadeno-pathy*	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	
* If Yes please specify site:								
Ascites	☐ Yes	☐ No	If yes, start date:		Stop Date:		Treatment:	

 # Please provide details in section 7

3. Details of SEROQUEL (quetiapine) Therapy:

Start Date: **Stop Date:** **Dosage:**

Indication:

Was SEROQUEL stopped or the dosage altered due to the event(s)? ☐ Yes, permanently ☐ Yes, temporally ☐ No ☐ n/a

If yes, did the event(s) improve after stopping/altering Seroquel? ☐ Yes ☐ No ☐ n/a

If applicable, please provide date Seroquel was stopped/dosage altered:

Was SEROQUEL re-introduced? ☐ Yes ☐ No ☐ n/a

If yes, did the event(s) reoccur after reintroduction? ☐ Yes ☐ No ☐ n/a

If applicable, please provide date SEROQUEL was re-introduced:

In your medical judgment is there a reasonable possibility that SEROQUEL may have caused the event(s)? ☐ Yes ☐ No

4. Details of Other Suspect Drugs, if applicable:

Please only include other drugs you consider to be causality related to the adverse event(s) and not concomitant medications.

Suspect Drug Name	Indication	Daily Dosage	Route	Start Date	Stop Date	Was this suspect medication withdrawn?
						☐ Yes, prior to event ☐ Yes, after event ☐ No
						☐ Yes, prior to event ☐ Yes, after event ☐ No
						☐ Yes, prior to event ☐ Yes, after event ☐ No

If any of the above drug(s) were withdrawn, did the event(s) improve after stopping? ☐ Yes ☐ No ☐ n/a

If applicable, please provide date drug was stopped/altered:

Did the event(s) reoccur after reintroduction? ☐ Yes ☐ No ☐ n/a

If applicable, please provide date drug was re-introduced:

5. Concomitant Medication(s): Include OTC, herbal, and all meds up to one month prior to event. Exclude drugs used to treat the event	Indication	Daily Dosage	Route	Start Date	Stop Date	Was this concomitant medication withdrawn?
						☐ Yes, prior to event ☐ Yes, after event ☐ No ☐ n/a
						☐ Yes, prior to event ☐ Yes, after event ☐ No ☐ n/a
						☐ Yes, prior to event ☐ Yes, after event ☐ No ☐ n/a
						☐ Yes, prior to event ☐ Yes, after event ☐ No ☐ n/a
						☐ Yes, prior to event ☐ Yes, after event ☐ No ☐ n/a
						☐ Yes, prior to event ☐ Yes, after event ☐ No ☐ n/a
						☐ Yes, prior to event ☐ Yes, after event ☐ No ☐ n/a
						☐ Yes, prior to event ☐ Yes, after event ☐ No ☐ n/a

6. Does the patient possess any of the following risk factors for the event:		Status	Start Date	Stop Date	If yes, please provide details
Hepatobiliary disorder	☐ Yes ☐ No	☐ Current ☐ History			
Pancreatic disorder	☐ Yes ☐ No	☐ Current ☐ History			
Allergy	☐ Yes ☐ No	☐ Current ☐ History			
Drug allergy	☐ Yes ☐ No	☐ Current ☐ History			
Previous drug reactions	☐ Yes ☐ No	☐ Current ☐ History			
Auto-immune disease	☐ Yes ☐ No	☐ Current ☐ History			
Cardiovascular disease	☐ Yes ☐ No	☐ Current ☐ History			
Respiratory conditions	☐ Yes ☐ No	☐ Current ☐ History			
Surgical procedures	☐ Yes ☐ No	☐ Current ☐ History			

Blood transfusion	☐ Yes ☐ No	☐ Current ☐ History			
Alcohol consumption	☐ Yes ☐ No	☐ Current ☐ History			Indicate amount/day and duration
Tattoo or acupuncture	☐ Yes ☐ No	☐ Current ☐ History			
Travel to Asia or Africa	☐ Yes ☐ No	☐ Current ☐ History			
Sexually transmitted diseases	☐ Yes ☐ No	☐ Current ☐ History			
IV drug abuse	☐ Yes ☐ No	☐ Current ☐ History			
Occupational toxic agent exposure	☐ Yes ☐ No	☐ Current ☐ History			

7. Please provide details of any other relevant medical history / concurrent diseases, including approximate dates of diagnosis and resolution if applicable.

8. Laboratory Results.
Please provide details of the following relevant lab tests, if carried out.

Test (insert reference values in brackets)	**Units**	**Baseline Value** (pre-treatment)	**At Event Onset**	**Peak**	**8 days following drug withdrawal**	**30 days following drug withdrawal**	**180 days following drug withdrawal**	**Returned to normal**
	Test Date:							
AST (ULN <.....)								
ALT (ULN <.....)								
GGT (ULN <.....)								
Alk Phos (ULN <.....)								
CPK (ULN <.....)								
Total bilirubin (ULN <.....)								
Albumin (..... to .....)								
Creatinine (..... to .....)								
Urea (..... to .....)								
Prothrombin time (test/control) (..... to .....)								
Haemoglobin (..... to .....)								

WBC (..... to .....)								
Neutrophils (..... to .....)								
Eosinophils (..... to .....)								

Serology:		**Present**	**Test performed and Titre**
Hepatitis A	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Hepatitis B	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Hepatitis C	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Hepatitis D	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Hepatitis E	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Hepatitis F	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Hepatitis G	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Anti-CMV	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Anti-EBV	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Anti-nuclear Ab	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Anti-ds DNA Ab	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Anti-smooth muscle Ab	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Anti-mitochondrial Ab	☐ Not Tested ☐ Tested, date:	☐ Yes ☐ No	
Other serology (specify):	Date:	☐ Yes ☐ No	
Other serology (specify):	Date:	☐ Yes ☐ No	

Other investigations:		Results
Ultrasound	☐ Not Tested ☐ Tested, date:	
CT/MRI	☐ Not Tested ☐ Tested, date:	
Liver biopsy	☐ Not Tested ☐ Tested, date:	
Other (specify):	Date:	
Other (specify):	Date:	

9. Please provide any further relevant information about the Adverse Event

Include any other treatments received that have not been previously stated.

Thank you for completing this form.

AstraZeneca SEROQUEL® CARDIOMYOPATHY/MYOCARDITIS QUESTIONNAIRE
(Page 1)

Please **check the appropriate Adverse Event/ Serious Adverse Event Box**:

☐ *Myocarditis*
☐ *Cardiomyopathy (type if known:_____)*

Date:	Reporter's Name: Reporter's Specialty:
AE Number:	Reporter's Address: Phone Number:
1. Patient's age:	2. Patient's Gender/ Height/ Weight:
3. **SEROQUEL**® Formulation (*please circle*): IR/ XR/ UNK	4. INDICATION for use of **SEROQUEL**® ?
5. **SEROQUEL**® Start Date? **SEROQUEL**® Stop Date?	6. **SEROQUEL**® Dosage?

7. Was the patient receiving any other medications at the time of the event in addition to on SEROQUEL®? If Yes, please provide drug, dates of use and indication for use. Please indicate if drugs were continued or discontinued due to the event.

Drug	**Indication**	**Dates of Use**

8. Please **circle** the signs and symptoms observed (indicate temporal relationship to event (before or during) and duration

Fever

Flu like symptoms (including headache, muscle aches, sore throat, running nose, diarrhea, rashes)

Fatigue

Decreased exercise tolerance

Chest pain

Joint pain

Joint swelling

Arrhythmia

Palpitations

Syncope/Pre-syncope/Loss of consciousness

OTHER: Please specify:

Deleted:

9. Has the patient had or presently have any of the following **risk factors** and/ or **concomitant diseases**? If Yes, please **CIRCLE** and provide date of diagnosis or duration

- Heart disease. If yes, type and date of diagnosis or duration
- Cardiac surgery/procedures. If yes, type and date of diagnosis or duration
- Cardiac arrhythmia. If yes, type and date of diagnosis or duration
- Myocarditis. If yes, type and date of diagnosis or duration
- Cardiomyopathy. If yes, type and date of diagnosis or duration
- Cancer therapy. If yes, provide cancer diagnosis and type of chemotherapy (include dose and dates of use) and/or radiotherapy (include location and dates of treatment.
- Hypertension. If yes, provide date of diagnosis or duration and whether controlled or uncontrolled.
- Renal failure. If yes, provide date of diagnosis or duration, severity, eGFR (if available), if dialysis required
- Systemic or autoimmune diseases. If yes, specify type, date of diagnosis or duration.
- Play competitive sports/exercise. If yes, provide details.
- Smoking. If yes, provide number of packs smoked per year. If previous history of smoking please indicate.
- Lung disease/COPD. If yes, provide severity, date of diagnosis or duration.
- Alcohol use. If yes, provide frequency (eg, #drinks per day; # drinks per month; # drinks per year)
- Drug abuse. If yes, specify type and duration.
- Any other important medical history. If yes, provide details.

Deleted:

10. Did the patient experience heart failure (yes/no)—if yes please answer questions below

- Was patient hospitalized or visited emergency room due to heart failure (if yes)
  - Date of visit
  - Duration of hospitalization
  - Hospital diagnosis of heart failure: NYHA class (I, II, III, IV)
  - Cause of heart failure (if given)
  - Vital signs: Temp , Pulse bpm, Respiratory rate breaths/minute, Blood pressure mmHg
  - Physical exam findings (circle if yes): Peripheral edema, Hepatomegaly, Hepato-jugular reflex, Increased jugular venous pressure
- ECG findings (ie, arrhythmia, conduction abnormalities)
- Lab findings

- Imaging/test results (Echo, X-ray, CT scan, MR, MUGA, RH/LH cath, etc.) (If available please attach reports/results)
    - Cardiac size (esp. chamber dilatation)
    - LV function (%EF, diastolic function parameters)
    - Regional wall motion abnormalities
    - Other meaningful finding (eg. Valvular abnormalities, wall thickness, myocardial perfusion abnormalities, delayed enhancement on MR, evidence of pulmonary edema

11. Did the patient *receive any treatment? If Yes,* please specify.

Did the patient Improve?

12. Did the symptoms resolve or improve while continuing SEROQUEL®?

13. Was SEROQUEL stopped? Did the symptoms improve?

Was the treatment started again? Did the symptoms reoccur?

14. Did the patient die? If Yes, please provide date of death, cause of death and autopsy as well as toxicology results if done.

15. Please include narrative of the course of disease development or progression

Deleted: ¶

Deleted: ¶

Deleted: ¶

Deleted: ¶

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PANCREATITIS DATA QUESTIONNAIRE FOR SPONTANEOUS REPORTS (version 1.0)

AstraZeneca Report #

1. Patient Initials: **2**. Age Sex Race:

3. Seroquel® **dose & indication** at the time of the event: **4.** Seroquel ® **start date**:

5. **Date** Seroquel ® was **stopped** or temporarily stopped: **6**. **Date and dose** Seroquel ® **restarted** if applicable:

7. Please list each adverse event in the table below (criteria for seriousness is listed below the table)

Adverse Event	**Event start date:**	**Event stop date: (If not ongoing)**	****Serious (S) or Non-serious (NS)** *If serious, circle all criteria of seriousness listed below the table*	**Causally related to Seroquel ® *(Y/N)***	**Action taken with Seroquel® S=stopped TS= temporarily stopped DD= dose decreased**	**Outcome *(Has the patient recovered)***

** **Criteria for seriousness 1)** Results in hospitalization or prolongation of existing hospitalization; **2)** Persistent or significant disability/incapacity; **3)** Death; **4)** Life threatening; **5)** A congenital abnormality/birth defect; **6)** Important medical event jeopardizing the patient and requiring medical or surgical intervention to prevent a serious outcome.

8. Briefly describe the clinical presentation including signs& symptoms e.g. abdominal pain, rigidity or guarding, rebound tenderness, vomiting, dimunition or loss of bowel sounds, or weight loss.

- **Please indicate if the events were new or pre-existing conditions**

- **Please provide date of hospitalization if relevant.**

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9. Medical History /Concurrent Illness

Condition	Check if applicable	Onset Date (mm/dd/yy)	Ongoing (Y/N)	Inves-tigated (Y/N)	Ruled-out (Y/N)	Additional Information
Hist of Pancreatitis (incl. Congenital pancreatitis)						
Hypertriglyceridemia						
Biliary tract disease (incl. cholelithiasis)						
Alcohol use (significant)						
Infections						
Abnormalities of pancreatic or bile ducts (e.g. ampullary obstruction by tumor, choledochocele, periampullary duodenal diverticulum, pancreas divisum, annular pancreas, primary or metastatic pancreatic tumor, parasites in pancreas ducts)						
Surgery of stomach or biliary tract						
Vascular disease						
Hyperparathyroidism						
Hypercalcemia						
Penetrating duodenal ulcer						
Organ transplantation						
Crohn's disease of duodenum						
Trauma (e.g blunt abdominal						

Condition	Check if applicable	Onset Date (mm/dd/yy)	Ongoing (Y/N)	Inves-tigated (Y/N)	Ruled-out (Y/N)	Additional Information
trauma)						
ERCP						
Cardiopulmonary bypass						
Exposure to toxins (e.g. methanol, organophosphorus, insecticides, scorpion venom)						

10. Provide concomitant medications including ACE inhibitors, estrogens, NSAIDS and other medications (include dosage, indication, **and if medication was stopped**). *Exclude medications used to treat the event(s).*

11. Please list laboratory results and diagnostic tests in the tables below.

Laboratory test	Date:		Date:		Date:		Date:	
	BASELINE Value	Reference range/units	PEAK Value	Reference range/units	SUBSEQUENT Value	Reference range/units	SUBSEQUENT Value	Reference range/units
Blood amylase								
Blood lipase								
Alkaline phosphatase								
Triglycerides								
WBC								
Bilirubin								

Diagnostic test:	Date:	Result:
Ultrasound		
Other Imaging technique (please specify) _____		

12. Any additional information about the clinical course, including treatment, outcome of the event(s), and possible cause(s) for the event? If applicable, please provide autopsy results by attaching the autopsy report to this fax.

Print name and title of person completing form	signature of person completing form	if physician, specify specialty

If completed by a person in proxy for a physician, please **also** indicate the following:

Name of physician	specialty

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MUSCLE DATA COLLECTION FORM

Date Received by AstraZeneca (dd/mm/yyyy):_____

Clintrace/AZ reference #: _____

AstraZeneca drug: _____

AstraZeneca study number (if applicable): _____

Instructions for :	☐ Investigator ☐ Clintrace Data Entry Site ☐ Marketing companies
This questionnaire should be completed for the following events (PTs)	
Please provide verbatim term as report by reporter/investigator	

Patient details

Initials	**Age (years)**

Weight	**Height**	**Ethnic Origin**
(check one) ☐ lbs ☐ kg	*(check one)* ☐ in ☐ cm	

Gender	**Marital status**
☐ M ☐ F	☐ Single ☐ Married ☐ Widowed ☐ Separated ☐ Divorced

Reporter details

Reporter Name:	**Date of this report (dd/mm/yyyy):**
(Optional) Reporter Address:	**Reporter's Signature:**
Telephone Number:	

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Muscle related events

Reported events

Adverse event	Start date (dd/mm/yyyy)	Stop date (dd/mm/yyyy)	Outcome	
			☐ Recovered ☐ Ongoing ☐ Improved	☐ Recovered with sequelae ☐ Death ☐ Worsened
			☐ Recovered ☐ Ongoing ☐ Improved	☐ Recovered with sequelae ☐ Death ☐ Worsened
			☐ Recovered ☐ Ongoing ☐ Improved	☐ Recovered with sequelae ☐ Death ☐ Worsened

If patient recovered but with sequelae please describe here:

Please include cause of death and a description of events:

If patient died was an autopsy performed? ☐ Yes ☐ No *(If yes, please provide relevant results)*

Describe clinical course of treatment:

Did patient require dialysis ☐ Yes ☐ No ☐ Temporary ☐ No

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Symptoms

Symptoms		Start date (dd/mm/yyyy)	Stop date (dd/mm/yyyy)	Additional information
Fever	☐ Yes ☐ No			
Changes in urine color	☐ Yes ☐ No			
Muscle weakness	☐ Yes ☐ No			
Muscle aching	☐ Yes ☐ No			
Fatigue	☐ Yes ☐ No			
Nausea	☐ Yes ☐ No			
Vomiting	☐ Yes ☐ No			

Suspect drug(s): *(Please only include drugs considered to be causally related to the adverse event(s) and not concomitant medications)*

Suspect Drug Name *Provide formulation if applicable*	**Indication**	**Daily Dose**	**Start Date**	**Stop Date**	**Was this medication withdrawn or dose altered?**
					☐ Yes, prior to event ☐ Yes, after event ☐ No
					☐ Yes, prior to event ☐ Yes, after event ☐ No
					☐ Yes, prior to even ☐ Yes, after event ☐ No

If any of the above drug(s) were withdrawn, what was the reason? *If applicable, please provide name of drug(s)withdrawn*

If any of the above drug(s) were withdrawn, did the event(s) improve after stopping? ☐ Yes ☐ No ☐ n/a
If applicable, please provide name of drug(s)withdrawn

Was the drug(s) re-introduced? ☐ Yes ☐ No
If yes, please provide each date drug was re-introduced

Did the event(s) reoccur/worsen after reintroduction? ☐ Yes ☐ No ☐ n/a
If yes, please provide date that event recurred.

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Medical history relevant for the event

History or risk factors			Onset date (dd/mm/yyyy)	If yes, please provide details
Renal impairment	☐ Yes ☐ No	☐ Current ☐ Past		
Dialysis	☐ Yes ☐ No	☐ Current ☐ Past		
Previous muscle problems ☐ Related to statins/fibrates ☐ Related to other medications ☐ Other	☐ Yes ☐ No	☐ Current ☐ Past		
Hereditary muscle disorders	☐ Yes ☐ No			
Hypothyroidism *If yes provide status of control*	☐ Yes ☐ No	☐ Current ☐ Past		
Heavy or significant alcohol use	☐ Yes ☐ No	☐ Current ☐ Past		
Strenuous exercise or activity	☐ Yes ☐ No	☐ Current ☐ Past		
Dehydration	☐ Yes ☐ No	☐ Current ☐ Past		
Infections	☐ Yes ☐ No	☐ Current ☐ Past		
Surgery	☐ Yes ☐ No	☐ Current ☐ Past		
Trauma	☐ Yes ☐ No	☐ Current ☐ Past		

History or risk factors			Onset date (dd/mm/yyyy)	If yes, please provide details
Falls	☐ Yes ☐ No	☐ Current ☐ Past		
Epilepsy	☐ Yes ☐ No	☐ Current ☐ Past		
Diabetes *If yes provide degree of control*	☐ Yes ☐ No	☐ Current ☐ Past		
Drug abuse	☐ Yes ☐ No	☐ Current ☐ Past		
Hypothermia	☐ Yes ☐ No	☐ Current ☐ Past		
IM injections	☐ Yes ☐ No	☐ Current ☐ Past		
Other relevant concomitant medical conditions (*If any please specify*) ☐ Yes ☐ No				
Nutritional problems (*If any please specify*) ☐ Yes ☐ No				

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Concomitant medication(s): (*Include all prescription, OTC drugs, herbal/dietary supplements. Exclude suspect drugs listed above*)

Drug(s): Exclude drugs used to treat the event	**Indication for use**	**Daily Dose**	**Start Date**	**Stop Date**	**Was this medication withdrawn?**
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a
					☐ Yes, prior to event ☐ No ☐ Yes, after event ☐ n/a

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Laboratory values

Laboratory parameter	Baseline Date (dd/mm/yyyy) ____/____/_____	Follow-up Date (dd/mm/yyyy) ____/____/_____	Follow-up Date (dd/mm/yyyy) ____/____/_____	Follow-up Date (dd/mm/yyyy) ____/____/_____	Follow-up Date (dd/mm/yyyy) ____/____/_____
Creatine Kinase (U/L)					
Creatinine	☐ mg/dL ☐ µmol/L	☐ mg/dL ☐ µmol/L	☐ mg/dL ☐ µmol/L	☐ mg/dL ☐ µmol/L	☐ mg/dL ☐ µmol/L
CK-MB (%)					
Troponin					
Serum myoglobin (µg/L)					
Urinalysis (include myoglobinuria & hematuria)					

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Please provide any other relevant information:

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AstraZeneca SEROQUEL® /SEROQUEL XR®

SEROTONIN SYNDROME COLLECTION FORM

AZ CASE #: _____

Patient Initials:	Gender: ☐ M ☐ F	Age (years):	Ethnic Origin:

Reporter Name, Address, Phone Number, Email	Date

Serotonin syndrome is a **potentially serious neurologic disorder,** which is typically associated with the use of certain medicines. Your assistance with this **brief questionnaire** helps AstraZeneca improve its safety surveillance.

Please summarize any relevant information:

Serotonin syndrome is a diagnosis of exclusion. Please check these disorders *only* if they have been *ruled out*:

☐ NMS ☐ epilepsy/seizure ☐ drug or alcohol abuse/overdose
☐ drug withdrawal ☐ hyperthyroidism ☐ hypoglycemia
☐ stroke/migraine ☐ infection, ☐ anti-cholinergic toxidrome
☐ malignant hyperthermia (post-anesthesia)

Serotonin syndrome consists of a symptom complex (i.e. mental status, autonomic & motor). Please check if any of the following have been documented:

☐ mental status changes ☐ altered level of consciousness ☐ restlessness/akathisia
☐ myoclonic jerks ☐ increased reflexes ☐ increased muscle tone
☐ tremor ☐ incoordination ☐ fever
☐ increased sweating ☐ unstable vital signs ☐ nausea, vomiting, diarrhea
☐ abnormal pupil size ☐ convulsions ☐ abnormal eye movements/nystagmus
☐ elevated heart rate/blood pressure

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Neurotoxic syndromes may be associated with abnormal labs. Please check any of the following that were abnormal:

☐ liver function tests ☐ complete blood count ☐ muscle enzymes
☐ lithium level ☐ imaging studies ☐ drug levels ☐ toxicology labs

Serotonin syndrome has been reported with certain classes of drugs. Please indicate if any of these were present at the time of the adverse even or in the recent past:

☐ Antidepressants (eg MAOI's, TCA's, SSRI's, SNRI's)
☐ Painkillers/Migraine drugs (eg opiates, tramadol, meperidine, sumatriptan, zolmitriptan)
☐ Herbs (eg St John's Wort)
☐ Illicit drugs (eg amphetamines, cocaine, LSD, ecstasy)
☐ Others (eg lithium, anticholinergics, buspirone, dextromethorphan, tryptophan, L-dopa, carbamazepine)

Other questions:

- **Over what period of time did the symptoms and/or abnormal labs above develop?**

- **Did this event begin after the addition of a drug, or a change in dose/administration? If so, please briefly describe (also see table on page 3).**

- **Did event improve after the discontinuation of any drug(s)? If so, how long after?**

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Suspect drug(s): *(Please only include drugs considered to be causally related to the adverse event(s) and not concomitant medications)*

Suspect Drug Name *Provide formulation if applicable*	**Indication for use**	**Daily dose**	**Start Date**	**Stop Date**

Concomitant medications(s): *(Include all prescription, OTC drugs, herbal/dietary supplements. Exclude suspect drugs listed above)*

Drug(s): *exclude drugs used to treat the event*	**Indication for use**	**Daily dose**	**Start Date**	**Stop Date**

Suicidality Data Collection Form

Patient Initials: ___ ___ ___

Date of Birth (mm/dd/yy): ___/___/___

Sex: □ male □ female

Marital Status: □ married □ single □ separated/divorced □ widowed

Type of Suicidality: Completed suicide □ Suicide Attempt □ Suicidal Ideation □

For Suicidal Ideation <u>only</u>: Contemplated □ Threatened □

Concomitant Conditions (check all that apply):
Akathisia □, Tardive Dyskinesia □, Treatment Refractory Schizophrenia □,
Previous Ideation/Attempt □, Depression □, or Substance Abuse □

Relevant Family History (check all that apply for family members and state relationship to patient):
Suicide □, Mental Disorders □, Substance Abuse □, Violence or Sexual/Physical Abuse □

Methods:

□ Drug Overdose
- □ Single Drug Overdose □ Multiple Drug Overdose
- Specify which drugs_____
- Was this confirmed with toxicology studies (complete below)?

□ Other Method (non-drug overdose)
- Specify specific method(s)_____

Toxicology: Please provide results indicating if pre- or post-mortem toxicology, compounds identified, type of specimen tested (e.g., blood, gastric contents, liver, etc.), concentration, and reference ranges

_____	_____	_____	_____
Compound	Specimen	Concentration	Reference range
_____	_____	_____	_____
Compound	Specimen	Concentration	Reference range
_____	_____	_____	_____
Compound	Specimen	Concentration	Reference range

Suspect Drug Information

Name of Drug #1: _____

Indication for therapy: _____

Date Started (mm/dd/yy): ___/___/___

Dose/Route/Schedule:_____

Date Stopped (mm/dd/yy): ___/___/___

Reason: _____

Name of Drug #2: _____

Indication for therapy: _____

Date Started (mm/dd/yy): ___/___/___

Dose/Route/Schedule:_____

Date Stopped (mm/dd/yy): ___/___/___

Reason: _____

Concomitant Drug Information

Name of Drug #1: _____

Indication for therapy: _____

Date Started (mm/dd/yy): ___/___/___

Dose/Route/Schedule:_____

Date Stopped (mm/dd/yy): ___/___/___

Name of Drug #2: _____

Indication for therapy: _____

Date Started (mm/dd/yy): ___/___/___

Dose/Route/Schedule:_____

Date Stopped (mm/dd/yy): ___/___/___

Was the drug discontinued (dechallenge)? □ yes □ no

If yes, what was the outcome related to suicidality?

□ Resolved

□ Not resolved

Was the drug re-introduced (rechallenge)? □ yes □ no

If yes: Date drug was reintroduced (mm/dd/yy): ___/___/___

Dose/Route/Schedule: _____

Did symptoms recur?

If so, how soon after reintroduction?

Outcome:

□ Recovered

□ Died

□ Unknown

Reporter's causality: In your medical judgment, is there a reasonable possibility that the AZ drug may have caused this? □ yes □ no

Why? _____

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Patient Safety

TOXIC SKIN REACTIONS DATA COLLECTION FORM

AZ Date of Receipt: _____

AZ ref: _____

1. Patient Details

Initials:	Sex:	Age:	Ethnic Origin:
	☐ Male ☐ Female		

2. Details of AstraZeneca Drug Therapy

Drug Name: **Start Date:** **Stop Date:** **Dosage:**

Indication: **Stage:**_____ ☐**Initial diagnosis** ☐ **Recurrent**

Was the drug stopped or the dosage adjusted due to the event(s)? ☐ Yes, permanently ☐ Yes, temporarily ☐ No ☐ Unknown

If yes, did the event(s) improve after stopping/adjusting the drug? ☐ Yes ☐ No ☐ N/A ☐ Unknown

Was the drug re-introduced? ☐ Yes ☐ No ☐ N/A ☐ Unknown

If yes, did the event(s) recur after reintroduction? ☐ Yes ☐ No ☐ N/A ☐ Unknown

3. Details of Adverse Event(s)

Note: Please indicate worsening of a preexisting condition.

Adverse Event(s)	Start/Stop Dates	Severity	Outcome	Causal Relation
		☐ Mild ☐ Mod. ☐ Severe	☐ Recovered/ ☐ with sequelae ☐ Event ongoing ☐ Death	☐ Yes ☐ No
		☐ Mild ☐ Mod. ☐ Severe	☐ Recovered/ ☐ with sequelae ☐ Event ongoing ☐ Death	☐ Yes ☐ No
		☐ Mild ☐ Mod. ☐ Severe	☐ Recovered/ ☐ with sequelae ☐ Event ongoing ☐ Death	☐ Yes ☐ No

Did the patient experience any of the following signs/symptoms?

Sign/Symptom	Start Date	Stop Date	Treatment and Response (ex: antihistamines, corticosteroids)
☐ Malaise			
☐ Fever			
☐ Chills			
☐ Headache			
☐ Cough			
☐ Conjunctivitis			
☐ Itching			
☐ Pigmentation changes			
☐ Erythema			
☐ Pain *(please describe)* _____			
☐ Skin sloughing			
☐ Necrotic epithelium			
☐ Oral/mucosal involvement			
☐ Positive Nikolsky sign			
☐ Other *(specify)* _____			
☐ Skin lesions (*specify site* _____)			

Type of lesions: ☐ Macupapular ☐ Vesicles ☐Pustules ☐Other:_____

Severity of lesions: ☐ Mild ☐ Moderate ☐Severe

Lesion distribution: ☐ Single ☐ Multiple ☐Random ☐Patterned ☐Other:_____

Lesion configuration: ☐ Linear ☐ Annular ☐Target ☐Other: _____

Lesion texture: ☐Verrucous ☐Indurated ☐Other:_____

Lesion color: ☐ Red ☐ Blue ☐Black ☐Violet ☐Other:_____

Body surface area involvement: ☐ **<10%** ☐ **≥10%** **Affected area (specify):** _____

4. Does the patient have any of the following risk factors for the event? *(Mark all that apply)*	**Onset Date (dd/mm/yyyy)**	**Please provide further details:**
Previous skin problems ☐ Due to chemotherapy ☐ Due to other medications ☐ Other		
☐ Infections *(recent or ongoing)*		
☐ Sun exposure		Length of time:
☐ Immune suppression *(specify):* ☐ HIV ☐ Skin graft ☐ Other: _____		
☐ Surgery ☐ Radiation therapy ☐ Other malignancy (_____) ☐ Illicit drug use / ☐ alcohol use		
Other relevant concomitant medical conditions / comorbidities *(If any, please specify)* ☐ Yes ☐ No		

5. Details of other drugs that might be causally related to the event if applicable

For example; carbamazepine, phenytoin, NSAIDS, allopurinol, penicillin, sulfonamides (Exclude drugs used to treat the event)

Drug Name and Indication	Suspected	Dosage	Start Date	Stop Date	Withdrawn If yes, before or after event?	If yes, did event improve	Restarted	If yes, did event recur
1)	☐ Yes ☐ No				☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A
2)	☐ Yes ☐ No				☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A
3)	☐ Yes ☐ No				☐ Yes ☐ Before ☐ No ☐ After	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A

6. Details of other concomitant drugs if applicable

Exclude drugs used to treat the event

Drug Name and Indication	Dosage	Start Date	Stop Date	Drug Name and Indication	Dosage	Start Date	Stop Date
1)				3)			
2)				4)			

7. Laboratory Values

Date (dd/mm/yyyy); Please provide units and normal range if known

Laboratory parameter	Baseline	Peak	Follow-up
WBC	Date: Value: Normal Range: ☐ Normal ☐ Elevated ☐ Not Measured	Date: Value: Normal Range: ☐ Normal ☐ Elevated ☐ Not Measured	Date: Value: Normal Range: ☐ Normal ☐ Elevated ☐ Not Measured
Eosinophils	Date: Value: Normal Range: ☐ Normal ☐ Elevated ☐ Not Measured	Date: Value: Normal Range: ☐ Normal ☐ Elevated ☐ Not Measured	Date: Value: Normal Range: ☐ Normal ☐ Elevated ☐ Not Measured
Skin biopsy	Date: Result: ☐ Normal ☐ Abnormal ☐ Not Performed	Date: Result: ☐ Normal ☐ Abnormal ☐ Not Performed	Date: Result: ☐ Normal ☐ Abnormal ☐ Not Performed
Immunofluorescence	Date: Result: ☐ Normal ☐ Abnormal ☐ Not Performed	Date: Result: ☐ Normal ☐ Abnormal ☐ Not Performed	Date: Result: ☐ Normal ☐ Abnormal ☐ Not Performed

8. Please provide details of the clinical course if applicable *(i.e. use of IVIG, corticosteroids, immunosuppressants, plasmapheresis for treatment)*

9. Reporter Details

Reporter Name: *(Please print)* ☐ Health Care Professional ☐ Other	**Date of this Report :** *(dd/mm/yyy)*

Thank you for completing this form.

EU RMP Part VII Annex 8

Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	12
Data lock point for this module	12 June 2013

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® AND SEROQUEL XR®)

Part VII ANNEX 8 - PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL® and SEROQUEL XR®
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

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1. PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

There were no ongoing or planned post-authorisation efficacy studies during this period.

EU RMP Part VII Annex 9	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	13
Data lock point for this module	06 December 2016

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® AND SEROQUEL XR®)

Part VII ANNEX 9 - NEWLY AVAILABLE STUDY REPORTS FOR RMP PARTS III & IV

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL® and SEROQUEL XR®
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

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1. NEWLY AVAILABLE STUDY REPORTS FOR RMP PARTS III & IV

During this reporting period, there was 1 newly available study report summarized in Parts III or IV:

- D1443C00056 SE-SLS Part III safety evaluation Study Final Report.

PASS Study Report

Active substance	Quetiapine fumarate
Product reference	D1443C00056
Version number	1.0
Date	29 July 2016

A pharmacoepidemiological program of quetiapine XR in the treatment of major depressive disorder in Sweden: Safety evaluation study.

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU United Kingdom
MAH contact person	[redacted] Milsten Building, Granta Park Gothenburg CB 21 6 GH Sweden [redacted]

Approved by: [redacted]

Principal Investigator Date

PASS INFORMATION

Title	A pharmacoepidemiological program of quetiapine XR in the treatment of major depressive disorder in Sweden: Safety evaluation study.
Version identifier of the final study report	1.0
Date of last version of the final study report	29 July 2016
EU PAS register number	N/A
Active substance	quetiapine fumarate, ATC code N05AH04
Medicinal product	SEROQUEL XR 50, 150, 200, 300, and 400 mg prolonged-release tablets SEROQUEL 25, 100, 150, 200, and 300 mg film-coated tablets
Product reference	SEROQUEL XR: 50 mg: PL 17901/0249 150 mg: PL 17901/0259 200 mg: PL 17901/0250 300 mg: PL 17901/0251 400 mg: PL 17901/0252 SEROQUEL: 25 mg: PL 17901/0038 100mg: PL 17901/0039 150 mg: PL 17901/0041 200 mg: PL 17901/0040 300 mg: PL 17901/0088
Procedure number	N/A
Marketing authorisation holder(s)	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU United Kingdom

Joint PASS	No
Research question and objectives	This report aims to evaluate the safety of quetiapine in Sweden from 2011-2014 with regard to the following outcomes: death from all causes, acute myocardial infarction, stroke, suicide and self-harm, diabetes mellitus, extrapyramidal disorders, and somnolence.
Country of study	Sweden
Authors	[redacted] Centre for Pharmacoepidemiology, Karolinska Institutet, Karolinska University Hospital Solna Clinical Epidemiology Unit T2, SE-171 76 Stockholm, Sweden [redacted] [redacted] Centre for Pharmacoepidemiology, Karolinska Institutet, Karolinska University Hospital, Solna Clinical Epidemiology Unit T2, SE-171 76 Stockholm, Sweden [redacted]

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APPENDICES

LIST OF TABLES

1. ABSTRACT

Title

A pharmacoepidemiological program of Quetiapine XR in the treatment of major depressive disorder in Sweden: Safety evaluation study

8 June, 2016

Johan Reutfors

Morten Andersen

Centre for Pharmacoepidemiology, Karolinska Institutet.

Keywords

Quetiapine, major depressive disorder, safety study

Rationale and background

In January 2011 quetiapine XR was launched in Sweden for treatment as an add-on (adjunctive treatment) treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy. AstraZeneca has committed to conducting post-approval studies (PAS) for approved indications.

Research question and objectives

This report aims to evaluate the safety of quetiapine in Sweden from 2011-2014 with regard to the following outcomes: death from all causes, acute myocardial infarction, stroke, suicide and self-harm, diabetes mellitus, extrapyramidal disorders, and somnolence.

Study design

Retrospective cohort study in which the Swedish Prescribed Drug Register was used to identify cohorts of users of quetiapine and other antidepressant drugs during 2011-2014. Two user cohorts were followed, a treatment change cohort (treated with another antidepressant during the year before the index date) and a new user with MDD cohort, where no other antidepressants were dispensed in the year before, but where all users had a record of an MDD diagnosis during the past year. Nested case-control analyses matched on age, sex and index year were performed for each of the safety outcomes, comparing use of quetiapine with use of other antidepressants.

Setting

Population based register study in Sweden (9.4 million inhabitants 2011) using health care databases.

Subjects and study size, including dropouts

After exclusion of individuals with schizophrenia-related or bipolar disorder diagnoses, as well as individuals previously using mood stabilizers or antipsychotics, the treatment change cohort consisted of 7 421 quetiapine users and 281 303 users of other antidepressants, and the new user with MDD cohort of 819 quetiapine users and 37 953 other antidepressant users.

Variables and data sources

Data sources were the Prescribed Drug Register, the National Patient Register, the Total Population Register and the Cause of Death Register, all with complete national coverage, linked using Personal Identification Numbers. Information included drugs dispensed outside hospital: ATC codes, product names, dispensing date, amount, prescribed doses (extracted from dose texts) and prescriber category. Treatment episodes were constructed based on estimated days' supply, and exposed person years calculated. Medication patterns (one or multiple substances) were characterised. Diagnoses from inpatients (since 1997) and outpatients (since 2001) were retrieved (ICD-10 codes). User's history of psychiatric and somatic morbidity was characterized and used for confounder adjustment.

Results

In the treatment change cohort, a significantly higher risk of death from all causes was identified among current users of combination therapy with quetiapine, adjusted OR 1.31 (1.12-1.54) compared to combinations of other antidepressants. No significant associations between quetiapine use and the outcomes acute myocardial infarction, stroke and diabetes were found. A higher risk of self-harm and suicide was identified among current users of a combination therapy with quetiapine, adjusted OR 1.52 (1.26-1.84). The OR was also significantly elevated in an analysis including those with a prior history of self-harm. A significantly higher risk of extrapyramidal disorder was identified among current users of quetiapine, with an adjusted OR 13.5 (5.0-36.7) for monotherapy and 6.2 (3.6-10.6) for combination therapy. Use of other antipsychotics was associated with an even higher risk, adjusted OR 19.9 (13.8-28.9). An association between somnolence and current quetiapine combination therapy was also seen, adjusted OR 2.45 (1.45-4.13), with anxiolytics and hypnotics also leading to an increased risk, adjusted OR 1.95 (1.54-2.46). The analysis of the new user with MDD cohort revealed no significant risks, but the analysis should be interpreted with caution because of the small numbers.

Discussion

The analyses of the treatment change cohort found associations between quetiapine treatment and death from all causes and between quetiapine use and an increased risk of self-harm and suicide. The increased risk may be explained by selective prescribing of these treatments to patients at high risk for the outcomes in question. Unmeasured and residual confounding is likely to have biased the results towards a higher relative risk. Quetiapine is prescribed to individuals with a higher burden of psychiatric comorbidity, including a history of previous self-harm and more frequent admissions for MDD. As quetiapine and combinations of antidepressants are second-line therapy, the populations receiving these treatments would be

expected to have more severe or more difficult to treat depression, and thus be at higher risk for self-harm and suicide.

Marketing Authorisation Holder(s)

AstraZeneca UK Ltd
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Names and affiliations of principal investigators

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2. LIST OF ABBREVIATIONS

Abbreviation	Explanation
AMI	Acute myocardial infarction
ATC	Anatomical therapeutic chemical classification system
DDD	Defined Daily Doses
EMA	European Medicines Agency
GAD	Generalized anxiety disorder
ICD	International classification of diseases
IHD	Ischaemic heart disease
MI	Myocardial infarction
MDD	Major depressive disorder
NPR	National patient register
OCD	Obsessive compulsive disorder
OTC	Over the counter
PAS	Post-approval study
PASS	Post-approval safety study
PDR	Prescribed drug register
PIN	Personal identity number

SD Standard Deviation

3. INVESTIGATORS

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[redacted]

4. OTHER RESPONSIBLE PARTIES

[redacted]
Centre for Pharmacoepidemiology
Karolinska Institutet
Karolinska University Hospital Solna
Clinical Epidemiology Unit T2
SE-171 76 Stockholm, Sweden

5. MILESTONES

Table I Milestones

Milestone	Date	Comments
Draft protocol	June 2010	
Final protocol	October 2010	
Start of data collection - pilot study	July 1, 2005	Retrospectively collected register data back to 1997 used. Dates refer to data on medication
End of data collection - pilot study	December 31, 2010	
Pilot study report	December 2012	This final report is for Part I of the study
Start of data collection - first utilisation study	January 1, 2011	

End of data collection - first utilisation report	December 31, 2011	
Utilisation study first report	June 2013	This interim report for Part II of the study covers the first year of the utilisation study
Start of data collection - second utilisation study	January 1, 2011	
End of data collection - second utilisation report	December 31, 2012	
Utilisation study Statistical Analysis Plan	May 2014	
Utilisation study second report	May 2014	This final report for Part II of the study covers the second year of the utilisation study
Safety study and Final report of study results	July 2016	This final report for the safety study covers four years
Annual progress report 1	July 2012	
Annual progress report 2	June 2013	
Annual progress report 3	July 2014	
Annual progress report 4	June 2015	

6. RATIONALE AND BACKGROUND

Quetiapine XR (quetiapine fumarate extended release tablets, Seroquel XR) is an atypical antipsychotic drug which affects not only dopamine receptors as an antagonist but also has an antagonistic action on serotonin, histamine and adrenergic alfa$_1$ receptors (SmPC 2014). The drug quetiapine was first approved for clinical use in Sweden in 2003, as an immediate-release form (IR). Its indications are the treatment of schizophrenia and bipolar disorder. Subsequently the formulation with extended release, quetiapine XR was approved for the treatment of schizophrenia including preventing relapse in stable schizophrenic patients who have been maintained on quetiapine XR, and for the treatment of bipolar disorder including moderate to severe manic episodes in bipolar disorder, major depressive episodes in bipolar disorder, and for the prevention of recurrence in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment.

Subsequently, studies have been published which support the use of atypical antipsychotics such as quetiapine for treatment-resistant major depressive disorder (Papakostas et al. 2007). In April 2010, the European Medicines Agency (EMA) gave the recommendation that quetiapine XR can be used as an add-on (adjunctive treatment) treatment of major depressive

episodes in patients with major depressive disorder (MDD) who have had sub-optimal response to antidepressant monotherapy. In October 2010, the Swedish Medical Products Agency granted quetiapine XR the above new indication for use in Sweden. Quetiapine XR was launched for this indication in Sweden in January 2011.

AstraZeneca has committed to conducting a post-authorisation safety study (PASS) for approved indications. The present register based study of the use of quetiapine is conducted according to a research contract between AstraZeneca and Centre for Pharmacoepidemiology, Karolinska Institutet.

For the new indication of use in MDD it was anticipated that psychiatrists in specialist care would be the main prescribers. The present study, however, includes prescribing in primary care as well as specialist care.

In a pilot study report we evaluated the methodology to deliver the data of interest for a study of quetiapine XR among MDD patients using the national Swedish registers. Methods for identifying the drugs of interest, estimating prescribed doses, including the assessment of search procedures for identifying the prescribed dose in text fields of prescription records were described. Exposure periods for quetiapine XR and other antidepressants were defined taking into account prescribed amount and estimates of prescribed daily dose based on the dose text information. Furthermore, because of the absence of a recorded indication for each prescription, we developed a stepwise algorithm to identify patients with likely MDD indication. The algorithm was based on the history of previous psychiatric diagnoses and use of mood stabilizers.

In two reports we described the use of quetiapine XR in Sweden in 2011-2012, focusing on new users treated for MDD and including quetiapine used as an add-on to conventional antidepressant treatment.

Several generic or parallel-imported products containing quetiapine are on the market in Sweden – these were all studied in the above mentioned drug utilisation studies. Furthermore, it was shown that use of quetiapine immediate release (IR) tablets also occurred in the studied cohorts with MDD as a likely indication, often interchangeably with the extended release tablets. From a safety perspective, it would also seem appropriate to focus on the pharmacologically active molecule and to maximise the number of patients using that substance. It was therefore chosen not to distinguish between the IR and XR formulations in the safety analyses. Finally, initial monotherapy with quetiapine also took place, and although this is not among the indications in the summary of product characteristics (SmPC 2014), this treatment pattern was also of interest from a safety perspective and was therefore added as an objective as part of the Statistical Analysis Plan for the study.

In the present report we evaluate the safety of quetiapine in Sweden from 2011-2014 with regard to the following outcomes: death from all causes, acute myocardial infarction, stroke, suicide and self-harm, diabetes mellitus, extrapyramidal disorders, and somnolence.

7. RESEARCH QUESTION AND OBJECTIVES

This study aimed to evaluate the safety of quetiapine in Sweden from 2011-2014.

The following outcomes were included:

- Death from all causes
- Acute myocardial infarction
- Stroke
- Suicide and self-harm
- Diabetes mellitus
- Extrapyramidal disorders
- Somnolence

The risk of these events in patients treated with quetiapine is compared to the risk among patients treated with other antidepressants. Add-on treatment with quetiapine or switching to quetiapine (i.e. a change of treatment) is compared in patients all undergoing a change in antidepressant treatment, and incident treatment with quetiapine will be compared to incident treatment with other antidepressants in a restricted cohort of patients with a recent diagnosis of MDD.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

9.1 Study design

This is a population-based retrospective cohort study in which the Prescribed Drug Register (PDR) was used to identify new users of antidepressant drugs. For each of the seven outcomes of interest, we also performed a case-control study nested within each of the two cohorts.

9.1.1. Cohort studies

The study encompassed two cohorts of patients which were followed up to estimate crude event rates of the seven outcomes of interest. The two cohorts were:

A. The treatment change cohort: Patients with dispensing of a new antidepressant substance (including quetiapine) who have had another antidepressant substance dispensed in the last year.

B. The new user cohort: Patients with dispensing of a new antidepressant (including quetiapine) who had a contact to a specialist psychiatric clinic with a recorded MDD diagnosis within one year before.

The treatment change cohort was intended to represent patients who were undergoing antidepressant drug treatment and who had made a treatment change, reasons for which could be side effects developed due to the initial antidepressant drug or a suboptimal response to this drug.

The new user cohort allowed the study of initial monotherapy or combination therapy with quetiapine. Restricting the cohort to those with a recently recorded MDD diagnosis excludes the large population of incident antidepressant users treated in primary care only, with no recorded psychiatric specialist care and presumably less severe depression – or other indications for antidepressants than depression.

9.1.2. Nested case-control studies

In each of the two cohorts, we performed nested case-control studies for each outcome. This was done to estimate the relative risk for each outcome allowing control of confounding. A dynamic study population was created so that each individual could contribute with several episodes of use, entering the population when the criteria above were fulfilled and leaving the population at the time where no new dispensing had occurred during 365 days.

Incidence density sampling was used to randomly select the controls. For every case, five controls that had not been diagnosed with the outcome were randomly selected from the cohort at risk at the time a case was defined (matching of controls is described below). The controls were selected with replacement and they could therefore end up as cases later on (Rothman et al. 2008).

9.2 Setting

National population based register study in Sweden. Study cohorts identified 2011-2014.

9.3 Subjects

9.3.1 Cohort studies

We identified all patients who filled a prescription for an antidepressant (ATC code N06A, excluding bupropion under the brand name of Zyban, indication for smoking cessation) and quetiapine IR or XR (ATC code N05AH04) from 2011-2014. The following antidepressant drug groups were defined:

Quetiapine XR and IR (N05AH04).

Other antidepressants, including the subgroups

SSRI: N06AB.

SNRI: venlafaxine (N06AX16), duloxetine (N06AX21).

Remaining antidepressants: (non-selective monoamine reuptake inhibitors) N06AA, (monoamine oxidase inhibitors, non-selective) N06AF, (monoamine oxidase A inhibitors) N06AG, and N06AX except venlafaxine (N06AX16) and duloxetine (N06AX21).

Cohort A. The treatment change cohort:

Among the patients undergoing antidepressant treatment we identified those who within one year from treatment initiation had filled a prescription for a new drug (defined below) on or after 1 January, 2011. Treatment with the first antidepressant drug could occur during 2010.

The day of cohort entry (index date) was the day of the first treatment change (index dispensing, i.e. add-on or switch).

Cohort B. The new user cohort:

Members of the cohort were identified as patients with a diagnosis of MDD (ICD-10 F32-F33) in a specialist psychiatric clinic within one year before a dispensing of a new antidepressant drug on or after 1 January 2011 and no other antidepressant drug dispensing in the year prior to this (washout period of at least one year). Psychiatric clinics also included clinics specialized in substance use disorders.

The day of cohort entry (index date) was the date of the first new dispensing. Patients remain in the cohort, irrespectively of later fulfilling the criterion of treatment change.

In the cohort definitions "new" meant first-time dispensing of an antidepressant substance that had not been dispensed during the previous year. Furthermore, as individuals could enter the population multiple times, the term ‘user’ in the cohort study refers to episodes of use.

9.3.2 Exclusion criteria

Age <18 years at the date of cohort entry.

Individuals not resident in Sweden at least one least year before cohort entry.

Patients with diagnoses related to schizophrenia or bipolar disorder from January 1, 1997 to the date of the index dispensing.

Patients with previous dispensing of lithium or mood stabilizers of antiepileptic type from July 1, 2005 to the date of the index dispensing, defined as lithium (N05AN01), carbamazepine

(N03AF01), lamotrigine (N03AX09), or valproate (N03AG01), because these can be considered markers of bipolar disorder in this population.

Patients with dispensing of any antipsychotic (N05A excluding lithium N05AN01) in the year prior to cohort entry.

Patients with a history of dementia (ICD-10 F00-F03, F051, F10.7A, G30, G311).

Both diagnoses from outpatient visits and inpatient hospitalizations were included in the definitions above.

Patients who experienced an event corresponding to any of the above exclusion criteria during the follow-up were censored on the date of the event.

9.3.3 Case-control studies

For each of the seven outcomes we performed a nested case-control study nested within each of the two cohorts A and B. For every case up to 5 controls were individually matched. Controls were selected using incidence density sampling among those alive and with no outcome events occurring before the event date of the matching case. In density-sampled case-control studies, controls are sampled from the unique set of subjects in the study cohort who are at risk of becoming a case at the time a case is defined. Using density sampling, the probability of any person from the study cohort being selected as control is proportional to the contribution of that person to the person-time at risk. If the sampling of controls is conducted independently of exposure, the odds ratio estimated from the case-control study is a valid estimate of the incidence rate ratio (Rothman et al. 2008). Sampling of controls was with replacement and controls were allowed to be selected as case later if they were diagnosed with an outcome. Matching criteria were age ±5 years, sex, calendar year of cohort entry and event date.

9.4 Variables

9.4.1 Exposures

The exposure was classified based on the information in drug dispensing records. Information on the prescribed dose is not coded in the PDR in a structured way. However, the dose information can be obtained through free text search. This information was used for assessing the length of treatment episodes of individual drugs and subsequently for determining the treatment pattern at specific points in time (index date, event date). The approach was developed in the pilot study (Pilot Study Report 2012).

In the previous study reports, medication exposure patterns were characterised using several categories: monotherapy, combination therapy, add-on, switching, uncertain, and complex pattern (Pilot Study Report 2012, Drug Utilisation Study First Report 2013, Drug Utilisation Study Second Report 2014). When a person during the treatment episode with a drug A was dispensed a new drug B, the treatment pattern was categorized as ‘uncertain’. This meant that it could not be determined whether dispensing of drug B represented add-on to treatment A or

a switch from A to B. If the A episode ended, the pattern was considered compatible with a switch to monotherapy with drug B on that date. If another dispensing of A occurred, B was considered an add-on from that date. With such a detailed exposure definition, it was found that the person time spent by an individual within a particular pattern was relatively short with several changes in exposure category over time. In the present study, the uncertain category was used only in the initial descriptive tables. In cohort and case-control analyses, medication exposure was categorized as monotherapy or combination therapy, with the uncertain period included as combination therapy.

In the cohort analyses, the exposure was based on the index medication (treatment at cohort entry, index dispensing), categorized as including quetiapine or other antidepressants only and further as either monotherapy or combination therapy including switching or add-on treatment groups as defined above.

Incident antidepressant users were defined as those with treatment initiated within one year prior to cohort entry and a treatment-free gap (washout period) of at least one year before initiation of treatment.

In the case-control studies, two exposures were investigated, current medication on the case defining event date (or matched control date) and index medication.

Using current treatment as exposure is equivalent to a cohort study with time-dependent exposure (time on drug, as-treated analysis), and using exposure at cohort entry is equivalent to an intention to treat analysis.

In the case-control analysis, current treatment was categorised as either monotherapy or combination therapy, with an exposure pattern according to the medications that were used on the event date.

In the new user cohort, only the treatment at cohort entry was relevant: monotherapy with quetiapine or other antidepressants, or polytherapy with or without quetiapine.

9.4.2 Outcomes

The safety outcomes were identified according to their ICD-10 diagnoses in the NPR and as the main cause of death in the cause of death register. For diabetes mellitus and extrapyramidal disorders (drug-induced parkinsonism) drug proxies were also used (ATC codes specified). A single dispensing was sufficient to define an outcome event.

The definitions of these outcomes were:

- Death (according to Cause of Death register).
- Acute myocardial infarction (AMI, ICD-10 I21).
- Stroke (ICD-10 I60-I69)

- Diabetes mellitus (ICD-10 E11, E13-E14, ATC A10 antidiabetics)
- Self-destructive acts and suicide (ICD-10 X60-X84 intentional self-harm and corresponding Y10-Y34 undetermined intent)
- Extrapyramidal disorders (ICD-10 G21 secondary parkinsonism, G24.0 drug-induced dystonia, ATC N04AA01 trihexyfenidyl, N04AA02 biperiden)
- Somnolence (ICD-10 R40)

Death was analysed as an independent outcome, irrespective of the occurrence of other events. For the outcomes acute myocardial infarction and stroke, death caused by these diagnoses were included (taking into account also cases not hospital admitted), while deaths from other causes were defined as censoring events.

We analysed incident events for all outcomes, excluding patients who had already experienced the event before cohort entry. For self-harm and suicide, we performed an additional analysis of all cases, including those with a previous history of self-harm, but adjusting for this.

For outcomes identified as inpatient hospital admissions in the NPR, the date of the event was the date of admission, while for drug proxies it was the date of the first dispensing of the drug defining the outcome event. For outcomes which were also relevant to identify in outpatient data (diabetes mellitus, extrapyramidal disorders, somnolence, and self-harm), the date of the event was defined as the date of diagnosis. Except for self-harm, we included incident outcome events only, and thus patients with the specific outcome event occurring before cohort entry were excluded. For self-destructive acts and suicide, separate estimates were calculated both for patients with and without previous self-harm.

Both cohorts were followed until December 31, 2014, or the first occurrence of a censoring event: exclusion criterion (below), migration or death prior to this date. Patients without prescription fillings of any antidepressant in 365 days were censored. Patients censored could fulfil the criterion for inclusion in one or both of the cohorts later on and were then included.

9.4.3 Potential confounders

In addition to the matching variables (age and sex), possible confounders available for adjustments were co-morbidities or co-medications that may be associated both with the patient being prescribed quetiapine and the outcomes of interest:

- Ischaemic heart disease other than myocardial infarction
- Transient cerebral ischemic attacks
- Peripheral arterial disease including extracerebral, non-coronary arterial thromboembolism
- Hypertension or antihypertensive drug use (all drug groups with the indication)

- Hyperlipidemia or lipid modifying agent use
- Low dose ASA or antianginal drugs (nitrates)
- Chronic respiratory disease: COPD, asthma
- Prior somatic admission history including number of previous admissions
- Psychiatric admission history including number of previous admissions
- History of self-harm (including both psychiatric and somatic admissions)
- Anxiolytic and hypnotic use
- Drug and alcohol abuse

These potential confounding variables (corresponding ICD-10 and ATC codes) have been evaluated as co-morbidity and co-medication patterns in the Pilot Study (Pilot Study Report 2012). Definitions are found in the Appendix.

Another potential confounder was severity of psychiatric illness, measured as history of psychiatric care follows: the number of hospital admissions for MDD (in the past year and since 1997) as: 0, 1, 2, ≥3. Severity of somatic illness was addressed in a similar way. Because of the relatively few expected outcome events, the number of confounders that could be included was limited and the relevant confounders were assumed to differ between outcomes. For example, relevant confounding factors were history of self-harm for suicide and cardiovascular comorbidities for myocardial infarction. A Charlson Comorbidity Score was calculated and used for adjustment for three of the outcomes. The predefined categories and their priorities are shown in the table below. We planned to include an increasing number of confounders while ensuring that there are at least 10 events per variable and sufficient numbers in each stratum. In case the analysis indicated a strong confounding factor where adjustment was not possible, an analysis matching on the particular confounder was planned as an alternative.

9.4.4 Pre-defined confounding factors and priorities

Outcome	Factors for adjustment
I Death of all causes	1. Charlson Comorbidity Score 2. Alcohol use disorder Other substance use disorder 3. Number of somatic hospitalizations in the year before index filling and since 1997 (0, 1, 2, ≥3)

	4. Number of hospitalizations for MDD in the year before index filling and since 1997 (0, 1, 2, ≥3)
II Acute myocardial infarction	1. Alcohol use disorder Cerebrovascular Disease Congestive Heart Failure Diabetes with complications Diabetes without complications Paraplegia and Hemiplegia Peripheral Vascular Disease Renal Disease IHD other than MI Low dose ASA or antianginal drug use Hypertension diagnosis or antihypertensive drug use Hyperlipidemia diagnosis or lipid modifying agent use 2. Charlson Comorbidity Score 3. Number of somatic hospitalizations in the year before index filling and since 1997 (0, 1, 2, ≥3) 4. Number of hospitalizations for MDD in the year before index filling and since 1997 (0, 1, 2, ≥3)
Stroke	1. Cerebrovascular Disease other than stroke Alcohol use disorder Congestive Heart Failure Diabetes with complications Diabetes without complications Myocardial Infarction Peripheral Vascular Disease Renal Disease IHD other than MI Low dose ASA or antianginal drug use Hypertension diagnosis or antihypertensive drug use Hyperlipidemia diagnosis or lipid modifying agent use 2. Charlson Comorbidity Score

	3. Number of somatic hospitalizations in the year before index filling and since 1997 (0, 1, 2, ≥3) 4. Number of hospitalizations for MDD in the year before index filling and since 1997 (0, 1, 2, ≥3)
Diabetes mellitus	1. Cerebrovascular Disease Congestive Heart Failure Myocardial Infarction Paraplegia and Hemiplegia Peripheral Vascular Disease Renal Disease Obesity 2. Number of somatic hospitalizations in the year before index filling and since 1997 (0, 1, 2, ≥3) 3. Number of hospitalizations for MDD in the year before index filling and since 1997 (0, 1, 2, ≥3)
Suicide and self-harm	1. Previous self-harm Other organic, including symptomatic, mental disorder Disorders of adult personality and behaviour Alcohol use disorder Other substance use disorder Anxiety disorder incl. GAD
Extrapyramidal symptoms	1. Current use of other antipsychotics.
Somnolence	1. Use of benzodiazepines or benzodiazepine-like hypnotics

*Index dispensing meaning first dispensing of the new drug meeting the inclusion criteria.

9.5 Data sources and measurement

The data utilized for the studies is obtained from national Swedish registers maintained by the National Board of Health and Welfare. Individual data is linked within and between registers by the unique personal identification number (PIN) (Ludvigsson et al. 2009).

9.5.1 The Prescribed Drug Register

The PDR was started July 1, 2005 and comprises all purchases of prescribed drugs at pharmacies (dispensed drugs) (Wettermark et al. 2006). It is estimated that the register annually contains 82% of all Defined Daily Doses (DDD) and 74% of all drug sales in Sweden. The remainder concerns drugs used in in-patient care, OTC drugs and requisitions

(purchase orders) from physicians. Drug Register was started July 1, 2005 and is updated each month. The variables include the patient's PIN and place of residence as well as information about prescribed and dispensed drugs by ATC-code, dates, dosage and for an unknown proportion indication in free text, DDDs, and expenditure. Information on the prescriber's profession (physician or other) and specialist code are registered. Additionally, information on the prescriber's workplace includes ownership (public, private), level of care (primary or specialist), and type of care (i.e. internal medicine, surgery, psychiatry). Indication of the drug is not included as a separate code, the amount of dispensed drug is available both as the number of dosage units (e.g. tablets) and DDDs, but the prescribed dosage for the particular drug is written as free text which is only partly structured.

9.5.2 The National Patient Register

The NPR was established in the first county in 1964 (Ludvigsson et al. 2011). From 1987 the NPR includes all in-patient care in Sweden. It contains 50 million discharges during the period 1964 to 2006. From 2001 the register also contains information on outpatient visits at hospitals, including day surgery carried out by both private and public caregivers. The variables include patient data (PIN, sex, age, place of residence), geographic data (county council, type of clinic, or department), administrative data (dates of admission and discharge, length of stay for inpatients, acute/planned admission, admitted from, discharged to) and medical data (the main diagnosis, secondary diagnoses, external cause of injury and poisoning, procedures and surgery). Information on primary care visits is not included in the NPR.

9.5.3 The Total Population Register

To ascertain a correct population and calculate durations and person time in the data analysis, information on dates of emigration and death for all patients is retrieved from the Total Population Register that is maintained by Statistics Sweden.

9.5.4 The Causes of Death Register

The Causes of Death Register contains information on all deaths of Swedish residents since 1960. Information is based on death certificates and contains main and contributory causes of death coded according to international versions of ICD.

9.6 Bias

The study is based on population-based data including all patients in Sweden meeting the inclusion criteria. Thus, there is no selection bias affecting the dynamic study population. As data were prospectively registered recall bias is not a concern. The PDR does not contain information on medication use in hospitals and misclassification of exposure status might therefore occur. However, as the average duration of hospitalization is relatively short and patients receive prescription for their medications after hospital discharge such bias would be minimal. We used a 12-month wash-out period as an attempt to restrict the subjects to incident users.

Indications as well as comorbidities may differ between the treatment groups; this is likely to be the case also for factors not captured in the registers. Patients with MDD who are prescribed an antipsychotic drug such as quetiapine may be more severely ill than those only receiving other antidepressants. This leads to confounding by indication or confounding by severity. This is sometimes also referred to as a type of selection bias, or channelling bias. We do not have access to direct information on the clinical status of the patient. Thus, some residual confounding and bias due to unmeasured confounders is expected. This bias would lead to an apparently increased risk of the adverse outcome.

Misclassification of outcome events is a possible source of information bias. Low completeness of the data sources used or in the recording of specific diagnoses could lead to non-differential misclassification and bias towards the null, while differential misclassification among users of quetiapine and other antidepressants could lead to bias away from the null.

The Cause of Death Register and the National Patient Register have complete coverage of the population. Inpatient diagnoses of stroke and myocardial infarction are known to have a high validity (Ludvigsson et al. 2011). Using only diabetes diagnoses from the patient register (in- and outpatients) may lead to incomplete ascertainment of diabetes, but the use of antidiabetic drugs as a proxy should lead to almost complete coverage of drug-treated diabetes. Suicide is captured by the Cause of Death Register, but less severe cases of self-harm and cases not leading to a health care encounter may not be captured. Differential misclassification, however, is not considered likely.

With regard to diagnoses of extrapyramidal disorders and somnolence, it could be expected that coverage is low because many events may only be recorded in primary care. Both extrapyramidal disorders and somnolence are mentioned as very frequent adverse effects in the SmPC of quetiapine (SmPC 2014) and it cannot be excluded that increased awareness would lead to non-differential misclassification and an increase in the risk estimate for quetiapine due to more frequent recording of the diagnoses after dispensing of this drug.

9.7 Study size

Not applicable. The study concerns a total population of antidepressant users fulfilling the inclusion criteria.

9.8 Data transformation

Not applicable.

9.9 Statistical methods

9.9.1 Main summary measures

9.9.1.1 Cohort studies

Descriptive statistics including numbers, proportions, mean, standard deviations, medians, quartiles, minimum, maximum and mode were used to characterise the cohorts.

Crude incidence rates with confidence intervals of each of the outcomes were calculated from cohort entry (index dispensing) to outcome event, meeting exclusion criteria, emigration or end of follow-up, whichever came first. The crude incidence rates were reported as number of cases per 1,000 person-years.

9.9.1.2 Nested case-control studies

For each of the seven outcomes, we performed a case-control study nested within each of the two cohorts. Descriptive statistics including numbers, proportions, mean, standard deviations, medians, quartiles, minimum, maximum and mode were used to characterise the cases and controls for each outcome in each cohort.

The odds ratio (OR) and 95% CI for each outcome was estimated by comparing exposure between cases and controls.

9.9.2 Main statistical methods

9.9.2.1 Cohort studies

Cohorts A and B were analysed separately.

Two types of analyses were performed:

An intention-to-treat analysis where follow-up started at the index date, potentially including all dispensings of the index episode of medication use, censoring at the outcome, migration, death or at the time when 365 days after a dispensing had elapsed, whichever event occurred first.

A time-dependent exposure (time on drug) analysis where follow-up started on the index date, censoring at the outcome, migration, death or at the switch or discontinuation of the index dispensing. This was used to calculate rates for monotherapy or combination therapy.

Exact 95% confidence intervals, according to Poisson distributions were calculated for the incidence rates. However, as the rates are presented with descriptive purposes, neither formal statistical tests of differences nor adjustments were performed.

9.9.2.2 Nested case-control studies

The data was analysed separately for each of the two cohorts. Each of the seven outcomes were analysed using conditional logistic regression models conditioning on the case and matched controls sets comparing the exposure to quetiapine monotherapy or combination treatment among cases and controls, thus assessing any contrasts between quetiapine treatment and other treatment patterns, with combinations of other antidepressants as reference category. In some models the categories quetiapine use as monotherapy and in combination were collapsed due to small numbers. The statistical modelling was done with the logistic procedure in SAS version 9.4, SAS Institute Inc., Cary, NC, USA

Both current treatment at the time of the respective event and treatment at cohort entry, i.e. index dispensing, was analysed. These analyses are equivalent to cohort studies with time-

dependent exposure or intent-to-treat analysis, respectively. From the analysis of current medication, cases hospitalized for more than 30 days immediately prior to an outcome event identified in the cause of death register were omitted along with their controls, since medications given during hospitalisation are unknown.

Conditional logistic regression models were used to estimate ORs and their 95% CIs. Crude ORs are estimated for each covariate. Adjusted ORs are estimated with a model including all pre-specified covariates (see sections 9.4.3 and 9.4.4). In the present nested case-control design the odds ratio (OR) of cases' exposure to a particular medication vs. the reference medication is an estimate of the incidence rate ratio of the outcome event in users of the medication vs. users of the reference medication.

9.9.3 Missing values

Not applicable.

9.9.4 Sensitivity analyses

The following sensitivity analyses were performed with the nested case-control approach:

- Analyses repeated after exclusion of patients with a diagnosis of alcohol or substance misuse
- Stratified on age groups 18-64 years and 65+ years
- A separate analysis of death by suicide
- Analysis of self-harm and suicides with violent methods in a subsample of patients without a history of previous self-harm
- Self-harm and suicides with non-violent methods in a subsample of patients without previous self-harm.
- Analyses repeated after exclusion of patients on quetiapine IR at date of event.

9.9.5 Amendments to the statistical analysis plan

The clinic of the prescriber of the index drug was added in Tables 16 and 17.

In the result tables (Appendix 1) adjusted analyses for the pre-defined full models are presented. In Appendix 5, a Type 3 test is shown for variables and estimates of the full models and for estimates from a reduced model with only significant covariates selected using a backward elimination approach. This alternative modelling strategy was performed to check the robustness of the results in the pre-specified main analysis.

The above approach was not detailed in the statistical analysis plan.

9.10 Quality control

Routine quality checks and cleaning procedures were used for register data received. The study has been conducted as described in the study protocol and in the statistical analysis plan. We followed the internal quality guidelines of the Centre for Pharmacoepidemiology when conducting the statistical analyses.

The procedure for extracting information from dose texts has previously been validated at the Centre for Pharmacoepidemiology.

10. RESULTS

10.1 Participants

Descriptive data on the number of included new users and cohort follow-up time are shown in a flowchart, **Figure 1**. Because an individual can enter the study more than once, the term 'user' and the numbers refer to new episodes of use. A total of 1 514 368 new users of antidepressants (including quetiapine) between 2011 and 2014 were eligible for study. The initial exclusion criteria including age, migration status, and no use of antipsychotic drugs in the previous year were subsequently applied.

For 505 105 new users another antidepressant had been dispensed in the previous year. After applying further exclusion criteria related to the psychiatric history, the treatment change cohort (Cohort A) consisted of 288 724 users. Of these, the number with an index dispensing of quetiapine XR, quetiapine IR and other antidepressants was 2 823, 4 598, and 281 303, respectively.

In the parallel path of cohort formation, 855 379 new users had no other antidepressant dispensed in the previous year. After including only those with MDD diagnosed in a psychiatric clinic in the previous year and applying further exclusion criteria related to the psychiatric history, 38 772 entered the users with MDD cohort (Cohort B). The number of users with an index dispensing of quetiapine XR, quetiapine IR and other antidepressants was 337, 482, and 37 953, respectively.

Table 1 shows for each cohort and treatment group the number of users excluded due to a previous diagnosis of a schizophrenia related disorder, dementia or bipolar disorder or previous use of mood stabilizing medication.

The number of antidepressant users initiating treatment with quetiapine in this study is 7 412 in Cohort A and 819 in Cohort B. In both cohorts, however, those with an index dispensing of another antidepressant than quetiapine may start to use quetiapine later during follow-up. Thus, the nested case-control studies cover *all* quetiapine-exposed patients during 2011-2014 in these cohorts. Treatment with quetiapine as add-on to another antidepressant is included in the treatment change cohort. The total number of patients who at some point during follow up use quetiapine XR and do not use quetiapine IR is 5481 in Cohort A and 767 in Cohort B.

10.2 Descriptive data

Table 2 shows the history of MDD, other psychiatric diagnoses and self-harm since 1997 in the two study cohorts.

In the treatment change cohort, 85.6% of quetiapine users had a recorded psychiatric diagnosis from specialist care, whereas a much lower proportion, 47.2%, of users of other antidepressants had such a diagnosis. A diagnosis of MDD had been given to a considerably higher proportion of quetiapine users than to those treated with other antidepressants (74.6 % vs. 37.5%). A higher prevalence of psychiatric illness among quetiapine users was seen for all diagnostic groups. Quetiapine users had a higher prevalence than other antidepressant users of alcohol use disorders (10.3% vs. 3.5%) other substance use (12.5% vs. 2.7%), anxiety disorders including GAD (45.1% vs. 16.9%), OCD, stress-related and somatoform disorders (26.5% vs. 9.5%) adult personality disorders (12.8% vs. 2.7%) and disorders of psychological development (18.1% vs. 4.9%). A history of self-harm was nearly three times more prevalent in the quetiapine group compared to the other antidepressant group (15.0% vs. 5.6%).

In the new user with MDD cohort, all by definition had a previous psychiatric diagnosis of MDD. A pattern of a higher burden of psychiatric illness was seen in quetiapine users compared to other antidepressant users for all other specified psychiatric diagnostic groups except for the group behavioural syndromes associated with physiological disturbances and physical factors (including for instance eating disorders and sleep disorders). In this cohort representing naïve users, a history of self-harm was more prevalent in the quetiapine group compared to the other antidepressant group (17.1% vs. 10.4%).

Table 3 shows descriptive characteristics of the study cohorts. For the treatment change cohort, the clinic of the prescriber differed considerably between the index drugs. A markedly higher proportion of the prescriptions for quetiapine than prescriptions for other antidepressants were written in specialized psychiatric care (82.6% vs. 23.1%).

In the treatment change cohort, age at cohort entry was lower for new users of quetiapine than other antidepressants, mean age 43.0 years vs. 51.0 years, and median 41 years vs. 49 years, respectively. There were more women than men in both exposure groups, 58.2% women for quetiapine and 66.5% for other antidepressants. A higher proportion of quetiapine users than other antidepressant users had been hospitalised due to a diagnosis of MDD in the year prior to the index prescription, 10.7% vs. 2.5%. Likewise, a higher proportion of quetiapine users than other antidepressant users had been hospitalised due to a diagnosis of MDD from 1997 until the index date, 19.7% vs. 6.1%. In contrast, a similar proportion of quetiapine and other antidepressant users had been hospitalised for a somatic condition in the year prior to the index prescription, 76.3% vs. 78.5%, and in the period from 1997 to the index prescription, 70.3% vs. 71.6%.

In the new user with MDD cohort a very high proportion of the prescriptions were written in specialized psychiatric care. A markedly lower proportion of the prescriptions were written in primary care for quetiapine than for other antidepressants (1.0% vs. 8.8%).

The age was relatively similar in new users of quetiapine and other antidepressants, mean 37.6 years vs. 36.9 years, and median 35 years vs. 33 years, respectively. Women were more prevalent; 52.4% among quetiapine and 66.5% among other antidepressant users. A higher proportion of quetiapine users than other antidepressant users had been hospitalised due to a diagnosis of MDD in the year prior to the index date, 29.5% vs. 16.3%. Likewise, a higher proportion of quetiapine users than other antidepressant users had been hospitalised due to a diagnosis of MDD from 1997 until index date, 39.1% vs. 21.1%. In contrast, a similar proportion of quetiapine and other antidepressant users had been hospitalised for a somatic condition in the year prior to the index date, 19.8% vs. 18.4%, and in the period from 1997 to the index date, 66.5% vs. 62.0%.

Table 4 shows the history of psychiatric diagnoses in the year before the index dispensing in the two study cohorts. Overall, the pattern was similar to that described above for Table 2, in that the burden of psychiatric illness treated in specialist care was higher for users of quetiapine than for other antidepressants.

In the treatment change cohort, 82.6 % of quetiapine users had a recorded psychiatric diagnosis from specialist care, whereas only 41.2% of users of other antidepressants had such a diagnosis. A diagnosis of MDD had been given to a considerably larger proportion of patients with quetiapine than to patients treated with other antidepressants (49.7 % vs. 24.8%). A higher burden of psychiatric illness among quetiapine users than among users of other antidepressants was seen for other diagnostic groups as well.

In the new user with MDD cohort, all patients by definition had a previous psychiatric diagnosis of MDD. In all other psychiatric diagnostic groups except two, a higher burden of psychiatric illness treated in specialised care was seen in quetiapine users than in other antidepressant users. For the group behavioural syndromes associated with physiological disturbances and physical factors (including for instance eating disorders and sleep disorders) and the group other organic, including symptomatic, mental disorders, excluding dementia, the prevalence was similar in users of quetiapine and other antidepressants.

A history of self-harm was more prevalent in the quetiapine group compared to the other antidepressant group, both in the treatment change cohort (7.2% vs. 2.1%) and in the new user with MDD cohort (8.8% vs. 5.6%).

Table 5 shows the history of psychiatric diagnoses from psychiatric departments in the year before the index dispensing. Overall, the pattern was very similar to that found in Tables 2 and 4.

In the treatment change cohort, a majority of quetiapine users had a recorded psychiatric diagnosis from specialist care, whereas about one third of users of other antidepressants had such a diagnosis.

In the new user with MDD cohort, all patients by definition had a previous psychiatric diagnosis of MDD. In all other diagnostic groups except the same two groups as above, a

higher burden of psychiatric illness treated in specialised care was seen in quetiapine users compared to other antidepressant users.

Table 6 shows the somatic comorbidity profile (diagnoses as of 1997) prior to the index dispensing, according to Charlson comorbidity groups (Quant et al. 2005, Appendix 2) and IHD excluding MI.

In the treatment change cohort, quetiapine users overall had a slightly lower burden of somatic disease according to the Charlson comorbidity index: 74.3 % of quetiapine users vs. 70.1% of users of other antidepressants had a score of 0. The mean Charlson comorbidity score was 0.38 (SD 0.76) for quetiapine users and 0.52 (SD 1.00) for other antidepressant users. This trend was observed for most of the specific Charlson comorbidity diagnostic groups, including ischaemic heart disease of which the prevalence among quetiapine uses was 3.7 % compared to 7.0% among users of other antidepressants.

In the new user with MDD cohort, quetiapine users and users of other antidepressants had similar Charlson comorbidity scores: 80.8% of quetiapine users vs. 81.8% of users of other antidepressants had a score of 0. The mean Charlson comorbidity score was 0.27 (SD 0.64) for quetiapine users and 0.27 (SD 0.68) for other antidepressant users. Quetiapine users had overall a slightly lower prevalence of ischaemic heart disease: 1.3% of quetiapine users vs. 2.4% of users of other antidepressants.

Table 7 shows the patterns of dispensing during the index medication episode of the new antidepressant among patients in the two study cohorts.

In the treatment change cohort, a smaller proportion of quetiapine users than other antidepressant users used monotherapy (16.4% vs. 27.2%). and a larger proportion were classified as having a combination or add on therapy (28.1% vs. 11.5%). The overall number of dispensings was higher for other antidepressants than for quetiapine; more than five dispensings were seen in 25.9% of quetiapine users and 31.1% of other antidepressant users. Also, the duration of the drug treatment episode was longer for other antidepressants than for quetiapine; a duration of more than 30 days was seen in 86.9% of quetiapine users and 94.4% of other antidepressant users.

In the new user with MDD cohort, a smaller proportion of quetiapine users than other antidepressant users used monotherapy (59.5% vs. 96.8%) and a much larger proportion of quetiapine users than other antidepressant users was classified as having a combination or add on therapy (40.5% vs. 3.2%). The overall number of dispensings was higher for other antidepressants than for quetiapine with more than five in 21.0% of quetiapine users and 27.0% of other antidepressant users. Furthermore, the duration of the drug treatment episode was longer for other antidepressants than for quetiapine, more than 30 days was in 37.5% of quetiapine users vs. 52.6% of other antidepressant users.

The majority of quetiapine users, 86.6% in the treatment change cohort and 91.0% in the new users with MDD cohort, used only one formulation.

Table 8 shows the patterns of medication at study entry and in the preceding year in the treatment change cohort. A larger proportion in the quetiapine group than in the other antidepressant group had filled prescriptions for more than two drugs (14.9% vs. 5.7%). The length of the antidepressant treatment episode preceding the index episode did not differ markedly between the quetiapine and other antidepressant groups.

Table 9 shows the patterns of censoring and observed person time in the two study cohorts.

In the treatment change cohort, a notably larger proportion of quetiapine users than other antidepressant users were censored during follow up because of exclusion criteria, i.e. a diagnosis of schizophrenia, bipolar disorder or dementia or filling a prescription of a mood-stabilizing medication (19.9% vs. 6.4%). A slightly lower proportion of quetiapine users than other antidepressant users died during the follow up (3.2% vs. 4.5%). The total observation time was 11 307.4 person years for the quetiapine users and 472 124.6 person years for the other antidepressant users. The mean follow up time is 1.52 years for quetiapine users and 1.68 for other antidepressant users.

Likewise, in the new user with MDD cohort, a notably larger proportion of quetiapine users than other antidepressant users were censored because of exclusion criteria (18.1% vs. 7.4%). In this cohort, a similar proportion of quetiapine users and other antidepressant users died during follow up (1.3% vs. 1.4%). The total observation time was 957.3 person years for the quetiapine users and 54663.2 person years for the other antidepressant users. The mean follow up time is 1.17 years for quetiapine users and 1.44 years for other antidepressant users.

Table 10 shows the history of events and comorbidities from 1997 until the date of the index prescription in the study cohorts. Overall, there was no uniform pattern found for the different treatment groups.

In the treatment change cohort, the proportion of patients with a history of extrapyramidal disorders, somnolence, and self-harm was higher among quetiapine users than among other antidepressant users: However, a lower proportion of quetiapine users had a history of acute myocardial infarction, stroke, and diabetes mellitus. As for comorbidities, a markedly higher proportion of quetiapine users than users of other antidepressants had a history of alcohol abuse, substance abuse and anxiolytic and hypnotic use, whereas a higher proportion of users of other antidepressants had IHD other than AMI, peripheral arterial disease, hypertension and hyperlipidaemia.

In the new user with MDD cohort, quetiapine users more frequently had a history of diabetes mellitus, extrapyramidal disorders, somnolence, and self-harm but less frequently a history of acute myocardial infarction and stroke. A markedly higher proportion of quetiapine users than users of other antidepressants had a previous history of alcohol abuse, substance abuse, anxiolytic and hypnotic use.

10.3 Outcome data

Table 11 shows the number of events of interest and the first source of identification of the events in the National Patient Register, Prescription Register and Cause of Death Register. All causes of death were identified in the Cause of Death Register. For diabetes mellitus and extrapyramidal disorders, the majority of cases were identified in the Prescription Register whereas the majority of other outcome events were identified in the National Patient Register.

10.4 Main results

10.4.1 Cohort analysis

Incidence rates are presented by cohort and exposure to index medication for descriptive purposes.

Table 12 shows the crude incidence rates of outcome events with 95% CI analysed using an intention-to-treat principle with follow-up until event, or censoring 365 days after the last dispensing of any antidepressant. In the treatment change cohort, quetiapine users had a lower incidence rate of death from all causes, acute myocardial infarction and diabetes mellitus than other antidepressant users. In contrast, quetiapine users had higher total incidence rates of extrapyramidal disorders, somnolence, self-harm and suicides (incident cases), and self-harm and suicides (all cases). Incidence rates of all cause death, acute myocardial infarction and stroke increased with age. For diabetes mellitus, the highest incidence rate was found among the 50-74 year olds. The highest rates of self-harm and suicide were found among the 18-49 year olds.

In the new user with MDD cohort, quetiapine users had higher total incidence rates for extrapyramidal disorders and self-harm and suicides (for all cases but not for incident cases). No major differences in incidence rates were found for the other investigated outcome events. There were, however, only few events among the quetiapine users. The highest incidence rates for most outcome events were found in the age group 75 years or more. However, for self-harm and suicides, the highest incidence rate was found in the youngest age group, the 18-49 year olds.

Table 13 shows incidence rates of outcome events for users of combination therapy with the index substance, censoring at switch or discontinuation of index medication, i.e. only events during treatment with the initial medication pattern were included.

In the treatment change cohort, other antidepressant users had a higher total incidence rate for death of all causes, and diabetes mellitus compared to quetiapine users. In contrast, higher total incidence rates for extrapyramidal disorders, self-harm and suicides (incident and all cases and both violent and non-violent methods) were found among quetiapine users. In the new user with MDD cohort, quetiapine users had a higher total incidence rate for extrapyramidal disorders. No major differences in incidence rates were observed for the other outcome events investigated.

Table 14 shows incidence rates of outcome events in users of monotherapy with the index substance, censoring at switch or discontinuation of index medication, i.e. only events during treatment with the initial medication pattern were included.

In the treatment change cohort, quetiapine users had higher total incidence rates for extrapyramidal disorders, somnolence, self-harm and suicides (incident cases and all cases and both violent and non-violent methods), compared to other antidepressant users.

In the new user with MDD cohort, quetiapine users had a higher total incidence rate for extrapyramidal disorders, self-harm and suicides (all cases). No major differences in incidence rates were found for the other outcome events investigated.

10.4.2 Case-control analyses

In all analyses, cases were compared to controls matched by the year of the index dispensing, age and sex. The exposure category combination therapy including other antidepressants was used as reference in the treatment change cohort, monotherapy with other antidepressants as a reference in the new user with MDD cohort.

10.4.2.1 Death from all causes

Table 15 shows descriptive characteristics of cases and controls for the analysis of death from all causes. A total of 13 126 deaths were identified in the treatment change cohort (cohort A). The mean (SD) age was 77.3 (14.7) years and 60.1% were women. In the new user with MDD cohort (cohort B), 527 deaths were identified. The mean (SD) age at death was 62.4 (21.0) years and 36.8% were women.

Table 16 shows odds ratios from the case control analysis of death from all causes with regard to current medication at the date of death.

In the treatment change cohort, a significantly higher risk of death was identified only among current users of a combination therapy with quetiapine, adjusted OR 1.49 (1.27-1.75). Having filled a prescription for monotherapy with quetiapine was associated with a borderline significantly higher risk, adjusted OR 1.37 (0.99-1.89).

In the new user with MDD cohort, the number of events was small and associations with quetiapine exposure not significant.

Table 17 shows odds ratios from the case control analysis of death from all causes with index treatment. In the treatment change cohort, a significantly higher risk of death was identified among index users of monotherapy with quetiapine, adjusted OR 1.69 (1.18-2.42) and combination therapy with quetiapine, adjusted OR 1.25 (1.05-1.48).

In the new user with MDD cohort, adjusted ORs for quetiapine monotherapy and for combination therapy with quetiapine were also above one, but lower than in cohort A, and the associations were not significant.

Other factors associated with death from all causes (**Tables 16-17**) were the index prescriber (prescriptions from a somatic clinic and other clinic showed a higher risk but a prescription from psychiatry lowered the risk compared to a prescription from primary care), comorbidity including the Charlson comorbidity score and the number of somatic hospitalizations, and the number of hospitalizations for MDD in the year before the index date. In addition, having a history of alcohol or substance use increased the risk of death significantly compared to no such history.

10.4.2.2 Acute myocardial infarction

Table 18 shows descriptive characteristics of cases and controls included in the analysis of acute myocardial infarction (AMI). In the treatment change cohort, 2 018 cases were identified. The mean (SD) age was 73.8 (13.35) years and 56.7% were women.

In the new user with MDD cohort, 89 cases of AMI were identified, with a mean (SD) age of 62.4 (14.72) years. A majority were men (61.8%).

Table 19 shows odds ratios from the case-control analysis of acute myocardial infarction (AMI) with regard to current medication at the date of the event.

In the adjusted analyses, no significant associations between type of current medication and acute myocardial infarction were found.

In the new user with MDD cohort, no cases and only few controls were exposed to quetiapine and ORs could not be estimated.

Table 20 shows odds ratios from the case-control analysis of AMI with regard to type of index treatment.

No significant associations between categories of drug use and acute myocardial infarction were identified. In the new user with MDD cohort, no cases were exposed to quetiapine and ORs could not be estimated.

Several comorbidities, including alcohol use disorder, cerebrovascular disease, congestive heart failure, diabetes, paraplegia and hemiplegia, IHD other than AMI, low dose ASA or antianginal drug use, hypertension and hyperlipidaemia were found to be associated with a higher risk of AMI in the crude analysis, with ORs attenuated after multivariable adjustment. A high Charlson comorbidity score (including several of the factors mentioned) and an increasing number of somatic hospitalizations was also associated with a higher risk of AMI.

10.4.2.3 Stroke

Table 21 shows descriptive characteristics of cases and controls for the case control analysis of stroke. In the treatment change cohort, 2 913 cases were identified. The mean (SD) age was 74.6 (13.8) years and 64.5% were women. In the new user with MDD cohort, 130 cases were identified, with a mean (SD) age of 64.3 (16.2) years and 38.5% women.

Table 22 shows odds ratios from the case control analysis of the outcome stroke with regard to current medication.

No significant associations between categories of drug use and stroke were identified in either of the two cohorts. .

Other factors found to be associated with stroke were a high Charlson comorbidity score, corresponding comorbidity groups, a history of alcohol use disorder, IHD other than AMI, low dose ASA or antianginal drug use, hypertension, hyperlipidaemia, and the number of previous somatic hospitalizations.

Table 23 shows odds ratios from the case control analysis of the outcome stroke with regard to the index treatment.

No significant associations between categories of drug use and stroke were identified.

In the new user with MDD cohort, the number of cases and controls with the exposures of interest were too few to estimate their associations with stroke.

10.4.2.4 Diabetes mellitus

Table 24 shows descriptive characteristics of cases and controls for the case control analysis of diabetes mellitus. In the treatment change cohort, 2 941 cases were identified. The mean (SD) age was 58.8 (15.2) years and 59% were women. In the new user with MDD cohort, 229 cases were identified, with a mean (SD) age of 48.3 (15.6) years, 52% were women.

Table 25 shows odds ratios from the case control analysis for diabetes mellitus with regard to current medication at the event and **Table 26** shows odds ratios with regard to the index treatment. In the treatment change cohort, neither of these analyses demonstrated significant associations with quetiapine monotherapy or quetiapine combination therapy. In the new user with MDD cohort, there were only few cases exposed to quetiapine. Exposure to quetiapine monotherapy and combination was collapsed into one category, but no significant associations were found.

Other factors associated with diabetes were cerebrovascular disease, myocardial infarction, peripheral vascular disease, renal disease, obesity, a high Charlson comorbidity score, previous somatic hospitalisations and more than 2 hospitalisations for MDD during the year prior to the index date.

10.4.2.5 Self-harm and suicide

Table 27A shows descriptive characteristics of cases and controls for the analysis of all cases of self-harm and suicide, *including* patients who had a recorded history of self-harm prior to the index date. In the treatment change cohort 5 714 cases were identified. The mean (SD) age was 41.3 (18.2) years and the majority were women (60.4%). In the new user with MDD cohort there were 1 513 cases with a mean (SD) age of 33.9 (15.8) years of whom 52% were women.

Table 27B shows descriptive characteristics of cases and controls for the analysis of incident cases of self-harm and suicide, *excluding* patients and controls with a history of self-harm before the index date. In the treatment change cohort 3 918 cases were identified. The mean (SD) age was 42.3 (18.7) years and the majority were women (59.0%). In the new user with MDD cohort there were 1 028 cases with a mean (SD) age of 32.6 (14.3) years of whom 55.5% were women.

Table 28 shows odds ratios from the case control analysis of self-harm and suicide (all cases) with regard to current treatment at time of event.

In the treatment change cohort, a significantly increased risk of self-harm was identified among current users of combination therapy with quetiapine, adjusted OR 1.53 (1.31-1.79). A significantly lower risk of the outcome was found for those with no medication, adjusted OR 0.52 (0.47-0.58) but also in users of monotherapy with quetiapine and monotherapy with other antidepressants.

Psychiatric comorbidity was found to be associated with this outcome, with the highest risk presented by previous self-harm, crude OR 6.83 (6.32-7.37). Other factors associated with the outcome were other organic, including symptomatic, mental disorder, disorders of adult personality, alcohol and other substance use as well as anxiety disorder including GAD. Furthermore, the number of previous hospitalizations with MDD was strongly associated with self-harm and suicide, both hospitalizations in the year prior to the index date and the long-term history since 1997. The number of somatic hospitalizations was also associated with the outcome, although to a lesser degree than psychiatric comorbidity.

In the new user with MDD cohort, no increased risk of self-harm was identified among current users of monotherapy or a combination therapy with quetiapine. Having no current medication or monotherapy with other antidepressants was associated with a significantly a lower risk of the outcome.

In this cohort, a history of self-harm was strongly associated with the outcome. Other factors of psychiatric comorbidity and previous hospitalizations were also associated, but to a lesser degree than in the treatment change cohort.

Table 29 shows odds ratios from the case control analysis of self-harm and suicide (all cases) with regard to the index treatment.

In the treatment change cohort, a significantly higher risk was identified only among index users of combination therapy with quetiapine, adjusted OR 1.21 (1.03-1.43).

In the new user with MDD cohort, no significantly higher risk of self-harm was identified in any of the treatment groups.

Table 30 shows odds ratios from the case control analysis of the outcome self-harm and suicides for incident cases, with regard to the current medication at time of event.

In the treatment change cohort, a significantly higher risk of the outcome was identified only among current users of combination therapy with quetiapine, adjusted OR 1.52 (1.26-1.84). There was no increased risk with quetiapine monotherapy. In the new user with MDD cohort, the OR for quetiapine combination therapy was also above one, but not significant. Using monotherapy with other antidepressants and using no medication was again associated with a lower risk of the outcome compared to the reference of combinations with other antidepressants. The pattern of associations with other factors was also similar.

Table 31 shows odds ratios from the case control analysis of the outcome self-harm and suicides for incident cases, with regard to the index medication.

In the treatment change cohort, a significantly higher risk of the outcome was identified among patients on monotherapy with quetiapine, adjusted OR 1.61 (1.03-2.54), while there was no significantly increased risk with quetiapine combination therapy. In the new user with MDD cohort, there were no significant associations with quetiapine monotherapy or combination therapy.

10.4.2.6 Extrapyramidal disorders

Table 32 shows descriptive characteristics of cases and controls for the case control analysis of extrapyramidal disorders. In the treatment change cohort 523 cases were identified with a mean (SD) age of 55.3 (21.1) years, 59.1% were women. In the new user with MDD cohort, 67 cases were identified, with a mean (SD) age of 44.3 (19.8) years, 46.3% were women.

Table 33 shows odds ratios from the case control analysis for extrapyramidal disorders with regard to current treatment at time of event.

A significantly higher risk of extrapyramidal disorder was identified among current users of monotherapy with quetiapine, adjusted OR 13.51 (4.98-36.65) and a combination therapy with quetiapine, adjusted OR 6.15 (3.57-10.58). Current use of other antipsychotics than quetiapine was associated with an even higher risk, adjusted OR 19.94 (13.77-28.88) while using no current antidepressant medication was associated with a reduced risk, adjusted OR 0.70 (0.49-0.99).

In the new user with MDD cohort, no significantly higher risk of extrapyramidal disorders was identified among current users of monotherapy or a combination with quetiapine

(categories collapsed). Current use of other antipsychotics than quetiapine was associated with a very high risk, adjusted OR 54 (12-234).

Table 34 shows odds ratios from the case control analysis for extrapyramidal disorders with regard to the index treatment.

In the treatment change cohort, a similar pattern of associations with quetiapine monotherapy and combination therapy as that in Table 33 was found, although with somewhat lower ORs.

In the new user with MDD cohort, numbers were too few to estimate odds ratios.

10.4.2.7 Somnolence

Table 35 shows descriptive characteristics of cases and controls for the case control analysis of somnolence. In the treatment change cohort, 546 cases were identified. Their mean (SD) age was 57.5 (21.9) and 57.3% were women.

Table 36 shows odds ratios from the case control analysis for somnolence with regard to current treatment at time of event.

In the treatment change cohort, an association between the outcome and current quetiapine combination therapy was seen, adjusted OR 2.41 (1.42-4.11). Dispensing of anxiolytics and hypnotics before the index date and between the index date and the event date was also associated with the outcome, with only the latter being significant in the multivariable analysis, adjusted OR 1.95 (1.54-2.46).

In the new user with MDD cohort, numbers were too few to estimate odds ratios.

Table 37 shows odds ratios from the case control analysis for somnolence with regard to the index treatment and the results exhibit a similar pattern as Table 36.

In the new user with MDD cohort, numbers were too few to estimate odds ratios.

10.5 Other analyses

A number of sensitivity analyses were performed.

Table 38 shows the change in odds ratios in case-control analysis I-VII after exclusion of patients with a diagnosis of alcohol or substance misuse with regard to current treatment at the time of event.

In both cohorts, the adjusted ORs for the seven outcomes of interest changed only marginally in the different medication groups compared to those in Tables16, 19, 22, 25, 28, 30, 33 and 36. Exceptions were for diabetes mellitus, where the risk was significantly lower for patients using combination therapy with quetiapine, OR 0.63 (0.41-0.98), and for self-harm and suicide where the risk was significantly higher for users of a combination therapy with quetiapine, OR 1.42 (1.16-1.75),

Table 39 shows the case-control analysis I-VII stratified on age groups 18-64 years and 65+ years with regard to current treatment at time of the event.

In the treatment change cohort, in general the odds ratios for the seven outcomes of interest did not show any important differences between the age groups. Exceptions were found for the outcomes death all causes, stroke, and somnolence, where the older age groups had significantly increased risk of the outcome, but the lower age group had not. The new user cohort with MDD had too few numbers to analyse separately by age.

Table 40 shows the case-control analysis of death by suicide with regard to current treatment at time of event.

In the adjusted analyses, no higher risk of suicide was identified for any of the treatment groups. The odds ratios were of the same magnitude as those found for the combined outcome suicide and self-harm (Table 28).

In the new user with MDD cohort, events were too few to perform the analysis.

Table 41 shows the case-control analysis of death by suicide with regard to the index treatment.

In the treatment change cohort, the combined exposure group of quetiapine monotherapy or combination showed a lower point estimate for the outcome OR 0.82 (0.48-1.41), than the corresponding point estimates for the combined outcome suicide and self-harm (Table 29), but the ORs were not significant.

In the new user with MDD cohort, events were too few to perform the analysis.

Table 42 shows a case-control analysis of self-harm and suicides with violent methods in a subsample of patients without previous self-harm at index dispensing, with regard to current treatment at time of event.

In the treatment change cohort, users of quetiapine did not have a higher risk of the event which was in contrast to what was found for suicide and self-harm in monotherapy with quetiapine (Table 29).

In the new user with MDD cohort, no medication group had an increased risk.

Table 43 shows a case-control analysis of self-harm and suicides with violent methods in a subsample of patients without previous self-harm at index dispensing, with regard to the index treatment. Neither in the treatment change cohort, nor in the new user with MDD cohort, any significant associations between medication and the outcome was found.

Table 44 shows a case-control analysis of self-harm and suicides with non-violent methods in a subsample of patients without previous self-harm at index dispensing, with regard to current treatment at time of event. In the treatment change cohort users of a combination therapy with

quetiapine were at higher risk of the outcome similarly to the results reported in Table 30. However, no significant association was found in the new user with MDD cohort.

Table 45 reports the ORs of the case-control analysis of self-harm and suicides with non-violent methods in a subsample of patients without previous self-harm at index dispensing with regard to treatment at the index date.

In the treatment change cohort, combination therapy with quetiapine was associated with higher risk of the outcome but no significant association was found in the new user with MDD cohort.

Table 46 shows the change in odds ratios in case-control analysis I-VII with regard to current treatment after exclusion of patients on quetiapine IR at date of event.

In the treatment change cohort, overall, no important changes of the odds ratios were found. The only exceptions were for self-harm and suicides all cases where the adjusted OR for combination treatment with quetiapine changed from 0.99 (0.65-1.52) to 1.56 (1.22-1.98) and for somnolence where the adjusted OR for combination treatment with quetiapine changed from 2.41 (1.42-4.11) to a non-significant OR of 1.14 (0.42-3.13).

Table 47 shows the change in odds ratios in case-control analysis I-VII with regard to index treatment after exclusion of patients on quetiapine IR at date of index dispensing.

In the treatment change cohort, no important changes of the ORs were found.

10.6 Adverse events/adverse reactions

Not applicable.

11. DISCUSSION

11.1 Key results

In the following, results from the treatment change cohort are described. Patterns of associations were not consistent across cohorts, and the analysis of the new user with MDD cohort was often imprecise (wide CIs) or not possible because of small numbers.

Death from all causes: In the treatment change cohort, a significantly higher risk of death from all causes was identified among current users of combination therapy with quetiapine, adjusted OR 1.31 (1.12-1.54). Using both monotherapy and combination therapy with quetiapine as index medication was also associated with a higher risk of death, with adjusted ORs of 1.69 (1.18-2.42) and 1.25 (1.05-1.48), respectively. A high Charlson comorbidity score and a high number of previous somatic hospitalizations were factors strongly associated with death. Prescribing of the antidepressant from a somatic clinic, a history of alcohol or substance abuse, and the number of previous hospitalizations for MDD also increased the risk of death.

Acute myocardial infarction: No significant associations between categories of quetiapine use and acute myocardial infarction were identified. A history of alcohol abuse, IHD other than MI, diabetes, hypertension, a high Charlson comorbidity score and a high number of somatic hospitalisations were factors associated with a higher risk of acute myocardial infarction.

Stroke: No significant associations between categories of quetiapine use and stroke were identified. In the analysis, risk factors for stroke were found largely similar to those mentioned for acute myocardial infarction.

Diabetes: Analyses did not demonstrate significant associations between quetiapine monotherapy or quetiapine combination therapy and a diabetes diagnosis. A history of cerebrovascular disease, myocardial infarction, peripheral arterial disease, renal disease and obesity, a high Charlson comorbidity score and frequent somatic hospitalization was associated with a higher risk of a subsequent diabetes diagnosis or medication.

Self-harm and suicide: In the treatment change cohort, a higher risk of self-harm and suicide was identified among current users of a combination therapy with quetiapine, adjusted OR 1.53 (1.31-1.79). In the analysis of incident cases, excluding those with recorded self-harm prior to the index date, the adjusted OR of current treatment with quetiapine combination therapy was 1.52 (1.26-1.84). In the analysis with index medication as exposure, monotherapy with quetiapine was associated with a higher risk of self-harm, adjusted OR 1.61 (1.03-2.54), while there was no significantly increased risk for combination therapy with quetiapine. In the analysis of all cases, a history of previous self-harm was found to be a strong risk factor for self-harm and suicide, crude OR 6.83 (6.32-7.37). A history of three or more hospitalizations for MDD, alcohol and substance use disorders, disorders of adult personality and behavior, and anxiety disorders were also associated with a higher risk of self-harm and suicide.

Extrapyramidal disorders: A significantly higher risk of extrapyramidal disorder was identified among current users of monotherapy with quetiapine, adjusted OR 13.51 (4.98-36.65) and a combination therapy with quetiapine, adjusted OR 6.15 (3.57-10.58). Current use of other antipsychotics than quetiapine was associated with an even higher risk, adjusted OR 19.94 (13.77-28.88).

Somnolence: associations both with current quetiapine combination therapy was seen, adjusted OR 2.45 (1.45-4.13). Dispensing of anxiolytics and hypnotics between the index date and the event date was also associated with the outcome, adjusted OR 1.95 (1.54-2.46).

11.2 Limitations

A limitation in the study is that the patients' adherence to filled prescriptions is unknown. It is well known that non-adherence to medications is substantial. Misclassification of exposure may lead to bias, most likely an underestimate of relative risk (bias towards the null).

Because this is an observational study and not a randomized trial, confounding factors associated both with prescribing of the drug and with the outcome are involved. Quetiapine users in general had a higher burden of psychiatric co-morbidity, including a more frequent

history of self-harm, an important risk factor for new events of self-harm or suicide. They also more often had a previous history of alcohol and substance abuse, anxiolytic and hypnotic use. Although we adjusted for psychiatric comorbidity, alcohol and substance use in the analysis of self-harm and suicide, residual confounding may remain.

The severity of MDD is expected to be an important confounder. The study does not include clinical information from clinical health records and it has thus not been possible to assess the severity of depression directly; however, even if clinical records had been available, it is not likely that such information would be possible to extract for every patient. We adjusted for the history of hospitalizations for MDD in the year before index dispensing and since 1997 as a proxy for illness severity, together with the other factors described above. Nevertheless, indications as well as comorbidities differ between the treatment groups; this is likely to be the case also for unmeasured confounders, i.e. factors not recorded in the registers. Patients with MDD who are prescribed an antipsychotic drug such as quetiapine are likely to be more severely ill than those only receiving antidepressants. Although we have matched on age and sex and adjusted for information available in registers, residual confounding is expected to remain.

Another factor to consider is that patients may have been misclassified as having MDD as the focus of treatment because we identified MDD as both primary and secondary diagnoses to identify diagnoses in the NPR. Moreover, apart from those diagnoses recorded in the NPR, some patients may have had other psychiatric conditions which have been complicating the treatment, although those diagnoses may not have been recorded (e.g. personality disorder).

Certain diagnoses may not be recorded in the registers if they are not a chief complaint of the patient, for example somnolence. Regarding the diagnosis somnolence, it should also be noted that the ICD diagnostic code for that condition also includes stupor and coma; which of these conditions was the actual diagnosis treated was not possible to disentangle.

A higher proportion of quetiapine users than users of other antidepressants were censored during follow-up because they at some point met the exclusion criteria (schizophrenia-related or bipolar disorder diagnosis, or treatment with mood-stabilizers). This seems to indicate that psychiatric diagnoses are less stable among quetiapine users. It may in some patients reflect uncertainties about the initially recorded depression diagnosis, but it is also possible that the physicians' understanding of the underlying illness evolve over time. For example, in a patient initially treated for unipolar depression symptoms may emerge leading to a more informed diagnosis of bipolar disorder later which would be consistent both with the natural history and medical management of these diseases.

In the cohort analyses of the index medication an intention to treat approach was used, which means that bias may occur for analyses of outcomes with longer time of follow-up. This would tend to bias ORs against the null. This issue is similar to what happens in randomized clinical trials with intention to treat analysis and longer follow-up. This also pertains to the case-control analyses of exposure at cohort entry (index medication).

We did not have information on BMI, smoking and moderate alcohol abuse that may not be recorded with a diagnosis in the registers.

This study included patients using both the IR and XR formulations of quetiapine and the IR formulation was more common than the XR formulation. As we have shown, the study populations suffer from a range of comorbid conditions, and it possible that the pattern of comorbidities could be somewhat different between the users of XR and IR on a group level. Because the IR and XR formulations are often used interchangeably and the exact reasons for choosing the drug in clinical practice is not recorded in the available registers, it may be the case that indications in a broader sense may differ between the IR and XR formulations. In spite of the fact that this is a nationwide study performed in a population of more than 9 million residents, the statistical power to study the association between certain exposures and outcomes was low, especially in the new user cohort with MDD, and risk estimates were not always possible to calculate.

We refer to a result as significant when the 95% CI does not include unity. The results include analyses of several outcomes, two types of quetiapine exposure (monotherapy and combination therapy) in two different cohorts. The question is whether 'multiple testing' could be considered a limitation. The study, however, is neither an exploratory nor a signal detection exercise. We investigated seven pre-specified outcomes with clear definitions according to ICD and ATC codes. The protocol focused on add-on therapy with or switching to quetiapine. Thus, the primary analysis is the exposure to quetiapine in the treatment change cohort (cohort A), where there is an opportunity for add-on therapy (combination therapy with quetiapine) or switching (monotherapy with quetiapine). The additional exposures of quetiapine in the treatment-naïve patients in cohort B should be considered secondary analyses. We therefore do not believe that multiple testing is an issue, as long as the primary analysis is considered.

11.3 Interpretation

Associations between quetiapine use, a higher risk of death, and of self-harm and suicide were found, compared to combinations of other antidepressants. A likely explanation is that quetiapine is prescribed to patients with a high risk of the outcomes in question. However, as discussed above, there are several factors indicating a higher burden of disease among quetiapine users. It is not likely that it was possible to adjust or control for all such factors. A further indication of this, is the finding that more patients on quetiapine than other antidepressants were censored because they were diagnosed with schizophrenia, bipolar disorder or dementia or were dispensed mood-stabilizing medication after they entered the cohort. This suggests channelling, i.e. that patients using quetiapine had a more severe psychiatric illness already from the start, although they had not yet been diagnosed with a more severe disorder.

The results also showed that quetiapine users to a higher degree than other antidepressant users had a history of diabetes mellitus, extrapyramidal disorders, somnolence, and self-harm, as well as alcohol abuse, substance abuse, anxiolytic and hypnotic use. It can be presumed

also that more such diagnoses were not captured in our study because primary care diagnoses were not available. This may lead to residual confounding.

Self-harm may not be fully captured in the NPR, and as it is likely that patients with more severe illness perform more self-harm acts, this may also have contributed to self-harm being found more frequently as an outcome among users of quetiapine.

The use of antipsychotics has been associated with a number of adverse outcomes such as diabetes mellitus, obesity, and cardiovascular disease (Bodén et al. 2013; De Hert et al. 2012). Depression is known to be associated with cardiovascular disease and diabetes mellitus but whether an association between those diseases and antidepressants is causal has not been clarified (Kivimäki et al. 2011; Seligman & Nemeroff 2015). In this study, we found no significantly increased risk of acute myocardial infarction, stroke or receiving a diabetes diagnosis for quetiapine.

The comparison between those treated with quetiapine and those treated with other antidepressants indicates that quetiapine users are indeed a selected group with a higher burden of psychiatric comorbidity, including a higher prevalence of risk factors for self-harm and suicide. These risk factors included previous self-harm (in the analysis of all cases), the number of previous hospitalizations for MDD, alcohol and substance use disorders, disorders of adult personality and behavior, and anxiety disorders, all confirmed to be associated with a higher risk of self-harm and sucide in our analyses. While we adjusted for these confounding factors in the analyses, we did not have clinical information on the severity of depression, but used previous hospitalizations as a proxy. Thus, unmeasured and residual confounding may have biased results.

A study by Weisler et al. evaluated the effects of quetiapine XR on suicidality using data pooled from randomized clinical studies. Included patients had a diagnosis of major depressive disorder (MDD) and were considered not to be at high suicide risk at baseline (Weisler 2014). No increased incidence of treatment-emergent suicidality was found among patients treated with quetiapine XR compared to patients randomized to placebo. In the present study, the dominating pattern showed that the risk for self-harm and suicide was higher among users of quetiapine for both violent and non-violent methods. The method of suicide has previously been shown varying patterns in different mental disorders with more violent suicides in psychotic disorders (Reutfors et al. 2009) and a violent method of self-harm is associated with higher risk of completed suicide (Runeson et al. 2010).

11.4 Generalisability

The new user cohorts were identified using the Swedish PDR, a national register that has complete coverage of all prescribed drugs dispensed to patients outside hospitals in Sweden during 2011-2014. The register does not include dispensing to inpatients, but identifies treatments initiated during hospital admission and continued after discharge. Thus, the results apply to a complete outpatient population of new users in Sweden, and there are no generalisability problems concerning outpatients, but results may not be representative for inpatient use.

Results may also be generalizable to new user populations in other countries, but generalizability could depend on differences in the organisation of health care in general, and more specifically psychiatric care, as well as variation in diagnostic and therapeutic recommendations and traditions.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

The study found associations between use of quetiapine and death from all causes, and an increased risk of self-harm and suicide, when compared to the use of combinations of other antidepressants. These associations may be explained by selective prescribing of these treatments to patients at high risk for the outcomes in question (confounding by indication/severity), and possibly bias due to unmeasured or residual confounding. Quetiapine is prescribed to individuals with a higher burden of psychiatric comorbidity, including a history of previous self-harm and more frequent admissions for MDD. As quetiapine and combinations of antidepressants are second-line therapy, the populations receiving these treatments would be expected to have more severe or more difficult to treat depression, and thus be at higher risk for self-harm and suicide. The study also found significant associations between quetiapine use, extrapyramidal disorders and somnolence, but no significant associations between quetiapine and AMI, stroke or diabetes.

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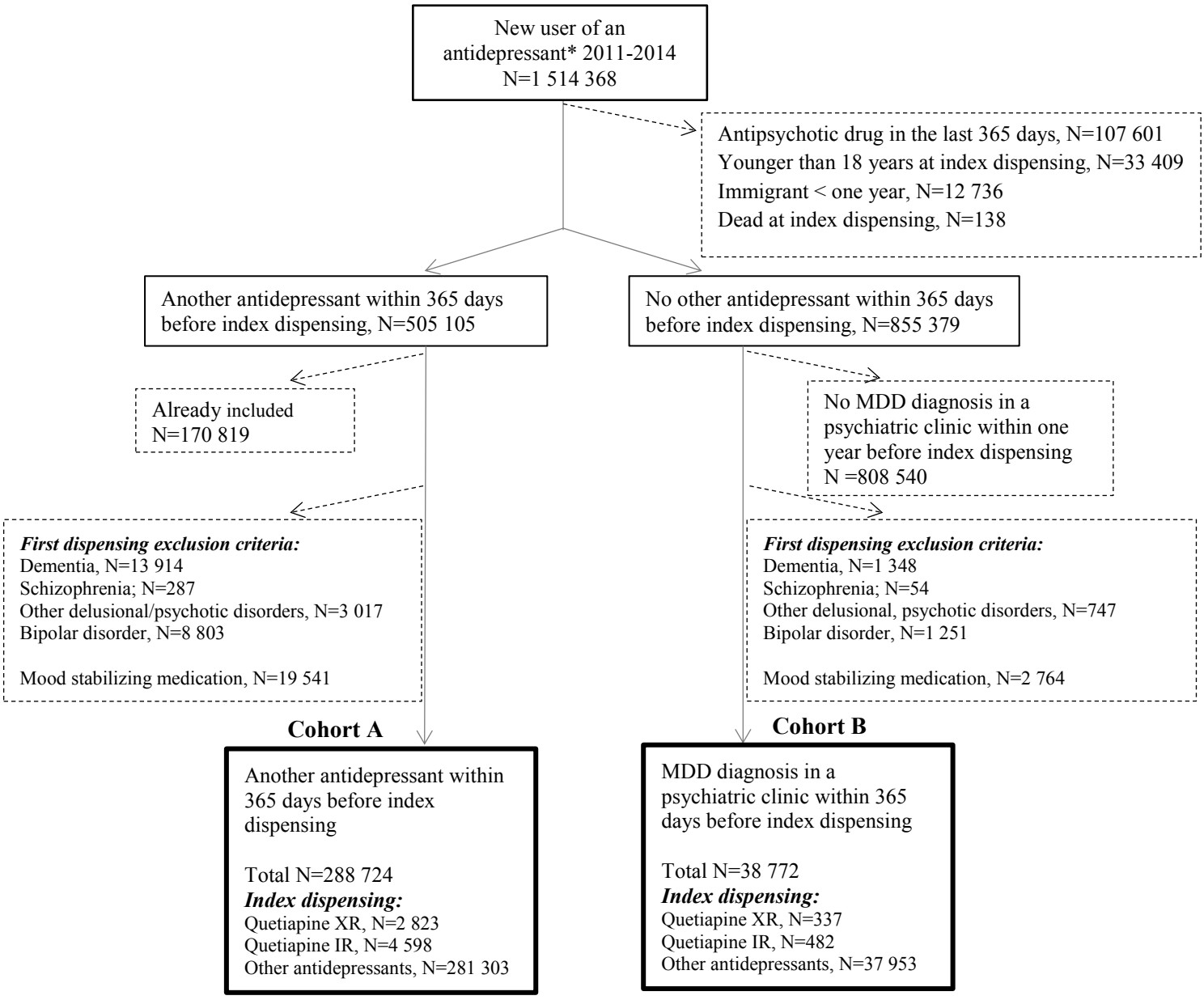
Appendix 1. Figures and Tables

Figure 1. Flowchart of study population and algorithm used for identifying the cohorts. New users refer to first-time users of a specific substance (washout period of one year) after January 1, 2011.



* Antidepressant medications are categorized at the substance level

Table 1. Exclusion of patients with a previous diagnosis of a schizophrenia related disorder, dementia or bipolar disorder or previous use of lithium, lamotrigine, carbamazepine, or valproate, generating the cohorts. Number of patients by treatment cohort and index medication.

	Cohort A Treatment change*				**Cohort B** New user with MDD**			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number before exclusion:	13 348		320 938		1 366		43 570	
Exclusion criteria***:								
Dementia	1 000	7.5	14 087	4.4	70	5.1	1424	3.3
Bipolar disorder	3 274	24.5	9 948	3.1	275	20.1	1491	3.4
Schizophrenia	67	0.5	434	0.1	9	0.7	84	0.2
Other delusional and psychotic disorders	584	4.4	3 034	0.9	92	6.7	754	1.7
Mood stabilizing medication	2 926	21.9	10 103	3.1	242	17.7	1 410	3.2
Excluded	5 927	44.4	39 635	12.3	547	40.0	5 617	12.9
Remaining	7 421	55.6	281 303	87.7	819	60.0	37 953	87.1

* Patients who initiate use of a particular antidepressant drug, who have not used this drug in the year prior to initiation, but who have used another antidepressant during this year.
** Patients who initiate antidepressant use after at least one year without antidepressant use, and who have a MDD diagnosis recorded at a psychiatric clinic during the year prior to initiation.
*** Diagnoses are identified by codes according to Appendix 2. More than one exclusion criterion may exist.

Table 2. History of MDD, other psychiatric diagnoses, and self-harm (since 1997), by study cohort and index medication.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number	7 421		281 303		819		37 953	
Diagnoses from 1997 until the index date								
No psychiatric diagnosis	1 071	14.4	148 473	52.8	0	-	0	-
MDD	4 181	56.3	78 775	28.0	819	100.0	37 953	100.0
Other psychiatric diagnoses*:	5 537	74.6	105556	37.5	628	76.7	22782	60.0
Mood disorder excluding MDD and bipolar disorder	495	6.7	6 829	2.4	50	6.1	1204	3.2
Other organic, including symptomatic, mental disorders, excluding dementia	168	2.3	4 375	1.6	14	1.7	431	1.1
Alcohol use disorder	1 223	16.5	19 196	6.8	166	20.3	4 912	12.9
Other substance use disorder	1 236	16.7	14 885	5.3	154	18.8	3 096	8.2
Anxiety disorder incl. GAD	3 636	49.0	59 368	21.1	341	41.6	10 390	27.4
GAD	624	8.4	8 840	3.1	53	6.5	1556	4.1
OCD, stress-related and somatoform disorders	2 391	32.2	38 496	13.7	271	33.1	9 099	24.0
Behavioural syndromes associated with physiological disturbances and physical factors	350	4.7	6 471	2.3	38	4.6	1 874	4.9
Disorders of adult personality and behaviour	900	12.1	8 284	2.9	121	14.8	2 179	5.7
Disorders of psychological development; Behavioural and emotional disorders with onset usually occurring in childhood and adolescence; Unspecified mental disorder	1 171	15.8	11 342	4.0	155	18.9	4 417	11.6
Self-harm**	1 112	15.0	15 629	5.6	140	17.1	3 962	10.4
Self-harm, violent method	316	4.3	5 177	1.8	42	5.1	1215	3.2
Self-harm, non-violent method	923	12.4	11 445	4.1	113	13.8	3 034	8.0

* The diagnoses are not mutually exclusive, meaning that the same patient can be found in more than one diagnostic group. Diagnoses according to Appendix 2.
**In ICD-10 external causes. The numbers add up to more than the total because some patients had used more than one type of method.

Table 3. Descriptive characteristics of study cohorts, by index medication.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number	7 421		281 303		819		37 953	
Clinic of the prescriber of the index drug dispensing								
Primary care	630	8.5	176 642	62.8	8	1.0	3344	8.8
Somatic care	442	6.0	23 958	8.5	7	0.9	624	1.6
Psychiatric/addiction care	6 128	82.6	65 104	23.1	788	96.2	33 542	88.4
Other	221	3.0	15 599	5.5	16	2.0	443	1.2
Age at inclusion								
Mean (SD)	43.0 (17.9)		51.0 (19.5)		37.6 (14.5)		36.8 (15.9)	
Median (quartiles)	41 (28;55)		49 (36;66)		35 (25;48)		33 (23;47)	
Min-max	18-99		18-105		18-86		18-99	
Age group (years)								
18-49	4 920	66.3	141 495	50.3	645	78.8	29 812	78.5
50-74	2 007	27.0	97 830	34.8	163	19.9	7 165	18.9
75+	494	6.7	41 978	14.9	11	1.3	976	2.6
Sex								
Men	3 102	41.8	94 297	33.5	390	47.6	17 120	45.1
Women	4 319	58.2	187 006	66.5	429	52.4	20 833	54.9
Number of hospitalizations for MDD in the year before index date								
0	6 629	89.3	274 240	97.5	577	70.5	31 773	83.7
1	602	8.1	5878	2.1	204	24.9	5530	14.6
2	137	1.8	927	0.3	30	3.7	566	1.5
≥3	53	0.7	258	0.1	8	1.0	84	0.2
Number of hospitalizations for MDD from 1997 until index date								
0	5960	80.3	264105	93.9	499	60.9	29 956	78.9
1	904	12.2	11954	4.2	208	25.4	6157	16.2
2	279	3.8	3 077	1.1	62	7.6	1 184	3.1
≥3	278	3.7	2167	0.8	50	6.1	656	1.7
Number of somatic hospitalizations in the year before index date								
0	5661	76.3	220791	78.5	657	80.2	30969	81.6
1	1084	14.6	33922	12.1	115	14.0	4666	12.3
2	320	4.3	12351	4.4	23	2.8	1251	3.3
≥3	356	4.8	14239	5.1	24	2.9	1067	2.8
Number of somatic hospitalizations from 1997 until index date								
0	2203	29.7	79833	28.4	274	33.5	14422	38.0
1	1488	20.1	53628	19.1	187	22.8	8171	21.5
2	1038	14.0	40457	14.4	115	14.0	5221	13.8
≥3	2692	36.3	107385	38.2	243	29.7	10139	26.7

Table 4. History of psychiatric diagnoses in the year before the index date, by study cohort and index medication.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number	7 421		281 303		819		37 953	
No psychiatric diagnosis	1 291	17.4	165 419	58.8	0	0.0	0	0.0
MDD	3 688	49.7	69 825	24.8	819	100.0	37 953	100.0
Other psychiatric diagnoses*:	5 415	73.0	92 694	33.0	628	76.7	24 112	63.5
Mood disorder excluding MDD and bipolar disorder	398	5.4	5 079	1.8	31	3.8	1054	2.8
Other organic, including symptomatic, mental disorders, excluding dementia	159	2.1	4 242	1.5	8	1.0	481	1.3
Alcohol use disorder	874	11.8	12 083	4.3	103	12.6	3 886	10.2
Other substance use disorder	1069	14.4	10 777	3.8	105	12.8	2 681	7.1
Anxiety disorder incl. GAD	3 504	47.2	56 366	20.0	345	42.1	11 961	31.5
GAD	654	8.8	9 461	3.4	57	7.0	1977	5.2
OCD, stress-related and somatoform disorders	2 043	27.5	30 930	11.0	246	30.0	8 754	23.1
Behavioural syndromes associated with physiological disturbances and physical factors	361	4.9	5 789	2.1	30	3.7	1939	5.1
Disorders of adult personality and behaviour	963	13.0	7 949	2.8	137	16.7	2614	6.9
Disorders of psychological development; Behavioural and emotional disorders with onset usually occurring in childhood and adolescence; Unspecified mental disorder	1364	18.4	14 220	5.1	178	21.7	5 379	14.2
Self-harm**	535	7.2	5 891	2.1	72	8.8	2 136	5.6
Self-harm, violent method	182	2.5	2 262	0.8	26	3.2	738	1.9
Self-harm, non-violent method	406	5.5	3 953	1.4	51	6.2	1 502	4.0

* The diagnoses are not mutually exclusive, meaning that the same patient can be found in more than one diagnostic group. Diagnoses according to Appendix 2.
** In ICD-10: Chapter 17, external causes. The numbers add up to more than the total because some patients had used more than one type of method.

Table 5. History of psychiatric diagnoses from psychiatric departments in the year before the index date, by study cohort and index medication.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number	7 421		281 303		819		37 953	
No psychiatric diagnosis	1 507	20.3	185 184	65.8	0	-	0	-
MDD	3 540	47.7	59 968	21.3	819	100.0	37 953	100.0
MDD in inpatient care	783	10.6	6 943	2.5	242	29.5	6 153	16.2
Other psychiatric diagnoses*	5 200	70.1	76 719	27.3	613	74.8	23 108	60.9
Mood disorder excluding MDD and bipolar disorder	384	5.2	4 679	1.7	31	3.8	1 021	2.7
Other organic, including symptomatic, mental disorders	95	1.3	1 790	0.6	7	0.9	341	0.9
Alcohol use disorder	767	10.3	9 723	3.5	94	11.5	3 393	8.9
Other substance use disorder	926	12.5	7 585	2.7	91	11.1	2 152	5.7
Anxiety disorder incl. GAD	3 347	45.1	47 575	16.9	327	39.9	11 365	29.9
GAD	631	8.5	8 646	3.1	57	7.0	1 931	5.1
OCD, stress-related and somatoform disorders	1 969	26.5	26 665	9.5	242	29.5	8 375	22.1
Behavioural syndromes associated with physiological disturbances and physical factors	327	4.4	4 326	1.5	26	3.2	1 738	4.6
Disorders of adult personality and behaviour	947	12.8	7 694	2.7	135	16.5	2 548	6.7
Disorders of psychological development; Behavioural and emotional disorders with onset usually occurring in childhood and adolescence; Unspecified mental disorder	1 341	18.1	13 655	4.9	175	21.4	5 316	14.0
Self-harm**	93	1.3	973	0.3	16	2.0	483	1.3
Self-harm, violent method	27	0.4	267	0.1	2	0.2	167	0.4
Self-harm, non-violent method	69	0.9	729	0.3	14	1.7	330	0.9

* The diagnoses are not mutually exclusive, meaning that the same patient can be found in more than one diagnostic group. Diagnoses according to Appendix 2.
** In ICD-10: Chapter 17, external causes. The numbers add up to more than the total because some patients had used more than one type of method.

Table 6. Comorbidity profile, diagnoses from 1997 until to the index date, by study cohort and index medication. Charlson comorbidity groups (Quan et al 2005, Appendix 3) and IHD excluding MI*.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number	7 421		281 303		819		37 953	
Charlson comorbidity index								
0	5 512	74.3	197 076	70.1	662	80.8	31 056	81.8
1-2	1 719	23.2	68 666	24.4	144	17.6	6 177	16.3
3-4	170	2.3	12 609	4.5	12	1.5	597	1.6
5-6	17	0.2	2 552	0.9	1	0.1	107	0.3
≥7	3	0.0	400	0.1	0	0.0	16	0.0
Median quartiles								
Mean (SD)	0 (0;1)		0 (0:1)		0 (0;0)		0 (0;0)	
Diagnoses from 1997 until the index date**	0.38 (0.76)		0.52 (1.00)		0.27 (0.64)		0.27 (0.68)	
No somatic diagnosis in the groups below, including IHD*	5 459	73.6	194 261	69.1	661	80.7	30 903	81.4
Charlson comorbidity groups								
Cancer	142	1.9	11 225	4.0	5	0.6	544	1.4
Cerebrovascular disease	145	2.0	10 748	3.8	4	0.5	454	1.2
Congestive heart failure	68	0.9	6 369	2.3	5	0.6	320	0.8
Chronic pulmonary disease	270	3.6	19 504	6.9	8	1.0	825	2.2
Dementia	0	-	0	-	0	-	0	-
Diabetes with complications	616	8.3	23 473	8.3	57	7.0	2 498	6.6
Diabetes without complications	112	1.5	7 028	2.5	4	0.5	354	0.9
AIDS/HIV	140	1.9	6 592	2.3	12	1.5	503	1.3
Metastatic carcinoma	313	4.2	5 399	1.9	39	4.8	968	2.6
Myocardial infarction	358	4.8	17 813	6.3	39	4.8	1 335	3.5
Mild liver disease	108	1.5	6 576	2.3	18	2.2	485	1.3
Moderate or severe liver disease	64	0.9	3 411	1.2	2	0.2	182	0.5
Paraplegia and hemiplegia	50	0.7	3 398	1.2	7	0.9	222	0.6
Peptic ulcer disease	294	4.0	20 511	7.3	14	1.7	1 075	2.8
Peripheral vascular disease	24	0.3	677	0.2	1	0.1	109	0.3
Renal disease	43	0.6	3 564	1.3	2	0.2	165	0.4
Rheumatic disease	4	0.1	165	0.1	3	0.4	62	0.2
IHD excl. MI*	277	3.7	19 574	7.0	11	1.3	921	2.4

* IHD is not included in Charlson comorbidity groups, but was also taken into account for the "No somatic diagnosis" category.
** The diagnoses are not mutually exclusive, meaning that the same patient can be found in more than one diagnostic group. Diagnoses according to Appendix 2.

Table 7. Patterns of dispensing during the index medication episode of the new antidepressant, by study cohort and index medication.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number	7 421		281 303		819		37 953	
Number of antidepressants at the start of the episode								
Monotherapy	1 217	16.4	76 631	27.2	487	59.5	36 741	96.8
Combination/add on	2 086	28.1	32 478	11.5	332	40.5	1 212	3.2
Uncertain*	4 118	55.5	172 194	61.2	-		-	
Number of dispensings during the index medication episode*								
1	3 006	40.5	90 226	32.1	368	44.9	11 619	30.6
2	1 134	15.3	42 653	15.2	144	17.6	6 358	16.8
3	594	8.0	26 359	9.4	61	7.4	4 237	11.2
4	425	5.7	19 578	7.0	40	4.9	3 093	8.1
5	337	4.5	15 003	5.3	34	4.2	2 380	6.3
>5	1 925	25.9	87 484	31.1	172	21.0	10 266	27.0
Length of first episode (days)*								
≤10	120	1.6	2 279	0.8	15	1.8	299	0.8
11-30	853	11.5	13 544	4.8	97	11.8	1 774	4.7
31-100	1 880	25.3	91 386	32.5	249	30.4	15 463	40.7
101-365	3 926	52.9	138 189	49.1	405	49.5	16 886	44.5
366-730	511	6.9	28 297	10.1	46	5.6	2 973	7.8
>730	131	1.8	7 608	2.7	7	0.9	558	1.5
Patterns of dispensing of quetiapine XR vs IR during the first episode								
Only one formulation	6 426	86.6	-		745	91.0	-	
Switch formulation once	597	8.0			50	6.1		
Dispensing of both types mixed/ switch more than once	398	5.4			24	2.9		
Antidepressant substances dispensed on index date								
Monotherapy								
quetiapine	1 217	16.4			487	59.5		
SSRI			26 529	9.4			9 357	24.7
SNRI			12 415	4.4			3 351	8.8
Other antidepressant substances			37 687	13.4			24 033	63.3
Combination								
quetiapine+SSRI	981	13.2	194	0.1	174	21.2	-	
quetiapine+SNRI	494	6.7	65	0.0	63	7.7	-	
quetiapine+other	438	5.9	139	0.0	69	8.4	-	
SSRI+SNRI	-		2 015	0.7	-		19	0.1
SSRI+other	-		22 948	8.2	-		888	2.3
SNRI+other	-		4 406	1.6	-		223	0.6
more than two groups or two substances from the same group	173	2.3	2 711	1.0	26	3.2	82	0.2
Uncertain*	4 118	55.5	172 194	61.2	-		-	

* Earlier dispensings of other antidepressants have not been consumed, if taken as prescribed, and we therefore cannot determine whether the new substance represents an add-on or switch.
** The first episode of the index substance, from index dispensing to first gap in medication, if taken as prescribed, with MPR 80%

Table 8. Patterns of dispensing at study entry and in the preceding year in the treatment change cohort, by index medication.

	Cohort A Treatment change			
	Quetiapine		Other antidepressant	
	N	%	N	%
Total number	7 421		281 303	
Group of antidepressant substances dispensed in the previous 365 days*				
quetiapine	-		2 716	1.0
SSRI	4 491	60.5	185 548	66.0
SNRI	1 524	20.5	28 898	10.3
Other antidepressant substances	2 471	33.3	79 016	28.1
Number of substances/ATC codes dispensed in the previous 365 days				
1	6 317	85.1	265 269	94.3
2	920	12.4	13 985	5.0
3+	184	2.5	2 049	0.7
Length of last antidepressant medication episode** before the new drug				
<30 days	1 201	16.2	36 864	13.1
30-90 days	2 124	28.6	80 684	28.7
91-365 days	2 701	36.4	115 742	41.1
>365 days	1 395	18.8	48 013	17.1

*Groups of substance are not mutually exclusive
** Length of episode of any antidepressant substance

Table 9. Patterns of censoring and observed person time, by study cohort and index medication.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number	7 421		281 303		819		37 953	
Follow-up								
Patients followed up until Dec 31, 2014	4 716	63.5	198 288	70.5	471	57.5	22 100	58.2
Censored due to no anti-depressant dispensing in one year	962	13.0	51 598	18.3	185	22.6	12 345	32.5
Emigration during follow-up	27	0.4	765	0.3	4	0.5	177	0.5
Diagnosis of schizophrenia, bipolar disorder or dementia or dispensing of mood-stabilizing medication	1 478	19.9	17 935	6.4	148	18.1	2 817	7.4
Died during follow-up	238	3.2	12 717	4.5	11	1.3	514	1.4
	Person years	%	Person years	%	Person years	%	Person years	%
Observed person time:								
Total	11307.4		472124.6		957.3		54663.2	
Monotherapy with index substance	1153.6	10.2	135368.6	28.7	232.1	24.2	22972.0	42.0
Combination with index substance	2708.4	24.0	60352.7	12.8	180.1	18.8	2854.3	5.2
Uncertain pattern*	1172.1	10.4	37283.6	7.9	49.0	5.1	606.7	1.1
Switch to other substance(s)	3993.8	35.3	129355.9	27.4	156.5	16.4	6747.4	12.3
No medication	2279.5	20.2	109763.8	23.2	339.6	35.5	21482.9	39.3

* Earlier dispensings of other antidepressants have not been consumed, if taken as prescribed, and we therefore cannot determine whether the new substance represents an add-on or switch.

Table 10. History of events of interest and comorbidity before the index date, by study cohort and index medication.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number	7 421		281 303		819		37 953	
Events of interest*								
Acute Myocardial infarction	100	1.3	8 236	2.9	4	0.5	420	1.1
Stroke	188	2.5	14 586	5.2	6	0.7	575	1.5
Diabetes mellitus	442	6.0	22 936	8.2	41	5.0	1 671	4.4
Extrapyramidal disorders	94	1.3	923	0.3	6	0.7	58	0.2
Somnolence	57	0.8	1 044	0.4	7	0.9	152	0.4
Self-harm	1 110	15.0	15 622	5.6	139	17.0	3 955	10.4
Self-harm, violent**	317	4.3	5 187	1.8	41	5.0	1 213	3.2
Self-harm, nonviolent**	921	12.4	11 433	4.1	113	13.8	3 029	8.0
Comorbidities*								
Ischaemic heart disease other than Myocardial infarction	836	11.3	54 093	19.2	44	5.4	2 542	6.7
Transient cerebral ischemic attacks	74	1.0	4 488	1.6	2	0.2	178	0.5
Peripheral arterial disease, including extra cerebral, non-coronary arterial thromboembolism	105	1.4	8 392	3.0	8	1.0	477	1.3
Hypertension	2 800	37.7	138 227	49.1	221	27.0	9 208	24.3
Hyperlipidaemia	861	11.6	55 698	19.8	54	6.6	2 791	7.4
Obesity	358	4.8	12 238	4.4	37	4.5	1 516	4.0
Alcohol abuse	1 215	16.4	19 106	6.8	167	20.4	4 809	12.7
Substance abuse	1 223	16.5	14 804	5.3	151	18.4	3 017	7.9
Anxiolytic and hypnotic use	6 668	89.9	224 734	79.9	585	71.4	21 639	57.0

* ICD-codes and ATC-codes found in Appendix 4.
** The numbers add up to more than the total because some patients had used more than one type of method.

Table 11. First source of identification of the outcome event: the National Patient Register, the Prescription Register or the Cause of Death Register, by study cohort and index medication.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine		Other antidepressant		Quetiapine		Other antidepressant	
	N	%	N	%	N	%	N	%
Total number	7 421		281 303		819		37 953	
Outcome events								
Death, all causes								
Cause of Death register	243	100.0	12 883	100.0	11	100.0	516	100.0
Acute myocardial infarction	**30**		**1 988**		**0**		**89**	
National Patient Register	19	63.3	1 564	78.7	0	0.0	75	84.3
Cause of Death register	11	36.7	424	21.3	0	0.0	14	15.7
Stroke	**54**		**2 859**		**3**		**127**	
National Patient Register	46	85.2	2 571	89.9	3	100.0	120	94.5
Cause of Death Register	8	14.8	288	10.1	0	0.0	7	5.5
Diabetes mellitus	**58**		**3 353**		**6**		**252**	
National Patient Register	18	31.0	946	28.2	1	16.7	72	28.6
Prescription Register	40	69.0	2364	70.5	5	83.3	179	71.0
Cause of Death Register	0	0.0	43	1.3	0	0.0	1	0.4
Extrapyramidal disorders	**54**		**469**		**11**		**56**	
National Patient Register	12	22.2	261	55.7	0	0.0	14	25.0
Prescription Register	42	77.8	208	44.3	11	100.0	42	75.0
Cause of Death Register	0	0.0	0	0.0	0	0.0	0	0.0
Somnolence	**28**		**518**		**1**		**82**	
National Patient Register	28	100.0	518	100.0	1	100.0	82	100.0
Cause of Death Register	0	0.0	0	0.0	0	0.0	0	0.0
Self-harm	**193**		**3 747**		**25**		**1 014**	
National Patient Register	179	92.7	3 337	89.1	24	96.0	920	90.7
Cause of Death Register	14	7.3	410	10.9	1	4.0	94	9.3
Self-harm, violent*	**68**		**1 444**		**13**		**365**	
National Patient Register	60	88.2	1 116	77.3	12	92.3	284	77.8
Cause of Death Register	8	11.8	328	22.7	1	7.7	81	22.2
Self-harm, nonviolent*	**169**		**2 813**		**16**		**812**	
National Patient Register	160	94.7	2 643	94.0	16	100.0	771	95.0
Cause of Death Register	9	5.3	170	6.0	0	0.0	41	5.0

* The numbers add up to more than the total because some patients had used more than one type of method

Table 12. Incidence rates of outcome events, by study cohort, index medication and age at index date. Intention-to-treat analysis with follow-up until event, censoring 365 days after last dispensing of any antidepressant.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine N=7 421		Other antidepressant N=281 303		Quetiapine N=819		Other antidepressant N=37 953	
	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)
Total person time (years)		11307.4		472124.6		957.3		54663.2
Outcome								
Death, all causes								
Total	243	21.5 (18.9-24.3)	12 883	27.3 (26.8-27.8)	11	11.5 (6.0-20.0)	516	9.4 (8.7-10.3)
18-49 years	52	7.2 (5.5-9.5)	737	3.1 (2.9-3.4)	3	4.0 (1.0-11.0)	143	3.4 (2.84-3.94)
50-74 years	81	23.5 (18.8-29.1)	3 667	21.0 (20.4-21.7)	5	25.3 (9.3-56.1)	197	18.4 (160.1-21.2)
75+ years	110	164.3 (135.6-197.2)	8 479	135.9 (133.1-138.8)	3	170.8 (43.4-464.7)	176	132.7 (114.2-153.4)
Acute myocardial infarction								
Total	30	2.7 (1.9-3.8)	1 988	4.3 (4.1-4.5)	0		89	1.6 (1.3-2.0)
18-49 years	2	0.3 (0.05-0.9)	123	0.5 (0.4-0.6)	0		17	0.4 (0.2-0.6)
50-74 years	15	4.5 (2.6-7.2)	835	5.0 (4.6-5.3)	0		51	5.0 (3.7-6.5)
75+ years	13	21.4 (11.9-35.7)	1 030	18.4 (17.2-19.5)	0		21	18.1 (11.5-27.2)
Stroke								
Total	54	4.9 (3.7-6.4)	2 859	6.4 (6.2-6.6)	3	3.2 (0.8-8.7)	127	2.4 (2.0-2.8)
18-49 years	6	0.8 (0.3-1.8)	172	0.7 (0.6-0.9)	1	1.4 (0.07-6.67)	25	0.6 (0.4-0.9)
50-74 years	25	7.6 (5.0-11.0)	1 062	6.5 (6.1-6.9)	1	5.3 (0.3-26.0)	67	6.6 (5.2-8.3)
75+ years	23	41.6 (27.0-61.4)	1 625	32.2 (30.6-33.8)	1	66.7 (0.3-32.9)	35	32.0 (22.7-44.1)
Diabetes mellitus								
Total	58	5.5 (4.2-7.1)	3 353	7.8 (7.5-8.0)	6	6.7 (2.7-13.8)	252	4.8 (4.3-5.5)
18-49 years	26	3.7 (2.5-5.4)	903	4.0 (3.7-4.2)	2	2.8 (0.3-10.0)	130	3.1 (2.6-3.7)
50-74 years	30	9.9 (6.8-14.0)	1877	12..3 (11.8-12.9)	4	2.5 (0.8-5.9)	107	11.3 (9.3-13.6)
75+ years	2	3.4 (0.6-11.2)	573	11.0 (10.0-11.9)	0		15	13.5 (0.8-21.7)

Table 12 (continued)

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine N=7 421		Other antidepressant N=281 303		Quetiapine N=819		Other antidepressant N=37 953	
	N	N / 1000 PYR (95% CI*)	N	N / 1000 PYR (95% CI*)	N	N / 1000 PYR (95% CI*)	N	N / 1000 PYR (95% CI*)
Extrapyramidal disorders								
Total	54	4.9 (3.7-6.3)	469	1.0 (0.9-1.1)	11	11.7 (6.2-20.4)	56	1.0 (0.8-1.3)
18-49 years	33	4.6 (3.2-6.4)	177	0.8 (0.6-0.9)	8	10.9 (5.1-20.8)	33	0.8 (0.5-1.1)
50-74 years	15	4.5 (2.6-7.2)	187	1.1 (0.9-1.2)	2	10.5 (0.2-34.6)	18	1.7 (1.02.6)
75+ years	6	9.6 (3.9-20.1)	105	1.7 (1.4-2.0)	1	67.5 (3.4-333.0)	5	3.8 (1.4-8.4)
Somnolence								
Total	28	2.5 (1.7-3.6)	533	1.1 (1.0-1.2)	1	1.1 (0.1-5.2)	83	1.5 (1.2-1.9)
18-49 years	14	2.0 (1.1-3.2)	197	0.8 (0.7-1.0)	1	1.4 (0.1-6.7)	61	1.4 (1.1-1.8)
50-74 years	8	2.3 (1.1-4.5)	177	1.0 (0.9-1.2)	0		18	1.7 (1.0-2.6)
75+ years	6	9.1 (3.7-18.9	159	2.6 (2.2-3.0)	0		4	3.0 (1.0-7.3)
Self-harm and suicides, incident cases								
Total	193	20.4 (17.7-23.42)	3 747	8.5 (8.2-8.7)	25	32.0 (21.2 (46.6)	1 014	21.1 (19.8-22.4)
Violent method*	68	6.3 (4.9-7.9)	1 444	3.1 (3.0-3.3)	13	14.4 (8.0-23.9)	365	6.9 (6.2-7.7)
Non-violent method*	169	17.3 (14.9-20.1)	2 813	6.3 (6.0-6.5)	16	16.6 (11.6-31.2)	812	16.4 (15.3-17.6)
Total								
18-49 years	147	25.4 (21.6-29.8)	2 513	11.6 (11.2-12.1)	23	38.4 (24.9-56.7)	860	22.9 (21.4-24.5)
50-74 years	42	13.8 (10.0-18.5)	970	5.8 (5.5-6.2)	2	12.2 (2.0-40.4)	145	15.4 (13.1-18.1)
75+ years	4	6.3 (2.0-15.1)	264	4.4 (3.9-4.9)	0		9	8.2 (4.0-15.0)
Self-harm and suicides, all cases								
Total	361	33.1 (29.8-36.7)	5 353	11.5 (11.2-11.8)	45	49.0 (36.2-65.0)	1 468	27.6 (26.2-29.0)
Violent method*	102	9.1 (7.5-11.0)	1 714	3.6 (3.5-3.8)	19	20.2 (12.5-30.9)	441	8.1 (7.4-8.9)
Non-violent method*	297	27.0 (24.1-30.3)	3 954	8.5 (8.2-8.7)	31	33.3 (23.0-46.7)	1 118	20.9 (19.7-22.2)
Total								
18-49 years	286	41.6 (37.0-46.7)	3 709	16.0 (15.5-16.6)	43	61.1 (44.7-81.5)	1 211	29.3 (27.6-30.9)
50-74 years	69	20.5 (16.1-25.8)	1 326	7.7 (7.3-8.1)	2	10.2 (1.7-33.5)	223	21.3 (18.6-24.2)
75+ years	6	9.0 (3.7-18.8)	318	5.1 (4.6-5.7)	0		34	26.3 (18.5-36.4)

* The numbers add up to more than the total because some patients had used more than one type of method

Table 13. Incidence rates of outcome events, by study cohort, index medication and age at index date. *Combination therapy with index substance*, censoring at switch or discontinuation of index dispensing.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine N=7 421		Other antidepressant N=281 303		Quetiapine N=819		Other antidepressant N=37 953	
	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)
Total person time (years)**		2708.4		60352.7		180.1		2854.3
Outcome* **								
Death, all causes								
Total	75	27.7 (21.9-34.5)	3 231	53.4 (51.7-55.4)	4	22.2 (7.1-53.6)	59	20.7 (15.9-26.5)
18-49 years	10	65.0 (33.01-115.8)	132	5.60 (4.7-6.6)	0		12	6.1 (3.3-10.4)
50-74 years	25	27.8 (18.4-40.4)	716	30.7 (28.5-33.0)	2	51.9 (8.7-171.5)	23	31.2 (20.3-46.1)
75+ years	40	147.9 (107.1-199.4)	2 383	177.1 (170.1-184.3)	2	262.0 (439.5-866.0)	24	158.3 (103.8-236.2)
Acute myocardial infarction								
Total	12	4.5 (2.5-7.7)	400	6.9 (6.3-7.6)	0		6	2.2 (0.9-4.5)
18-49 years	0		14	0.6 (0.3-1.0)	0		1	0.5 (0.03-2.5)
50-74 years	7	8.1 (3.6-16.1)	141	6.3 (5.3-7.4)	0		2	2.9 (0.5-9.5)
75+ years	5	20.3 (7.4-45.0)	245	20.4 (18.0-23.1)	0		3	23.2 (5.9-63.2)
Stroke								
Total	25	9.5 (6.3-13.9)	576	10.5 (9.7-11.4)	1	5.7 (0.3-28.2)	16	5.8 (3.4-9.2)
18-49 years	1	0.7 (0.03-3.2)	23	1.0 (0.6-1.5)	0		1	0.5 (0.03-2.5)
50-74 years	10	11.6 (5.9-20.7)	174	8.2 (7.0-9.5)	0		12	17.3 (9.4-29.4)
75+ years	14	61.0 (34.7-99.9)	379	37.0 (33.4-40.9)	1	140.3(0.7-691.7)	3	25.6 (6.5-69.8)
Diabetes mellitus								
Total	17	6.1 (3.7-9.6)	663	12.4 (11.5-13.4)	1	6.1 (0.3-30.1)	28	10.4 (7.0-14.9)
18-49 years	7	3.6 (1.6-7.1)	139	6.2 (5.2-7.3)	1	7.8 (0.4-38.3)	15	7.9 (4.6-12.7)
50-74 years	9	13.0 (6.3-23.8)	371	18.7 (16.9-20.7)	0		12	18.7 (10.1-31.8)
75+ years	1	8.5 (0.4-42.1)	153	13.8 (11.8-16.2)	0		1	7.3 (1.0-52.0)

Table 13 (continued)

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine N=7 421		Other antidepressant N=281 303		Quetiapine N=819		Other antidepressant N=37 953	
	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)
Extrapyramidal disorders								
Total	18	6.8 (4.2-10.5)	83	1.4 (1.1-1.7)	6	34.6 (14.0-72.0)	8	2.8 (1.3-5.3)
18-49 years	11	7.2 (3.8-12.59	31	1.3 (0.9-1.8)	3	22.9 (5.8-62.4)	7	3.6 (1.6-7.4)
50-74 years	5	5.7 (2.1-12.7)	36	1.6 (1.1-2.1)	2	53.3 (8.9-17.6)	0	
75+ years	2	8.0 (1.3-26.4)	16	1.2 (0.7-1.9)	1	202.4 (101.3-998.4)	1	6.6 (0.3-32.7)
Somnolence								
Total	7	2.6 (1.1-5.2)	90	1.5 (1.2-1.8)	0		6	2.1 (0.9-4.4)
18-49 years	3	2.0 (0.5-5.3)	21	0.9 (0.6-1.3)	0		3	1.5 (0.4-4.2)
50-74 years	1	1.1 (0.1-5.5)	35	1.5 (1.1-2.1)	0		3	4.1 (1.0-11.2)
75+ years	3	11.2 (2.9-30.6)	34	2.5 (1.8-3.5)	0		0	
Self-harm and suicides, incident cases								
Total	58	25.6 (19.6-32.8)	644	11.5 (10.6-12.4)	6	41.0 (16.6-85.3)	127	52.1 (43.6-61.8)
Violent method*	17	6.6 (4.0-10.4)	240	4.1 (3.6-4.6)	3	17.5 (4.4-47.8)	38	13.9 (10.0-18.9)
Non-violent method*	56	23.9 (18.3-30.9)	476	8.3 (7.6-9.1)	3	19.6 (5.0-53.3)	97	38.5 (31.4-46.7)
Total								
18-49 years	40	32.6 (23.6-44.0)	384	17.9 (16.2-19.8)	5	4.6 (1.7-10.1)	103	60.5 (49.7-73.1)
50-74 years	18	22.9 (14.0-35.5)	201	9.2 (8.0-10.5)	1	34.1 (1.7-168.6)	24	39.1 (25.6-57.2)
75+ years	0		59	4.6 (3.5-5.8)	0		0	
Self-harm and suicides, all cases								
Total	119	45.2 (37.6-53.9)	936	15.7 (14.7-16.7)	10	57.0 (29.0-101-6)	172	62.6 (53.8-72.6)
Violent method*	28	10.4 (7.1-14.9)	297	4.9 (4.4-5.5)	5	28.1 (10.9-62.2)	48	17.0 (12.6-22.3)
Non-violent method*	102	38.5 (31.6-46.6)	687	11.5 (10.6-12.4)	5	28.2 (10.4-62.6)	132	47.7 (40.1-56.4)
Total								
18-49 years	89	60.1 (48.6-73.6)	580	25.0 (23.1-27.1)	9	69.6 (33.9-127.7)	138	72.90 (61.5-85.9)
50-74 years	28	31.6 (21.4-45.1)	284	12.3 (10.9-13.8)	1	26.0 (13.0-128.0)	32	45.2 (31.5-63.0)
75+ years	2	7.4 (1.2-24.5)	72	5.4 (4.2-6.7)	0		2	13.8 (2.32-45.7)

***** The numbers add up to more than the total because some patients had used more than one type of method

Table 14. Incidence rates of outcome events, by study cohort, index medication and age at index date. *Monotherapy with index substance*, censoring at switch or discontinuation of index dispensing.

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine N=7 421		Other antidepressant N=281 303		Quetiapine N=819		Other antidepressant N=37 953	
	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)
Total person time (years)	1153.6		13568.6		232.1		22972.0	
Outcome* **								
Death, all causes	33	28.6 (20.0-39.7)	3 943	29.1 (28.2-30.0)	2	8.6 (1.4-28.5)	240	10.4 (9.2-11.8)
Total	3	3.8 (1.0-10.4)	164	2.4 (2.0-2.8)	2	10.7 (1.8-35.4)	59	3.3 (2.5-4.2)
18-49 years	11	39.1 (20.6-68.0)	960	20.1 (18.9-21.4)	0		78	17.6 (14.0-21.8)
50-74 years	19	215.4 (133.5-330.2)	2 819	149.1 (143.6-154.7)	0		103	154.2 (126.5-186.3)
75+ years								
Acute myocardial infarction								
Total	6	5.3 (2.1-11.0)	562	4.3 (3.9-4.6)	0		41	1.8 (1.3-2.4)
18-49 years	1	1.3 (0.1-6.3)	32	0.5 (0.3-0.7)	0		6	0.3 (1.4-7.0)
50-74 years	2	7.2 (1.2-23.9)	225	4.9 (4.3-5.6)	0		23	5.4 (3.5-7.9)
75+ years	3	37.5 (9.5-102.0)	305	18.0 (16.1-20.1)	0		12	21.1 (11.4-35.8)
Stroke								
Total	8	7.2 (3-3-13.6)	856	6.7 (6.2-7.1)	1	4.3 (0.2-21.3)	52	2.3 (1.7-3.0)
18-49 years	1	1.3 (0.1-6.4)	48	0.7 (0.5-0.9)	0		6	0.3 (0.1-0.7)
50-74 years	3	10.9 (2.8-29.7)	300	6.7 (6.0-7.5)	1	22.8 (1.1-112.2)	28	6.7 (4.5-9.5)
75+ years	4	58.0 (18.4-140.0)	508	33.5 (30.7-36.6)	0		18	33.1 (20.2-51.2)
Diabetes mellitus								
Total	9	8.2 (4.0-15.0)	898	7.2 (6.8-7.7)	1	4.5 (0.2-22.2)	110	5.0 (4.1-6.0)
18-49 years	4	5.2 (1.7-12.6)	246	3.7 (3.3-4.2)	0		50	2.9 (2.2-3.8)
50-74 years	5	19.7 (7.2-43.7)	503	12.0 (11.0-13.1)	1	25.6 (1.3-126.1)	51	13.0 (9.7-16.9)
75+ years	0		149	9.4 (8.0-11.0)	0		9	16.6 (8.1-30.4)

Table 14 (continued)

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Quetiapine N=7 421		Other antidepressant N=281 303		Quetiapine N=819		Other antidepressant N=37 953	
	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)	N	N / 1000 PYR (95% CI)
Extrapyramidal disorders								
Total	10	8.9 (4.5-15.8)	124	0.9 (0.8-1.1)	3	13.1 (3.3-35.7)	19	0.8 (0.5-1.3)
18-49 years	4	5.2 (1.6-12.4)	40	0.6 (0.4-0.8)	3	16.2 (4.1-44.1)	8	0.4 (0.2-0.9)
50-74 years	4	14.7 (4.7-35.4)	46	9.7 (7.2-12.8)	0		9	2.0 (1.0-3.7)
75+ years	2	26.2 (4.4-86.6)	38	2.0 (1.5-2.8)	0		2	3.0 (0.5-10.0)
Somnolence								
Total	5	4.4 (1.6-9.8)	141	1.0 (0.9-1.2)	1	4.4 (0.2-21.6)	32	1.4 (1.0-2.0)
18-49 years	1	1.3 (0.6-6.4)	48	0.7 (0.5-0.9)	1	5.5 (0.3-27.0)	25	1.4 (0.9-2.0)
50-74 years	4	14.5 (4.6-34.9)	40	0.8 (0.6-1.1)	0		5	1.1 (0.4-2.5)
75+ years	0		53	2.8 (2.1-3.7)	0		2	3.0 (0.5-10.0)
Self-harm and suicides, incident cases								
Total	17	17.7 (10.7-27.8)	910	7.1 (6.6-7.6)	7	37.6 (16.4-74.3)	481	23.3 (21.3-25.5)
Violent method*	7	6.4 (2.8-12.6)	336	2.5 (2.3-2.8)	5	22.8 (8.4-50.6)	160	7.2 (6.1-8.4)
Non-violent method*	14	14.2 (8.1-23.2)	698	5.4 (5.0-5.8)	3	15.3 (3.9-41.7)	394	18.7 (16.9-20.6)
Total								
18-49 years	14	22.5 (12.8-36.8)	658	10.3 (9.5-11.1)	7	47.5 (20.8-94.0	406	25.2 (22.8-27.8)
50-74 years	1	4.0 (0.2-19.7)	187	4.1 (3.5-4.7)	0		71	17.9 (14.1-22.5)
75+ years	2	23.3 (3.9-77.1)	65	3.5 (2.7-4.5)	0		4	7.4 (2.3-17.8)
Self-harm and suicides, all cases								
Total	33	29.5 (20.7-41.0)	1331	9.9 (9.4-10.4)	16	70.9 (41.9-112.6)	709	31.4 (29.1-33.7)
Violent method*	13	11.3 (6.3-18.9)	403	3.0 (2.7-3.3)	7	30.46 (13.3-60.2)	198	8.7 (7.5-9.9)
Non-violent method*	25	22.3 (14.8-32.4)	988	7.3 (6.9-7.8)	10	43.90 (22.3-78.2)	540	23.8 (21.8-25.9)
Total								
18-49 years	29	38.5 (26.2-54.5)	992	14.6 (13.7-15.5)	16	88.7 (52.5-141.0)	577	32.8 (30.2-35.6)
50-74 years	2	7.2 (1.2-23.9)	262	5.5 (4.9-6.2)	0		110	25.1 (20.7-30.1)
75+ years	2	22.9 (2.8-75.6)	77	4.1 (3.2-5.1)	0		22	33.7 (21.6-50.2)

***** The numbers add up to more than the total because some patients had used more than one type of method

Table 15. Case control analysis I. Cases of *Death from all causes*. Controls matched on calendar year of index dispensing* sex, and age ±5 years. Characteristics of cases and controls.

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	13 126	65625	527	2625
Age at event		(matched)		(matched)
Mean (SD)	77.3 (14.7)	76.5 (14.4)	62.4 (21.0)	61.7 (20.5)
Median (quartiles)	81 (70;88)	81 (69-87)	67 (48;80)	66 (47;79)
Min**-max	18-108	18-104	18-97	18-95
Mode	86	87	68	82
Sex, n (%)		(matched)		(matched)
Men	5 232 (39.9%)	26 159 (39.9%)	333 (63.2%)	1 658 (63.2%)
Women	7 894 (60.1%)	39 466 (60.1%)	194 (36.8%)	967 (36.8%)
Clinic of the prescriber of the index dispensing n (%)				
Primary care	8 052 (61.3%)	48 067 (73.2%)	54 (10.2%)	271 (10.3%)
Somatic care	3 089 (23.5%)	7 171 (10.9%)	83 (15.7%)	179 (6.8%)
Psychiatric/addiction care	1 125 (8.6%)	7 372 (11.2%)	374 (71.0%)	2 129 (81.1%)
Other	860 (6.6%)	3 015 (4.6%)	16 (3.0%)	46 (1.8%)
Number of hospitalizations for MDD in the year before index date				
0	12 805 (97.6%)	64 196 (97.8%)	319 (60.5%)	1 842 (70.2%)
1	242 (1.8%)	1 184 (1.8%)	178 (33.8%)	681 (25.9%)
2	51 (0.4%)	170 (0.3%)	26 (4.9%)	83 (3.2%)
≥3	28 (0.2%)	75 (0.1%)	4 (0.8%)	19 (0.7%)
Number of hospitalizations for MDD from 1997 until index date				
0	12 305 (93.7%)	61 939 (94.4%)	290 (55.0%)	1 694 (64.5%)
1	504 (3.8%)	2 413 (3.7%)	180 (34.2%)	673 (25.6%)
2	164 (1.2%)	668 (1.0%)	36 (6.8%)	158 (6.0%)
≥3	153 (1.2%)	605 (0.9%)	21 (4.0%)	100 (3.8%)
Number of somatic hospitalizations in the year before index date				
0	5 103 (38.9%)	41 936 (63.9%)	215 (40.8%)	1 657 (63.1%)
1	2 643 (20.1%)	11 239 (17.1%)	102 (19.4%)	477 (18.2%)
2	1 676 (12.8%)	5 684 (8.7%)	66 (12.5%)	215 (8.2%)
≥3	3 704 (28.2%)	6 766 (10.3%)	144 (27.3%)	276 (10.5%)
Number of somatic hospitalizations from 1997 until the index date				
0	822 (6.3%)	10 646 (16.2%)	87 (16.5%)	688 (26.2%)
1	1 026 (7.8%)	9 677 (14.7%)	56 (10.6%)	456 (17.4%)
2	1 117 (8.5%)	8 218 (12.5%)	55 (10.4%)	335 (12.8%)
≥3	10 161 (77.4%)	37 084 (56.5%)	329 (62.4%)	1 146 (43.7%)

Table 15 (continued)

	Cohort A Treatment change				**Cohort B** New user with MDD			
	Cases		Controls		Cases		Controls	
Total number	13 126		65 625		527		2631	
No somatic diagnosis in the groups below	2 600	(19.8%)	27 207	(41.5%)	206	(39.1%)	1 473	(56.1%)
Charlson comorbidity groups *from 1997 until the index date*								
Cancer	2 418	(18.4%)	7 512	(11.4%)	67	(12.7%)	237	(9.0%)
Cerebrovascular disease	3 318	(25.3%)	8 043	(12.3%)	92	(17.5%)	239	(9.1%)
Congestive heart failure	1 456	(11.1%)	3 990	(6.1%)	52	(9.9%)	138	(5.3%)
Chronic pulmonary disease	3 592	(27.4%)	12 862	(19.6%)	90	(17.1%)	284	(10.8%)
Dementia	Excluded							
Diabetes with complications	2 604	(19.8%)	7 425	(11.3%)	70	(13.3%)	217	(8.3%)
Diabetes without complications	979	(7.5%)	3 374	(5.1%)	27	(5.1%)	88	(3.4%)
AIDS/HIV	921	(7.0%)	3 030	(4.6%)	22	(4.2%)	99	(3.8%)
Metastatic carcinoma	383	(2.9%)	803	(1.2%)	34	(6.5%)	97	(3.7%)
Myocardial infarction	2 540	(19.4%)	7 853	(12%)	79	(15%)	227	(8.6%)
Mild liver disease	1 065	(8.1%)	2 863	(4.4%)	37	(7.0%)	71	(2.7%)
Moderate or severe liver disease	559	(4.3%)	1 439	(2.2%)	5	(0.9%)	29	(1.1%)
Paraplegia and hemiplegia	980	(7.5%)	1 869	(2.8%)	45	(8.5%)	63	(2.4%)
Peptic ulcer disease	3 844	(29.3%)	10 080	(15.4%)	111	(21.1%)	303	(11.5%)
Peripheral vascular disease	116	(0.9%)	180	(0.3%)	11	(2.1%)	16	(0.6%)
Renal disease	1 376	(10.5%)	1 017	(1.5%)	24	(4.6%)	28	(1.1%)
Rheumatic disease	9	(0.1%)	17	(0.0%)	1	(0.2%)	6	(0.2%)
IHD excl. MI**	3 580	(27.3%)	13 177	(20.1%)	107	(20.3%)	384	(14.6%)
Charlson comorbidity index from 1997								
0	2 745	(20.9%)	28 843	(44.0%)	211	(40.0%)	1 514	(57.7%)
1-2	6 070	(46.2%)	27 387	(41.7%)	200	(38.0%)	844	(32.2%)
3-4	3 203	(24.4%)	7 615	(11.6%)	78	(14.8%)	216	(8.2%)
≥5	1 108	(8.4%)	1 780	(2.7%)	38	(7.2%)	51	(1.9%)
Median quartiles	2 (1;3)		1 (0;2)		1 (0;2)		0 (0;1)	
Mean (SD)	1.99 (1.67)		1.10 (1.34)		1.46 (1.69)		0.82 (1.26)	
Alcohol disorder diagnosis ever (since 1997)	921	(7.0%)	3 030	(4.6%)	22	(4.2%)	99	(3.8%)
Substance disorder diagnosis ever (since 1997)	383	(2.9%)	803	(1.2%)	34	(6.5%)	97	(3.7%)

Table 16. Case control analysis I. Cases of *Death from all causes*. Controls matched on calendar year of index dispensing, sex, and age ±5 years. Exposure: current medication at the date of the event.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=13 126		Controls n=65625		Conditional logistic regression		Cases n=527		Controls n=2 625		Conditional logistic regression	
	n	%	N	%	Crude OR (95% CI)	Adjusted OR (95% CI)	n	%	n	%	Crude OR (95% CI)	Adjusted OR (95% CI)
Current medication at the date of event												
No medication	2 124	16.2	10 864	16.6	0.88 (0.83-0.93)	0.96 (0.90-1.02)	151	28.7	806	30.7	0.66 (0.48-0.91)	0.74 (0.53-1.04)
Monotherapy with quetiapine	56	0.4	195	0.3	1.30 (0.96-1.76)	1.37 (0.99-1.89)	4	0.8	8	0.3	1.76 (0.52-6.00)	1.73 (0.45-6.66)
Combination therapy including quetiapine	231	1.8	853	1.3	1.23 (1.06-1.43)	1.31 (1.12-1.54)	7	1.3	28	1.1	0.89 (0.38-2.13)	1.22 (0.49-3.04)
Monotherapy with other antidepressants	6 078	46.3	32 672	49.8	0.84 (0.80-0.88)	0.88 (0.84-0.92)	293	55.6	1527	58.2	0.68 (0.51-0.91)	0.75 (0.55-1.02)
Combination therapy including other antidepressants	4 637	35.3	21 041	32.1	Ref=1		72	13.7	256	9.8	Ref=1	
Charlson Comorbidity Score												
0	2 745	20.9	28 843	44.0	Ref=1		211	40.0	1514	57.7	Ref=1	
1-2	6 070	46.2	27 387	41.7	2.69 (2.55-2.83)	1.90 (1.79-2.01)	200	38.0	844	32.2	2.13 (1.68-2.70)	1.44 (1.10-1.89)
3-4	3 203	24.4	7 615	11.6	5.43 (5.11-5.77)	2.99 (2.79-3.21)	78	14.8	216	8.2	3.47 (2.49-4.83)	1.77 (1.19-2.61)
≥5	1 108	8.4	1 780	2.7	8.17 (7.47-8.93)	3.93 (3.56-4.33)	38	7.2	51	1.9	7.82 (4.8-12.74)	3.34 (1.91-5.83)
Clinic of the prescriber of the index dispensing												
Primary care	8 052	61.3	48 067	73.2	Ref=1		54	10.2	271	10.3	Ref=1	
Somatic care	3 089	23.5	7 171	10.9	2.59 (2.47-2.72)	1.52 (1.44-1.61)	83	15.7	179	6.8	2.57 (1.72-3.84)	1.76 (1.14-2.71)
Psychiatric/addiction care	1 125	8.6	7 372	11.2	0.90 (0.83-0.96)	0.80 (0.74-0.86)	374	71.0	2129	81.1	0.84 (0.61-1.15)	0.89 (0.64-1.25)
Other	860	6.6	3 015	4.6	1.70 (1.57-1.84)	1.40 (1.29-1.53)	16	3.0	46	1.8	1.84 (0.96-3.52)	1.46 (0.74-2.91)
History of alcohol use disorder (since 1997)	923	7.0	2 538	3.9	1.96 (1.81-2.13)	1.55 (1.42-1.7)	117	22.2	371	14.1	1.84 (1.44-2.35)	1.42 (1.08-1.87)
History of other substance use disorder (since 1997)	837	6.4	2 040	3.1	2.17 (1.99-2.36)	1.37 (1.25-1.51)	81	15.4	194	7.4	2.30 (1.73-3.05)	1.55 (1.13-2.13)
Number of hospitalizations for MDD in the year before index date												
0	12 805	97.6	64 196	97.8	Ref=1		319	60.5	1842	70.2	Ref=1	
1	242	1.8	1 184	1.8	1.03 (0.89-1.18)	1.12 (0.93-1.35)	178	33.8	681	25.9	1.54 (1.25-1.90)	1.29 (0.8-2.08)
2	51	0.4	170	0.3	1.51 (1.10-2.07)	1.54 (1.06-2.24)	26	4.9	83	3.2	1.80 (1.14-2.84)	1.91 (0.92-3.95)
≥3	28	0.2	75	0.1	1.87 (1.21-2.89)	1.67 (0.99-2.79)	4	0.8	19	0.7	1.30 (0.42-3.99)	1.67 (0.44-6.36)
Number of hospitalizations for MDD from 1997 until index date												
0	12 305	93.7	61 939	94.4	Ref=1		290	55.0	1 694	64.5	Ref=1	
1	504	3.8	2 413	3.7	1.05 (0.95-1.16)	0.98 (0.87-1.11)	180	34.2	673	25.6	1.60 (1.29-1.98)	1.17 (0.73-1.89)
2	164	1.2	668	1.0	1.24 (1.04-1.47)	1.09 (0.89-1.33)	36	6.8	158	6.0	1.35 (0.92-1.98)	0.86 (0.46-1.63)
≥3	153	1.2	605	0.9	1.28 (1.07-1.53)	1.02 (0.81-1.27)	21	4.0	100	3.8	1.26 (0.77-2.06)	0.91 (0.46-1.79)
Number of somatic hospitalizations in the year before index date												
0	5 103	38.9	41 936	63.9	Ref=1		215	40.8	1657	63.1	Ref=1	
1	2 643	20.1	11 239	17.1	2.01 (1.91-2.12)	1.44 (1.36-1.52)	102	19.4	477	18.2	2.09 (1.58-2.75)	1.53 (1.12-2.09)
2	1 676	12.8	5 684	8.7	2.57 (2.41-2.73)	1.55 (1.45-1.66)	66	12.5	215	8.2	3.34 (2.38-4.68)	1.99 (1.35-2.94)
≥3	3 704	28.2	6 766	10.3	4.73 (4.49-4.98)	2.3 (2.16-2.44)	144	27.3	276	10.5	5.99 (4.48-8.02)	2.68 (1.83-3.91)
Number of somatic hospitalizations from 1997 until index date												
0	822	6.3	10 646	16.2	Ref=1		87	16.5	688	26.2	Ref=1	
1	1 026	7.8	9 677	14.7	1.46 (1.33-1.61)	1.16 (1.05-1.28)	56	10.6	456	17.4	1.01 (0.71-1.44)	0.80 (0.55-1.17)
2	1 117	8.5	8 218	12.5	1.95 (1.77-2.15)	1.30 (1.18-1.44)	55	10.4	335	12.8	1.42 (0.98-2.05)	1.02 (0.69-1.53)
≥3	10 161	77.4	37 084	56.5	4.13 (3.82-4.47)	1.50 (1.37-1.64)	329	62.4	1146	43.7	2.70 (2.05-3.56)	1.06 (0.74-1.52)

Table 17. Case control analysis I. Cases of *Death from all causes*- Controls matched on calendar year of index dispensing, sex, and age ±5 years. Exposure: Index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=13126		Controls n=65625		Conditional logistic regression		Cases n=527		Controls n=2625		Conditional logistic regression	
	n	%	n	%	Crude OR (95% CI)	Adjusted OR (95% CI)	n	%	n	%	Crude OR (95% CI)	Adjusted OR (95% CI)
Index medication												
Monotherapy with quetiapine	45	0.3	142	0.2	1.57 (1.12-2.19)	1.69 (1.18-2.42)	6	1.1	23	0.9	1.09 (0.42-2.86)	1.39 (0.50-3.86)
Combination therapy including quetiapine	198	1.5	766	1.2	1.28 (1.09-1.50)	1.25 (1.05-1.48)	5	0.9	21	0.8	1.01 (0.35-2.88)	1.14 (0.36-3.59)
Monotherapy with other antidepressants	3 081	23.5	16414	25.0	0.93 (0.89-0.97)	0.89 (0.85-0.94)	480	91.1	2430	92.6	0.82 (0.57-1.20)	0.93 (0.62-1.39)
Combination therapy including other antidepressants	9 802	74.7	48303	73.6	Ref=1		36	6.8	151	5.8	Ref=1	
Charlson Comorbidity Score												
0	2 745	20.9	28 843	44.0	Ref=1		211	40.0	1514	57.7	Ref=1	
1-2	6 070	46.2	27 387	41.7	2.69 (2.55-2.83)	1.89 (1.79-2.00)	200	38.0	844	32.2	2.13 (1.68-2.70)	1.43 (1.09-1.88)
3-4	3 203	24.4	7 615	11.6	5.43 (5.11-5.77)	2.99 (2.79-3.21)	78	14.8	216	8.2	3.47 (2.49-4.83)	1.77 (1.20-2.62)
≥5	1 108	8.4	1 780	2.7	8.17 (7.47-8.93)	3.92 (3.56-4.33)	38	7.2	51	1.9	7.82 (4.8-12.74)	3.31 (1.89-5.77)
Clinic of the prescriber of the index dispensing												
Primary care	8 052	61.3	48 067	73.2	Ref=1		54	10.2	271	10.3	Ref=1	
Somatic care	3 089	23.5	7 171	10.9	2.59 (2.47-2.72)	1.52 (1.44-1.61)	83	15.7	179	6.8	2.57 (1.72-3.84)	1.73 (1.12-2.66)
Psychiatric/addiction care	1 125	8.6	7 372	11.2	0.90 (0.83-0.96)	0.80 (0.74-0.87)	374	71.0	2129	81.1	0.84 (0.61-1.15)	0.88 (0.63-1.23)
Other	860	6.6	3 015	4.6	1.70 (1.57-1.84)	1.40 (1.29-1.52)	16	3.0	46	1.8	1.84 (0.96-3.52)	1.44 (0.72-2.87)
History of alcohol use disorder (since 1997)	923	7.0	2 538	3.9	1.96 (1.81-2.13)	1.55 (1.42-1.70)	117	22.2	371	14.1	1.84 (1.44-2.35)	1.42 (1.08-1.86)
History of other substance use disorder (since 1997)	837	6.4	2 040	3.1	2.17 (1.99-2.36)	1.38 (1.25-1.51)	81	15.4	194	7.4	2.30 (1.73-3.05)	1.56 (1.14-2.14)
Number of hospitalizations for MDD in the year before the index date												
0	12 805	97.6	64 196	97.8	Ref=1		319	60.5	1842	70.2	Ref=1	
1	242	1.8	1 184	1.8	1.03 (0.89-1.18)	1.12 (0.93-1.35)	178	33.8	681	25.9	1.54 (1.25-1.90)	1.29 (0.80-2.08)
2	51	0.4	170	0.3	1.51 (1.10-2.07)	1.55 (1.06-2.25)	26	4.9	83	3.2	1.80 (1.14-2.84)	1.89 (0.91-3.91)
≥3	28	0.2	75	0.1	1.87 (1.21-2.89)	1.67 (0.99-2.79)	4	0.8	19	0.7	1.30 (0.42-3.99)	1.66 (0.44-6.29)
Number of hospitalizations for MDD from 1997 until index date												
0	12 305	93.7	61 939	94.4	Ref=1		290	55.0	1 694	64.5	Ref=1	
1	504	3.8	2 413	3.7	1.05 (0.95-1.16)	0.99 (0.88-1.12)	180	34.2	673	25.6	1.60 (1.29-1.98)	1.18 (0.74-1.91)
2	164	1.2	668	1.0	1.24 (1.04-1.47)	1.10 (0.89-1.35)	36	6.8	158	6.0	1.35 (0.92-1.98)	0.87 (0.46-1.65)
≥3	153	1.2	605	0.9	1.28 (1.07-1.53)	1.03 (0.82-1.28)	21	4.0	100	3.8	1.26 (0.77-2.06)	0.90 (0.46-1.77)
Number of somatic hospitalizations in the year before index date												
0	5 103	38.9	41 936	63.9	Ref=1		215	40.8	1657	63.1	Ref=1	
1	2 643	20.1	11 239	17.1	2.01 (1.91-2.12)	1.44 (1.36-1.52)	102	19.4	477	18.2	2.09 (1.58-2.75)	1.56 (1.14-2.12)
2	1 676	12.8	5 684	8.7	2.57 (2.41-2.73)	1.56 (1.45-1.67)	66	12.5	215	8.2	3.34 (2.38-4.68)	2.02 (1.37-2.98)
≥3	3 704	28.2	6 766	10.3	4.73 (4.49-4.98)	2.31 (2.18-2.46)	144	27.3	276	10.5	5.99 (4.48-8.02)	2.71 (1.86-3.97)
Number of somatic hospitalizations from 1997 until the index date												
0	822	6.3	10 646	16.2	Ref=1		87	16.5	688	26.2	Ref=1	
1	1 026	7.8	9 677	14.7	1.46 (1.33-1.61)	1.16 (1.05-1.28)	56	10.6	456	17.4	1.01 (0.71-1.44)	0.79 (0.54-1.16)
2	1 117	8.5	8 218	12.5	1.95 (1.77-2.15)	1.30 (1.18-1.44)	55	10.4	335	12.8	1.42 (0.98-2.05)	1.01 (0.68-1.51)
≥3	10 161	77.4	37 084	56.5	4.13 (3.82-4.47)	1.50 (1.37-1.64)	329	62.4	1146	43.7	2.70 (2.05-3.56)	1.06 (0.74-1.52)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 18. Case control analysis II. Incident cases of *Acute myocardial infarction (AMI)*. Controls matched on calendar year of index dispensing*, sex, and age ±5 years. Characteristics of cases and controls.

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	2 018	10090	89	445
Age at event*		(matched)		(matched)
Mean (SD)	73.8 (13.35)	73.2 (13.27)	62.4 (14.72)	61.8 (14.70)
Median (quartiles)	76 (65;84)	75 (65;84)	63 (53;73)	62 (53;73)
Min**-max	19-100	18-102	27-88	23-92
Mode	81	81	53	55
Sex, n (%)		(matched)		(matched)
Men	873 (43.3%)	4 365 (43.3%)	55 (61.8%)	275 (61.8%)
Women	1 145 (56.7%)	5 725 (56.7%)	34 (38.2%)	170 (38.2%)
Clinic of the prescriber of the index dispensing n (%)				
Primary care	1 415 (70.1%)	7 183 (71.2%)	12 (13.5%)	42 (9.4%)
Somatic care	280 (13.9%)	1 085 (10.8%)	9 (10.1%)	25 (5.6%)
Psychiatric/addiction care	238 (11.8%)	1 345 (13.3%)	66 (74.2%)	371 (83.4%)
Other	85 (4.2%)	477 (4.7%)	2 (2.2%)	7 (1.6%)
Number of hospitalizations for MDD in the year before index date				
0	1 969 (97.6%)	9 826 (97.4%)	56 (62.9%)	332 (74.6%)
1	35 (1.7%)	217 (2.2%)	29 (32.6%)	94 (21.1%)
2	11 (0.5%)	39 (0.4%)	2 (2.2%)	14 (3.1%)
≥3	3 (0.1%)	8 (0.1%)	2 (2.2%)	5 (1.1%)
Number of hospitalizations for MDD from 1997 until index date				
0	1 886 (93.5%)	9 467 (93.8%)	53 (59.6%)	309 (69.4%)
1	83 (4.1%)	394 (3.9%)	29 (32.6%)	98 (22.0%)
2	27 (1.3%)	121 (1.2%)	1 (1.1%)	27 (6.1%)
≥3	22 (1.1%)	108 (1.1%)	6 (6.7%)	11 (2.5%)
Number of somatic hospitalizations in the year before index date				
0	1 148 (56.9%)	6 974 (69.1%)	52 (58.4%)	307 (69.0%)
1	367 (18.2%)	1 548 (15.3%)	16 (18%)	64 (14.4%)
2	187 (9.3%)	709 (7%)	6 (6.7%)	32 (7.2%)
≥3	316 (15.7%)	859 (8.5%)	15 (16.9%)	42 (9.4%)
Number of somatic hospitalizations from 1997 until the index date				
0	267 (13.2%)	2 086 (20.7%)	18 (20.2%)	131 (29.4%)
1	254 (12.6%)	1 682 (16.7%)	11 (12.4%)	81 (18.2%)
2	227 (11.2%)	1 351 (13.4%)	7 (7.9%)	65 (14.6%)
≥3	1 270 (62.9%)	4 971 (49.3%)	53 (59.6%)	168 (37.8%)

***** For controls: age at the event of the case.

Table 18 (continued)

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	2 018	10090	89	445
No somatic diagnosis in the groups below	630 (31.2%)	4 894 (48.5%)	38 (42.7%)	270 (60.7%)
Charlson comorbidity groups from 1997 until the index date				
Cancer	183 (9.1%)	295 (2.9%)	8 (9%)	13 (2.9%)
Cerebrovascular disease	286 (14.2%)	812 (8%)	5 (5.6%)	21 (4.7%)
Congestive heart failure	218 (10.8%)	521 (5.2%)	10 (11.2%)	11 (2.5%)
Chronic pulmonary disease	443 (22%)	1 617 (16%)	13 (14.6%)	36 (8.1%)
Dementia	Excluded			
Diabetes with complications	373 (18.5%)	1 076 (10.7%)	11 (12.4%)	37 (8.3%)
Diabetes without complications	155 (7.7%)	429 (4.3%)	3 (3.4%)	13 (2.9%)
AIDS/HIV	154 (7.6%)	387 (3.8%)	7 (7.9%)	10 (2.2%)
Metastatic carcinoma	49 (2.4%)	162 (1.6%)	6 (6.7%)	26 (5.8%)
Myocardial infarction	440 (21.8%)	1 066 (10.6%)	18 (20.2%)	41 (9.2%)
Mild liver disease	208 (10.3%)	366 (3.6%)	10 (11.2%)	13 (2.9%)
Moderate or severe liver disease	61 (3.0%)	215 (2.1%)	1 (1.1%)	1 (0.2%)
Paraplegia and hemiplegia	98 (4.9%)	198 (2.0%)	3 (3.4%)	9 (2.0%)
Peptic ulcer disease	299 (14.8%)	1 450 (14.4%)	8 (9.0%)	34 (7.6%)
Peripheral vascular disease	8 (0.4%)	27 (0.3%)	2 (2.2%)	7 (1.6%)
Renal disease	32 (1.6%)	132 (1.3%)	2 (2.2%)	3 (0.7%)
Rheumatic disease	0 (0%)	6 (0.1%)	0 (0%)	4 (0.9%)
IHD excl. MI**	495 (24.5%)	1 227 (12.2%)	19 (21.3%)	39 (8.8%)
Charlson comorbidity index from 1997				
0	698 (34.6%)	5 136 (50.9%)	41 (46.1%)	280 (62.9%)
1-2	863 (42.8%)	3 988 (39.5%)	32 (36%)	134 (30.1%)
3-4	340 (16.8%)	813 (8.1%)	12 (13.5%)	31 (7%)
≥5	117 (5.8%)	153 (1.5%)	4 (4.5%)	0 (0%)
Median quartiles	1 (0;2)	0 (0;1)	1 (0;2)	0 (0;1)
Mean (SD)	1.49 (1.59)	0.87 (1.17)	1.20 (1.58)	0.62 (0.98)
Alcohol disorder diagnosis (since 1997)	146 (7.2%)	527 (5.2%)	16 (18%)	72 (16.2%)
Substance disorder diagnosis (since 1997)	109 (5.4%)	341 (3.4%)	11 (12.4%)	37 (8.3%)

Table 19. Case control analysis II. Incident cases of *Acute myocardial infarction (AMI).* Controls matched on calendar year of index dispensing, sex, and age ±5 years. Exposure: Current medication at the date of the event.

	Cohort A Treatment change						**Cohort B** New user with MDD			
	Cases n=2 018		Controls n=10090		Conditional logistic regression		Cases =89		Controls n=455	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%
Current medication at the date of event										
No medication	371	18.4	1 802	17.9	0.97 (0.84-1.12)	1.01 (0.87-1.18)	32	36.0	150	33.7
Monotherapy with quetiapine	6	0.3	27	0.3	1.05 (0.43-2.54)	1.31 (0.54-3.20)	0	0.0	1	0.2
Combination with quetiapine	29	1.4	139	1.4	0.99 (0.65-1.48)	0.98 (0.64-1.51)	0	0.0	3	0.7
Monotherapy with other antidepressants	980	48.6	5 139	50.9	0.90 (0.80-1.00)	0.93 (0.83-1.05)	48	53.9	239	53.7
Combination with other antidepressants	632	31.3	2 983	29.6	Ref=1		9	10.1	52	11.7
History of diagnoses from 1997 and of drugs from 1 July 2005 until index date										
Alcohol use disorder	146	7.2	527	5.2	1.44 (1.18-1.75)	1.25 (1.01-1.53)				
Cerebrovascular disease	286	14.2	812	8.0	2.00 (1.72-2.33)	0.88 (0.73-1.05)				
Congestive heart failure	218	10.8	521	5.2	2.24 (1.89-2.64)	1.12 (0.92-1.35)				
Diabetes with complications	373	18.5	1 076	10.7	1.91 (1.68-2.18)	1.20 (1.03-1.39)				
Diabetes without complications	155	7.7	429	4.3	1.89 (1.56-2.29)	1.24 (1.01-1.53)				
Paraplegia and hemiplegia	98	4.9	198	2.0	2.62 (2.04-3.37)	1.18 (0.88-1.56)				
Peripheral vascular disease	8	0.4	27	0.3	1.48 (0.67-3.26)	0.66 (0.29-1.53)				
Renal disease	32	1.6	132	1.3	1.22 (0.82-1.80)	0.74 (0.49-1.12)				
IHD other than MI	495	24.5	1 227	12.2	2.45 (2.17-2.77)	1.55 (1.34-1.78)				
Low dose ASA or antianginal drug use	1 140	56.5	4 135	41.0	2.11 (1.89-2.34)	1.35 (1.19-1.53)				
Hypertension diagnosis or antihypertensive drug use	1 741	86.3	7 753	76.8	2.11 (1.82-2.44)	1.47 (1.25-1.73)				
Hyperlipidaemia diagnosis or lipid modifying agent use	930	46.1	3 602	35.7	1.58 (1.43-1.75)	0.98 (0.87-1.11)				
Charlson Comorbidity Score										
0	698	34.6	5 136	50.9	Ref=1					
1-2	863	42.8	3 988	39.5	1.73 (1.54-1.93)	1.31 (1.15-1.50)				
3-4	340	16.8	813	8.1	3.45 (2.95-4.04)	1.97 (1.59-2.44)				
≥5	117	5.8	153	1.5	6.29 (4.86-8.16)	2.91 (2.04-4.15)				
Number of somatic hospitalizations in the year before index date										
0	1 148	56.9	6 974	69.1	Ref=1					
1	367	18.2	1 548	15.3	1.46 (1.28-1.67)	1.12 (0.98-1.30)				
2	187	9.3	709	7.0	1.64 (1.38-1.96)	1.13 (0.94-1.36)				
≥3	316	15.7	859	8.5	2.31 (1.99-2.67)	1.35 (1.14-1.60)				
Number of somatic hospitalizations from 1997 until the index date										
0	267	13.2	2 086	20.7	Ref=1					
1	254	12.6	1 682	16.7	1.21 (1.01-1.45)	1.04 (0.86-1.26)				
2	227	11.2	1 351	13.4	1.37 (1.13-1.66)	1.04 (0.85-1.28)				
≥3	1 270	62.9	4 971	49.3	2.13 (1.84-2.47)	1.08 (0.90-1.29)				
Number of hospitalizations for MDD in the year before index date										
0	1 969	97.6	9 826	97.4	Ref=1					
1	35	1.7	217	2.2	0.80 (0.56-1.15)	0.72 (0.46-1.12)				
≥2	14	0.7	47	0.5	1.49 (0.82-2.71)	1.46 (0.70-3.04)				
Number of hospitalizations for MDD from 1997 until index date										
0	1 886	93.5	9 467	93.8	Ref=1					
1	83	4.1	394	3.9	1.06 (0.83-1.35)	1.15 (0.86-1.54)				
≥2	49	2.4	229	2.3	1.07 (0.79-1.47)	0.92 (0.61-1.37)				

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling
**pre-specified categories collapsed due to small number

Table 20. Case control analysis II. Incident cases of *Acute myocardial infarction*. Controls matched on calendar year of index dispensing, sex, age ±5 years-. Exposure: index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD			
	Cases n=2 018		Controls n=10090		Conditional logistic regression		Cases =89		Controls n=455	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%
Index medication										
Monotherapy with quetiapine,	2	0.1	26	0.3	collapsed		0	0.0	3	0.7
Combination with quetiapine*	28	1.4	133	1.3	collapsed		0	0.0	4	0.9
Monotherapy with other antidepressants	501	24.8	2 508	24.9	1.00 (0.89-1.12)	0.98 (0.87-1.10)	8	9.0	24	5.4
Combination with other antidepressants*	1 487	73.7	7 423	73.6	Ref=1	Ref=1	81	91.0	414	93.0
Quetiapine monotherapy or combination	30		159		0.94 (0.63-1.40)	0.93 (0.62-1.40)				
History of diagnoses from 1997 and of drugs from 1 July 2005 until index date										
Alcohol use disorder	146	7.2	527	5.2	1.44 (1.18-1.75)	1.25 (1.02-1.54)				
Cerebrovascular disease	286	14.2	812	8.0	2.00 (1.72-2.33)	0.88 (0.73-1.05)				
Congestive heart failure	218	10.8	521	5.2	2.24 (1.89-2.64)	1.12 (0.92-1.35)				
Diabetes with complications	373	18.5	1076	10.7	1.91 (1.68-2.18)	1.20 (1.03-1.39)				
Diabetes without complications	155	7.7	429	4.3	1.89 (1.56-2.29)	1.25 (1.01-1.53)				
Paraplegia and hemiplegia	98	4.9	198	2.0	2.62 (2.04-3.37)	1.18 (0.89-1.57)				
Peripheral vascular disease	8	0.4	27	0.3	1.48 (0.67-3.26)	0.66 (0.29-1.52)				
Renal disease	32	1.6	132	1.3	1.22 (0.82-1.80)	0.74 (0.49-1.12)				
IHD other than MI	495	24.5	1 227	12.2	2.45 (2.17-2.77)	1.54 (1.34-1.78)				
Low dose ASA or antianginal drug use since	1 140	56.5	4 135	41.0	2.11 (1.89-2.34)	1.35 (1.19-1.53)				
Hypertension diagnosis or antihypertensive drug use	1 741	86.3	7 753	76.8	2.11 (1.82-2.44)	1.48 (1.26-1.74)				
Hyperlipidaemia diagnosis or lipid modifying agent use	930	46.1	3 602	35.7	1.58 (1.43-1.75)	0.99 (0.88-1.11)				
Charlson Comorbidity Score										
0	698	34.6	5 136	50.9	Ref=1					
1-2	863	42.8	3 988	39.5	1.73 (1.54-1.93)	1.31 (1.15-1.5)				
3-4	340	16.8	813	8.1	3.45 (2.95-4.04)	1.97 (1.59-2.44)				
≥5	117	5.8	153	1.5	6.29 (4.86-8.16)	2.91 (2.04-4.15)				
Number *of somatic hospitalizations in the year before index date*										
0	1 148	56.9	6 974	69.1	Ref=1					
1	367	18.2	1 548	15.3	1.46 (1.28-1.67)	1.13 (0.98-1.30)				
2	187	9.3	709	7.0	1.64 (1.38-1.96)	1.13 (0.94-1.37)				
Number of somatic hospitalizations from 1997 until the index date*										
0	267	13.2	2 086	20.7	Ref=1					
1	254	12.6	1 682	16.7	1.21 (1.01-1.45)	1.04 (0.86-1.26)				
2	227	11.2	1 351	13.4	1.37 (1.13-1.66)	1.04 (0.85-1.27)				
≥3	1 270	62.9	4 971	49.3	2.13 (1.84-2.47)	1.08 (0.90-1.29)				
Number of hospitalizations for MDD in the year before index date*										
0	1 969	97.6	9 826	97.4	Ref=1					
1	35	1.7	217	2.2	0.80 (0.56-1.15)	0.73 (0.47-1.13)				
≥2	14	0.7	47	0.5	1.49 (0.82-2.71)	1.49 (0.71-3.11)				
Number of hospitalizations for MDD from 1997 until index date*										
0	1 886	93.5	9 467	93.8	Ref=1					
1	83	4.1	394	3.9	1.06 (0.83-1.35)	1.16 (0.87-1.55)				
≥2	49	2.4	229	2.3	1.07 (0.79-1.47)	0.93 (0.62-1.39)				

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 21. Case control analysis III. Incident cases of *Stroke*. Controls matched on calendar year of index dispensing* sex, and age ±5 years. Characteristics of cases and controls.

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	2 913	14 565	130	650
Age at event*		(matched)		(matched)
Mean (SD)	74.6 (13.8)	74.0 (13.7)	64.3 (16.2)	63.3 (16.0)
Median (quartiles)	77 (67;85)	77 (66;84)	67 (54;77)	66 (54;75)
Min**-max	19-102	18-103	27-94	23-93
Mode	82	82	68	67
Sex, n (%)		(matched)		(matched)
Men	1 035 (35.5%)	5 175 (35.5%)	80 (61.5%)	400 (61.5%)
Women	1 878 (64.5%)	9 390 (64.5%)	50 (38.5%)	250 (38.5%)
Clinic of the prescriber of the index dispensing n (%)				
Primary care	137 (4.7%)	603 (4.1%)	2 (1.5%)	16 (2.5%)
Somatic care	2 074 (71.2%)	10 600 (72.8%)	14 (10.8%)	67 (10.3%)
Psychiatric/addiction care	363 (12.5%)	1 477 (10.1%)	10 (7.7%)	44 (6.8%)
Other	339 (11.6%)	1 885 (12.9%)	104 (80%)	523 (80.5%)
Number of hospitalizations for MDD in the year before index dispensing				
0	2 845 (97.7%)	14 249 (97.8%)	83 (63.8%)	491 (75.5%)
1	56 (1.9%)	258 (1.8%)	39 (30%)	134 (20.6%)
2	11 (0.4%)	40 (0.3%)	7 (5.4%)	24 (3.7%)
≥3	1 (0%)	18 (0.1%)	1 (0.8%)	1 (0.2%)
Number of hospitalizations for MDD from 1997 until index dispensing				
0	2 715 (93.2%)	13 736 (94.3%)	79 (60.8%)	439 (67.5%)
1	118 (4.1%)	514 (3.5%)	36 (27.7%)	147 (22.6%)
2	45 (1.5%)	173 (1.2%)	8 (6.2%)	40 (6.2%)
≥3	35 (1.2%)	142 (1.0%)	7 (5.4%)	24 (3.7%)
Number of somatic hospitalizations in the year before index date				
0	1 713 (58.8%)	10 057 (69%)	67 (51.5%)	440 (67.7%)
1	560 (19.2%)	2 289 (15.7%)	24 (18.5%)	105 (16.2%)
2	269 (9.2%)	1 053 (7.2%)	15 (11.5%)	39 (6%)
≥3	371 (12.7%)	1 166 (8.0%)	24 (18.5%)	66 (10.2%)
Number of somatic hospitalizations from 1997 until the index dispensing				
0	341 (11.7%)	2 879 (19.8%)	23 (17.7%)	173 (26.6%)
1	400 (13.7%)	2 487 (17.1%)	21 (16.2%)	109 (16.8%)
2	358 (12.3%)	2 062 (14.2%)	12 (9.2%)	97 (14.9%)
≥3	1 814 (62.3%)	7 137 (49.0%)	74 (56.9%)	271 (41.7%)

***** For controls age at the event of the case.

Table 21 (continued)

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	2 913	14565	130	650
No somatic diagnosis in the groups below	1 093 (37.5%)	7 339 (50.4%)	58 (44.6%)	368 (56.6%)
Charlson comorbidity groups from 1997 until the index date				
Cancer	364 (12.5%)	1 363 (9.4%)	13 (10.0%)	45 (6.9%)
Cerebrovascular disease	427 (14.7%)	1 345 (9.2%)	18 (13.8%)	46 (7.1%)
Congestive heart failure	228 (7.8%)	715 (4.9%)	15 (11.5%)	23 (3.5%)
Chronic pulmonary disease	353 (12.1%)	722 (5.0%)	4 (3.1%)	20 (3.1%)
Dementia	Excluded			
Diabetes with complications	394 (13.5%)	1 559 (10.7%)	14 (10.8%)	57 (8.8%)
Diabetes without complications	186 (6.4%)	731 (5%)	6 (4.6%)	26 (4%)
AIDS/HIV	139 (4.8%)	584 (4%)	7 (5.4%)	37 (5.7%)
Metastatic carcinoma	81 (2.8%)	202 (1.4%)	5 (3.8%)	23 (3.5%)
Myocardial infarction	495 (17.0%)	1 542 (10.6%)	20 (15.4%)	78 (12%)
Mild liver disease	223 (7.7%)	534 (3.7%)	13 (10%)	28 (4.3%)
Moderate or severe liver disease	33 (1.1%)	91 (0.6%)	0 (0%)	3 (0.5%)
Paraplegia and hemiplegia	129 (4.4%)	308 (2.1%)	7 (5.4%)	14 (2.2%)
Peptic ulcer disease	455 (15.6%)	2 117 (14.5%)	18 (13.8%)	56 (8.6%)
Peripheral vascular disease	13 (0.4%)	37 (0.3%)	0 (0%)	4 (0.6%)
Renal disease	67 (2.3%)	212 (1.5%)	1 (0.8%)	5 (0.8%)
Rheumatic disease	2 (0.1%)	4 (0%)	2 (1.5%)	1 (0.2%)
IHD excl. MI**	628 (21.6%)	2 496 (17.1%)	22 (16.9%)	86 (13.2%)
Charlson comorbidity index from 1997				
0	1 156 (39.7%)	7 749 (53.2%)	61 (46.9%)	380 (58.5%)
1-2	1 260 (43.3%)	5 498 (37.7%)	50 (38.5%)	219 (33.7%)
3-4	410 (14.1%)	1 118 (7.7%)	14 (10.8%)	47 (7.2%)
≥5	87 (3%)	200 (1.4%)	5 (3.8%)	4 (0.6%)
Median quartiles	1 (0;2)	1 (0;2)	1 (0;2)	1 (0;2)
Mean (SD)	1.23 (1.39)	0.83 (1.15)	1.10 (1.45)	0.72 (1.05)
Alcohol disorder diagnosis since 1997	217 (7.4%)	644 (4.4%)	29 (22.3%)	72 (11.1%)
Substance disorder diagnosis since 1997	162 (5.6%)	454 (3.1%)	10 (7.7%)	37 (5.7%)

Table 22. Case control analysis III. Incident cases of *Stroke*. Controls matched calendar year of index dispensing, sex, age ±5 years. Exposure: Current medication at the date of the event.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=2 913		Controls =14565		Conditional logistic regression		Cases =130		Controls n=650		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Current medication at the date of event												
No medication	487	16.7	2 589	17.8	0.85 (0.75-0.97)	0.90 (0.80-1.02)	42	32.3	232	35.7	0.63 (0.33-1.19)	0.78 (0.38-1.61)
Monotherapy with quetiapine	10	0.3	43	0.3	1.07 (0.53-2.14)	1.21 (0.60-2.45)	2	1.5	3	0.5	Collapsed	
Combination with quetiapine	51	1.8	190	1.3	1.23 (0.89-1.68)	1.26 (0.91-1.74)	3	2.3	6	0.9	Collapsed	
Monotherapy with other antidepressants	1 419	48.7	7 405	50.8	0.87 (0.8-0.96)	0.89 (0.81-0.98)	65	50.0	344	52.9	0.67 (0.36-1.21)	0.75 (0.38-1.47)
Combination with other antidepressants	946	32.5	4 338	29.8	Ref=1	Ref=1	18	13.8	65	10.0	Ref=1	
Quetiapine monotherapy or combination							5		9		2.03 (0.60-6.86)	0.38 (0.11-1.24)
History of diagnoses from 1997 and of drugs from 1 July 2005 until index date												
Alcohol use disorder	217	7.4	644	4.4	1.80 (1.53-2.12)	1.58 (1.33-1.87)	29	22.3	107	16.5	1.50 (0.93-2.42)	1.18 (0.69-2.01)
Cerebrovascular disease (excl. Stroke)	427	14.7	1 345	9.2	1.75 (1.55-1.97)	1.06 (0.92-1.23)	18	13.8	46	7.1	2.16 (1.19-3.90)	1.25 (0.60-2.58)
Congestive heart failure	228	7.8	715	4.9	1.65 (1.41-1.93)	0.99 (0.83-1.18)	15	11.5	23	3.5	3.87 (1.89-7.94)	2.22 (0.98-5.03)
Diabetes with complications	394	13.5	1 559	10.7	1.31 (1.16-1.47)	0.82 (0.72-0.94)	14	10.8	57	8.8	1.27 (0.68-2.37)	0.89 (0.42-1.89)
Diabetes without complications	186	6.4	731	5.0	1.29 (1.09-1.53)	0.90 (0.75-1.08)	6	4.6	26	4.0	1.17 (0.46-2.95)	0.90 (0.32-2.53)
Myocardial infarction	495	17.0	1 542	10.6	1.74 (1.55-1.94)	1.05 (0.91-1.21)	20	15.4	78	12.0	1.33 (0.78-2.27)	0.83 (0.43-1.63)
Peripheral vascular disease	13	0.4	37	0.3	1.77 (0.94-3.34)	0.84 (0.43-1.62)	0	0.0	4	0.6	-	
Renal disease	67	2.3	212	1.5	1.60 (1.21-2.11)	1.03 (0.76-1.38)	1	0.8	5	0.8	-	
IHD other than MI	628	21.6	2 496	17.1	1.35 (1.22-1.49)	0.77 (0.68-0.87)	22	16.9	86	13.2	1.39 (0.80-2.39)	0.54 (0.26-1.14)
Low dose ASA or antianginal drug use	1 587	54.5	6 156	42.3	1.78 (1.63-1.94)	1.44 (1.30-1.60)	55	42.3	184	28.3	2.17 (1.40-3.38)	1.82 (1.03-3.21)
Hypertension diagnosis or antihypertensive drug use	2 502	85.9	11 303	77.6	1.91 (1.69-2.15)	1.52 (1.33-1.73)	89	68.5	375	57.7	1.80 (1.14-2.83)	1.16 (0.66-2.01)
Hyperlipidaemia diagnosis or lipid modifying agent use	1 226	42.1	5 297	36.4	1.29 (1.19-1.40)	0.88 (0.80-0.98)	45	34.6	178	27.4	1.46 (0.95-2.23)	1.15 (0.64-2.05)
Charlson Comorbidity Score												
0	1 156	39.7	7 749	53.2	Ref=1		61	46.9	380	58.5	Ref=1	
1-2	1 260	43.3	5 498	37.7	1.60 (1.46-1.75)	1.33 (1.19-1.48)	50	38.5	219	33.7	1.52 (1-2.33)	1.02 (0.57-1.82)
3-4	410	14.1	1 118	7.7	2.62 (2.29-2.99)	1.95 (1.58-2.41)	14	10.8	47	7.2	Collapsed	
≥5	87	3.0	200	1.4	3.15 (2.42-4.11)	2.35 (1.61-3.44)	5	3.8	4	0.6	Collapsed	
≥3							19		51		2.52 (1.36-4.65)	1.24 (0.42-3.62)
Number of somatic hospitalizations in the year before index date												
0	1 713	58.8	10 057	69.0	Ref=1		67	51.5	440	67.7	Ref=1	
1	560	19.2	2 289	15.7	1.46 (1.31-1.62)	1.14 (1.02-1.27)	24	18.5	105	16.2	1.58 (0.94-2.67)	1.28 (0.72-2.29)
2	269	9.2	1 053	7.2	1.54 (1.33-1.77)	1.09 (0.93-1.27)	15	11.5	39	6.0	2.89 (1.46-5.72)	2.01 (0.90-4.48)
≥3	371	12.7	1 166	8.0	1.91 (1.67-2.17)	1.25 (1.08-1.44)	24	18.5	66	10.2	2.79 (1.57-4.98)	1.62 (0.78-3.34)
Number of somatic hospitalizations from 1997 until the index dispensing												
0	341	11.7	2 879	19.8	Ref=1		23	17.7	173	26.6	Ref=1	
1	400	13.7	2 487	17.1	1.39 (1.19-1.62)	1.23 (1.05-1.45)	21	16.2	109	16.8	1.45 (0.77-2.75)	1.44 (0.73-2.84)
2	358	12.3	2 062	14.2	1.53 (1.30-1.79)	1.26 (1.07-1.49)	12	9.2	97	14.9	0.96 (0.46-2.02)	0.75 (0.33-1.68)
≥3	1 814	62.3	7 137	49.0	2.29 (2.01-2.6)	1.51 (1.3-1.75)	74	56.9	271	41.7	2.24 (1.32-3.81)	1.45 (0.73-2.88)
Number of hospitalizations for MDD in the year before index date**												
0	2 845	97.7	14 249	97.8	Ref=1		83	63.8	491	75.5	Ref=1	
1	56	1.9	258	1.8	1.09 (0.81-1.46)	0.89 (0.62-1.27)	39	30.0	134	20.6	1.75 (1.13-2.71)	3.72 (1.13-12.23)
≥2	12	0.4	58	0.4	1.04 (0.56-1.93)	0.77 (0.38-1.56)	8	6.2	25	3.8	1.89 (0.82-4.35)	4.98 (0.97-25.64)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	2 715	93.2	13 736	94.3	Ref=1		79	60.8	439	67.5	Ref=1	
1	118	4.1	514	3.5	1.16 (0.95-1.42)	1.04 (0.82-1.33)	36	27.7	147	22.6	1.38 (0.88-2.14)	0.38 (0.11-1.24)
2	45	1.5	173	1.2	1.32 (0.95-1.84)	1.27 (0.89-1.83)	8	6.2	40	6.2	1.12 (0.5-2.51)	0.24 (0.05-1.12)
≥3	35	1.2	142	1.0	1.25 (0.86-1.81)	1.13 (0.74-1.72)	7	5.4	24	3.7	1.65 (0.68-4.05)	0.54 (0.15-2.00)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 23. Case control analysis III. Incident cases of *Stroke*. Controls matched calendar year of index dispensing, sex, age ±5 years. Exposure: Index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD			
	Cases n=2 913		Controls =14565		Conditional logistic regression		Cases =130		Controls n=650	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%
Index medication										
Monotherapy with quetiapine	9	0.3	29	0.2	1.57 (0.74-3.31)	1.53 (0.71-3.29)	1	0.8	4	0.6
Combination with quetiapine	45	1.5	168	1.2	1.35 (0.97-1.88)	1.37 (0.97-1.92)	2	1.5	2	0.3
Monotherapy with other antidepressants	747	25.6	3 685	25.3	1.03 (0.94-1.12)	1.01 (0.92-1.11)	113	86.9	620	95.4
Combination with other antidepressants	2 112	72.5	10 683	73.3	Ref=1		14	10.8	24	3.7
History of diagnoses from 1997 and of drugs from 1 July 2005 until index date										
Alcohol use disorder	217	7.4	644	4.4	1.80 (1.53-2.12)	1.58 (1.33-1.87)				
Cerebrovascular disease (excl. Stroke)	427	14.7	1 345	9.2	1.75 (1.55-1.97)	1.06 (0.92-1.23)				
Congestive heart failure	228	7.8	715	4.9	1.65 (1.41-1.93)	1.00 (0.83-1.19)				
Diabetes with complications	394	13.5	1 559	10.7	1.31 (1.16-1.47)	0.82 (0.72-0.95)				
Diabetes without complications	186	6.4	731	5.0	1.29 (1.09-1.53)	0.90 (0.75-1.07)				
Myocardial infarction	495	17.0	1 542	10.6	1.74 (1.55-1.94)	1.05 (0.91-1.21)				
Peripheral vascular disease	13	0.4	37	0.3	1.77 (0.94-3.34)	0.81 (0.42-1.57)				
Renal disease	67	2.3	212	1.5	1.60 (1.21-2.11)	1.03 (0.77-1.39)				
IHD other than MI	628	21.6	2 496	17.1	1.35 (1.22-1.49)	0.77 (0.68-0.87)				
Low dose ASA or antianginal drug use	1 587	54.5	6 156	42.3	1.78 (1.63-1.94)	1.44 (1.30-1.60)				
Hypertension diagnosis or antihypertensive drug use	2 502	85.9	11 303	77.6	1.91 (1.69-2.15)	1.52 (1.33-1.73)				
Hyperlipidaemia diagnosis or lipid modifying agent use	1 226	42.1	5 297	36.4	1.29 (1.19-1.40)	0.88 (0.80-0.98)				
Charlson Comorbidity Score										
0	1 156	39.7	7 749	53.2	Ref=1					
1-2	1 260	43.3	5 498	37.7	1.60 (1.46-1.75)	1.32 (1.18-1.48)				
3-4	410	14.1	1 118	7.7	2.62 (2.29-2.99)	1.95 (1.58-2.42)				
≥5	87	3.0	200	1.4	3.15 (2.42-4.11)	2.35 (1.61-3.43)				
Number of somatic hospitalizations in the year before index date										
0	1 713	58.8	10 057	69.0	Ref=1					
1	560	19.2	2 289	15.7	1.46 (1.31-1.62)	1.14 (1.02-1.27)				
2	269	9.2	1 053	7.2	1.54 (1.33-1.77)	1.09 (0.93-1.27)				
≥3	371	12.7	1 166	8.0	1.91 (1.67-2.17)	1.25 (1.08-1.44)				
Number of somatic hospitalizations from 1997 until the index dispensing										
0	341	11.7	2 879	19.8	Ref=1					
1	400	13.7	2 487	17.1	1.39 (1.19-1.62)	1.24 (1.05-1.45)				
2	358	12.3	2 062	14.2	1.53 (1.30-1.79)	1.26 (1.07-1.49)				
≥3	1 814	62.3	7 137	49.0	2.29 (2.01-2.6)	1.52 (1.31-1.76)				
Number of hospitalizations for MDD in the year before index date**										
0	2 845	97.7	14 249	97.8	Ref=1					
1	56	1.9	258	1.8	1.09 (0.81-1.46)	0.88 (0.62-1.26)				
≥2	12	0.4	58	0.4	1.04 (0.56-1.93)	0.76 (0.38-1.54)				
Number of hospitalizations for MDD from 1997 until index dispensing										
0	2 715	93.2	13 736	94.3	Ref=1					
1	118	4.1	514	3.5	1.16 (0.95-1.42)	1.06 (0.83-1.34)				
2	45	1.5	173	1.2	1.32 (0.95-1.84)	1.32 (0.92-1.89)				
≥3	35	1.2	142	1.0	1.25 (0.86-1.81)	1.15 (0.75-1.75)				

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 24. Case control analysis IV. Incident cases of *Diabetes mellitus*. Controls matched on calendar year of index dispensing* sex, and age ±5 years. Characteristics of cases and controls.

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	2 941	14 705	229	1 145
Age at event*		(matched)		(matched)
Mean (SD)	58.8 (15.2)	58.5 (15.2)	48.3 (15.6)	47.8 (15.7)
Median (quartiles)	59 (49;69)	58 (48;69)	49 (36;58)	48 (37;58)
Min**-max	18-99	18-101	18-86	18-88
Mode	54	53	53	50
Sex, n (%)		(matched)		(matched)
Men	1 207 (41%)	6 035 (41%)	110 (48%)	550 (48%)
Women	1 734 (59%)	8 670 (59%)	119 (52%)	595 (52%)
Clinic of the prescriber of the index dispensing n (%)				
Primary care	135 (4.6%)	852 (5.8%)	4 (1.7%)	20 (1.7%)
Somatic care	1 924 (65.4%)	9 433 (64.1%)	21 (9.2%)	98 (8.6%)
Psychiatric/addiction care	262 (8.9%)	1 202 (8.2%)	6 (2.6%)	27 (2.4%)
Other	620 (21.1%)	3 218 (21.9%)	198 (86.5%)	1 000 (87.3%)
Number of hospitalizations for MDD in the year before index date				
0	2 856 (97.1%)	14 323 (97.4%)	166 (72.5%)	932 (81.4%)
1	65 (2.2%)	330 (2.2%)	50 (21.8%)	180 (15.7%)
2	15 (0.5%)	34 (0.2%)	10 (4.4%)	28 (2.4%)
≥3	5 (0.2%)	18 (0.1%)	3 (1.3%)	5 (0.4%)
Number of hospitalizations for MDD from 1997 until index dispensing				
0	2 742 (93.2%)	13 735 (93.4%)	152 (66.4%)	862 (75.3%)
1	137 (4.7%)	658 (4.5%)	47 (20.5%)	196 (17.1%)
2	36 (1.2%)	160 (1.1%)	14 (6.1%)	58 (5.1%)
≥3	26 (0.9%)	152 (1%)	16 (7%)	29 (2.5%)
Number of somatic hospitalizations in the year before index date				
0	2 234 (76%)	11 817 (80.4%)	171 (74.7%)	928 (81%)
1	424 (14.4%)	1 760 (12%)	32 (14%)	128 (11.2%)
2	143 (4.9%)	583 (4%)	15 (6.6%)	49 (4.3%)
≥3	140 (4.8%)	545 (3.7%)	11 (4.8%)	40 (3.5%)
Number of somatic hospitalizations from 1997 until the index dispensing				
0	749 (25.5%)	4 547 (30.9%)	65 (28.4%)	395 (34.5%)
1	556 (18.9%)	3 002 (20.4%)	46 (20.1%)	246 (21.5%)
2	435 (14.8%)	2 156 (14.7%)	29 (12.7%)	182 (15.9%)
≥3	1 201 (40.8%)	5 000 (34%)	89 (38.9%)	322 (28.1%)

Table 24 (continued)

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	2 941	14 705	229	1 145
No somatic diagnosis in the groups below	1 987 (67.6%)	11 071 (75.3%)	170 (74.2%)	966 (84.4%)
Charlson comorbidity groups from 1997 until the index date				
Cancer	184 (6.3%)	547 (3.7%)	9 (3.9%)	30 (2.6%)
Cerebrovascular disease	142 (4.8%)	413 (2.8%)	9 (3.9%)	27 (2.4%)
Congestive heart failure	72 (2.4%)	290 (2%)	5 (2.2%)	11 (1%)
Chronic pulmonary disease	288 (9.8%)	1 100 (7.5%)	12 (5.2%)	33 (2.9%)
Dementia	Excluded			
Diabetes with complications	Prevalent cases excluded in the analysis			
Diabetes without complications	89 (3%)	338 (2.3%)	5 (2.2%)	18 (1.6%)
AIDS/HIV	82 (2.8%)	299 (2%)	13 (5.7%)	43 (3.8%)
Metastatic carcinoma	13 (0.4%)	17 (0.1%)	2 (0.9%)	2 (0.2%)
Myocardial infarction	2 (0.1%)	5 (0%)	1 (0.4%)	0 (0%)
Mild liver disease	53 (1.8%)	178 (1.2%)	1 (0.4%)	6 (0.5%)
Moderate or severe liver disease	44 (1.5%)	103 (0.7%)	2 (0.9%)	9 (0.8%)
Paraplegia and hemiplegia	284 (9.7%)	1 183 (8%)	14 (6.1%)	45 (3.9%)
Peptic ulcer disease	15 (0.5%)	34 (0.2%)	5 (2.2%)	3 (0.3%)
Peripheral vascular disease	52 (1.8%)	169 (1.1%)	2 (0.9%)	7 (0.6%)
Renal disease	3 (0.1%)	7 (0%)	0 (0%)	5 (0.4%)
Rheumatic disease	89 (3%)	338 (2.3%)	5 (2.2%)	18 (1.6%)
IHD excl. MI**	330 (11.2%)	1 017 (6.9%)	15 (6.6%)	53 (4.6%)
Charlson comorbidity index from 1997				
0	2 073 (70.5%)	11 344 (77.1%)	175 (76.4%)	983 (85.9%)
1-2	764 (26%)	3 091 (21%)	49 (21.4%)	142 (12.4%)
3-4	96 (3.3%)	250 (1.7%)	5 (2.2%)	20 (1.7%)
≥5	8 (0.3%)	20 (0.1%)	0 (0%)	0 (0%)
Median quartiles	0 (0;1)	0 (0;0)	0 (0;0)	0 (0;0)
Mean (SD)	0.45 (0.83)	0.31 (0.68)	0.35 (0.74)	0.21 (0.60)
Alcohol disorder diagnosis since 1997	212 (7.2%)	1 019 (6.9%)	38 (16.6%)	170 (14.8%)
Substance disorder diagnosis since 1997	157 (5.3%)	680 (4.6%)	19 (8.3%)	90 (7.9%)

Table 25. Case control analysis IV. Incident cases of *Diabetes mellitus*. Controls matched calendar year of index dispensing, sex, age ±5 years. Exposure: Current medication at the date of the event.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=2 941		Controls =14705		Conditional logistic regression		Cases =229		Controls n=1 145		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Current medication at the date of event												
No medication	566	19.2	3 100	21.1	0.74 (0.66-0.84)	0.76 (0.68-0.86)	83	36.2	394	34.4	0.86 (0.53-1.42)	0.88 (0.52-1.48)
Monotherapy with quetiapine	11	0.4	54	0.4	0.84 (0.44-1.61)	0.86 (0.45-1.66)	3	1.3	9	0.8	Collapsed	
Combination with quetiapine	46	1.6	221	1.5	0.86 (0.62-1.19)	0.87 (0.62-1.22)	6	2.6	16	1.4	Collapsed	
Monotherapy with other antidepressants	877	29.8	3 646	24.8	0.77 (0.70-0.84)	0.78 (0.71-0.86)	26	11.4	107	9.3	0.73 (0.45-1.18)	0.77 (0.46-1.27)
Combination with other antidepressants	1 441	49.0	7 684	52.3	Ref=1		111	48.5	619	54.1	Ref=1	
Quetiapine Monotherapy or combination							9		25		1.50 (0.62-3.64)	1.38 (0.53-3.56)
History of diagnoses from 1997 and of drugs from 1 July 2005 until index date												
Alcohol use disorder	212	7.2	1 019	6.9	1.05 (0.89-1.22)	0.97 (0.82-1.14)	38	16.6	170	14.8	1.15 (0.77-1.71)	0.90 (0.59-1.37)
Cerebrovascular disease	142	4.8	413	2.8	1.84 (1.50-2.26)	1.36 (1.08-1.71)	9	3.9	27	2.4	1.80 (0.79-4.08)	1.05 (0.40-2.78)
Congestive heart failure	72	2.4	290	2.0	1.26 (0.96-1.64)	0.86 (0.64-1.15)	5	2.2	11	1.0	2.56 (0.81-8.06)	2.36 (0.69-8.14)
Myocardial infarction	13	0.4	17	0.1	3.82 (1.86-7.87)	2.74 (1.3-5.78)	2	0.9	2	0.2	5.00 (0.70-35.5)	3.62 (0.46-28.48)
Paraplegia and hemiplegia	44	1.5	103	0.7	2.18 (1.52-3.12)	1.48 (1.01-2.16)	2	0.9	9	0.8	1.11 (0.24-5.14)	0.46 (0.08-2.55)
Peripheral vascular disease	15	0.5	34	0.2	2.21 (1.2-4.05)	1.54 (0.81-2.91)	5	2.2	3	0.3	8.33 (1.99-34.87)	8.59 (1.57-46.99)
Renal disease	52	1.8	169	1.1	1.55 (1.13-2.12)	1.14 (0.82-1.60)	2	0.9	7	0.6	1.43 (0.30-6.88)	1.33 (0.24-7.40)
Obesity	184	6.3	375	2.6	2.58 (2.15-3.10)	2.29 (1.90-2.75)	21	9.2	30	2.6	3.77 (2.11-6.73)	3.91 (2.10-7.25)
Charlson Comorbidity Score												
0	2 073	70.5	11 344	77.1	Ref=1		175	76.4	983	85.9		
1-2	764	26.0	3 091	21.0	1.44 (1.31-1.59)	1.23 (1.09-1.37)	49	21.4	142	12.4	2.07 (1.41-3.03)	1.73 (1.08-2.77)
3-4	96	3.3	250	1.7	2.36 (1.84-3.03)	1.63 (1.20-2.23)	5	2.2	20	1.7	Collapsed	
≥5	8	0.3	20	0.1	2.48 (1.08-5.69)	1.41 (0.56-3.55)	0	0.0	0	0.0	Collapsed	
≥3							5		20		1.72 (0.61-4.81)	0.74 (0.19-2.84)
Number of somatic hospitalizations in the year before index date												
0	2 234	76.0	11 817	80.4	Ref=1		171	74.7	928	81.0	Ref=1	
1	424	14.4	1 760	12.0	1.28 (1.14-1.44)	1.09 (0.96-1.23)	32	14.0	128	11.2	1.39 (0.91-2.14)	1.15 (0.71-1.86)
2	143	4.9	583	4.0	1.31 (1.09-1.59)	1.01 (0.83-1.24)	15	6.6	49	4.3	1.74 (0.94-3.23)	1.03 (0.50-2.12)
≥3	140	4.8	545	3.7	1.38 (1.14-1.68)	0.99 (0.80-1.22)	11	4.8	40	3.5	1.63 (0.78-3.40)	0.77 (0.33-1.80)
Number of somatic hospitalizations from 1997 until index dispensing												
0	749	25.5	4 547	30.9	Ref=1		65	28.4	395	34.5	Ref=1	
1	556	18.9	3 002	20.4	1.14 (1.01-1.28)	1.09 (0.96-1.23)	46	20.1	246	21.5	1.15 (0.76-1.74)	1.03 (0.66-1.59)
2	435	14.8	2 156	14.7	1.25 (1.10-1.42)	1.16 (1.01-1.32)	29	12.7	182	15.9	1.00 (0.62-1.61)	0.85 (0.51-1.42)
≥3	1 201	40.8	5 000	34.0	1.51 (1.36-1.67)	1.25 (1.11-1.41)	89	38.9	322	28.1	1.76 (1.22-2.54)	1.27 (0.82-1.96)
Number of hospitalizations for MDD in the year before index date												
0	2 856	97.1	14 323	97.4	Ref=1		166	72.5	932	81.4	Ref=1	
1	65	2.2	330	2.2	0.99 (0.75-1.29)	1.01 (0.72-1.42)	50	21.8	180	15.7	1.58 (1.10-2.25)	1.55 (0.76-3.14)
≥2	20	0.7	52	0.4	1.93 (1.15-3.24)	2.51 (1.34-4.68)	13	5.7	33	2.9	2.26 (1.16-4.41)	1.98 (0.69-5.69)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	2 742	93.2	13 735	93.4	Ref=1		152	66.4	862	75.3	Ref=1	
1	137	4.7	658	4.5	1.04 (0.86-1.26)	1.00 (0.79-1.26)	47	20.5	196	17.1	1.37 (0.95-1.97)	1.03 (0.52-2.05)
2	36	1.2	160	1.1	1.13 (0.78-1.62)	0.89 (0.58-1.34)	14	6.1	58	5.1	1.37 (0.74-2.55)	0.75 (0.29-1.95)
≥3	26	0.9	152	1.0	0.86 (0.56-1.30)	0.63 (0.39-1.03)	16	7.0	29	2.5	3.09 (1.64-5.83)	2.07 (0.88-4.89)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 26. Case control analysis IV. Incident cases of *Diabetes mellitus*. Controls matched calendar year of index dispensing, sex, age ±5 years, both cohort separately. Exposure: Index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=2 941		Controls =14705		Conditional logistic regression		Cases =229		Controls n=1 145		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Index medication												
Monotherapy with quetiapine,	5	0.2	38	0.3	0.64 (0.25-1.62)	0.65 (0.25-1.65)	2	0.9	13	1.1	Collapsed	
Combination with quetiapine*	40	1.4	251	1.7	0.77 (0.55-1.08)	0.76 (0.54-1.07)	4	1.7	9	0.8	Collapsed	
Monotherapy with other antidepressants	674	22.9	3 675	25.0	0.89 (0.81-0.97)	0.89 (0.80-0.97)	209	91.3	1 069	93.4	0.75 (0.41-1.38)	0.98 (0.5-1.95)
Combination with other antidepressants*	2 222	75.6	10 741	73.0	Ref=1	Ref=1	14	6.1	54	4.7	Ref=1	Ref=1
Quetiapine monotherapy or combination							6		22		1.06 (0.36-3.15)	1.59 (0.48-5.27)
History of diagnoses from 1997 and of drugs from 1 July 2005 until index date												
Alcohol use disorder	212	7.2	1 019	6.9	1.05 (0.89-1.22)	0.98 (0.83-1.15)	38	16.6	170	14.8	1.15 (0.77-1.71)	0.89 (0.58-1.36)
Cerebrovascular disease	142	4.8	413	2.8	1.84 (1.50-2.26)	1.35 (1.08-1.70)	9	3.9	27	2.4	1.80 (0.79-4.08)	1.08 (0.41-2.86)
Congestive heart failure	72	2.4	290	2.0	1.26 (0.96-1.64)	0.87 (0.65-1.16)	5	2.2	11	1.0	2.56 (0.81-8.06)	2.34 (0.68-8.08)
Myocardial infarction	13	0.4	17	0.1	3.82 (1.86-7.87)	2.68 (1.27-5.65)	2	0.9	2	0.2		
Paraplegia and hemiplegia	44	1.5	103	0.7	2.18 (1.52-3.12)	1.46 (1.00-2.14)	2	0.9	9	0.8		
Peripheral vascular disease	15	0.5	34	0.2	2.21 (1.20-4.05)	1.52 (0.80-2.87)	5	2.2	3	0.3		
Renal disease	52	1.8	169	1.1	1.55 (1.13-2.12)	1.15 (0.82-1.60)	2	0.9	7	0.6		
Obesity	184	6.3	375	2.6	2.58 (2.15-3.10)	2.32 (1.93-2.79)	21	9.2	30	2.6	3.77 (2.11-6.73)	3.89 (2.09-7.23)
Charlson Comorbidity Score												
0	2 073	70.5	11 344	77.1	Ref=1		175	76.4	983	85.9	Ref=1	
1-2	764	26.0	3 091	21.0	1.44 (1.31-1.59)	1.23 (1.10-1.38)	49	21.4	142	12.4	2.07 (1.41-3.03)	0.75 (0.20-2.85)
3-4	96	3.3	250	1.7	2.36 (1.84-3.03)	1.65 (1.21-2.24)	5	2.2	20	1.7	Collapsed	
≥5	8	0.3	20	0.1	2.48 (1.08-5.69)	1.45 (0.58-3.63)	0	0.0	0	0.0	Collapsed	
≥3							5		20		1.72 (0.61-4.81)	1.75 (1.10-2.80)
Number of somatic hospitalizations in the year before index date												
0	2 234	76.0	11 817	80.4	Ref=1		171	74.7	928	81.0	Ref=1	
1	424	14.4	1 760	12.0	1.28 (1.14-1.44)	1.09 (0.97-1.24)	32	14.0	128	11.2	1.39 (0.91-2.14)	1.17 (0.72-1.90)
2	143	4.9	583	4.0	1.31 (1.09-1.59)	1.01 (0.83-1.24)	15	6.6	49	4.3	1.74 (0.94-3.23)	1.07 (0.52-2.19)
≥3	140	4.8	545	3.7	1.38 (1.14-1.68)	1.00 (0.81-1.23)	11	4.8	40	3.5	1.63 (0.78-3.40)	0.74 (0.32-1.72)
Number of somatic hospitalizations from 1997 until index dispensing												
0	749	25.5	4 547	30.9	Ref=1		65	28.4	395	34.5	Ref=1	
1	556	18.9	3 002	20.4	1.14 (1.01-1.28)	1.09 (0.96-1.23)	46	20.1	246	21.5	1.15 (0.76-1.74)	1.03 (0.67-1.60)
2	435	14.8	2 156	14.7	1.25 (1.10-1.42)	1.15 (1.01-1.32)	29	12.7	182	15.9	1.00 (0.62-1.61)	0.84 (0.50-1.39)
≥3	1 201	40.8	5 000	34.0	1.51 (1.36-1.67)	1.25 (1.11-1.41)	89	38.9	322	28.1	1.76 (1.22-2.54)	1.27 (0.82-1.96)
Number of hospitalizations for MDD in the year before index date												
0	2 856	97.1	14 323	97.4	Ref=1		166	72.5	932	81.4	Ref=1	
1	65	2.2	330	2.2	0.99 (0.75-1.29)	1.01 (0.72-1.42)	50	21.8	180	15.7	1.58 (1.10-2.25)	1.63 (0.80-3.31)
≥2	20	0.7	52	0.4	1.93 (1.15-3.24)	2.53 (1.35-4.73)	13	5.7	33	2.9	2.26 (1.16-4.41)	2.18 (0.75-6.35)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	2 742	93.2	13 735	93.4	Ref=1		152	66.4	862	75.3	Ref=1	
1	137	4.7	658	4.5	1.04 (0.86-1.26)	1.02 (0.81-1.29)	47	20.5	196	17.1	1.37 (0.95-1.97)	1-00 (0.50-1.99)
2	36	1.2	160	1.1	1.13 (0.78-1.62)	0.92 (0.60-1.39)	14	6.1	58	5.1	1.37 (0.74-2.55)	0.72 (0.28-1.88)
≥3	26	0.9	152	1.0	0.86 (0.56-1.30)	0.66 (0.40-1.06)	16	7.0	29	2.5	3.09 (1.64-5.83)	2.06 (0.87-4.88)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 27A. Case control analysis V. All cases of *Self-harm and suicides* including patients with recorded self-harm prior to index date. Controls matched on calendar year of index dispensing* sex, and age ±5 years. Characteristics of cases and controls.

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls*
Total number	5 714	28 570	1 513	7 562
Age at event*		(matched)		(matched)
Mean (SD)	41.3 (18.2)	41.5 (17.9)	33.9 (15.8)	34.0 (15.5)
Median (quartiles)	39 (25;53)	39 (26;53)	28 (21;44)	28 (22;44)
Min**-max	18-98	18-98	18-89	18-91
Mode	20	39	19	22
Sex, n (%)		(matched)		(matched)
Men	2 265 (39.6%)	11 325 (39.6%)	665 (44%)	3 322 (43.9%)
Women	3 449 (60.4%)	17 245 (60.4%)	848 (56%)	4 240 (56.1%)
Clinic of the prescriber of the index dispensing n (%)				
Primary care	192 (3.4%)	1 541 (5.4%)	19 (1.3%)	100 (1.3%)
Somatic care	2 206 (38.6%)	15 666 (54.8%)	78 (5.2%)	658 (8.7%)
Psychiatric/addiction care	296 (5.2%)	1 961 (6.9%)	17 (1.1%)	87 (1.2%)
Other	3 020 (52.9%)	9 402 (32.9%)	1 399 (92.5%)	6 717 (88.8%)
Number of hospitalizations for MDD in the year before index date				
0	4 959 (86.8%)	27 626 (96.7%)	997 (65.9%)	6 338 (83.8%)
1	540 (9.5%)	769 (2.7%)	433 (28.6%)	1 107 (14.6%)
2	157 (2.7%)	137 (0.5%)	72 (4.8%)	100 (1.3%)
≥3	58 (1%)	38 (0.1%)	11 (0.7%)	17 (0.2%)
Number of hospitalizations for MDD from 1997 until index dispensing				
0	4 380 (76.7%)	26 493 (92.7%)	891 (58.9%)	5 962 (78.8%)
1	761 (13.3%)	1 481 (5.2%)	432 (28.6%)	1 254 (16.6%)
2	301 (5.3%)	367 (1.3%)	117 (7.7%)	219 (2.9%)
≥3	272 (4.8%)	229 (0.8%)	73 (4.8%)	127 (1.7%)
Number of somatic hospitalizations in the year before index date				
0	3 747 (65.6%)	23 628 (82.7%)	1 077 (71.2%)	6 247 (82.6%)
1	1 117 (19.5%)	3 109 (10.9%)	269 (17.8%)	906 (12%)
2	364 (6.4%)	914 (3.2%)	84 (5.6%)	239 (3.2%)
≥3	486 (8.5%)	919 (3.2%)	83 (5.5%)	170 (2.2%)
Number of somatic hospitalizations from 1997 until the index dispensing				
0	1 301 (22.8%)	10 133 (35.5%)	465 (30.7%)	3 052 (40.4%)
1	1 039 (18.2%)	5 951 (20.8%)	306 (20.2%)	1 730 (22.9%)
2	825 (14.4%)	3 932 (13.8%)	209 (13.8%)	1 040 (13.8%)
≥3	2 549 (44.6%)	8 554 (29.9%)	533 (35.2%)	1 740 (23%)

*1512 cases has 5 controls, 1 case has 2 controls

Table 27A (continued)

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total numberS	5 714	28 570	1 513	7 562
No somatic diagnosis in the groups below	4 145 (72.5%)	22 219 (77.8%)	1 211 (80.0%)	6 289 (83.2%)
Charlson comorbidity groups from 1997 until the index date				
Cancer	145 (2.5%)	646 (2.3%)	20 (1.3%)	88 (1.2%)
Cerebrovascular disease	120 (2.1%)	514 (1.8%)	17 (1.1%)	82 (1.1%)
Congestive heart failure	77 (1.3%)	346 (1.2%)	16 (1.1%)	48 (0.6%)
Chronic pulmonary disease	242 (4.2%)	1 048 (3.7%)	32 (2.1%)	135 (1.8%)
Dementia	Excluded			
Diabetes with complications	560 (9.8%)	2 012 (7.0%)	123 (8.1%)	516 (6.8%)
Diabetes without complications	97 (1.7%)	404 (1.4%)	9 (0.6%)	60 (0.8%)
AIDS/HIV	103 (1.8%)	486 (1.7%)	21 (1.4%)	103 (1.4%)
Metastatic carcinoma	267 (4.7%)	508 (1.8%)	68 (4.5%)	143 (1.9%)
Myocardial infarction	306 (5.4%)	1 232 (4.3%)	53 (3.5%)	210 (2.8%)
Mild liver disease	101 (1.8%)	454 (1.6%)	20 (1.3%)	70 (0.9%)
Moderate or severe liver disease	71 (1.2%)	244 (0.9%)	9 (0.6%)	35 (0.5%)
Paraplegia and hemiplegia	56 (1.0%)	168 (0.6%)	7 (0.5%)	44 (0.6%)
Peptic ulcer disease	228 (4.0%)	1 177 (4.1%)	33 (2.2%)	168 (2.2%)
Peripheral vascular disease	21 (0.4%)	53 (0.2%)	5 (0.3%)	9 (0.1%)
Renal disease	36 (0.6%)	169 (0.6%)	2 (0.1%)	20 (0.3%)
Rheumatic disease	3 (0.1%)	23 (0.1%)	3 (0.2%)	13 (0.2%)
IHD excl. MI**	248 (4.3%)	1 113 (3.9%)	38 (2.5%)	158 (2.1%)
Charlson comorbidity index from 1997				
0	4 185 (73.2%)	22 396 (78.4%)	1 217 (80.4%)	6 317 (83.5%)
1-2	1 313 (23.0%)	5 395 (18.9%)	264 (17.4%)	1 137 (15.0%)
3-4	180 (3.2%)	662 (2.3%)	25 (1.7%)	94 (1.2%)
≥5	36 (0.6%)	117 (0.4%)	7 (0.5%)	14 (0.2%)
Median quartiles	0 (0;1)	0 (0;0)	0 (0;0)	0 (0;0)
Mean (SD)	0.42 (0.88)	0.33 (0.77)	0.29 (0.71)	0.23 (0.62)
Alcohol disorder diagnosis since 1997	1 468 (25.7%)	1 019 (3.6%)	384 (25.4%)	908 (12.0%)
Substance disorder diagnosis since 1997	1 237 (21.6%)	680 (2.4%)	279 (18.4%)	525 (6.9%)

Table 27B. Case control analysis V. Incident cases of *Self-harm and suicides,* excluding patients with recorded self-harm prior to index date. Controls matched on calendar year of index dispensing* sex, and age ±5 years. Characteristics of cases and controls.

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls*
Total number	3 918	19 590	1 028	5 140
Age at event*		(matched)		(matched)
Mean (SD)	42.3 (18.7)	42.6 (18.4)	32.3 (14.6)	32.6 (14.3)
Median (quartiles)	40 (25;50)	40 (26;55)	28 (21;44)	28 (22;44)
Min**-max	18-98	18-100	18-79	18-84
Mode	23	42	19	22
Sex, n (%)		(matched)		(matched)
Men	1 608 (41.0%)	8 040 (41.0%)	457 (44.5%)	2 285 (44.5%)
Women	2 310 (59.0%)	11 550 (59.0%)	571 (55.5%)	2 855 (55.5%)
Clinic of the prescriber of the index dispensing n (%)				
Primary care	1 754 (44.8%)	11 158 (57.0%)	58 (5.6%)	405 (7.9%)
Somatic care	216 (5.5%)	1 365 (7.0%)	7 (0.7%)	46 (0.9%)
Psychiatric/addiction care	1 804 (46.0%)	6 033 (30.8%)	953 (92.7%)	4 632 (90.1%)
Other	144 (3.7%)	1 034 (5.3%)	10 (1.0%)	57 (1.1%)
Number of hospitalizations for MDD in the year before index date				
0	3 509 (89.6%)	19 136 (97.7%)	723 (70.3%)	4 431 (86.2%)
1	312 (8.0%)	381 (1.9%)	262 (25.5%)	646 (12.6%)
2	78 (2.0%)	53 (0.3%)	40 (3.9%)	56 (1.1%)
≥3	19 (0.5%)	20 (0.1%)	3 (0.3%)	7 (0.1%)
Number of hospitalizations for MDD from 1997 until index dispensing				
0	3 284 (83.8%)	18 541 (94.6%)	678 (66.0%)	4 259 (82.9%)
1	431 (11.0%)	789 (4.0%)	267 (26.0%)	715 (13.9%)
2	127 (3.2%)	169 (0.9%)	57 (5.5%)	119 (2.3%)
≥3	76 (1.9%)	91 (0.5%)	26 (2.5%)	47 (0.9%)
Number of somatic hospitalizations in the year before index date				
0	2 923 (74.6%)	16 501 (84.2%)	845 (82.2%)	4 411 (85.8%)
1	597 (15.2%)	1 874 (9.6%)	121 (11.8%)	517 (10.1%)
2	163 (4.2%)	612 (3.1%)	27 (2.6%)	120 (2.3%)
≥3	235 (6.0%)	603 (3.1%)	35 (3.4%)	92 (1.8%)
Number of somatic hospitalizations from 1997 until the index dispensing				
0	1 192 (30.4%)	7 259 (37.1%)	423 (41.1%)	2 329 (45.3%)
1	756 (19.3%)	4 128 (21.1%)	214 (20.8%)	1 180 (23.0%)
2	568 (14.5%)	2 651 (13.5%)	145 (14.1%)	626 (12.2%)
≥3	1 402 (35.8%)	5 552 (28.3%)	246 (23.9%)	1 005 (19.6%)

*1027 cases has 5 controls, 1 case has 2 controls

Table 27B (continued)

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	5 714	28 570	1 513	7 562
No somatic diagnosis in the groups below	4 145 (72.5%)	22 219 (77.8%)	1 211 (80.0%)	6 289 (83.2%)
Charlson comorbidity groups from 1997 until the index date				
Cancer	145 (2.5%)	646 (2.3%)	20 (1.3%)	88 (1.2%)
Cerebrovascular disease	120 (2.1%)	514 (1.8%)	17 (1.1%)	82 (1.1%)
Congestive heart failure	77 (1.3%)	346 (1.2%)	16 (1.1%)	48 (0.6%)
Chronic pulmonary disease	242 (4.2%)	1 048 (3.7%)	32 (2.1%)	135 (1.8%)
Dementia	Excluded			
Diabetes with complications	357 (9.1%)	1 316 (6.7%)	68 (6.6%)	314 (6.1%)
Diabetes without complications	73 (1.9%)	301 (1.5%)	5 (0.5%)	23 (0.4%)
AIDS/HIV	62 (1.6%)	306 (1.6%)	4 (0.4%)	38 (0.7%)
Metastatic carcinoma	155 (4.0%)	319 (1.6%)	36 (3.5%)	105 (2.0%)
Myocardial infarction	191 (4.9%)	877 (4.5%)	22 (2.1%)	161 (3.1%)
Mild liver disease	63 (1.6%)	325 (1.7%)	7 (0.7%)	65 (1.3%)
Moderate or severe liver disease	38 (1.0%)	181 (0.9%)	8 (0.8%)	19 (0.4%)
Paraplegia and hemiplegia	43 (1.1%)	127 (0.6%)	4 (0.4%)	23 (0.4%)
Peptic ulcer disease	171 (4.4%)	888 (4.5%)	19 (1.8%)	105 (2.0%)
Peripheral vascular disease	13 (0.3%)	34 (0.2%)	3 (0.3%)	12 (0.2%)
Renal disease	27 (0.7%)	107 (0.5%)	1 (0.1%)	10 (0.2%)
Rheumatic disease	1 (0.0%)	10 (0.1%)	1 (0.1%)	11 (0.2%)
IHD excl. MI**	178 (4.5%)	789 (4.0%)	13 (1.3%)	69 (1.3%)
Charlson comorbidity index from 1997				
0	2 908 (74.2%)	15 354 (78.4%)	867 (84.3%)	4 364 (84.9%)
1-2	866 (22.1%)	3 650 (18.6%)	148 (14.4%)	723 (14.1%)
3-4	117 (3.0%)	486 (2.5%)	11 (1.1%)	47 (0.9%)
≥5	27 (0.7%)	100 (0.5%)	2 (0.2%)	6 (0.1%)
Median quartiles	0 (0;1)	0 (0;0)	0 (0;0)	0 (0;0)
Mean (SD)	0.41 (0.87)	0.34 (0.79)	0.21 (0.56)	0.21 (0.58)
Alcohol disorder diagnosis since 1997	675 (17.2%)	1 199 (6.1%)	176 (17.1%)	519 (10.1%)
Substance disorder diagnosis since 1997	551 (14.1%)	891 (4.5%)	127 (12.4%)	317 (6.2%)

Table 28. Case control analysis V. All cases of *Self-harm and suicides,* including patients with recorded self-harm prior to index date. Controls matched calendar year of index dispensing, sex, age ±5 years, both cohort separately. Exposure: Current medication at the date of the event.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=5 714		Controls n=28 570		Conditional logistic regression		Cases =1 513		Controls n=7 562		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Current medication at the date of event												
No medication	989	17.3	6 503	22.8	0.55 (0.50-0.60)	0.52 (0.47-0.58)	365	24.1	2 673	35.3	0.33 (0.27-0.40)	0.31 (0.25-0.38)
Monotherapy with quetiapine	70	1.2	207	0.7	1.27 (0.96-1.67)	0.71 (0.52-0.99)	19	1.3	45	0.6	1.06 (0.60-1.85)	0.69 (0.37-1.29)
Combination with quetiapine	404	7.1	642	2.2	2.37 (2.07-2.71)	1.53 (1.31-1.79)	46	3.0	100	1.3	1.17 (0.79-1.72)	0.99 (0.65-1.52)
Monotherapy with other antidepressants	2 403	42.1	14 103	49.4	0.63 (0.59-0.68)	0.66 (0.61-0.71)	883	58.4	4 240	56.1	0.51 (0.43-0.62)	0.54 (0.44-0.65)
Combination with other antidepressants	1 848	32.3	7 115	24.9	Ref=1		200	13.2	504	6.7	Ref=1	
History of diagnoses from 1997 until index date												
Previous self-harm	1 796	31.4	1 871	6.5	6.83 (6.32-7.37)	3.34 (3.05-3.67)	485	32.1	751	9.9	4.28 (3.74-4.90)	2.83 (2.41-3.31)
Other organic, including symptomatic, mental disorder	100	1.8	272	1.0	1.87 (1.48-2.35)	1.11 (0.85-1.46)	8	0.5	78	1.0	0.51 (0.24-1.05)	0.36 (0.16-0.83)
Disorders of adult personality and behaviour	640	11.2	1 156	4.0	3.06 (2.76-3.39)	1.32 (1.17-1.50)	155	10.2	400	5.3	2.05 (1.69-2.50)	1.32 (1.05-1.67)
Alcohol use disorder	1 468	25.7	2 257	7.9	4.16 (3.86-4.49)	1.94 (1.77-2.13)	384	25.4	908	12.0	2.55 (2.22-2.93)	1.49 (1.27-1.75)
Other substance use disorder	1 237	21.6	1 805	6.3	4.17 (3.84-4.52)	1.79 (1.62-1.98)	279	18.4	525	6.9	3.09 (2.64-3.63)	1.84 (1.53-2.22)
Anxiety disorder incl. GAD	2 374	41.5	7 542	26.4	2.03 (1.91-2.15)	1.25 (1.16-1.34)	475	31.4	2 060	27.2	1.22 (1.09-1.38)	1.01 (0.89-1.16)
Number of somatic hospitalizations in the year before index dispensing												
0	3 747	65.6	23 628	82.7	Ref=1		1 077	71.2	6 247	82.6	Ref=1	
1	1 117	19.5	3 109	10.9	2.31 (2.14-2.49)	1.45 (1.32-1.59)	269	17.8	906	12.0	1.78 (1.53-2.07)	1.16 (0.97-1.40)
2	364	6.4	914	3.2	2.68 (2.36-3.05)	1.43 (1.23-1.67)	84	5.6	239	3.2	2.18 (1.68-2.82)	1.09 (0.80-1.48)
≥3	486	8.5	919	3.2	3.60 (3.19-4.05)	1.88 (1.62-2.17)	83	5.5	170	2.2	3.22 (2.42-4.28)	1.58 (1.12-2.23)
Number of somatic hospitalizations from 1997 until index dispensing												
0	1 301	22.8	10 133	35.5	Ref=1		465	30.7	3 052	40.4	Ref=1	
1	1 039	18.2	5 951	20.8	1.40 (1.28-1.52)	1.01 (0.92-1.12)	306	20.2	1 730	22.9	1.19 (1.02-1.39)	0.87 (0.73-1.03)
2	825	14.4	3 932	13.8	1.74 (1.58-1.92)	1.08 (0.97-1.21)	209	13.8	1 040	13.8	1.39 (1.16-1.66)	1.00 (0.82-1.22)
≥3	2 549	44.6	8 554	29.9	2.58 (2.38-2.78)	1.10 (1.00-1.21)	533	35.2	1 740	23.0	2.22 (1.92-2.57)	1.13 (0.94-1.36)
Number of hospitalizations for MDD in the year before the index date												
0	4 959	86.8	27 626	96.7	Ref=1		997	65.9	6 338	83.8	Ref=1	
1	540	9.5	769	2.7	3.94 (3.51-4.43)	1.92 (1.61-2.30)	433	28.6	1 107	14.6	2.56 (2.24-2.92)	1.68 (1.28-2.22)
2	157	2.7	137	0.5	6.32 (5.01-7.97)	2.33 (1.69-3.22)	72	4.8	100	1.3	4.75 (3.47-6.51)	2.98 (1.87-4.77)
≥3	58	1.0	38	0.1	8.55 (5.66-12.91)	2.13 (1.24-3.64)	11	0.7	17	0.2	4.92 (2.28-10.6)	2.50 (0.95-6.54)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	4 380	76.7	26 493	92.7	Ref=1		891	58.9	5 962	78.8	Ref=1	
1	761	13.3	1 481	5.2	3.17 (2.88-3.48)	1.43 (1.24-1.65)	432	28.6	1 254	16.6	2.37 (2.07-2.70)	1.19 (0.91-1.56)
2	301	5.3	367	1.3	4.97 (4.25-5.82)	1.50 (1.21-1.87)	117	7.7	219	2.9	3.83 (3.01-4.88)	1.21 (0.83-1.78)
≥3	272	4.8	229	0.8	7.23 (6.03-8.66)	1.37 (1.06-1.77)	73	4.8	127	1.7	4.25 (3.14-5.76)	1.27 (0.84-1.94)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 29. Case control analysis V. All cases of *Self-harm and suicides*, including patients with recorded self-harm prior to the index date. Controls matched calendar year of index dispensing, sex, age ±5 years, both cohort separately. Exposure: Index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=5 714		Controls n=28 570		Conditional logistic regression		Cases =1 513		Controls n=7 562		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Index medication												
Monotherapy with quetiapine,	55	1.0	160	0.6	2.47 (1.64-3.70)	0.85 (0.59-1.23)	28	1.9	62	0.8	0.86 (0.41-1.82)	1.21 (0.55-2.65)
Combination with quetiapine	306	5.4	693	2.4	1.72 (1.43-2.08)	1.21 (1.03-1.43)	17	1.1	55	0.7	0.98 (0.48-2.00)	0.93 (0.43-1.97)
Monotherapy with other antidepressants	1 409	24.7	7 717	27.0	0.90 (0.83-0.97)	0.87 (0.81-0.93)	1 392	92.0	7 243	95.8	0.64 (0.45-0.91)	0.95 (0.65-1.39)
Combination with other antidepressants	3 944	69.0	20 000	70.0	Ref=1		76	5.0	202	2.7	Ref=1	
History of diagnoses from 1997 until index date												
Previous self-harm	1 796	31.4	1 871	6.5	6.83 (6.32-7.37)	3.35 (3.06-3.67)	485	32.1	751	9.9	4.28 (3.74-4.90)	2.72 (2.32-3.18)
Other organic, including symptomatic, mental disorder	100	1.8	272	1.0	1.87 (1.48-2.35)	1.15 (0.89-1.51)	8	0.5	78	1.0	0.51 (0.24-1.05)	0.36 (0.16-0.83)
Disorders of adult personality and behaviour	640	11.2	1 156	4.0	3.06 (2.76-3.39)	1.34 (1.18-1.52)	155	10.2	400	5.3	2.05 (1.69-2.50)	1.25 (1.00-1.57)
Alcohol use disorder	1 468	25.7	2 257	7.9	4.16 (3.86-4.49)	1.92 (1.75-2.10)	384	25.4	908	12.0	2.55 (2.22-2.93)	1.48 (1.26-1.73)
Other substance use disorder	1 237	21.6	1 805	6.3	4.17 (3.84-4.52)	1.78 (1.62-1.97)	279	18.4	525	6.9	3.09 (2.64-3.63)	1.77 (1.47-2.12)
Anxiety disorder incl. GAD	2 374	41.5	7 542	26.4	2.03 (1.91-2.15)	1.29 (1.20-1.38)	475	31.4	2 060	27.2	1.22 (1.09-1.38)	1.02 (0.89-1.16)
Number of somatic hospitalizations in the year before the index date												
0	3 747	65.6	23 628	82.7	Ref=1		1 077	71.2	6 247	82.6	Ref=1	
1	1 117	19.5	3 109	10.9	2.31 (2.14-2.49)	1.45 (1.32-1.59)	269	17.8	906	12.0	1.78 (1.53-2.07)	1.15 (0.96-1.38)
2	364	6.4	914	3.2	2.68 (2.36-3.05)	1.45 (1.24-1.69)	84	5.6	239	3.2	2.18 (1.68-2.82)	1.11 (0.82-1.50)
≥3	486	8.5	919	3.2	3.60 (3.19-4.05)	1.94 (1.68-2.25)	83	5.5	170	2.2	3.22 (2.42-4.28)	1.58 (1.13-2.22)
Number of somatic hospitalizations from 1997 until index dispensing												
0	1 301	22.8	10 133	35.5	Ref=1		465	30.7	3 052	40.4	Ref=1	
1	1 039	18.2	5 951	20.8	1.40 (1.28-1.52)	1.01 (0.92-1.11)	306	20.2	1 730	22.9	1.19 (1.02-1.39)	0.89 (0.75-1.06)
2	825	14.4	3 932	13.8	1.74 (1.58-1.92)	1.07 (0.96-1.19)	209	13.8	1 040	13.8	1.39 (1.16-1.66)	1.01 (0.83-1.23)
≥3	2 549	44.6	8 554	29.9	2.58 (2.38-2.78)	1.10 (1.00-1.21)	533	35.2	1 740	23.0	2.22 (1.92-2.57)	1.13 (0.94-1.36)
Number of hospitalizations for MDD in the year before the index date												
0	4 959	86.8	27 626	96.7	Ref=1		997	65.9	6 338	83.8	Ref=1	
1	540	9.5	769	2.7	3.94 (3.51-4.43)	1.90 (1.59-2.27)	433	28.6	1 107	14.6	2.56 (2.24-2.92)	1.70 (1.29-2.23)
2	157	2.7	137	0.5	6.32 (5.01-7.97)	2.41 (1.75-3.33)	72	4.8	100	1.3	4.75 (3.47-6.51)	2.93 (1.85-4.65)
≥3	58	1.0	38	0.1	8.55 (5.66-12.91)	2.21 (1.30-3.78)	11	0.7	17	0.2	4.92 (2.28-10.6)	2.62 (1.02-6.75)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	4 380	76.7	26 493	92.7	Ref=1		891	58.9	5 962	78.8	Ref=1	
1	761	13.3	1 481	5.2	3.17 (2.88-3.48)	1.46 (1.27-1.69)	432	28.6	1 254	16.6	2.37 (2.07-2.70)	1.20 (0.92-1.56)
2	301	5.3	367	1.3	4.97 (4.25-5.82)	1.55 (1.25-1.92)	117	7.7	219	2.9	3.83 (3.01-4.88)	1.26 (0.87-1.84)
≥3	272	4.8	229	0.8	7.23 (6.03-8.66)	1.43 (1.11-1.84)	73	4.8	127	1.7	4.25 (3.14-5.76)	1.30 (0.86-1.96)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 30. Case control analysis V. Incident cases of *Self-harm and suicides,* excluding patients with recorded self-harm prior to the index date. Controls matched on calendar year of index dispensing, sex, age ±5 years. Exposure: Current medication at the date of the event.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=3 918		Controls n=19 590		Conditional logistic regression		Cases n=1 028		Controls n=5 140		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Current medication at the date of event												
No medication	681	17.4	4 501	23.0	0.53 (0.47-0.59)	0.52 (0.47-0.58)	234	22.8	1 807	35.2	0.30 (0.24-0.39)	0.29 (0.22-0.37)
Monotherapy with quetiapine	39	1.0	101	0.5	1.37 (0.94-2.00)	1.02 (0.68-1.53)	8	0.8	32	0.6	0.58 (0.26-1.29)	0.36 (0.16-0.81)
Combination with quetiapine	223	5.7	423	2.2	1.93 (1.62-2.30)	1.52 (1.26-1.84)	35	3.4	64	1.2	1.29 (0.82-2.04)	1.39 (0.85-2.26)
Monotherapy with other antidepressants	1 665	42.5	9 670	49.4	0.62 (0.57-0.67)	0.64 (0.59-0.7)	610	59.3	2 900	56.4	0.51 (0.41-0.63)	0.49 (0.39-0.62)
Combination with other antidepressants	1 310	33.4	4 895	25.0	Ref=1		141	13.7	337	6.6	Ref=1	
History of diagnoses from 1997 until index date												
Previous self-harm	excluded											
Other organic, including symptomatic, mental disorder	63	1.6	199	1.0	1.60 (1.20-2.14)	1.21 (0.89-1.65)	3	0.3	38	0.7	-	
Disorders of adult personality and behaviour	223	5.7	585	3.0	1.98 (1.69-2.32)	1.25 (1.05-1.50)	66	6.4	228	4.4	1.48 (1.11-1.96)	1.29 (0.96-1.74)
Alcohol use disorder	675	17.2	1 199	6.1	3.29 (2.96-3.64)	2.32 (2.07-2.61)	176	17.1	519	10.1	1.87 (1.55-2.26)	1.55 (1.26-1.91)
Other substance use disorder	551	14.1	891	4.5	3.46 (3.09-3.88)	2.26 (1.99-2.56)	127	12.4	317	6.2	2.16 (1.73-2.69)	1.81 (1.42-2.30)
Anxiety disorder incl. GAD	1 326	33.8	4 798	24.5	1.61 (1.49-1.73)	1.25 (1.16-1.36)	282	27.4	1 375	26.8	1.04 (0.89-1.21)	1.00 (0.85-1.17)
Number of somatic hospitalizations in the year before the index date												
0	2 923	74.6	16 501	84.2	Ref=1		845	82.2	4 411	85.8	Ref=1	
1	597	15.2	1 874	9.6	1.83 (1.66-2.03)	1.45 (1.29-1.62)	121	11.8	517	10.1	1.24 (1.00-1.54)	1.13 (0.89-1.43)
2	163	4.2	612	3.1	1.59 (1.33-1.90)	1.16 (0.95-1.42)	27	2.6	120	2.3	1.20 (0.78-1.83)	0.89 (0.56-1.42)
≥3	235	6.0	603	3.1	2.33 (1.99-2.74)	1.72 (1.44-2.07)	35	3.4	92	1.8	2.04 (1.37-3.03)	1.49 (0.94-2.36)
Number of somatic hospitalizations from 1997 until index dispensing												
0	1 192	30.4	7 259	37.1	Ref=1		423	41.1	2 329	45.3	Ref=1	
1	756	19.3	4 128	21.1	1.13 (1.03-1.25)	0.98 (0.88-1.08)	214	20.8	1 180	23.0	1.01 (0.84-1.21)	0.94 (0.77-1.13)
2	568	14.5	2 651	13.5	1.36 (1.22-1.52)	1.10 (0.97-1.24)	145	14.1	626	12.2	1.31 (1.06-1.62)	1.15 (0.91-1.44)
≥3	1 402	35.8	5 552	28.3	1.66 (1.52-1.82)	1.16 (1.04-1.29)	246	23.9	1 005	19.6	1.41 (1.17-1.70)	1.20 (0.96-1.49)
Number of hospitalizations for MDD in the year before the index date												
0	3 509	89.6	19 136	97.7	Ref=1		723	70.3	4 431	86.2	Ref=1	
1	312	8.0	381	1.9	4.56 (3.90-5.34)	2.56 (2.02-3.24)	262	25.5	646	12.6	2.55 (2.15-3.01)	1.35 (0.92-1.99)
2	78	2.0	53	0.3	8.11 (5.68-11.59)	4.14 (2.58-6.63)	40	3.9	56	1.1	Collapsed	
≥3	19	0.5	20	0.1	5.34 (2.84-10.05)	2.07 (0.94-4.56)	3	0.3	7	0.1	Collapsed	
≥2							43		63		4.40 (2.93-6.62)	3.04 (1.61-5.72)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	3 284	83.8	18 541	94.6	Ref=1		678	66.0	4 259	82.9	Ref=1	
1	431	11.0	789	4.0	3.11 (2.74-3.52)	1.54 (1.28-1.86)	267	26.0	715	13.9	2.4 (2.03-2.83)	1.75 (1.20-2.56)
2	127	3.2	169	0.9	4.29 (3.39-5.43)	1.59 (1.15-2.19)	57	5.5	119	2.3	3.16 (2.26-4.4)	1.48 (0.88-2.48)
≥3	76	1.9	91	0.5	4.84 (3.55-6.61)	1.70 (1.12-2.58)	26	2.5	47	0.9	3.73 (2.28-6.1)	2.07 (1.10-3.87)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 31. Case control analysis V. Incident cases of *Self-harm and suicides,* excluding patients with recorded self-harm prior to the index date. Controls matched calendar year of index dispensing, sex, age ±5 years. Exposure: index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=3 918		Controls n=18 371		Conditional logistic regression		Cases n=1 028		Controls n=4 637		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Index medication												
Monotherapy with quetiapine	35	0.9	71	0.4	2.47 (1.64-3.70)	1.61 (1.03-2.54)	11	1.1	42	0.8	0.86 (0.41-1.82)	1.21 (0.55-2.64)
Combination with quetiapine	156	4.0	452	2.3	1.72 (1.43-2.08)	1.15 (0.94-1.41)	13	1.3	43	0.8	0.98 (0.48-2.00)	0.89 (0.42-1.89)
Monotherapy with other antidepressants	942	24.0	5 217	26.6	0.90 (0.83-0.97)	0.87 (0.80-0.94)	961	93.5	4 913	95.6	0.64 (0.45-0.91)	0.94 (0.65-1.38)
Combination with other antidepressants	2 785	71.1	13 850	70.7	Ref=1		43	4.2	142	2.8	Ref=1	
History of diagnoses from 1997 until index date												
Previous self-harm	excluded											
Other organic, including symptomatic, mental disorder	63	1.6	199	1.0	1.60 (1.20-2.14)	1.21 (0.89-1.65)	3	0.3	38	0.7	-	
Disorders of adult personality and behaviour	223	5.7	585	3.0	1.98 (1.69-2.32)	1.25 (1.05-1.50)	66	6.4	228	4.4	1.48 (1.11-1.96)	1.29 (0.96-1.74)
Alcohol use disorder	675	17.2	1 199	6.1	3.29 (2.96-3.64)	2.32 (2.07-2.61)	176	17.1	519	10.1	1.87 (1.55-2.26)	1.55 (1.26-1.91)
Other substance use disorder	551	14.1	891	4.5	3.46 (3.09-3.88)	2.26 (1.99-2.56)	127	12.4	317	6.2	2.16 (1.73-2.69)	1.81 (1.42-2.30)
Anxiety disorder incl. GAD	1 326	33.8	4 798	24.5	1.61 (1.49-1.73)	1.25 (1.16-1.36)	282	27.4	1 375	26.8	1.04 (0.89-1.21)	1.00 (0.85-1.17)
Number of somatic hospitalizations in the year before the index date												
0	2 923	74.6	16 501	84.2	Ref=1		845	82.2	4 411	85.8	Ref=1	
1	597	15.2	1 874	9.6	1.83 (1.66-2.03)	1.45 (1.29-1.62)	121	11.8	517	10.1	1.24 (1-1.54)	1.13 (0.89-1.43)
2	163	4.2	612	3.1	1.59 (1.33-1.90)	1.16 (0.95-1.42)	27	2.6	120	2.3	1.2 (0.78-1.83)	0.89 (0.56-1.42)
≥3	235	6.0	603	3.1	2.33 (1.99-2.74)	1.72 (1.44-2.07)	35	3.4	92	1.8	2.04 (1.37-3.03)	1.49 (0.94-2.36)
Number of somatic hospitalizations from 1997 until index dispensing												
0	1 192	30.4	7 259	37.1	Ref=1		423	41.1	2 329	45.3	Ref=1	
1	756	19.3	4 128	21.1	1.13 (1.03-1.25)	0.98 (0.88-1.08)	214	20.8	1 180	23.0	1.01 (0.84-1.21)	0.94 (0.77-1.13)
2	568	14.5	2 651	13.5	1.36 (1.22-1.52)	1.10 (0.97-1.24)	145	14.1	626	12.2	1.31 (1.06-1.62)	1.15 (0.91-1.44)
≥3	1 402	35.8	5 552	28.3	1.66 (1.52-1.82)	1.16 (1.04-1.29)	246	23.9	1 005	19.6	1.41 (1.17-1.70)	1.20 (0.96-1.49)
Number of hospitalizations for MDD in the year before the index date												
0	3 509	89.6	19 136	97.7	Ref=1		723	70.3	4 431	86.2	Ref=1	
1	312	8.0	381	1.9	4.56 (3.90-5.34)	2.56 (2.02-3.24)	262	25.5	646	12.6	2.55 (2.15-3.01)	1.35 (0.92-1.99)
2	78	2.0	53	0.3	8.11 (5.68-11.59)	4.14 (2.58-6.63)	40	3.9	56	1.1	Collapsed	
≥3	19	0.5	20	0.1	5.34 (2.84-10.05)	2.07 (0.94-4.56)	3	0.3	7	0.1	Collapsed	
≥2							43		63		4.40 (2.93-6.62)	3.04 (1.61-5.72)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	3 284	83.8	18 541	94.6	Ref=1		678	66.0	4 259	82.9	Ref=1	
1	431	11.0	789	4.0	3.11 (2.74-3.52)	1.54 (1.28-1.86)	267	26.0	715	13.9	2.4 (2.03-2.83)	1.75 (1.20-2.56)
2	127	3.2	169	0.9	4.29 (3.39-5.43)	1.59 (1.15-2.19)	57	5.5	119	2.3	3.16 (2.26-4.4)	1.48 (0.88-2.48)
≥3	76	1.9	91	0.5	4.84 (3.55-6.61)	1.70 (1.12-2.58)	26	2.5	47	0.9	3.73 (2.28-6.1)	2.07 (1.10-3.87)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 32. Case control analysis VI. Incident cases of *Extrapyramidal disorder.* Controls matched on calendar year of index dispensing* sex, and age ±5 years. Characteristics of cases and controls.

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls*
Total number	523	2 615	67	335
Age at event*		(matched)		(matched)
Mean (SD)	55.3 (21.1)	55.3 (20.8)	44.3 (19.8)	43.9 (19.8)
Median (quartiles)	58 (37;74)	58 (36;73)	41 (25;63)	42 (26;61)
Min**-max	18-92	18-97	18-82	18-91
Mode	77	76	22	22
Sex, n (%)		(matched)		(matched)
Men	214 (40.9%)	1 070 (40.9%)	36 (53.7%)	180 (53.7%)
Women	309 (59.1%)	1 545 (59.1%)	31 (46.3%)	155 (46.3%)
Clinic of the prescriber of the index dispensing n (%)				
Primary care	27 (5.2%)	157 (6.0%)	1 (1.5%)	6 (1.8%)
Somatic care	238 (45.5%)	1 634 (62.5%)	5 (7.5%)	28 (8.4%)
Psychiatric/addiction care	71 (13.6%)	216 (8.3%)	5 (7.5%)	13 (3.9%)
Other	187 (35.8%)	608 (23.3%)	56 (83.6%)	288 (86.0%)
Number of hospitalizations for MDD in the year before the index date				
0	483 (92.4%)	2 528 (96.7%)	43 (64.2%)	270 (80.6%)
1	30 (5.7%)	70 (2.7%)	21 (31.3%)	52 (15.5%)
2	7 (1.3%)	15 (0.6%)	2 (3.0%)	13 (3.9%)
≥3	3 (0.6%)	2 (0.1%)	1 (1.5%)	-
Number of hospitalizations for MDD from 1997 until index dispensing				
0	445 (85.1%)	2 438 (93.2%)	41 (61.2%)	254 (75.8%)
1	45 (8.6%)	115 (4.4%)	19 (28.4%)	58 (17.3%)
2	14 (2.7%)	39 (1.5%)	4 (6.0%)	15 (4.5%)
≥3	19 (3.6%)	23 (0.9%)	3 (4.5%)	8 (2.4%)
Number of somatic hospitalizations in the year before the index date				
0	354 (67.7%)	2 030 (77.6%)	47 (70.1%)	246 (73.4%)
1	92 (17.6%)	324 (12.4%)	12 (17.9%)	44 (13.1%)
2	26 (5.0%)	138 (5.3%)	4 (6.0%)	18 (5.4%)
≥3	51 (9.8%)	123 (4.7%)	4 (6.0%)	27 (8.1%)
Number of somatic hospitalizations from 1997 until the index dispensing				
0	117 (22.4%)	745 (28.5%)	20 (29.9%)	116 (34.6%)
1	91 (17.4%)	501 (19.2%)	12 (17.9%)	66 (19.7%)
2	75 (14.3%)	371 (14.2%)	8 (11.9%)	42 (12.5%)
≥3	240 (45.9%)	998 (38.2%)	27 (40.3%)	111 (33.1%)

Table 32 (continued)

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	523	2 615	67	335
No somatic diagnosis in the groups below	318 (60.8%)	1 693 (64.7%)	50 (74.6%)	237 (70.7%)
Charlson comorbidity groups from 1997 until the index date				
Cancer	21 (4.0%)	132 (5.0%)	2 (3.0%)	11 (3.3%)
Cerebrovascular disease	22 (4.2%)	102 (3.9%)	2 (3.0%)	10 (3.0%)
Congestive heart failure	14 (2.7%)	82 (3.1%)	0 (0.0%)	7 (2.1%)
Chronic pulmonary disease	43 (8.2%)	225 (8.6%)	2 (3.0%)	18 (5.4%)
Dementia	Excluded			
Diabetes with complications	41 (7.8%)	210 (8%)	3 (4.5%)	28 (8.4%)
Diabetes without complications	11 (2.1%)	65 (2.5%)	1 (1.5%)	8 (2.4%)
AIDS/HIV	18 (3.4%)	62 (2.4%)	1 (1.5%)	10 (3.0%)
Metastatic carcinoma	21 (4.0%)	44 (1.7%)	3 (4.5%)	10 (3.0%)
Myocardial infarction	35 (6.7%)	182 (7.0%)	2 (3.0%)	21 (6.3%)
Mild liver disease	14 (2.7%)	67 (2.6%)	2 (3.0%)	8 (2.4%)
Moderate or severe liver disease	9 (1.7%)	29 (1.1%)	0 (0.0%)	5 (1.5%)
Paraplegia and hemiplegia	9 (1.7%)	37 (1.4%)	0 (0.0%)	4 (1.2%)
Peptic ulcer disease	50 (9.6%)	223 (8.5%)	5 (7.5%)	28 (8.4%)
Peripheral vascular disease	1 (0.2%)	2 (0.1%)	0 (0.0%)	2 (0.6%)
Renal disease	7 (1.3%)	29 (1.1%)	1 (1.5%)	0 (0.0%)
Rheumatic disease	2 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IHD excl. MI	51 (9.8%)	251 (9.6%)	3 (4.5%)	15 (4.5%)
Charlson comorbidity index from 1997				
0	327 (62.5%)	1 734 (66.3%)	50 (74.6%)	237 (70.7%)
1-2	168 (32.1%)	737 (28.2%)	16 (23.9%)	79 (23.6%)
3-4	23 (4.4%)	109 (4.2%)	1 (1.5%)	16 (4.8%)
≥5	5 (1.0%)	35 (1.3%)	0 (0%)	3 (0.9%)
Median quartiles	0 (0;1)	0 (0;1)	0 (0;1)	0 (0;1)
Mean (SD)	0.61 (1.01)	0.57 (1.03)	0.36 (0.73)	0.51 (1.03)
Alcohol disorder diagnosis since 1997	53 (10.1%)	172 (6.6%)	11 (16.4%)	54 (16.1%)
Substance disorder diagnosis since 1997	63 (12.0%)	138 (5.3%)	14 (20.9%)	24 (7.2%)

Table 33. Case control analysis VI. Incident cases of *Extrapyramidal disorders.* Controls matched calendar year of index dispensing, sex, age ±5 years. Exposure: Current medication at the date of the event.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=523		Controls n=2615		Conditional logistic regression		Cases =67		Controls n=335		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Current medication at the date of event												
No medication	81	15.5	592	22.6	0.66 (0.49-0.91)	0.70 (0.49-0.99)	19	5.7	104	31.0	0.52 (0.18-1.45)	0.50 (0.15-1.69)
Monotherapy with quetiapine	16	3.1	8	0.3	9.23 (3.84-22.17)	13.51 (4.98-36.65)	2	0.6	1	0.3	collapsed	
Combination with quetiapine	51	9.8	46	1.8	5.61 (3.53-8.90)	6.15 (3.57-10.58)	10	3.0	12	3.6	collapsed	
Monotherapy with other antidepressants	246	47.0	1 342	51.3	0.88 (0.69-1.11)	1.05 (0.81-1.37)	29	8.7	197	58.8	0.45 (0.17-1.17)	0.47 (0.15-1.44)
Combination with other antidepressants	129	24.7	627	24.0	Ref=1	Ref=1	7	2.1	21	6.3	Ref=1	Ref=1
Quetiapine monotherapy or combination							12		13		2.39 (0.75-7.65)	1.67 (0.41-6.73)
Current use of other antipsychotics	154	29.4	51	2.0	19.33 (13.54-27.6)	19.94 (13.77-28.88)	25	7.5	3	0.9	61.05 (14.45-257.92)	54.83 (12.83-234.32)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 34. Case control analysis VI. Incident cases of *Extrapyramidal disorders*. Controls matched on calendar year of index dispensing, sex, age ±5 years. Exposure: Index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD			
	Cases n=523		Controls n=2615		Conditional logistic regression		Cases =67		Controls n=335	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%
Index medication										
Monotherapy with quetiapine	10	1.9	6	0.2	8.45 (8.45-23.35)	8.84 (2.72-28.82)	4	1.2	3	0.9
	44	8.4	51	2.0	4.64 (4.64-7.09)	4.30 (2.61-7.06)	7	2.1	5	1.5
	119	22.8	687	26.3	0.92 (0.92-1.15)	0.99 (0.77-1.27)	52	15.5	319	95.2
Combination with quetiapine	350	66.9	1 871	71.5	Ref=1	Ref=1	4	1.2	8	2.4
Monotherapy with other antidepressants										
Current use of other antipsychotics	154	29.4	51	2.0	19.33 (13.54-27.6)	18.92 (13.18-27.18)				

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 35. Case control analysis VII. Incident cases of *Somnolence*. Controls matched on calendar year of index dispensing* sex, and age ±5 years. Characteristics of cases and controls.

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls*
Total number	546	2 730	83	415
Age at event*		(matched)		(matched)
Mean (SD)	57.5 (21.9)	57.4 (21.6)	37.8 (17.1)	37.7 (16.7)
Median (quartiles)	59 (39;77)	59 (40;77)	34 (23;52)	33 (23;50)
Min**-max	18-96	18-97	18-80	18-85
Mode	70	81	19	21
Sex, n (%)		(matched)		(matched)
Men	233 (42.7%)	1 165 (42.7%)	39 (47%)	195 (47%)
Women	313 (57.3%)	1 565 (57.3%)	44 (53%)	220 (53%)
Clinic of the prescriber of the index dispensing n (%)				
Primary care	259 (47.4%)	1 757 (64.4%)	7 (8.4%)	32 (7.7%)
Somatic care	91 (16.7%)	231 (8.5%)	2 (2.4%)	10 (2.4%)
Psychiatric/addiction care	169 (31%)	604 (22.1%)	73 (88%)	364 (87.7%)
Other	27 (4.9%)	138 (5.1%)	1 (1.2%)	9 (2.2%)
Number of hospitalizations for MDD in the year before the index date				
0	502 (91.9%)	2 657 (97.3%)	52 (62.7%)	337 (81.2%)
1	29 (5.3%)	65 (2.4%)	27 (32.5%)	72 (17.3%)
2	11 (2%)	8 (0.3%)	3 (3.6%)	5 (1.2%)
≥3	4 (0.7%)	0 (0%)	1 (1.2%)	1 (0.2%)
Number of hospitalizations for MDD from 1997 until index dispensing				
0	457 (83.7%)	2 556 (93.6%)	46 (55.4%)	314 (75.7%)
1	44 (8.1%)	112 (4.1%)	31 (37.3%)	77 (18.6%)
2	15 (2.7%)	32 (1.2%)	2 (2.4%)	11 (2.7%)
≥3	30 (5.5%)	30 (1.1%)	4 (4.8%)	13 (3.1%)
Number of somatic hospitalizations in the year before the index date				
0	260 (47.6%)	2 049 (75.1%)	54 (65.1%)	324 (78.1%)
1	113 (20.7%)	357 (13.1%)	14 (16.9%)	64 (15.4%)
2	52 (9.5%)	154 (5.6%)	5 (6%)	20 (4.8%)
≥3	121 (22.2%)	170 (6.2%)	10 (12%)	7 (1.7%)
Number of somatic hospitalizations from 1997 until the index dispensing				
0	72 (13.2%)	706 (25.9%)	20 (24.1%)	151 (36.4%)
1	63 (11.5%)	486 (17.8%)	17 (20.5%)	107 (25.8%)
2	57 (10.4%)	388 (14.2%)	7 (8.4%)	61 (14.7%)
≥3	354 (64.8%)	1 150 (42.1%)	39 (47%)	96 (23.1%)

Table 35 (continued)

	Cohort A Treatment change		**Cohort B** New user with MDD	
	Cases	Controls	Cases	Controls
Total number	546	2 730	83	415
No somatic diagnosis in the groups below	246 (45.1%)	1 685 (61.7%)	59 (71.1%)	338 (81.4%)
Charlson comorbidity groups from 1997 until the index date				
Cancer	64 (11.7%)	163 (6.0%)	2 (2.4%)	6 (1.4%)
Cerebrovascular disease	70 (12.8%)	162 (5.9%)	2 (2.4%)	3 (0.7%)
Congestive heart failure	40 (7.3%)	94 (3.4%)	3 (3.6%)	5 (1.2%)
Chronic pulmonary disease	100 (18.3%)	299 (11.0%)	4 (4.8%)	13 (3.1%)
Dementia	Excluded			
Diabetes with complications	79 (14.5%)	232 (8.5%)	10 (12%)	22 (5.3%)
Diabetes without complications	20 (3.7%)	82 (3.0%)	0 (0%)	1 (0.2%)
AIDS/HIV	23 (4.2%)	97 (3.6%)	0 (0%)	6 (1.4%)
Metastatic carcinoma	35 (6.4%)	32 (1.2%)	5 (6%)	10 (2.4%)
Myocardial infarction	89 (16.3%)	222 (8.1%)	7 (8.4%)	14 (3.4%)
Mild liver disease	46 (8.4%)	91 (3.3%)	3 (3.6%)	5 (1.2%)
Moderate or severe liver disease	22 (4.0%)	46 (1.7%)	2 (2.4%)	3 (0.7%)
Paraplegia and hemiplegia	24 (4.4%)	37 (1.4%)	2 (2.4%)	3 (0.7%)
Peptic ulcer disease	65 (11.9%)	242 (8.9%)	2 (2.4%)	10 (2.4%)
Peripheral vascular disease	7 (1.3%)	8 (0.3%)	0 (0%)	0 (0%)
Renal disease	12 (2.2%)	18 (0.7%)	0 (0%)	1 (0.2%)
Rheumatic disease	1 (0.2%)	1 (0%)	0 (0%)	0 (0%)
IHD excl. MI**	98 (17.9%)	327 (12%)	2 (2.4%)	9 (2.2%)
Charlson comorbidity index from 1997				
0	251 (46.0%)	1 737 (63.6%)	59 (71.1%)	339 (81.7%)
1-2	183 (33.5%)	790 (28.9%)	20 (24.1%)	69 (16.6%)
3-4	77 (14.1%)	159 (5.8%)	3 (3.6%)	6 (1.4%)
≥5	35 (6.4%)	44 (1.6%)	1 (1.2%)	1 (0.2%)
Median quartiles	1 (0;2)	0 (0;1)	0 (0;1)	0 (0;0)
Mean (SD)	1.28 (1.70)	0.67 (1.14)	0.51 (1.03)	0.25 (0.64)
Alcohol disorder diagnosis since 1997	95 (17.4%)	184 (6.7%)	26 (31.3%)	57 (13.7%)
Substance disorder diagnosis since 1997	100 (18.3%)	137 (5%)	25 (30.1%)	37 (8.9%)

Table 36. Case control analysis VII. Incident cases of *Somnolence*. Controls matched by calendar year of index dispensing, sex, age ±5 years. Exposure: Current medication at the date of the event.

	Cohort A Treatment change						**Cohort B** New user with MDD			
	Cases n=546		Controls n=2730		Conditional logistic regression		Cases =83		Controls n=415	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%
Current medication at the date of event										
No medication	95	17.4	603	22.1	0.69 (0.51-0.92)	0.70 (0.52-0.93)	27	6.5	168	40.5
Monotherapy with quetiapine	5	0.9	15	0.5	1.48 (0.52-4.17)	1.52 (0.53-4.33)	1	0.2	0	0.0
Combination with quetiapine	25	4.6	45	1.6	2.45 (1.45-4.13)	2.41 (1.42-4.11)	1	0.2	8	1.9
Monotherapy with other antidepressants	153	28.0	680	24.9	0.85 (0.68-1.06)	0.86 (0.69-1.07)	6	1.4	28	6.7
Combination with other antidepressants	268	49.1	1 387	50.8	Ref=1	Ref=1	48	11.6	211	50.8
Anxiolytic or hypnotic dispensing before index date	484	88.6	2 241	82.1	1.75 (1.31-2.33)	1.24 (0.91-1.69)	53	63.9	250	60.2
Anxiolytic or hypnotic dispensing from index date to date of event	423	77.5	1 724	63.2	2.07 (1.66-2.58)	1.95 (1.54-2.46)	68	81.9	261	62.9

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 37. Case control analysis VII. Incident cases of *Somnolence*. Controls matched calendar year of index dispensing, sex, age ±5 years. Exposure: index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD			
	Cases n=546		Controls n=2730		Conditional logistic regression		Cases =83		Controls n=415	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%
Index medication										
Monotherapy with quetiapine	4	0.7	8	0.3	collapsed		1	0.2	2	0.5
Combination with quetiapine	24	4.4	45	1.6	collapsed		0	0.0	3	0.7
Monotherapy with other antidepressants	138	25.3	675	24.7	1.08 (0.87-1.34)	1.08 (0.87-1.34)	78	18.8	393	94.7
Combination with other antidepressants	380	69.6	2 002	73.3	Ref=1		4	1.0	17	4.1
Quetiapine monotherapy or combination	28		53		2.84 (1.76-4.58)	2.90 (1.78-4.72)				
Anxiolytic or hypnotic dispensing before index date	484	88.6	2 241	82.1	1.75 (1.31-2.33)	1.27 (0.93-1.73)	53	63.9	250	60.2
Anxiolytic or hypnotic dispensing from index date to date of event	423	77.5	1 724	63.2	2.07 (1.66-2.58)	1.96 (1.54-2.48)	68	81.9	261	62.9

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 38- Change in estimates in case-control analysis I-VII after exclusion of patients with a diagnosis of alcohol or substance misuse. Exposure: Current treatment at the time of the event. Adjusted for the same variables as in table 16, 19, 22, 25, 28, 30, 33 and 36.

	Cohort A Treatment change			**Cohort B** New user with MDD	
	Total cohort	Cohort without patients with alcohol or substance misuse diagnosis		Total cohort	Cohort without patients with alcohol or substance misuse diagnosis
	Adjusted OR (95% CI)	Adjusted OR (95% CI)		Adjusted OR (95% CI)	Adjusted OR (95% CI)
Death all causes					
No medication	0.96 (0.90-1.02)	0.96 (0.90-1.03)	No medication	0.76 (0.54-1.06)	0.63 (0.42-0.95)
Monotherapy with quetiapine	1.37 (0.99-1.89)	1.40 (0.97-2.01)	Monotherapy with other antidepressants	0.75 (0.55-1.02)	0.77 (0.54-1.1)
Combination with quetiapine	1.31 (1.12-1.54)	1.29 (1.07-1.54)	Combination with other antidepressants	Ref=1	Ref=1
Monotherapy with other antidepressants	0.88 (0.84-0.92)	0.88 (0.84-0.93)	Quetiapine monotherapy or combination	1.35 (0.63-2.9)	1.01 (0.36-2.84)
Combination with other antidepressants	Ref=1	Ref=1			
Acute myocardial infarction			too few		
No medication	1.01 (0.87-1.18)	1.08 (0.92-1.27)			
Monotherapy with quetiapine	1.31 (0.54-3.20)	1.85 (0.7-4.85)			
Combination with quetiapine	0.98 (0.64-1.51)	0.87 (0.52-1.46)			
Monotherapy with other antidepressants	0.93 (0.83-1.05)	0.98 (0.86-1.11)			
Combination with other antidepressants	Ref=1	Ref=1			
Stroke			too few		
No medication	0.90 (0.80-1.02)	0.89 (0.78-1.02)			
Monotherapy with quetiapine	1.21 (0.60-2.45)	1.42 (0.68-2.96)			
Combination with quetiapine	1.26 (0.91-1.74)	1.24 (0.87-1.77)			
Monotherapy with other antidepressants	0.89 (0.81-0.98)	0.88 (0.80-0.98)			
Combination with other antidepressants	Ref=1	Ref=1			
Diabetes mellitus			too few		
No medication	0.76 (0.68-0.86)	0.77 (0.68-0.88)			
Monotherapy with quetiapine	0.86 (0.45-1.66)	0.75 (0.33-1.71)			
Combination with quetiapine	0.87 (0.62-1.22)	0.63 (0.41-0.98)			
Monotherapy with other antidepressants	0.78 (0.71-0.86)	0.77 (0.69-0.85)			
Combination with other antidepressants	Ref=1	Ref=1			

Table 38 (continued)

	Cohort A Treatment change			**Cohort B** New user with MDD	
	Total cohort	Cohort without patients with alcohol or substance misuse diagnosis		Total cohort	Cohort without patients with alcohol or substance misuse diagnosis
	Adjusted OR (95% CI)	Adjusted OR (95% CI)		Adjusted OR (95% CI)	Adjusted OR (95% CI)
Self-harm and suicides all cases					
No medication	0.52 (0.47-0.58)	0.47 (0.42-0.53)	No medication	0.31 (0.25-0.38)	0.30 (0.23-0.40)
Monotherapy with quetiapine	0.71 (0.52-0.99)	0.71 (0.44-1.13)	Monotherapy with quetiapine	0.69 (0.37-1.29)	0.63 (0.26-1.55)
Combination with quetiapine	1.53 (1.31-1.79)	1.42 (1.16-1.75)	Combination with quetiapine	0.99 (0.65-1.52)	1.39 (0.82-2.35)
Monotherapy with other antidepressants	0.66 (0.61-0.71)	0.59 (0.54-0.65)	Monotherapy with other antidepressants	0.54 (0.44-0.65)	0.55 (0.43-0.70)
Combination with other antidepressants	Ref=1	Ref=1	Combination with other antidepressants	Ref=1	Ref=1
Self-harm and suicides, incident cases, no previous diagnosis of self-harm					
No medication	0.52 (0.47-0.58)	0.46 (0.40-0.52)	No medication	0.29 (0.22-0.37)	0.30 (0.22-0.40)
Monotherapy with quetiapine	1.02 (0.68-1.53)	1.00 (0.58-1.72)	Monotherapy with quetiapine	0.36 (0.16-0.81)	0.49 (0.16-1.54)
Combination with quetiapine	1.52 (1.26-1.84)	1.54 (1.23-1.94)	Combination with quetiapine	1.39 (0.85-2.26)	1.42 (0.78-2.58)
Monotherapy with other antidepressants	0.64 (0.59-0.7)	0.60 (0.54-0.66)	Monotherapy with other antidepressants	0.49 (0.39-0.62)	0.56 (0.43-0.74)
Combination with other antidepressants	Ref=1	Ref=1	Combination with other antidepressants	0.29 (0.22-0.37)	Ref=1
Extrapyramidal disorders					
No medication	0.70 (0.49-0.99)	0.70 (0.48-1.04)	No medication	0.50 (0.15-1.69)	0.79 (0.19-3.28)
Monotherapy with other antidepressants	1.05 (0.80-1.37)	1.17 (0.87-1.56)	Monotherapy with other antidepressants	0.47 (0.15-1.44)	0.81 (0.22-3.02)
Combination with other antidepressants	Ref=1	Ref=1	Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	7.26 (4.42-11.91)	8.14 (4.39-15.08)	Quetiapine monotherapy or combination	1.67 (0.41-6.73)	1.47 (0.26-8.27)
Somnolence					
No medication	0.70 (0.52-0.93)	0.62 (0.44-0.88)	too few		
Monotherapy with other antidepressants	0.86 (0.69-1.07)	0.84 (0.65-1.09)			
Combination with other antidepressants	Ref=1	Ref=1			
Quetiapine monotherapy or combination	2.19 (1.35-3.55)	2.16 (1.09-4.27)			

Table 39. Case-control analysis 1-7, stratified on age, in two groups 18-64 years, 65+ years. Exposure: Current treatment at time of event. Adjusted for the same variables as in table 16, 19, 22, 25, 28, 30, 33 and 36.

	Cohort A Treatment change	
	Age 18-64 Adjusted OR (95% CI)	Age 65+ Adjusted OR (95% CI)
Death all causes		
No medication	0.77 (0.66-0.90)	0.98 (0.92-1.05)
Monotherapy with quetiapine	1.17 (0.65-2.11)	1.37 (0.93-2.01)
Combination with quetiapine	1.20 (0.87-1.66)	1.31 (1.09-1.58)
Monotherapy with other antidepressants	0.66 (0.58-0.75)	0.91 (0.87-0.96)
Combination with other antidepressants	Ref=1	Ref=1
acute myocardial infarction		
No medication	0.80 (0.59-1.08)	1.10 (0.93-1.32)
Monotherapy with other antidepressants	0.83 (0.65-1.08)	0.96 (0.84-1.09)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	0.64 (0.28-1.44)	1.28 (0.82-2.00)
Stroke		
No medication	0.94 (0.72-1.23)	0.90 (0.78-1.04)
Monotherapy with quetiapine	1.56 (0.53-4.55)	0.98 (0.37-2.61)
Combination with quetiapine	0.78 (0.39-1.56)	1.47 (1.01-2.12)
Monotherapy with other antidepressants	0.99 (0.79-1.24)	0.87 (0.78-0.96)
Combination with other antidepressants	Ref=1	Ref=1
Diabetes mellitus		
No medication	0.71 (0.61-0.83)	0.85 (0.69-1.04)
Monotherapy with other antidepressants	0.77 (0.68-0.87)	0.79 (0.68-0.93)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	1.01 (0.72-1.41)	0.46 (0.22-0.98)
Self-harm and suicides all cases		
No medication	0.50 (0.45-0.56)	0.75 (0.58-0.99)
Monotherapy with other antidepressants	0.66 (0.61-0.72)	0.65 (0.53-0.79)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	1.34 (1.15-1.56)	1.22 (0.71-2.08)
Self-harm and suicides, no previous diagnosis of self-harm		
No medication	0.48 (0.43-0.54)	0.71 (0.53-0.94)
Monotherapy with other antidepressants	0.61 (0.55-0.67)	0.59 (0.48-0.73)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	1.38 (1.15-1.66)	0.85 (0.48-1.52)
Extrapyramidal disorders		
No medication	0.50 (0.29-0.84)	0.96 (0.59-1.55)
Monotherapy with other antidepressants	0.76 (0.5-1.16)	1.30 (0.91-1.86)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	6.65 (3.53-12.49)	6.65 (2.69-16.41)
Somnolence		
No medication	0.71 (0.48-1.04)	0.68 (0.43-1.08)
Monotherapy with other antidepressants	0.82 (0.6-1.13)	0.89 (0.65-1.22)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	1.66 (0.9-3.05)	3.55 (1.57-8.05)

Table 40. Subgroup analysis of *death by suicide* in case- control analysis V. Exposure: current treatment at time of event. Controls matched on calendar year of index dispensing, sex, age ±5 years.

	Cohort A Treatment change						**Cohort B** New user with MDD			
	Cases n=549		Controls n=2 745		Conditional logistic regression		Cases n=134		Controls n=670	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%
Current medication at the date of event										
No medication	92	16.8	589	21.5	0.45 (0.34-0.60)	0.44 (0.33-0.60)	37	27.6	253	37.8
Monotherapy with quetiapine	4	0.7	16	0.6	0.77 (0.25-2.35)	0.54 (0.16-1.86)	1	0.7	5	0.7
Combination with quetiapine	31	5.6	55	2.0	1.67 (1.05-2.67)	1.24 (0.73-2.10)	2	1.5	12	1.8
Monotherapy with other antidepressants	231	42.1	741	27.0	0.42 (0.34-0.53)	0.45 (0.35-0.57)	22	16.4	55	8.2
Combination with other antidepressants	191	34.8	1 344	49.0	Ref=1		72	53.7	345	51.5
History of diagnoses from 1997 until index date										
Previous self-harm	121	22.0	128	4.7	5.73 (4.35-7.54)	3.32 (2.39-4.62)				
Other organic, including symptomatic, mental disorder	12	2.2	41	1.5	1.48 (0.77-2.84)	0.89 (0.42-1.88)				
Disorders of adult personality and behaviour	39	7.1	70	2.6	2.95 (1.97-4.44)	1.36 (0.83-2.23)				
Alcohol use disorder	135	24.6	240	8.7	3.61 (2.82-4.61)	1.98 (1.48-2.64)				
Other substance use disorder	103	18.8	172	6.3	3.45 (2.64-4.50)	1.65 (1.19-2.29)				
Anxiety disorder incl. GAD	174	31.7	567	20.7	1.79 (1.46-2.19)	1.16 (0.91-1.47)				
Number of somatic hospitalizations in the year before the index date										
0	380	69.2	2 129	77.6	Ref=1					
1	96	17.5	311	11.3	1.75 (1.35-2.26)	1.33 (0.97-1.81)				
2	32	5.8	134	4.9	1.38 (0.92-2.08)	1.01 (0.63-1.63)				
≥3	41	7.5	171	6.2	1.38 (0.96-1.99)	0.99 (0.62-1.56)				
Number of somatic hospitalizations from 1997 until index dispensing										
0	142	25.9	850	31.0	Ref=1					
1	107	19.5	546	19.9	1.18 (0.90-1.55)	0.90 (0.67-1.21)				
2	86	15.7	387	14.1	1.35 (1.00-1.81)	0.91 (0.65-1.27)				
≥3	214	39.0	962	35.0	1.37 (1.08-1.75)	0.73 (0.53-0.99)				
Number of hospitalizations for MDD in the year before the index date										
0	469	85.4	2 647	96.4	Ref=1					
1	56	10.2	76	2.8	4.17 (2.90-6.01)	1.38 (0.81-2.35)				
2	17	3.1	17	0.6	5.66 (2.84-11.27)	1.20 (0.48-3.03)				
≥3	7	1.3	5	0.2	7.00 (2.22-22.06)	1.18 (0.25-5.53)				
≥2										
Number of hospitalizations for MDD from 1997 until index dispensing										
0	407	74.1	2 539	92.5	Ref=1					
1	82	14.9	137	5.0	3.75 (2.78-5.05)	2.19 (1.43-3.38)				
2	34	6.2	41	1.5	5.32 (3.30-8.59)	2.49 (1.32-4.69)				
≥3	26	4.7	28	1.0	5.52 (3.20-9.52)	1.97 (0.90-4.32)				

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 41. Subgroup analysis of *death by suicide* in case- control analysis V. Exposure: Index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD			
	Cases n=549		Controls n=2 745		Conditional logistic regression		Cases n=134		Controls n=670	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%
Index medication										
Monotherapy with quetiapine,	2	0.4	9	0.3	collapsed		1	0.7	8	1.2
Combination with quetiapine	24	4.4	69	2.5	collapsed		1	0.7	2	0.3
Monotherapy with other antidepressants	125	22.8	727	26.5	0.84 (0.67-1.04)	0.80 (0.63-1.01)	125	93.3	636	94.9
Combination with other antidepressants	398	72.5	1 940	70.7	Ref=1	Ref=1	7	5.2	24	3.6
Quetiapine monotherapy or combination	26		78		1.61 (1.03-2.53)	0.82 (0.48-1.41)	1	0.7	8	1.2
History of diagnoses from 1997 until index date										
Previous self-harm	121	22.0	128	4.7	5.73 (4.35-7.54)	3.19 (2.31-4.41)				
Other organic, including symptomatic, mental disorder	12	2.2	41	1.5	1.48 (0.77-2.84)	0.92 (0.44-1.92)				
Disorders of adult personality and behaviour	39	7.1	70	2.6	2.95 (1.97-4.44)	1.45 (0.89-2.37)				
Alcohol use disorder	135	24.6	240	8.7	3.61 (2.82-4.61)	1.99 (1.50-2.65)				
Other substance use disorder	103	18.8	172	6.3	3.45 (2.64-4.50)	1.68 (1.22-2.33)				
Anxiety disorder incl. GAD	174	31.7	567	20.7	1.79 (1.46-2.19)	1.22 (0.97-1.54)				
Number of somatic hospitalizations in the year before the index date										
0	380	69.2	2 129	77.6	Ref=1					
1	96	17.5	311	11.3	1.75 (1.35-2.26)	1.34 (0.98-1.81)				
2	32	5.8	134	4.9	1.38 (0.92-2.08)	1.08 (0.67-1.73)				
≥3	41	7.5	171	6.2	1.38 (0.96-1.99)	1.07 (0.68-1.67)				
Number of somatic hospitalizations from 1997 until index dispensing										
0	142	25.9	850	31.0	Ref=1					
1	107	19.5	546	19.9	1.18 (0.90-1.55)	0.88 (0.66-1.18)				
2	86	15.7	387	14.1	1.35 (1.00-1.81)	0.90 (0.65-1.25)				
≥3	214	39.0	962	35.0	1.37 (1.08-1.75)	0.71 (0.53-0.97)				
Number of hospitalizations for MDD in the year before the index date										
0	469	85.4	2 647	96.4	Ref=1					
1	56	10.2	76	2.8	4.17 (2.90-6.01)	1.44 (0.85-2.44)				
2	17	3.1	17	0.6	5.66 (2.84-11.27)	1.40 (0.56-3.54)				
≥3	7	1.3	5	0.2	7.00 (2.22-22.06)	1.47 (0.32-6.78)				
≥2										
Number of hospitalizations for MDD from 1997 until index dispensing										
0	407	74.1	2 539	92.5	Ref=1					
1	82	14.9	137	5.0	3.75 (2.78-5.05)	2.26 (1.48-3.46)				
2	34	6.2	41	1.5	5.32 (3.30-8.59)	2.51 (1.32-4.74)				
≥3	26	4.7	28	1.0	5.52 (3.20-9.52)	2.04 (0.94-4.41)				

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 42. Subgroup analysis of case control analysis V. All cases of *Self-harm and suicides, violent methods,* including patients with recorded self-harm prior to index date.. Controls matched calendar year of index dispensing, sex, age ±5 years. Exposure: Current medication at the date of the event.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=1 817		Controls n=9 080		Conditional logistic regression		Cases n=460		Controls n=2 297		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Current medication at the date of event												
No medication	355	19.5	2 106	23.2	0.63 (0.54-0.74)	0.62 (0.52-0.74)	123	26.7	815	35.5	0.42 (0.29-0.61)	0.35 (0.24-0.53)
Monotherapy with quetiapine	23	1.3	67	0.7	1.30 (0.78-2.15)	0.77 (0.43-1.38)	8	1.7	11	0.5	1.79 (0.67-4.8)	1.43 (0.46-4.48)
Combination with quetiapine	119	6.6	200	2.2	1.88 (1.43-2.45)	1.31 (0.97-1.77)	10	2.2	34	1.5	0.71 (0.31-1.63)	0.50 (0.20-1.28)
Monotherapy with other antidepressants	582	32.0	2 336	25.7	0.64 (0.56-0.73)	0.67 (0.59-0.77)	60	13.0	176	7.7	0.56 (0.39-0.78)	0.53 (0.36-0.77)
Combination with other antidepressants	737	40.6	4 371	48.1	Ref=1		259	56.3	1 261	54.9	Ref=1	
History of diagnoses from 1997 until index date												
Previous self-harm	533	29.4	602	6.6	6.09 (5.31-6.99)	3.51 (2.99-4.12)	150	32.6	225	9.8	4.45 (3.48-5.68)	3.39 (2.54-4.52)
Other organic, including symptomatic, mental disorder	32	1.8	88	1.0	1.85 (1.22-2.78)	1.21 (0.76-1.92)	2	0.4	31	1.3	-	
Disorders of adult personality and behaviour	201	11.1	330	3.6	3.38 (2.81-4.08)	1.48 (1.19-1.85)	53	11.5	116	5.1	2.43 (1.73-3.41)	1.48 (0.99-2.21)
Alcohol use disorder	374	20.6	729	8.0	3.07 (2.67-3.53)	1.53 (1.30-1.81)	108	23.5	279	12.1	2.32 (1.79-3.01)	1.56 (1.16-2.09)
Other substance use disorder	332	18.3	555	6.1	3.43 (2.96-3.98)	1.67 (1.40-1.99)	78	17.0	179	7.8	2.45 (1.83-3.28)	1.47 (1.05-2.05)
Anxiety disorder incl. GAD	742	40.9	2 328	25.6	2.05 (1.84-2.28)	1.36 (1.20-1.53)	155	33.7	609	26.5	1.41 (1.14-1.75)	1.25 (0.99-1.6)
Number of somatic hospitalizations in the year before the index date												
0	1 218	67.1	7 416	81.7	Ref=1		339	73.7	1 917	83.5	Ref=1	
1	331	18.2	1 010	11.1	2.01 (1.75-2.31)	1.37 (1.17-1.62)	73	15.9	263	11.4	1.63 (1.22-2.18)	0.99 (0.7-1.41)
2	105	5.8	322	3.5	2.09 (1.66-2.64)	1.28 (0.98-1.67)	21	4.6	65	2.8	1.87 (1.13-3.09)	1.13 (0.63-2.01)
≥3	162	8.9	332	3.7	3.21 (2.61-3.94)	1.87 (1.46-2.40)	27	5.9	52	2.3	3.21 (1.96-5.27)	1.60 (0.87-2.93)
Number of somatic hospitalizations from 1997 until index dispensing												
0	468	25.8	3 254	35.8	Ref=1		164	35.7	1 008	43.9	Ref=1	
1	353	19.4	1 863	20.5	1.34 (1.15-1.56)	1.05 (0.89-1.24)	104	22.6	491	21.4	1.32 (1.01-1.73)	0.94 (0.7-1.27)
2	247	13.6	1 244	13.7	1.44 (1.22-1.71)	0.92 (0.77-1.12)	57	12.4	298	13.0	1.21 (0.87-1.69)	0.88 (0.61-1.27)
≥3	748	41.2	2 719	29.9	2.06 (1.8-2.35)	0.97 (0.82-1.14)	135	29.3	500	21.8	1.75 (1.34-2.29)	0.87 (0.62-1.22)
Number of hospitalizations for MDD in the year before the index date												
0	1 614	88.9	8 756	96.4	Ref=1		305	66.3	1 917	83.5	Ref=1	
1	144	7.9	264	2.9	2.97 (2.40-3.67)	1.63 (1.18-2.26)	132	28.7	345	15.0	2.50 (1.97-3.19)	2.19 (1.27-3.77)
2	39	2.1	45	0.5	4.70 (3.05-7.25)	1.91 (1.07-3.42)	22	4.8	30	1.3	collapsed	
≥3	19	1.0	15	0.2	6.78 (3.44-13.39)	1.60 (0.66-3.89)	1	0.2	5	0.2	collapsed	
≥2							23		35		4.34 (2.51-7.49)	4.15 (1.77-9.73)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	1 450	79.8	8 401	92.5	Ref=1		280	60.9	1 803	78.5	Ref=1	
1	208	11.5	470	5.2	2.57 (2.16-3.05)	1.18 (0.91-1.53)	136	29.6	391	17.0	2.31 (1.82-2.94)	0.88 (0.52-1.49)
2	84	4.6	131	1.4	3.71 (2.80-4.90)	1.36 (0.93-1.99)	34	7.4	65	2.8	3.58 (2.29-5.60)	1.11 (0.54-2.26)
≥3	74	4.1	78	0.9	5.51 (3.98-7.62)	1.48 (0.94-2.31)	10	2.2	38	1.7	1.81 (0.89-3.72)	0.38 (0.15-0.99)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 43. Subgroup analysis of case control analysis V. All cases of *Self-harm and suicides*, *violent methods*, including patients with recorded self-harm prior to the index date. Controls matched calendar year of index dispensing, sex, age ±5 years. Exposure: Index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=1 817		Controls n=9 080		Conditional logistic regression		Cases n=460		Controls n=2 297		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Index medication												
Monotherapy with quetiapine	18	1.0	48	0.5	1.67 (0.94-2.95)	0.90 (0.47-1.73)	13	2.8	26	1.1	1.54 (0.65-3.64)	1.48 (0.57-3.89)
Combination with quetiapine	84	4.6	232	2.6	1.57 (1.18-2.07)	0.79 (0.58-1.09)	6	1.3	10	0.4	2.55 (0.8-8.15)	2.48 (0.70-8.80)
Monotherapy with other antidepressants	454	25.0	2 473	27.2	0.87 (0.77-0.99)	0.82 (0.72-0.94)	419	91.1	2 184	95.1	0.66 (0.4-1.09)	0.92 (0.53-1.60)
Combination with other antidepressants	1 260	69.4	6 327	69.7	Ref=1		22	4.8	77	3.4	Ref=1	
History of diagnoses from 1997 until index date												
Previous self-harm	533	29.4	602	6.6	6.09 (5.31-6.99)	3.49 (2.98-4.1)	150	32.6	225	9.8	4.45 (3.48-5.68)	3.28 (2.47-4.37)
Other organic, including symptomatic, mental disorder	32	1.8	88	1.0	1.85 (1.22-2.78)	1.23 (0.78-1.95)	2	0.4	31	1.3	-	
Disorders of adult personality and behaviour	201	11.1	330	3.6	3.38 (2.81-4.08)	1.47 (1.18-1.84)	53	11.5	116	5.1	2.43 (1.73-3.41)	1.36 (0.91-2.01)
Alcohol use disorder	374	20.6	729	8.0	3.07 (2.67-3.53)	1.53 (1.29-1.80)	108	23.5	279	12.1	2.32 (1.79-3.01)	1.51 (1.13-2.03)
Other substance use disorder	332	18.3	555	6.1	3.43 (2.96-3.98)	1.71 (1.43-2.04)	78	17.0	179	7.8	2.45 (1.83-3.28)	1.43 (1.03-1.98)
Anxiety disorder incl. GAD	742	40.9	2 328	25.6	2.05 (1.84-2.28)	1.41 (1.25-1.59)	155	33.7	609	26.5	1.41 (1.14-1.75)	1.28 (1.01-1.62)
Number of somatic hospitalizations in the year before the index date												
0	1 218	67.1	7 416	81.7	Ref=1		339	73.7	1 917	83.5	Ref=1	
1	331	18.2	1 010	11.1	2.01 (1.75-2.31)	1.39 (1.18-1.64)	73	15.9	263	11.4	1.63 (1.22-2.18)	1.01 (0.71-1.44)
2	105	5.8	322	3.5	2.09 (1.66-2.64)	1.32 (1.01-1.72)	21	4.6	65	2.8	1.87 (1.13-3.09)	1.10 (0.61-1.95)
≥3	162	8.9	332	3.7	3.21 (2.61-3.94)	1.97 (1.53-2.52)	27	5.9	52	2.3	3.21 (1.96-5.27)	1.59 (0.87-2.89)
Number of somatic hospitalizations from 1997 until index dispensing												
0	468	25.8	3 254	35.8	Ref=1		164	35.7	1 008	43.9	Ref=1	
1	353	19.4	1 863	20.5	1.34 (1.15-1.56)	1.04 (0.88-1.22)	104	22.6	491	21.4	1.32 (1.01-1.73)	0.97 (0.72-1.3)
2	247	13.6	1 244	13.7	1.44 (1.22-1.71)	0.93 (0.77-1.12)	57	12.4	298	13.0	1.21 (0.87-1.69)	0.86 (0.60-1.25)
≥3	748	41.2	2 719	29.9	2.06 (1.8-2.35)	0.95 (0.80-1.12)	135	29.3	500	21.8	1.75 (1.34-2.29)	0.88 (0.63-1.24)
Number of hospitalizations for MDD in the year before the index date												
0	1 614	88.9	8 756	96.4	Ref=1		305	66.3	1 917	83.5	Ref=1	
1	144	7.9	264	2.9	2.97 (2.40-3.67)	1.61 (1.17-2.23)	132	28.7	345	15.0	2.50 (1.97-3.19)	2.02 (1.18-3.46)
2	39	2.1	45	0.5	4.70 (3.05-7.25)	2.08 (1.16-3.72)	22	4.8	30	1.3	collapsed	
≥3	19	1.0	15	0.2	6.78 (3.44-13.39)	1.76 (0.72-4.30)	1	0.2	5	0.2	collapsed	
≥2							23		35		4.34 (2.51-7.49)	3.65 (1.54-8.62)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	1 450	79.8	8 401	92.5	Ref=1		280	60.9	1 803	78.5	Ref=1	
1	208	11.5	470	5.2	2.57 (2.16-3.05)	1.23 (0.94-1.59)	136	29.6	391	17.0	2.31 (1.82-2.94)	0.94 (0.56-1.59)
2	84	4.6	131	1.4	3.71 (2.80-4.90)	1.41 (0.96-2.05)	34	7.4	65	2.8	3.58 (2.29-5.60)	1.15 (0.56-2.36)
≥3	74	4.1	78	0.9	5.51 (3.98-7.62)	1.56 (1.00-2.43)	10	2.2	38	1.7	1.81 (0.89-3.72)	0.47 (0.18-1.18)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 44. Subgroup analysis of case control analysis V. All cases of *Self-harm and suicides*, *non-violent methods*, including patients with recorded self-harm prior to the index date. Controls matched on calendar year of index dispensing, sex, age ±5 years. Exposure: Current medication at the date of event.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=4 065		Controls n=20 350		Conditional logistic regression		Cases n=1 102		Controls n=5 510		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Current medication at the date of event												
No medication	662	16.3	4 577	22.5	0.51 (0.46-0.57)	0.48 (0.43-0.54)	252	22.9	1 949	35.4	0.29 (0.23-0.37)	0.28 (0.22-0.36)
Monotherapy with quetiapine	49	1.2	145	0.7	1.26 (0.9-1.75)	0.69 (0.47-1.02)	12	1.1	34	0.6	0.83 (0.42-1.66)	0.57 (0.27-1.23)
Combination with quetiapine	313	7.7	457	2.2	2.57 (2.19-3.01)	1.61 (1.34-1.94)	38	3.4	69	1.3	1.37 (0.88-2.15)	1.16 (0.71-1.90)
Monotherapy with other antidepressants	1 314	32.3	5 021	24.7	0.63 (0.58-0.68)	0.64 (0.59-0.71)	145	13.2	350	6.4	0.50 (0.40-0.62)	0.53 (0.42-0.67)
Combination with other antidepressants	1 727	42.5	10 125	49.8	Ref=1		655	59.4	3 108	56.4	Ref=1	
History of diagnoses from 1997 until index date												
Previous self-harm	1 336	32.9	1 333	6.6	7.29 (6.65-7.99)	3.30 (2.95-3.68)	354	32.1	555	10.1	4.24 (3.62-4.96)	2.66 (2.20-3.21)
Other organic, including symptomatic, mental disorder	70	1.7	190	0.9	1.87 (1.42-2.47)	1.07 (0.77-1.48)	6	0.5	48	0.9	0.62 (0.27-1.46)	0.34 (0.12-0.96)
Disorders of adult personality and behaviour	473	11.6	860	4.2	3.05 (2.70-3.44)	1.30 (1.12-1.51)	110	10.0	299	5.4	1.95 (1.54-2.45)	1.19 (0.90-1.56)
Alcohol use disorder	1 145	28.2	1 605	7.9	4.73 (4.33-5.16)	2.15 (1.93-2.40)	289	26.2	665	12.1	2.62 (2.23-3.07)	1.48 (1.22-1.78)
Other substance use disorder	952	23.4	1 301	6.4	4.58 (4.17-5.04)	1.85 (1.64-2.08)	209	19.0	362	6.6	3.40 (2.82-4.11)	1.96 (1.57-2.46)
Anxiety disorder incl. GAD	1 730	42.6	5 459	26.9	2.06 (1.92-2.22)	1.23 (1.13-1.34)	336	30.5	1 521	27.6	1.15 (1.00-1.33)	0.92 (0.79-1.08)
Number of somatic hospitalizations in the year before the index date												
0	2 626	64.6	16 911	83.2	Ref=1		771	70.0	4 537	82.3	Ref=1	
1	823	20.2	2 192	10.8	2.48 (2.26-2.71)	1.49 (1.33-1.66)	206	18.7	670	12.2	1.87 (1.57-2.23)	1.24 (1.00-1.53)
2	274	6.7	613	3.0	3.09 (2.66-3.60)	1.53 (1.27-1.84)	65	5.9	179	3.2	2.33 (1.73-3.15)	1.12 (0.78-1.61)
≥3	342	8.4	609	3.0	3.89 (3.37-4.49)	1.94 (1.62-2.33)	60	5.4	124	2.3	3.29 (2.35-4.60)	1.65 (1.10-2.48)
Number of somatic hospitalizations from 1997 until index dispensing												
0	862	21.2	7 196	35.4	Ref=1		313	28.4	2 150	39.0	Ref=1	
1	720	17.7	4 287	21.1	1.45 (1.30-1.61)	1.00 (0.89-1.13)	216	19.6	1 296	23.5	1.18 (0.98-1.42)	0.86 (0.70-1.06)
2	608	15.0	2 805	13.8	1.95 (1.74-2.18)	1.19 (1.05-1.35)	159	14.4	772	14.0	1.50 (1.22-1.86)	1.06 (0.84-1.35)
≥3	1 875	46.1	6 037	29.7	2.92 (2.66-3.21)	1.18 (1.05-1.32)	414	37.6	1 292	23.4	2.49 (2.09-2.96)	1.25 (1.01-1.56)
Number of hospitalizations for MDD in the year before the index date												
0	3 485	85.7	19 667	96.8	Ref=1		722	65.5	4 632	84.1	Ref=1	
1	412	10.1	533	2.6	4.38 (3.83-5.02)	2.04 (1.65-2.51)	317	28.8	791	14.4	2.62 (2.25-3.06)	1.50 (1.09-2.05)
2	127	3.1	98	0.5	7.20 (5.50-9.41)	2.55 (1.75-3.73)	52	4.7	74	1.3	4.76 (3.29-6.88)	2.51 (1.45-4.35)
≥3	41	1.0	27	0.1	8.75 (5.36-14.3)	2.09 (1.09-4.00)	11	1.0	13	0.2	6.29 (2.79-14.19)	2.33 (0.81-6.69)
Number of hospitalizations for MDD from 1997 until index dispensing												
0	3 048	75.0	18 865	92.8	Ref=1		312	28.3	895	16.2	Ref=1	
1	580	14.3	1 054	5.2	3.50 (3.13-3.91)	1.58 (1.33-1.86)	88	8.0	162	2.9	2.43 (2.08-2.84)	1.38 (1.01-1.88)
2	230	5.7	247	1.2	5.79 (4.81-6.98)	1.58 (1.21-2.05)	65	5.9	94	1.7	4.00 (3.03-5.28)	1.37 (0.88-2.12)
≥3	207	5.1	159	0.8	8.14 (6.57-10.08)	1.33 (0.98-1.81)	97	8.8	0	0.0	5.29 (3.77-7.40)	1.73 (1.07-2.77)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 45. Subgroup analysis of case control analysis V. All cases of *Self-harm and suicides, non-violent methods,* including patients with recorded self-harm prior to the index date. Controls matched calendar year of index dispensing, sex, age ±5 years. Exposure: Index medication.

	Cohort A Treatment change						**Cohort B** New user with MDD					
	Cases n=4 065		Controls n=20 350		Conditional logistic regression		Cases n=1 102		Controls n=5 510		Conditional logistic regression	
	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)	N	%	N	%	Crude OR (95% CI)	Adjusted OR* (95% CI)
Index medication												
Monotherapy with quetiapine	49	1.2	113	0.6	1.79 (1.24-2.58)	0.85 (0.55-1.32)	17	1.5	37	0.7	1.09 (0.57-2.09)	1.04 (0.49-2.19)
Combination with quetiapine	313	7.7	478	2.4	2.57 (2.19-3.02)	1.43 (1.18-1.73)	11	1.0	47	0.9	0.55 (0.27-1.15)	0.50 (0.22-1.12)
Monotherapy with other antidepressants	1 314	32.3	14 275	70.2	0.95 (0.87-1.02)	0.89 (0.82-0.97)	56	5.1	133	2.4	0.45 (0.33-0.62)	0.66 (0.46-0.95)
Combination with other antidepressants	1 727	42.5	5 459	26.9	Ref=1		1 018	92.4	5 293	96.1	Ref=1	
History of diagnoses from 1997 until index date												
Previous self-harm	1 336	32.9	1 333	6.6	7.29 (6.65-7.99)	3.32 (2.98-3.70)	354	32.1	555	10.1	4.24 (3.62-4.96)	2.54 (2.11-3.06)
Other organic, including symptomatic, mental disorder	70	1.7	190	0.9	1.87 (1.42-2.47)	1.12 (0.81-1.55)	6	0.5	48	0.9	0.62 (0.27-1.46)	0.33 (0.12-0.91)
Disorders of adult personality and behaviour	473	11.6	860	4.2	3.05 (2.70-3.44)	1.33 (1.14-1.54)	110	10.0	299	5.4	1.95 (1.54-2.45)	1.15 (0.88-1.51)
Alcohol use disorder	1 145	28.2	1 605	7.9	4.73 (4.33-5.16)	2.10 (1.88-2.33)	289	26.2	665	12.1	2.62 (2.23-3.07)	1.48 (1.23-1.78)
Other substance use disorder	952	23.4	1 301	6.4	4.58 (4.17-5.04)	1.81 (1.61-2.04)	209	19.0	362	6.6	3.40 (2.82-4.11)	1.88 (1.51-2.34)
Anxiety disorder incl. GAD	1 730	42.6	5 459	26.9	2.06 (1.92-2.22)	1.26 (1.16-1.37)	336	30.5	1 521	27.6	1.15 (1.00-1.33)	0.93 (0.79-1.09)
Number of somatic hospitalizations in the year before index date												
0	2 626	64.6	16 911	83.2	Ref=1		771	70.0	4 537	82.3	Ref=1	
1	823	20.2	2 192	10.8	2.48 (2.26-2.71)	1.47 (1.32-1.64)	206	18.7	670	12.2	1.87 (1.57-2.23)	1.22 (0.99-1.50)
2	274	6.7	613	3.0	3.09 (2.66-3.60)	1.55 (1.29-1.86)	65	5.9	179	3.2	2.33 (1.73-3.15)	1.17 (0.82-1.67)
≥3	342	8.4	609	3.0	3.89 (3.37-4.49)	2.00 (1.67-2.39)	60	5.4	124	2.3	3.29 (2.35-4.60)	1.66 (1.11-2.47)
Number of somatic hospitalizations from 1997 until index date												
0	862	21.2	7 196	35.4	Ref=1		313	28.4	2 150	39.0	Ref=1	
1	720	17.7	4 287	21.1	1.45 (1.30-1.61)	1.01 (0.90-1.13)	216	19.6	1 296	23.5	1.18 (0.98-1.42)	0.89 (0.73-1.09)
2	608	15.0	2 805	13.8	1.95 (1.74-2.18)	1.17 (1.03-1.33)	159	14.4	772	14.0	1.50 (1.22-1.86)	1.08 (0.86-1.37)
≥3	1 875	46.1	6 037	29.7	2.92 (2.66-3.21)	1.19 (1.06-1.33)	414	37.6	1 292	23.4	2.49 (2.09-2.96)	1.26 (1.01-1.56)
Number of hospitalizations for MDD in the year before index date												
0	3 485	85.7	19 667	96.8	Ref=1		722	65.5	4 632	84.1	Ref=1	
1	412	10.1	533	2.6	4.38 (3.83-5.02)	2.01 (1.63-2.47)	317	28.8	791	14.4	2.62 (2.25-3.06)	1.56 (1.15-2.13)
2	127	3.1	98	0.5	7.20 (5.50-9.41)	2.61 (1.79-3.80)	52	4.7	74	1.3	4.76 (3.29-6.88)	2.61 (1.53-4.46)
≥3	41	1.0	27	0.1	8.75 (5.36-14.3)	2.12 (1.11-4.03)	11	1.0	13	0.2	6.29 (2.79-14.19)	2.84 (1.02-7.95)
Number of hospitalizations for MDD from 1997 until index date												
0	3 048	75.0	18 865	92.8	Ref=1		312	28.3	895	16.2	Ref=1	
1	580	14.3	1 054	5.2	3.50 (3.13-3.91)	1.61 (1.37-1.90)	88	8.0	162	2.9	2.43 (2.08-2.84)	1.36 (1.00-1.84)
2	230	5.7	247	1.2	5.79 (4.81-6.98)	1.63 (1.25-2.11)	65	5.9	94	1.7	4.00 (3.03-5.28)	1.38 (0.90-2.12)
≥3	207	5.1	159	0.8	8.14 (6.57-10.08)	1.38 (1.02-1.88)	97	8.8	0	0.0	5.29 (3.77-7.40)	1.72 (1.08-2.74)

*adjusted for full pre-specified model, see sections 9.4.3, 9.4.4 and appendix 5 for details on modelling

Table 46. Change in estimates in case-control analysis I-VII after exclusion of patients on Quetiapine IR at date of event from current treatment. Adjusted for the same variables as in tables 16, 19, 22, 25, 28, 30, 33 and 36.

	Cohort A Treatment change	
	Total cohort	Cohort without patients on quetiapine IR
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Death all causes		
No medication	0.96 (0.90-1.02)	0.96 (0.9-1.02)
Monotherapy with quetiapine	1.37 (0.99-1.89)	1.52 (0.71-3.24)
Combination with quetiapine	1.31 (1.12-1.54)	1.33 (0.96-1.84)
Monotherapy with other antidepressants	0.88 (0.84-0.92)	0.88 (0.84-0.92)
Combination with other antidepressants	Ref=1	Ref=1
Acute myocardial infarction		
No medication	1.02 (0.88-1.19)	1.03 (0.88-1.19)
Monotherapy with other antidepressants	0.93 (0.83-1.05)	0.94 (0.83-1.05)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	1.04 (0.70-1.53)	1.11 (0.53-2.33)
Stroke		
No medication	0.90 (0.8-1.03)	0.90 (0.79-1.02)
Monotherapy with other antidepressants	0.89 (0.81-0.98)	0.88 (0.80-0.97)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	1.25 (0.93-1.68)	1.02 (0.57-1.81)
Diabetes mellitus		
No medication	0.77 (0.68-0.86)	0.77 (0.68-0.86)
Monotherapy with other antidepressants	0.78 (0.71-0.86)	0.78 (0.71-0.86)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	0.88 (0.65-1.18)	1.28 (0.83-1.99)
Self-harm and suicides all cases		
No medication	0.31 (0.25-0.38)	0.52 (0.47-0.58)
Monotherapy with quetiapine	0.72 (0.39-1.33)	0.79 (0.45-1.38)
Combination with quetiapine	0.99 (0.65-1.52)	1.56 (1.22-1.98)
Monotherapy with other antidepressants	0.54 (0.44-0.65)	0.66 (0.61-0.71)
Combination with other antidepressants	Ref=1	Ref=1
Self-harm and suicides, no previous diagnosis of self-harm		
No medication	0.52 (0.47-0.58)	0.51 (0.45-0.57)
Monotherapy with quetiapine	1.02 (0.68-1.53)	0.69 (0.34-1.38)
Combination with quetiapine	1.52 (1.26-1.84)	1.51 (1.12-2.03)
Monotherapy with other antidepressants	0.64 (0.59-0.7)	0.61 (0.56-0.67)
Combination with other antidepressants	Ref=1	Ref=1
Extrapyramidal disorders		
No medication	0.70 (0.49-0.99)	0.70 (0.49-0.99)
Monotherapy with other antidepressants	1.05 (0.80-1.37)	1.06 (0.81-1.38)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	7.26 (4.42-11.91)	5.63 (2.48-12.81)
Somnolence		
No medication	0.70 (0.52-0.93)	0.82 (0.64-1.07)
Monotherapy with quetiapine	1.52 (0.53-4.33)	1.84 (0.19-18.12)
Combination with quetiapine	2.41 (1.42-4.11)	1.14 (0.42-3.13)
Monotherapy with other antidepressants	0.86 (0.69-1.07)	1.17 (0.94-1.47)
Combination with other antidepressants	Ref=1	Ref=1

Table 47. Change in estimates in case-control analysis I-VII after exclusion of patients who start Quetiapine IR. Exposure at index medication. Adjusted for the same variables as in table 17, 20, 23, 26, 29, 31, 34 and 37.

	Cohort A Treatment change	
	Total cohort	Cohort without patients on quetiapine IR
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Death all causes		
Monotherapy with quetiapine	1.69 (1.18-2.42)	1.43 (0.63-3.24)
Combination with quetiapine	1.25 (1.05-1.48)	1.14 (0.81-1.61)
Monotherapy with other antidepressants	0.89 (0.85-0.94)	0.90 (0.85-0.94)
Combination with other antidepressants	Ref=1	
Acute myocardial infarction		
Monotherapy with other antidepressants	0.98 (0.87-1.10)	0.98 (0.87-1.10)
Combination with other antidepressants	Ref=1	
Quetiapine monotherapy or combination	0.89 (0.59-1.34)	0.89 (0.43-1.84)
Stroke		
Monotherapy with other antidepressants	1.01 (0.92-1.11)	1.01 (0.92-1.11)
Combination with other antidepressants	Ref=1	
Quetiapine monotherapy or combination	1.39 (1.01-1.89)	0.66 (0.32-1.34)
Diabetes mellitus		
Monotherapy with other antidepressants	0.89 (0.81-0.97)	0.89 (0.81-0.98)
Combination with other antidepressants	Ref=1	
Quetiapine monotherapy or combination	0.75 (0.54-1.03)	0.75 (0.45-1.26)
Self-harm and suicides all cases		
Monotherapy with quetiapine	1.61 (1.03-2.54)	0.82 (0.48-1.40)
Combination with quetiapine	1.15 (0.94-1.41)	1.39 (1.09-1.77)
Monotherapy with other antidepressants	0.87 (0.8-0.94)	0.86 (0.80-0.93)
Combination with other antidepressants	Ref=1	
Self-harm and suicides subsample no previous diagnosis of self-harm		
Monotherapy with quetiapine	2.47 (1.64-3.70)	1.23 (0.63-2.37)
Combination with quetiapine	1.72 (1.43-2.08)	1.20 (0.89-1.60)
Monotherapy with other antidepressants	0.90 (0.83-0.97)	0.87 (0.80-0.94)
Combination with other antidepressants	Ref=1	Ref=1
Extrapyramidal disorders		
Monotherapy with other antidepressants	0.98 (0.77-1.26)	0.98 (0.76-1.26)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	4.76 (3.00-7.55)	2.8 (1.31-6.02)
Somnolence		
Monotherapy with other antidepressants	1.08 (0.87-1.34)	1.07 (0.86-1.33)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine monotherapy or combination	2.90 (1.78-4.72)	2.42 (1.12-5.23)

Appendix 2. Psychiatric diagnosis groups

Psychiatric diagnoses	ICD 10*	ATC**
Excluded		
Bipolar disorder	F30-F31	
Dementia	F00-F03, G30, F051, G311, F10.7A	
Schizophrenia	F20	
Other delusional and psychotic disorders	F21-F29	
Mood stabilizing medication		N05AN01 N03AX09 N03AG01 N03AF01
Included		
MDD	F32-F33	
Other psychiatric diagnoses	F00-F99 excl. previous groups	
Mood disorder excluding MDD and bipolar disorder	F34-F39	
Other organic, including symptomatic, mental disorders	F04-F09, Excl. F051	
Alcohol use disorder	F10	
Other substance use disorder	F11-F19	
Anxiety disorder incl. GAD	F40-F41	
OCD, stress-related and somatoform disorders	F42-F48	
Behavioural syndromes associated with physiological disturbances and physical factors	F50-F59	
Disorders of adult personality and behaviour	F60-F69	
Disorders of psychological development; Behavioural and emotional disorders with onset usually occurring in childhood and adolescence; Unspecified mental disorder	F80-F99	
Separate groups		
Generalized anxiety disorder (GAD)	F41.1	
Self-harm*** Self-harm violent method Self-harm non-violent method	X60-X84, Y10- Y34 X70-X84, Y20-Y34 X60-X69, Y10-Y19	

*International Statistical Classification of Diseases and Related Health problems, Tenth Revision, Swedish version (ICD10-s)
** Anatomic Therapeutic Chemical classification system
*** In ICD10 Chapter XX external causes, here included among psychiatric diagnoses.

Appendix 3. Charlson comorbidity groups

Charlson comorbidity groups	ICD 10*
Cancer	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96, C97
Cerebrovascular disease	G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, H340
Congestive heart failure	I43, I50, I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429, P290
Chronic pulmonary disease	J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, I278, I279, J684, J701, J703
Dementia	excluded
Diabetes with complications	E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147
Diabetes without complications	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149
AIDS/HIV	B20, B21, B22, B24
Metastatic carcinoma	C77, C78, C79, C80
Myocardial infarction (MI)	I21, I22, I252
Mild liver disease	B18, K73, K74, K700, K701, K702, K703, K709, K717, K713, K714, K715, K760, K762, K763, K764, K768, K769, Z944
Moderate or severe liver disease	K704, K711, K721, K729, K765, K766, K767, I850, I859, I864, I982
Paraplegia and hemiplegia	G81, G82, G041, G114, G801, G802, G830, G831, G832, G833, G834, G839
Peptic ulcer disease	K25, K26, K27, K28
Peripheral vascular disease	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
Renal disease	N18, N19, N052, N053, N054, N055, N056, N057, N250, I120, I131, N032, N033, N034, N035, N036, N037, Z490, Z491, Z492, Z940, Z992
Rheumatic disease	M05, M32, M33, M34, M06, M315, M351, M353, M360
Outside the Charlson groups	
Ischemic heart disease (IHD) excluding MI	I20, I24, I25

*International Statistical Classification of Diseases and Related Health problems, Tenth Revision, Swedish version (ICD10-s)

Appendix 4. ICD and ATC codes

ICD 10* codes (diagnoses) and ATC* codes (medications) used to identify outcome events and comorbidities.

	ICD 10*	ATC**
Outcome events		
Acute myocardial infarction	ICD-10 I21	
Stroke	I60-I69	
Diabetes mellitus	E11-E13-E14	A10 antidiabetics
Extrapyramidal disorders	G21 secondary parkinsonism	N04AA01 trihexyfenidyl
	G24.0 drug-induced dystonia	N04AA02 biperiden
Somnolence	R40	
Self-harm and suicide	X60-X84 intentional self-harm	
	Y10-Y34 undetermined intent	
Death	All causes	
Comorbidities		
Ischemic heart disease other than myocardial infarction	I20, I24, I25	B01AC06 Low dose ASA C01DA Nitrates
Transient cerebral ischemic attacks	G45.9	
Peripheral arterial disease including extra cerebral, non-coronary arterial thromboembolism	I70-I79	
Hypertension	I10, I11, I12, I13, I15	C02 Antihypertensives C03 Diuretics C04 Peripheral vasodilators C07 Beta blocking agents C08 Calcium channel blockers C09 Agents acting on the renin-angiotensin system
Hyperlipidemia	E78	C10 Lipid modifying agents
Alcohol abuse	F10	
Substance abuse	F11-F19	
Obesity	E66	

*International Statistical Classification of Diseases and Related Health problems, Tenth Revision, Swedish version (ICD10)
** Anatomic Therapeutic Chemical classification system

Appendix 5. Supplementary tables concerning model building

Table 16

	Pre-specified Full model			**Extended model**			**Significant model** after backwards elimination from extended		
	df	Wald $\chi 2$	p-value	df	Wald $\chi 2$	p-value	df	Wald $\chi 2$	p-value
Cohort A									
Type 3 Analysis of Effects									
Current medication at the date of event	4	50.24	<.0001	4	53.60	<.0001	4	53.75	<.0001
Charlson Comorbidity Score	3	1227.93	<.0001	3	1162.09	<.0001	3	1161.73	<.0001
History of alcohol use disorder since 1997	1	75.92	<.0001	1	90.66	<.0001	1	91.85	<.0001
History of other substance use disorder since 1997	1	35.26	<.0001	1	43.28	<.0001	1	43.80	<.0001
Number of somatic hospitalizations in the year before	3	3.90	0.27	3	8.56	0.04	3	13.93	0.003
Number of somatic hospitalizations from 1997	3	1.04	0.79	3	0.81	0.85			
Number of hospitalizations for MDD in the year before	3	1099.73	<.0001	3	719.47	<.0001	3	719.63	<.0001
Number of hospitalizations for MDD since 1997	3	101.10	<.0001	3	95.12	<.0001	3	95.38	<.0001
First prescriber				3	327.36	<.0001	3	327.62	<.0001
Adjusted estimates									
Current medication at the date of event									
No medication	0.97 (0.91-1.03)			0.96 (0.90-1.02)			0.95 (0.90-1.02)		
Monotherapy with quetiapine	1.38 (1.00-1.90)			1.37 (0.99-1.89)			1.37 (1.00-1.89)		
Combination with quetiapine	1.31 (1.12-1.54)			1.31 (1.12-1.54)			1.33 (1.13-1.56)		
Monotherapy with other antidepressants	0.89 (0.85-0.93)			0.88 (0.84-0.92)			0.88 (0.84-0.92)		
Combination with other antidepressants	Ref=1			Ref=1			Ref=1		

Cohort B	**Pre-specified Full model**			**Extended model**			**Significant model** after backwards elimination from extended		
	df	Wald $\chi 2$	p-value						
Type 3 Analysis of Effects									
Current medication at the date of event	4	5.89	0.21	4	6.14	0.1891	4	6.28	0.18
Charlson Comorbidity Score	3	19.97	0.0002	3	19.75	0.0002	3	23.98	<.0001
History of alcohol use disorder since 1997	1	6.08	0.014	1	6.27	0.0123	1	6.17	0.01
History of other substance use disorder since 1997	1	5.81	0.016	1	7.48	0.0062	1	8.05	0.00
Number of somatic hospitalizations in the year before	3	2.21	0.53	3	3.23	0.3579	3	34.59	<.0001
Number of somatic hospitalizations from 1997	3	1.44	0.70	3	1.45	0.6943	-		
Number of hospitalizations for MDD in the year before	3	43.71	<.0001	3	26.45	<.0001	3	11.88	0.01
Number of hospitalizations for MDD since 1997	3	2.57	0.46	3	2.50	0.4759	-		
First prescriber				3	14.76	0.002	3	14.81	0.002
Adjusted estimates									
Current medication at the date of event									
No medication	0.75 (0.53-1.05)			0.74 (0.53-1.04)			0.73 (0.52-1.03)		
Monotherapy with quetiapine	1.73 (0.45-6.65)			1.73 (0.45-6.66)			1.71 (0.45-6.52)		
Combination with quetiapine	1.16 (0.47-2.89)			1.22 (0.49-3.04)			1.18 (0.48-2.92)		
Monotherapy with other antidepressants	0.75 (0.55-1.02)			0.75 (0.55-1.02)			0.74 (0.55-1.01)		
Combination with other antidepressants	Ref=1			Ref=1			Ref=1		

Table 17

	Pre-specified Full model			**Extended model**			**Significant model** after backwards elimination from extended		
	df	Wald $\chi 2$	p-value	df	Wald $\chi 2$	p-value	df	Wald $\chi 2$	p-value
Cohort A									
Type 3 Analysis of Effects									
Index medication	3	35.22	<.0001	3	38.26	<.0001	3	38.35	<.0001
Charlson Comorbidity Score	3	1227.65	<.0001	3	1162.17	<.0001	3	1161.64	<.0001
History of alcohol use disorder since 1997	1	75.73	<.0001	1	90.41	<.0001	1	91.93	<.0001
History of other substance use disorder since 1997	1	35.50	<.0001	1	43.61	<.0001	1	44.31	<.0001
Number of somatic hospitalizations in the year before	3	3.96	0.27	3	8.58	0.04	3	730.34	<.0001
Number of somatic hospitalizations from 1997	3	0.85	0.84	3	0.87	0.83			
Number of hospitalizations for MDD in the year before	3	1112.37	<.0001	3	730.31	<.0001	3	96.82	<.0001
Number of hospitalizations for MDD since 1997	3	102.48	<.0001	3	96.46	<.0001	3	14.62	0.002
First prescriber				3	327.23	<.0001	3	327.25	<.0001
Adjusted estimates									
Index medication									
Monotherapy with quetiapine	1.72 (1.20-2.45)			1.69 (1.18-2.42)			1.71 (1.19-2.44)		
Combination with quetiapine	1.24 (1.05-1.47)			1.25 (1.05-1.48)			1.26 (1.06-1.50)		
Monotherapy with other antidepressants	0.90 (0.86-0.95)			0.89 (0.85-0.94)			0.89 (0.85-0.94)		
Combination with other antidepressants	Ref=1			Ref=1			Ref=1		

	Pre-specified Full model			**Extended model**			**Significant model** after backwards elimination from extended		
Cohort B	df	Wald $\chi 2$	p-value						
Type 3 Analysis of Effects									
Index medication	3	0.87	0.83	3	0.97	0.8091	3	0.89	0.83
Charlson Comorbidity Score	3	19.79	0.0002	3	19.61	0.0002	3	23.86	<.0001
History of alcohol use disorder since 1997	1	6.00	0.01	1	6.22	0.0126	1	6.08	0.01
History of other substance use disorder since 1997	1	6.06	0.01	1	7.77	0.0053	1	8.33	0.004
Number of somatic hospitalizations in the year before	3	2.12	0.55	3	3.13	0.3717	3	35.61	<.0001
Number of somatic hospitalizations from 1997	3	1.52	0.68	3	1.54	0.672			
Number of hospitalizations for MDD in the year before	3	44.94	<.0001	3	27.24	<.0001	3	11.84	0.01
Number of hospitalizations for MDD since 1997	3	2.67	0.45	3	2.60	0.4577			
First prescriber				3	14.60	0.0022	3	14.63	0.00
Adjusted estimates									
Index medication									
Monotherapy with quetiapine,	1.30 (0.47-3.62)			1.39 (0.50-3.86)			1.37 (0.50-3.79)		
Combination with quetiapine	1.17 (0.37-3.66)			1.14 (0.36-3.59)			1.15 (0.37-3.57)		
Monotherapy with other antidepressants	0.92 (0.61-1.37)			0.93 (0.62-1.39)			0.93 (0.62-1.39)		
Combination with other antidepressants	Ref=1			Ref=1			Ref=1		

Table 19

Cohort A	**Pre-specified Full model**			**Significant Model** After backwards elimination		
Type 3 Analysis of Effects	df	Wald $\chi 2$	p-value	Df	Wald $\chi 2$	p-value
Current medication at the date of event	4	2.58	0.63	4	2.58	0.631
Alcohol use disorder	1	4.34	0.04	1	4.54	0.033
Cerebrovascular Disease	1	2.01	0.16	-		
Congestive Heart Failure	1	1.30	0.25	-		
Diabetes with complications	1	5.51	0.02	1	5.81	0.016
Diabetes without complications	1	4.18	0.04	1	4.85	0.028
Paraplegia and Hemiplegia	1	1.22	0.27	-		
Peripheral Vascular Disease	1	0.92	0.34	-		
Renal Disease	1	2.05	0.15	-		
IHD other than MI	1	35.95	<.0001	1	36.44	<.0001
Low dose ASA or antianginal drug use	1	21.90	<.0001	1	25.27	<.0001
Hypertension diagnosis or antihypertensive drug use	1	22.05	<.0001	1	23.98	<.0001
Hyperlipidemia diagnosis or lipid modifying agent use	1	0.07	0.79	-		
Charlson Comorbidity Score	3	46.99	<.0001	3	69.25	<.0001
Number of somatic hospitalizations in the year before	3	12.26	0.01	3	15.03	0.002
Number of somatic hospitalizations from 1997	3	0.74	0.86	-		
Number of hospitalizations for MDD in the year before	2	3.71	0.16	-		
Number of hospitalizations for MDD since 1997	2	1.25	0.53	-		
Estimates						
Current medication at the date of event						
No medication	1.01 (0.87-1.18)			1.02 (0.88-1.19)		
Monotherapy with quetiapine	1.31 (0.54-3.20)			1.25 (0.51-3.09)		
Combination with quetiapine	0.98 (0.64-1.51)			0.99 (0.65-1.51)		
Monotherapy with other antidepressants	0.93 (0.83-1.05)			0.93 (0.83-1.05)		
Combination with other antidepressants	Ref=1			Ref=1		

Table 20

Cohort A	Pre-specified Full model			Significant model After backwards elimination		
Type 3 Analysis of Effects	df	Wald $\chi 2$	p-value	df	Wald $\chi 2$	p-value
Index medication	2	0.46	0.79	2	0.46	0.79
Alcohol use disorder	1	4.60	0.03	1	4.88	0.03
Cerebrovascular Disease	1	1.99	0.16	-		
Congestive Heart Failure	1	1.29	0.26	-		
Diabetes with complications	1	5.46	0.02	1	5.74	0.02
Diabetes without complications	1	4.36	0.04	1	5.04	0.02
Paraplegia and Hemiplegia	1	1.26	0.26	1	36.35	<.0001
Peripheral Vascular Disease	1	0.95	0.33	1	25.06	<.0001
Renal Disease	1	2.02	0.16	-		
IHD other than MI	1	35.80	<.0001	1	24.12	<.0001
Low dose ASA or antianginal drug use	1	21.73	<.0001	3	69.32	<.0001
Hypertension diagnosis or antihypertensive drug use	1	22.14	<.0001	3	15.16	0.002
Hyperlipidemia diagnosis or lipid modifying agent use	1	0.06	0.80	-		
Charlson Comorbidity Score	3	46.99	<.0001	3	69.32	<.0001
Number of somatic hospitalizations in the year before	3	12.33	0.01	3	15.16	0.002
Number of somatic hospitalizations from 1997	3	0.75	0.86	-		
Number of hospitalizations for MDD in the year before	2	3.73	0.15	-		
Number of hospitalizations for MDD since 1997	2	1.29	0.52	-		
Estimates						
Index medication						
Monotherapy with other antidepressants	0.98 (0.87-1.10)			0.98 (0.87-1.1)		
Combination with other antidepressants	Ref=1			Ref=1		
Quetiapine Monotherapy or combination	0.93 (0.62-1.40)			0.89 (0.59-1.33)		

Table 22

Cohort A	Pre-specified			Significant model After backwards elimination		
Type 3 Analysis of Effects	Full model			From extended		
Current medication at the date of event	4	9.98	0.041	4	10.64	0.031
Alcohol use disorder	1	26.92	<.0001	1	27.96	<.0001
Cerebrovascular Disease (excl. Stroke)	1	0.59	0.44			
Congestive Heart Failure	1	0.01	0.91			
Diabetes with complications	1	7.73	0.01	1	8.62	0.003
Diabetes without complications	1	1.34	0.25			
Myocardial Infarction	1	0.45	0.50			
Peripheral Vascular Disease	1	0.29	0.59			
Renal Disease	1	0.03	0.87			
IHD other than MI	1	17.12	<.0001	1	16.82	<.0001
Low dose ASA or antianginal drug use	1	48.45	<.0001	1	49.76	<.0001
Hypertension diagnosis or antihypertensive drug use	1	38.88	<.0001	1	39.19	<.0001
Hyperlipidemia diagnosis or lipid modifying agent use	1	5.95	0.015	1	5.77	0.016
Charlson Comorbidity Score	3	40.28	<.0001	3	82.01	<.0001
Number of somatic hospitalizations in the year before	3	11.08	0.011	3	11.31	0.01
Number of somatic hospitalizations from 1997	3	31.81	<.0001	3	31.77	<.0001
Number of hospitalizations for MDD in the year before	2	0.81	0.67			
Number of hospitalizations for MDD since 1997	3	1.82	0.61			
Estimates						
Current medication at the date of event						
No medication	0.90 (0.80-1.02)			0.90 (0.79-1.02)		
Monotherapy with quetiapine	1.21 (0.60-2.45)			1.20 (0.59-2.43)		
Combination with quetiapine	1.26 (0.91-1.74)			1.26 (0.92-1.75)		
Monotherapy with other antidepressants	0.89 (0.81-0.98)			0.89 (0.81-0.98)		
Combination with other antidepressants	Ref=1			Ref=1		

Cohort B	Pre-specified Full model			Significant model After backwards elimination		
	df	Wald $\chi 2$	p-value	df	Wald $\chi 2$	p-value
Type 3 Analysis of Effects						
Current medication at the date of event	3	6.09	0.107	3	5.4	0.14
Alcohol use disorder	1	0.37	0.54			
Cerebrovascular Disease (excl. Stroke)	1	0.35	0.55			
Congestive Heart Failure	1	3.68	0.06	1	9.9	0.002
Diabetes with complications	1	0.09	0.76			
Diabetes without complications	1	0.04	0.84			
Myocardial Infarction	1	0.28	0.59			
Peripheral Vascular Disease	1	2.62	0.11			
Low dose ASA or antianginal drug use	1	4.26	0.04	1	8.2	0.004
Hypertension diagnosis or antihypertensive drug use	1	0.26	0.61			
Hyperlipidemia diagnosis or lipid modifying agent use	1	0.21	0.65			
Charlson Comorbidity Score	2	0.21	0.90			
Number of somatic hospitalizations in the year before	3	3.37	0.34			

Number of somatic hospitalizations from 1997	3	4.23	0.24
Number of hospitalizations for MDD in the year before	2	5.62	0.06
Number of hospitalizations for MDD since 1997	3	4.01	0.26

Estimates		
Current medication at the date of event		
No medication	0.63 (0.33-1.19)	0.64 (0.34-1.22)
Monotherapy with other antidepressants	0.67 (0.36-1.21)	0.65 (0.36-1.19)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine Monotherapy or combination	2.03 (0.60-6.86)	2.04 (0.60-6.9)

Table 23

Cohort A

Type 3 Analysis of Effects	**Pre-specified Full model**			**Significant Model** After backwards elimination		
	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value
Index medication	3	4.40	0.22	3	4.34	0.23
Alcohol use disorder	1	26.78	<.0001	1	28.02	<.0001
Cerebrovascular Disease (excl. Stroke)	1	0.64	0.42			
Congestive Heart Failure	1	0.00	0.95			
Diabetes with complications	1	7.67	0.01	1	8.57	0.003
Diabetes without complications	1	1.38	0.24	1	17.01	<.0001
Myocardial Infarction	1	0.45	0.50			
Peripheral Vascular Disease	1	0.38	0.54			
Renal Disease	1	0.04	0.84			
IHD other than MI	1	17.33	<.0001	1	49.38	<.0001
Low dose ASA or antianginal drug use	1	48.04	<.0001	1	39.50	<.0001
Hypertension diagnosis or antihypertensive drug use	1	39.16	<.0001	1	5.77	0.016
Hyperlipidemia diagnosis or lipid modifying agent use	1	5.93	0.01	3	82.63	<.0001
Charlson Comorbidity Score	3	40.36	<.0001	3	11.58	0.009
Number of somatic hospitalizations in the year before	3	11.25	0.01	3	32.11	<.0001
Number of somatic hospitalizations from 1997	3	32.07	<.0001			
Number of hospitalizations for MDD in the year before	2	0.89	0.64			
Number of hospitalizations for MDD since 1997	3	2.39	0.50			

Estimates		
Index medication		
Monotherapy with quetiapine,	1.53 (0.71-3.29)	1.57 (0.73-3.36)
Combination with quetiapine	1.37 (0.97-1.92)	1.34 (0.96-1.88)
Monotherapy with other antidepressants	1.01 (0.92-1.11)	1.01 (0.92-1.10)
Combination with other antidepressants	Ref=1	Ref=1

Table 25

Cohort A

Type 3 Analysis of Effects	**Pre-specified Full model**			**Significant model** After backwards elimination		
	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value
Current medication at the date of event	4	28.73	<.0001	4	28.90	<.0001
Alcohol use disorder	1	0.18	0.68			
Cerebrovascular Disease	1	6.75	0.01	1	5.78	0.016
Congestive Heart Failure	1	1.08	0.30			
Myocardial Infarction	1	7.05	0.008	1	7.04	0.008
Paraplegia and Hemiplegia	1	3.99	0.046	1	3.86	0.0495
Peripheral Vascular Disease	1	1.74	0.19			
Renal Disease	1	0.63	0.43			
Obesity	1	75.76	<.0001	1	76.43	<.0001
Charlson Comorbidity Score	3	16.14	0.001	3	20.25	0.0002
Number of somatic hospitalizations in the year before	3	1.88	0.60			
Number of somatic hospitalizations from 1997	3	13.26	0.004	3	16.66	0.0008
Number of hospitalizations for MDD in the year before	2	8.38	0.015			
Number of hospitalizations for MDD since 1997	3	3.5127	0.32			

Estimates		
Current medication at the date of event		
No medication	0.76 (0.68-0.86)	0.90 (0.79-1.02)
Monotherapy with quetiapine	0.86 (0.45-1.66)	1.20 (0.59-2.43)
Combination with quetiapine	0.87 (0.62-1.22)	1.26 (0.92-1.75)
Monotherapy with other antidepressants	0.78 (0.71-0.86)	0.89 (0.81-0.98)
Combination with other antidepressants	Ref=1	Ref=1

Cohort B

Type 3 Analysis of Effects	**Significant**

	Pre-specified Full model			**model** After backwards elimination		
	df	Wald $\chi 2$	p-value	df	Wald $\chi 2$	p-value
Current medication at the date of event	3	2.50	0.48	3	2.73	0.435
Alcohol use disorder	1	0.25	0.62			
Cerebrovascular Disease	1	0.01	0.92			
Congestive Heart Failure	1	1.85	0.17			
Myocardial Infarction	1	1.49	0.22			
Paraplegia and Hemiplegia	1	0.80	0.37			
Peripheral Vascular Disease	1	6.15	0.01	1	5.87	0.015
Renal Disease	1	0.11	0.74			
Obesity	1	18.62	<.0001	1	21.28	<.0001
Charlson Comorbidity Score	2	7.44	0.02	2	10.69	0.005
Number of somatic hospitalizations in the year before	3	0.79	0.85			
Number of somatic hospitalizations from 1997	3	2.79	0.43			
Number of hospitalizations for MDD in the year before	2	2.08	0.35			
Number of hospitalizations for MDD since 1997	3	5.18	0.16	3	13.27	0.004
Estimates						
Current medication at the date of event						
No medication	0.88 (0.52-1.48)			0.88 (0.53-1.48)		
Quetiapine Monotherapy or combination	0.77 (0.46-1.27)			0.75 (0.46-1.24)		
Monotherapy with other antidepressants	Ref=1			Ref=1		
Combination with other antidepressants	1.38 (0.53-3.56)			1.33 (0.53-3.31)		

Table 26

Cohort A

	Pre-specified Full model			**Significant Model** After backwards elimination		
	df	Wald $\chi 2$	p-value	df	Wald $\chi 2$	p-value
Type 3 Analysis of Effects						
Index medication	3	8.97	0.03	3	9.3328	0.0252
Alcohol use disorder	1	0.09	0.76			
Cerebrovascular Disease	1	6.72	0.01	1	6.2311	0.0126
Congestive Heart Failure	1	0.95	0.33			
Myocardial Infarction	1	6.70	0.01	1	6.8493	0.0089
Paraplegia and Hemiplegia	1	3.73	0.05			
Peripheral Vascular Disease	1	1.63	0.20			
Renal Disease	1	0.65	0.42			
Obesity	1	78.58	<.0001	1	80.0118	<.0001
Charlson Comorbidity Score	3	16.80	0.0008	3	24.9715	<.0001
Number of somatic hospitalizations in the year before	3	2.13	0.55			
Number of somatic hospitalizations from 1997	3	13.47	0.004	3	17.302	0.0006
Number of hospitalizations for MDD in the year before	2	8.59	0.01	2	6.695	0.0352
Number of hospitalizations for MDD since 1997	3	3.08	0.38			
Estimates						
Index medication						
Monotherapy with quetiapine,	0.65 (0.25-1.65)			0.63 (0.25-1.61)		
Combination with quetiapine	0.76 (0.54-1.07)			0.75 (0.53-1.05)		
Monotherapy with other antidepressants	0.89 (0.80-0.97)			0.88 (0.80-0.97)		
Combination with other antidepressants	Ref=1			Ref=1		

Cohort B

	Pre-specified Full model			**Significant model** After backwards elimination		
Type 3 Analysis of Effects	df	Wald $\chi 2$	p-value	df	Wald $\chi 2$	p-value
Index medication	2	0.84	0.66	2.00	0.34	0.84
Alcohol use disorder	1	0.31	0.58			
Cerebrovascular Disease	1	0.03	0.87			
Congestive Heart Failure	1	1.82	0.18			
Myocardial Infarction	1	1.34	0.25			
Paraplegia and Hemiplegia	1	0.73	0.39	1.00	5.97	0.01
Peripheral Vascular Disease	1	6.08	0.01			
Renal Disease	1	0.11	0.74	1.00	21.08	<.0001
Obesity	1	18.47	<.0001	2.00	10.96	0.004
Charlson Comorbidity Score	2	7.72	0.02			
Number of somatic hospitalizations in the year before	3	1.12	0.77			
Number of somatic hospitalizations from 1997	3	3.11	0.37			
Number of hospitalizations for MDD in the year before	2	2.60	0.27			
Number of hospitalizations for MDD since 1997	3	5.62	0.13	3.00	13.57	0.004
Estimates						

Index medication		
Monotherapy with other antidepressants	0.98 (0.5-1.95)	0.95 (0.5-1.81)
Combination with other antidepressants	Ref=1	Ref=1
Quetiapine Monotherapy or combination	1.59 (0.48-5.27)	1.14 (0.37-3.52)

Table 28

Type 3 Analysis of Effects	**Extended Full model**			**Pre-specified Full model**			**Significant Model** after backwards elimination		
	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value
Current medication at the date of event	4	288.95	<.0001	4	153.97	<.0001	4	289.13	<.0001
Previous self-harm	1	665.61	<.0001	1	257.78	<.0001	1	694.99	<.0001
Other organic, including symptomatic, mental disorder	1	0.61	0.43	1	5.60	0.018			
Disorders of adult personality and behavior	1	19.06	<.0001	1	9.51	0.002	1	19.26	<.0001
Alcohol use disorder	1	202.54	<.0001	1	35.20	<.0001	1	208.47	<.0001
Other substance use disorder	1	134.22	<.0001	1	52.45	<.0001	1	139.59	<.0001
Anxiety disorder incl. GAD	1	38.47	<.0001	1	0.03	0.866	1	38.80	<.0001
Number of somatic hospitalizations in the year before	3	111.57	<.0001				3	159.33	<.0001
Number of somatic hospitalizations from 1997	3	4.91	0.18						
Number of hospitalizations for MDD in the year before	3	70.34	<.0001				3	68.61	<.0001
Number of hospitalizations for MDD since 1997	3	31.50	<.0001				3	33.14	<.0001

Estimates			
Current medication at the date of event			
No medication	0.31 (0.25-0.38)	0.52 (0.47-0.57)	0.31 (0.25-0.38)
Monotherapy with quetiapine	0.72 (0.39-1.33)	0.76 (0.56-1.05)	0.69 (0.37-1.29)
Combination with quetiapine	0.99 (0.65-1.52)	1.66 (1.42-1.93)	0.99 (0.65-1.52)
Monotherapy with other antidepressants	0.54 (0.44-0.65)	0.64 (0.59-0.69)	0.54 (0.44-0.65)
Combination with other antidepressants	Ref=1	Ref=1	Ref=1

Cohort B

Type 3 Analysis of Effects	**Extended Full model**			**Pre-specified Full model**			**Significant model** after backwards elimination		
	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value
Current medication at the date of event	4	135.07	<.0001	4	153.97	<.0001	4	135.44	<.0001
Previous self-harm	1	162.71	<.0001	1	257.78	<.0001	1	181.83	<.0001
Other organic, including symptomatic, mental disorder	1	5.78	0.02	1	5.60	0.02	1	5.79	0.02
Disorders of adult personality and behavior	1	5.64	0.02	1	9.51	0.002	1	7.15	0.01
Alcohol use disorder	1	23.55	<.0001	1	35.20	<.0001	1	24.79	<.0001
Other substance use disorder	1	40.93	<.0001	1	52.45	<.0001	1	42.23	<.0001
Anxiety disorder incl. GAD	1	0.04	0.84	1	0.03	0.87			
Number of somatic hospitalizations in the year before	3	8.13	0.04						
Number of somatic hospitalizations from 1997	3	7.52	0.06				3	14.07	0.003
Number of hospitalizations for MDD in the year before	3	26.45	<.0001				3	133.59	<.0001
Number of hospitalizations for MDD since 1997	3	2.15	0.54						

Estimates			
Current medication at the date of event			
No medication	0.33 (0.27-0.40)	0.29 (0.24-0.36)	0.31 (0.25-0.38)
Monotherapy with quetiapine	1.06 (0.60-1.85)	0.69 (0.37-1.27)	0.72 (0.39-1.33)
Combination with quetiapine	1.17 (0.79-1.72)	1.09 (0.72-1.65)	0.98 (0.64-1.5)
Monotherapy with other antidepressants	0.51 (0.43-0.62)	0.51 (0.42-0.62)	0.54 (0.44-0.66)
Combination with other antidepressants	Ref=1	Ref=1	Ref=1

Table 29

Type 3 Analysis of Effects	**Extended Full model**			**Pre-specified Full model**			**Significant model** after backwards elimination		
	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value
Index medication	3	22.61	<.0001	3	37.75	<.0001	3	22.27	<.0001
Previous self-harm	1	677.89	<.0001	1	1088.52	<.0001	1	707.87	<.0001
Other organic, including symptomatic, mental disorder	1	1.12	0.29	1	4.17	0.04	1	21.47	<.0001
Disorders of adult personality and behavior	1	21.12	<.0001	1	28.83	<.0001	1	202.38	<.0001

Alcohol use disorder	1	196.81	<.0001	1	264.08	<.0001	1	138.86	<.0001
Other substance use disorder	1	133.24	<.0001	1	183.29	<.0001	1	51.04	<.0001
Anxiety disorder incl. GAD	1	50.63	<.0001	1	66.19	<.0001	3	172.21	<.0001
Number of somatic hospitalizations in the year before	3	119.95	<.0001				3	69.72	<.0001
Number of somatic hospitalizations from 1997	3	4.89	0.18				3	39.02	<.0001
Number of hospitalizations for MDD in the year before	3	71.64	<.0001						
Number of hospitalizations for MDD since 1997	3	37.05	<.0001						

Estimates

Index medication			
Monotherapy with quetiapine	1.61 (1.03-2.54)	1.72 (1.12-2.64)	1.61 (1.02-2.52)
Combination with quetiapine	1.15 (0.94-1.41)	1.38 (1.14-1.69)	1.15 (0.93-1.41)
Monotherapy with other antidepressants	0.87 (0.80-0.94)	0.87 (0.80-0.95)	0.87 (0.80-0.95)
Combination with other antidepressants	Ref=1	Ref=1	Ref=1

Cohort B

Type 3 Analysis of Effects

	Extended Full model			**Pre-specified Full model**			**Significant Model** after backwards elimination		
	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value			
Index medication	3	7.33	0.06	3	21.83	<.0001	3	7.76	0.05
Previous self-harm	1	156.87	<.0001	1	255.33	<.0001	1	178.64	<.0001
Other organic, including symptomatic, mental disorder	1	5.81	0.02	1	5.63	0.02	1	5.81	0.02
Disorders of adult personality and behavior	1	3.73	0.05	1	6.88	0.01	1	5.00	0.03
Alcohol use disorder	1	23.60	<.0001	1	34.80	<.0001	1	27.28	<.0001
Other substance use disorder	1	37.07	<.0001	1	48.31	<.0001	1	41.45	<.0001
Anxiety disorder incl. GAD	1	0.05	0.83	1	0.05	0.82			
Number of somatic hospitalizations in the year before	3	8.10	0.04				3	13.80	0.003
Number of somatic hospitalizations from 1997	3	6.31	0.10						
Number of hospitalizations for MDD in the year before	3	26.99	<.0001				3	127.92	<.0001
Number of hospitalizations for MDD since 1997	3	2.62	0.45						

Estimates

Index medication			
Monotherapy with quetiapine	1.21 (0.55-2.65)	0.78 (0.37-1.66)	1.24 (0.57-2.71)
Combination with quetiapine	0.93 (0.43-1.97)	0.94 (0.46-1.95)	0.98 (0.46-2.08)
Monotherapy with other antidepressants	0.95 (0.65-1.39)	0.65 (0.45-0.93)	0.96 (0.66-1.4)
Combination with other antidepressants	Ref=1	Ref=1	Ref=1

Table 30

Type 3 Analysis of Effects

	Extended Full model			**Pre-specified Full model**			**Significant Model** after backwards elimination		
	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value	Df	Wald $\chi2$	p-value
Current medication at the date of event	4	253.91	<.0001	4	284.15	<.0001	4	225.963	<.0001
Other organic, including symptomatic, mental disorder	1	2.25	0.13	1	3.56	0.06			
Disorders of adult personality and behavior	1	8.18	0.004	1	13.73	0.0002	1	6.21	0.01
Alcohol use disorder	1	187.09	<.0001	1	273.62	<.0001	1	207.33	<.0001
Other substance use disorder	1	139.75	<.0001	1	207.16	<.0001	1	159.11	<.0001
Anxiety disorder incl. GAD	1	24.49	<.0001	1	40.27	<.0001	1	29.45	<.0001
Number of somatic hospitalizations in the year before	3	58.63	<.0001				3	63.30	<.0001
Number of somatic hospitalizations from 1997	3	8.04	0.05				3	11.92	0.01
Number of hospitalizations for MDD in the year before	3	50.66	<.0001				2	82.42	<.0001
Number of hospitalizations for MDD since 1997	3	31.61	<.0001				3	27.14	<.0001

Estimates

Current medication at the date of event			
No medication	0.52 (0.47-0.58)	0.51 (0.45-0.56)	0.52 (0.47-0.58)
Monotherapy with quetiapine	1.02 (0.68-1.53)	1.01 (0.68-1.51)	1.02 (0.68-1.53)
Combination with quetiapine	1.52 (1.26-1.84)	1.69 (1.41-2.03)	1.52 (1.26-1.83)
Monotherapy with other antidepressants	0.64 (0.59-0.7)	0.61 (0.56-0.67)	0.64 (0.59-0.70)
Combination with other antidepressants	Ref=1	Ref=1	Ref=1

Cohort B

Type 3 Analysis of Effects

	Extended Full model			**Pre-specified Full model**			**Significant model** after backwards elimination		
	Df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value
Current medication at the date of event	4	104.85	<.0001	4	125.33	<.0001	4	103.043	<.0001
Other organic, including symptomatic, mental disorder	1	6.01	0.01	1	7.90	0.00			

Disorders of adult personality and behavior	1	13.28	0.00	1	28.61	<.0001	1	16.0518	<.0001
Alcohol use disorder	1	26.33	<.0001	1	36.28	<.0001	1	33.6385	<.0001
Other substance use disorder	1	0.33	0.57	1	0.31	0.58			
Anxiety disorder incl. GAD	3	3.04	0.39						
Number of somatic hospitalizations in the year before	3	5.42	0.14						
Number of somatic hospitalizations from 1997	2	11.75	0.00				2	113.765	<.0001
Number of hospitalizations for MDD in the year before	3	4.87	0.18						
Number of hospitalizations for MDD since 1997	4	104.85	<.0001	4	125.33	<.0001	4	103.043	<.0001

Estimates

Current medication at the date of event			
No medication	0.52 (0.47-0.58)	0.29 (0.22-0.36)	0.31 (0.24-0.40)
Monotherapy with quetiapine	1.02 (0.68-1.53)	0.53 (0.23-1.18)	0.55 (0.24-1.25)
Combination with quetiapine	1.52 (1.26-1.83)	1.30 (0.82-2.07)	1.19 (0.74-1.91)
Monotherapy with other antidepressants	0.64 (0.59-0.70)	0.51 (0.41-0.63)	0.55 (0.44-0.69)
Combination with other antidepressants	Ref=1	Ref=1	Ref=1

Table 31

Cohort A

Type 3 Analysis of Effects

	Extended Full model			**Pre-specified Full model**			**Significant model** after backwards elimination		
	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value
Index medication	3	19.94	0.0002	3	7.27	0.06	3	17.68	0.0005
Other organic, including symptomatic, mental disorder	1	3.30	0.069	1	2.09	0.15			
Disorders of adult personality and behavior	1	9.06	0.003	1	5.43	0.0197	1	6.60	0.010
Alcohol use disorder	1	183.31	<.0001	1	26.97	<.0001	1	209.47	<.0001
Other substance use disorder	1	140.80	<.0001	1	30.62	<.0001	1	163.92	<.0001
Anxiety disorder incl. GAD	1	33.66	<.0001	1	0.12	0.73	1	35.98	<.0001
Number of somatic hospitalizations in the year before	3	62.72	<.0001				3	112.02	<.0001
Number of somatic hospitalizations from 1997	3	7.12	0.068						
Number of hospitalizations for MDD in the year before	3	49.36	<.0001				2	82.76	<.0001
Number of hospitalizations for MDD since 1997	3	37.23	<.0001				3	34.31	<.0001

Estimates

Index medication			
Monotherapy with quetiapine	1.61 (1.03-2.54)	0.78 (0.37-1.66)	1.59 (1.01-2.50)
Combination with quetiapine	1.15 (0.94-1.41)	0.94 (0.46-1.95)	1.14 (0.93-1.40)
Monotherapy with other antidepressants	0.87 (0.80-0.94)	0.65 (0.45-0.93)	0.87 (0.80-0.95)
Combination with other antidepressants	Ref=1	Ref=1	Ref=1

Cohort B

Type 3 Analysis of Effects

	Extended Full model			**Pre-specified Full model**			**Significant model** after backwards elimination		
	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value	df	Wald $\chi2$	p-value
Index medication									
Other organic, including symptomatic, mental disorder	3	0.60	0.90	3	7.44	0.06	3	0.59	0.90
Disorders of adult personality and behavior	1	3.74	0.05	1	5.29	0.02	1	4.89	0.03
Alcohol use disorder	1	12.00	0.0005	1	27.28	<.0001	1	13.36	0.0003
Other substance use disorder	1	21.93	<.0001	1	30.85	<.0001	1	23.94	<.0001
Anxiety disorder incl. GAD	1	0.10	0.75	1	0.11	0.74			
Number of somatic hospitalizations in the year before	3	2.96	0.40						
Number of somatic hospitalizations from 1997	3	5.58	0.13				3	8.94	0.03
Number of hospitalizations for MDD in the year before	2	13.15	0.00				2	125.65	<.0001
Number of hospitalizations for MDD since 1997	3	5.13	0.16						

Estimates

Index medication			
Monotherapy with quetiapine	1.21 (0.55-2.64)	1.52 (0.74-3.14)	1.21 (0.56-2.64)
Combination with quetiapine	0.89 (0.42-1.89)	1.23 (0.63-2.40)	0.91 (0.43-1.93)
Monotherapy with other antidepressants	0.94 (0.65-1.38)	1.26 (0.86-1.85)	0.95 (0.65-1.38)
Combination with other antidepressants	Ref=1	Ref=1	Ref=1

Appendix 6. List of standalone documents

None.

EU RMP Part VII Annex 10	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	12
Data lock point for this module	2 December 2016

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® AND SEROQUEL XR®)

Part VII ANNEX 10 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL® and SEROQUEL XR®
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

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1. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES

Additional Risk Minimisation Measures are in place for EPS, Somnolence, Metabolic and Nutritional Disorders (weight gain, lipid changes, hyperglycemia, diabetes mellitus, metabolic risk factors), off-label use and misdosing. Core elements of educational materials prepared for any of these risks are outlined in this Annex. The core elements include information on drug administration in patients with bipolar depression, monitoring of metabolic parameters to reduce the risk of metabolic adverse events and Seroquel XR use in add-on treatment of Major Depressive Disorder (MDD). The core document also includes safety messages regarding EPS and somnolence, in order to optimise the benefit-risk profile of patients taking SEROQUEL and Seroquel XR.

Local materials suitable for distribution to prescribing physicians can be derived from the core elements for approval nationally by national health authorities. Because of different legal environments and healthcare systems in EU member states, local AstraZeneca subsidiaries will implement activities according to local regulations while still maintaining the core principles of the risk minimization plan. This includes the details of the distribution plan for educational materials, which shall be agreed upon with the National Competent Authorities in each CMS where the product is marketed.

1.1 Core Elements of Educational Materials

1.1.1 Core Elements related to Extrapyramidal symptoms (EPS)/Somnolence

Educational pieces related to EPS/somnolence are required to include the following key elements to appropriately manage the benefit:risk profile:

EPS

- In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder. (Section 4.4. “Special Precautions and Warnings for Use”)

- EPS is classified as an adverse event that occurs very commonly (this means in greater than 10% of patients (Section 4.8. “Undesirable Effects”)

Somnolence

- The term somnolence refers to all adverse events potentially associated with somnolence (these are somnolence, sedation, lethargy and sluggishness)

- Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation. In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of

mild to moderate intensity (Section 4.4. "Special Precautions and Warnings for Use")

- Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered. (Section 4.4. "Special Precautions and Warnings for Use")

- Somnolence is classified as an adverse event that occurs very commonly (this means in greater than 10% of patients (Section 4.8. "Undesirable Effects")

1.1.2 Core Elements related to metabolic parameters

Educational pieces related to metabolic parameters are required to include the following key elements to appropriately manage the benefit:risk profile:

When treating patients with Seroquel IR/ Seroquel XR it is important to monitor metabolic parameters as described in the following sections of the SmPC:

SmPC Section 4.4. "Special Warnings and Precautions":

Weight

- Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines.*

Hyperglycaemia:

- Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines.

- Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids:

- Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine. Lipid changes should be managed as clinically appropriate.

Metabolic Risk

- Given the observed changes in weight, blood glucose (see hyperglycemia) and lipids seen in clinical studies, there may be possible worsening of the metabolic risk profile in individual patients, which should be managed as clinically appropriate.

*Antipsychotic guidelines relevant to [insert country name] include the following. Prescribers are encouraged to check for updates to relevant guidelines on a regular basis.

[insert guideline citation(s) as required during national phase]

1.1.3 Core Elements related to add-on treatment of major depressive disorder (MDD)

Educational pieces related to major depressive disorder (MDD) are required to include the following key elements to ensure appropriate use and thereby manage the benefit:risk profile:

- Seroquel XR should only be prescribed together with an antidepressant.
- Seroquel XR is not licensed as a monotherapy for major depressive disorder.
- As per section 4.1 of the SmPC, Seroquel XR is indicated as add-on treatment of major depressive episodes in patients with MDD who have had sub-optimal response to antidepressant monotherapy
- Please also note that Seroquel IR is not indicated for the treatment of MDD.

1.1.4 Core Elements related to drug administration in patients with bipolar depression

Educational pieces related to bipolar depression are required to include the following key elements to ensure appropriate dosing and thereby manage the benefit:risk profile.

- Dosing should be initiated according to the following titration schedule so that the recommended daily dose of 300 mg is reached by Day 4: 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3, and 300 mg on Day 4
- Quetiapine should be administered once daily at bedtime.
- Depending on patient response, the daily dose may be titrated up to 600 mg daily.
- The recommended dosing and titration schedule is applicable to both IR and XR formulations.

EU RMP Part VII Annex 11	
Drug Substance	Quetiapine fumarate
Version Number of RMP when last updated	12
Data lock point for this module	12 June 2013

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® AND SEROQUEL XR®)

Part VII ANNEX 11 - MOCK-UP OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES – NOT APPLICABLE

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL® and SEROQUEL XR®
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

AstraZeneca

EU RMP Part VII Annex 12

Drug Substance	Quetiapine fumarate
Version Number of RMP /PRMP when last updated	13
Data lock point for this module	12 June 2014

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR QUETIAPINE FUMARATE (SEROQUEL® AND SEROQUEL XR®)

Part VII ANNEX 12 - OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

Active substance(s) (INN or common name)	Quetiapine fumarate
Product(s) concerned (brand names(s))	SEROQUEL® and SEROQUEL XR®
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

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1. OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

1.1 Exposure

1.1.1 All trials

Table 1 Exposure to quetiapine by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
Population grouping	Total exposure in patient years	M	F	White	Black	Asian	Hispanic	Other[c]	<18	18-65	>65	>74
By indication												
Peds Schizophrenia[a]	100.2 (N=220)	58.1 (126)	42.1 (94)	58.5 (131)	13.7 (29)	20.7 (42)	5.8 (13)	1.5 (5)	100.2 (220)	NA	NA	NA
Schizophrenia[a]	3593.5 (N=10055)	2299.9 (6601)	1293.6 (3454)	2562.0 (6256)	502.1 (1748)	322.3 (1321)	138.6 (409)	68.5 (321)	NA	3558.1 (9986)	35.4 (69)	7.3 (19)
Bipolar depression	557.7 (N=2242)	233.5 (924)	324.2 (1318)	389.0 (1550)	76.7 (294)	60.0 (258)	24.1 (82)	8.0 (58)	NA	557.7 (2242)	NA	NA
BP mania/mixed	2368.0 (N=7117)	1096.2 (3386)	1271.7 (3731)	1857.0 (5302)	158.1 (670)	161.6 (601)	121.2 (319)	70.0 (225)	NA	2320.2 (7009)	47.7 (108)	4.3 (12)
Peds BP mania/mixed	104.5 (N=381)	62.4 (207)	42.0 (174)	82.6 (277)	14.6 (66)	0.5 (4)	4.2 (17)	2.6 (17)	104.5 (381)	NA	NA	NA
MDD	820.1 (N=3796)	283.0 (1355)	537.2 (2441)	696.1 (3153)	89.5 (454)	9.8 (66)	18.7 (94)	6.1 (29)	NA	795.0 (3629)	25.2 (167)	4.9 (36)
GAD	612.5 (N=3226)	213.2 (1129)	399.3 (2097)	523.1 (2759)	45.3 (262)	30.1 (118)	9.9 (55)	4.1 (32)	NA	577.3 (3002)	35.1 (224)	5.4 (37)
Mixed	0.9 (N=86)	0.7 (61)	0.3 (25)	0.5 (48)	0.2 (20)	0.0 (1)	0.2 (16)	0.0 (1)	NA	0.9 (86)	NA	NA
Other[b]	430.9 (N=1453)	167.2 (729)	263.7 (724)	372.2 (1069)	37.6 (210)	1.3 (31)	13.9 (122)	5.9 (21)	NA	55.4 (556)	375.6 (897)	265.8 (722)

By age group												
Pediatric <18	204.6 (N=601)	120.5 (333)	84.1 (268)	141.0 (408)	28.3 (95)	21.2 (46)	10.0 (30)	4.1 (22)	204.6 (601)	NA	NA	NA
Adult 18-65	7864.6 (N=26510)	4108.5 (13704)	3756.2 (12806)	5931.9 (18811)	876.2 (3581)	580.3 (2371)	315.0 (1062)	161.2 (685)	NA	7864.6 (26510)	NA	NA
Elderly >65	519.0 (N=1465)	185.1 (481)	333.9 (984)	468.0 (1326)	33.1 (77)	4.8 (25)	11.6 (35)	1.4 (2)	NA	NA	519.0 (1465)	NA
Elderly >74	287.6 (N=826)	84.2 (239)	203.3 (587)	259.2 (751)	20.2 (48)	0.6 (3)	7.5 (24)	NA	NA	NA	NA	287.6 (826)
Total	**8588.3 (N=28576)**	**4414.1 (14518)**	**4174.2 (14058)**	**6541.0 (20545)**	**937.6 (3753)**	**606.3 (2442)**	**336.7 (1127)**	**166.7 (709)**	**204.6 (601)**	**7864.6 (26510)**	**519.0 (1465)**	**287.6 (826)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem.SAS. Data version: V27. User: [redacted] 2014-07-21 13:18.

Table 2 Adult(>17 years old) exposure to quetiapine by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Otherb**	**18-65**	**>65**	**>74**
By indication											
Schizophrenia[a]	3593.5 (N=10055)	2299.9 (6601)	1293.6 (3454)	2562.0 (6256)	502.1 (1748)	322.3 (1321)	138.6 (409)	68.5 (321)	3558.1 (9986)	35.4 (69)	7.3 (19)
Bipolar depression	557.7 (N=2242)	233.5 (924)	324.2 (1318)	389.0 (1550)	76.7 (294)	60.0 (258)	24.1 (82)	8.0 (58)	557.7 (2242)	NA	NA
BP mania/mixed	2368.0 (N=7117)	1096.2 (3386)	1271.7 (3731)	1857.0 (5302)	158.1 (670)	161.6 (601)	121.2 (319)	70.0 (225)	2320.2 (7009)	47.7 (108)	4.3 (12)
MDD	820.1 (N=3796)	283.0 (1355)	537.2 (2441)	696.1 (3153)	89.5 (454)	9.8 (66)	18.7 (94)	6.1 (29)	795.0 (3629)	25.2 (167)	4.9 (36)
GAD	612.5 (N=3226)	213.2 (1129)	399.3 (2097)	523.1 (2759)	45.3 (262)	30.1 (118)	9.9 (55)	4.1 (32)	577.3 (3002)	35.1 (224)	5.4 (37)
Mixed	0.9 (N=86)	0.7 (61)	0.3 (25)	0.5 (48)	0.2 (20)	0.0 (1)	0.2 (16)	0.0 (1)	0.9 (86)	NA	NA
Other[b]	430.9 (N=1453)	167.2 (729)	263.7 (724)	372.2 (1069)	37.6 (210)	1.3 (31)	13.9 (122)	5.9 (21)	55.4 (556)	375.6 (897)	265.8 (722)
By age group											
Adult 18-65	7864.6 (N=26510)	4108.5 (13704)	3756.2 (12806)	5931.9 (18811)	876.2 (3581)	580.3 (2371)	315.0 (1062)	161.2 (685)	NA	NA	NA
Elderly >65	519.0 (N=1465)	185.1 (481)	333.9 (984)	468.0 (1326)	33.1 (77)	4.8 (25)	11.6 (35)	1.4 (2)	NA	NA	NA
Elderly >74	287.6 (N=826)	84.2 (239)	203.3 (587)	259.2 (751)	20.2 (48)	0.6 (3)	7.5 (24)	NA	NA	NA	NA
Total	**8383.6 (N=27975)**	**4293.6 (14185)**	**4090.0 (13790)**	**6399.9 (20137)**	**909.3 (3658)**	**585.1 (2396)**	**326.6 (1097)**	**162.6 (687)**	**7864.6 (26510)**	**519.0 (1465)**	**287.6 (826)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.

Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_adult.SAS. Data version: V27. User: [redacted] 2014-07-21 13:19.

Table 3 Exposure to quetiapine by indication and demographic characteristics in females: all studies

		Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**	**18-65**	**>65**	**>74**
By indication												
Peds Schizophrenia[a]	42.1 (N=94)	NA	42.1 (94)	26.2 (61)	5.6 (11)	7.9 (17)	1.6 (4)	0.7 (1)	42.1 (94)	NA	NA	NA
Schizophrenia[a]	1293.6 (N=3454)	NA	1293.6 (3454)	922.1 (2202)	194.0 (519)	120.7 (506)	33.1 (122)	23.7 (105)	NA	1277.0 (3422)	16.7 (32)	2.2 (9)
Bipolar depression	324.2 (N=1318)	NA	324.2 (1318)	214.5 (892)	51.8 (194)	37.6 (148)	16.0 (55)	4.3 (29)	NA	324.2 (1318)	NA	NA
BP mania/mixed	1271.7 (N=3731)	NA	1271.7 (3731)	963.6 (2735)	99.2 (388)	84.0 (281)	81.8 (198)	43.1 (129)	NA	1248.3 (3673)	23.4 (58)	2.3 (7)
Peds BP mania/mixed	42.0 (N=174)	NA	42.0 (174)	30.2 (122)	8.0 (35)	0.1 (1)	2.6 (8)	1.2 (8)	42.0 (174)	NA	NA	NA
MDD	537.2 (N=2441)	NA	537.2 (2441)	453.8 (2020)	60.3 (291)	4.3 (34)	14.1 (71)	4.7 (25)	NA	519.8 (2324)	17.4 (117)	3.3 (24)
GAD	399.3 (N=2097)	NA	399.3 (2097)	345.0 (1809)	27.9 (168)	18.7 (74)	5.3 (27)	2.4 (19)	NA	373.9 (1936)	25.3 (161)	4.2 (29)

Table 3 Exposure to quetiapine by indication and demographic characteristics in females: all studies

		Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**	**18-65**	**>65**	**>74**
Mixed	0.3 (N=25)	NA	0.3 (25)	0.1 (14)	0.1 (8)	NA	0.0 (3)	NA	NA	0.3 (25)	NA	NA
Other[b]	263.7 (N=724)	NA	263.7 (724)	234.8 (590)	19.8 (72)	0.2 (1)	8.7 (57)	0.3 (4)	NA	12.7 (108)	251.0 (616)	191.3 (518)
By age group												
Pediatric <18	84.1 (N=268)	NA	84.1 (268)	56.4 (183)	13.6 (46)	8.0 (18)	4.2 (12)	1.9 (9)	84.1 (268)	NA	NA	NA
Adult 18-65	3756.2 (N=12806)	NA	3756.2 (12806)	2831.5 (9362)	433.1 (1589)	263.0 (1036)	151.1 (509)	77.5 (310)	NA	3756.2 (12806)	NA	NA
Elderly >65	333.9 (N=984)	NA	333.9 (984)	302.5 (900)	19.9 (51)	2.5 (8)	8.1 (24)	1.0 (1)	NA	NA	333.9 (984)	NA
Elderly >74	203.3 (N=587)	NA	203.3 (587)	182.0 (533)	15.0 (36)	0.2 (1)	6.2 (17)	NA	NA	NA	NA	203.3 (587)
Total	**4174.2 (N=14058)**	**NA**	**4174.2 (14058)**	**3190.4 (10445)**	**466.6 (1686)**	**273.5 (1062)**	**163.3 (545)**	**80.3 (320)**	**84.1 (268)**	**3756.2 (12806)**	**333.9 (984)**	**203.3 (587)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_F.SAS. Data version: V27. User: [redacted] 2014-07-21 13:19.

Table 4 Exposure to Seroquel IR by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**	**18-65**	**>65**	**>74**
By indication												
Peds Schizophrenia[a]	100.2 (N=219)	58.1 (126)	42.1 (93)	58.4 (130)	13.7 (29)	20.7 (42)	5.8 (13)	1.5 (5)	100.2 (219)	NA	NA	NA
Schizophrenia[a]	3245.4 (N=7953)	2085.5 (5237)	1160.0 (2716)	2323.1 (5128)	453.4 (1318)	270.1 (859)	135.1 (366)	63.8 (282)	NA	3210.0 (7884)	35.4 (69)	7.3 (19)
Bipolar depression	522.3 (N=1958)	219.1 (807)	303.1 (1151)	377.3 (1449)	73.2 (266)	40.2 (109)	24.1 (82)	7.6 (52)	NA	522.3 (1958)	NA	NA
BP mania/mixed	2322.5 (N=6536)	1067.9 (3035)	1254.6 (3501)	1832.0 (5000)	153.8 (554)	146.2 (449)	121.2 (319)	69.3 (214)	NA	2274.8 (6428)	47.7 (108)	4.3 (12)
Peds BP mania/mixed	91.9 (N=289)	56.0 (162)	35.9 (127)	73.8 (212)	12.6 (52)	NA	4.2 (16)	1.4 (9)	91.9 (289)	NA	NA	NA
Mixed	0.2 (N=21)	0.2 (17)	0.0 (4)	0.1 (13)	0.0 (4)	NA	0.0 (4)	NA	NA	0.2 (21)	NA	NA
Other[b]	417.7 (N=1167)	159.9 (547)	257.7 (620)	362.8 (926)	35.4 (142)	1.3 (31)	12.5 (49)	5.8 (19)	NA	49.3 (337)	368.4 (830)	259.6 (666)

Table 4 Exposure to Seroquel IR by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
Population grouping	Total exposure in patient years	M	F	White	Black	Asian	Hispanic	Other[b]	<18	18-65	>65	>74
						By age group						
Pediatric <18	192.1 (N=508)	114.1 (288)	77.9 (220)	132.2 (342)	26.3 (81)	20.7 (42)	9.9 (29)	2.9 (14)	192.1 (508)	NA	NA	NA
Adult 18-65	6056.6 (N=16628)	3367.6 (9298)	2689.0 (7330)	4494.5 (11646)	682.9 (2209)	452.8 (1423)	281.3 (785)	145.1 (565)	NA	6056.6 (16628)	NA	NA
Elderly >65	451.5 (N=1007)	165.0 (345)	286.5 (662)	400.8 (870)	32.8 (75)	4.8 (25)	11.6 (35)	1.4 (2)	NA	NA	451.5 (1007)	NA
Elderly >74	271.2 (N=697)	79.3 (199)	191.9 (498)	242.8 (622)	20.2 (48)	0.6 (3)	7.5 (24)	NA	NA	NA	NA	271.2 (697)
Total	**6700.2 (N=18143)**	**3646.7 (9931)**	**3053.5 (8212)**	**5027.5 (12858)**	**742.1 (2365)**	**478.4 (1490)**	**302.9 (849)**	**149.4 (581)**	**192.1 (508)**	**6056.6 (16628)**	**451.5 (1007)**	**271.2 (697)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only immediate release quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_IR.SAS. Data version: V27. User: [redacted] 2014-07-21 13:18.

Table 5 Exposure to quetiapine by indication and demographic characteristics in males: all studies

Population grouping	Total exposure in patient years	Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
		M	F	White	Black	Asian	Hispanic	Other[b]	<18	18-65	>65	>74
By indication												
Peds Schizophrenia[a]	58.1 (N=126)	58.1 (126)	NA	32.3 (70)	8.1 (18)	12.8 (25)	4.1 (9)	0.8 (4)	58.1 (126)	NA	NA	NA
Schizophrenia[a]	2299.9 (N=6601)	2299.9 (6601)	NA	1639.9 (4054)	308.0 (1229)	201.6 (815)	105.5 (287)	44.9 (216)	NA	2281.1 (6564)	18.7 (37)	5.1 (10)
Bipolar depression	233.5 (N=924)	233.5 (924)	NA	174.5 (658)	24.9 (100)	22.3 (110)	8.0 (27)	3.7 (29)	NA	233.5 (924)	NA	NA
BP mania/mixed	1096.2 (N=3386)	1096.2 (3386)	NA	893.4 (2567)	58.9 (282)	77.6 (320)	39.5 (121)	26.9 (96)	NA	1072.0 (3336)	24.3 (50)	2.0 (5)
Peds BP mania/mixed	62.4 (N=207)	62.4 (207)	NA	52.4 (155)	6.6 (31)	0.4 (3)	1.7 (9)	1.4 (9)	62.4 (207)	NA	NA	NA
MDD	283.0 (N=1355)	283.0 (1355)	NA	242.3 (1133)	29.2 (163)	5.5 (32)	4.6 (23)	1.4 (4)	NA	275.2 (1305)	7.8 (50)	1.6 (12)
GAD	213.2 (N=1129)	213.2 (1129)	NA	178.0 (950)	17.4 (94)	11.4 (44)	4.6 (28)	1.7 (13)	NA	203.4 (1066)	9.8 (63)	1.1 (8)
Mixed	0.7 (N=61)	0.7 (61)	NA	0.4 (34)	0.1 (12)	0.0 (1)	0.1 (13)	0.0 (1)	NA	0.7 (61)	NA	NA
Other[b]	167.2 (N=729)	167.2 (729)	NA	137.5 (479)	17.8 (138)	1.1 (30)	5.2 (65)	5.6 (17)	NA	42.7 (448)	124.5 (281)	74.5 (204)

Table 5 Exposure to quetiapine by indication and demographic characteristics in males: all studies

		Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
Population grouping	Total exposure in patient years	M	F	White	Black	Asian	Hispanic	Other[b]	<18	18-65	>65	>74
						By age group						
Pediatric <18	120.5 (N=333)	120.5 (333)	NA	84.6 (225)	14.7 (49)	13.2 (28)	5.8 (18)	2.2 (13)	120.5 (333)	NA	NA	NA
Adult 18-65	4108.5 (N=13704)	4108.5 (13704)	NA	3100.4 (9449)	443.1 (1992)	317.2 (1335)	164.0 (553)	83.7 (375)	NA	4108.5 (13704)	NA	NA
Elderly >65	185.1 (N=481)	185.1 (481)	NA	165.5 (426)	13.2 (26)	2.4 (17)	3.5 (11)	0.5 (1)	NA	NA	185.1 (481)	NA
Elderly >74	84.2 (N=239)	84.2 (239)	NA	77.2 (218)	5.3 (12)	0.4 (2)	1.3 (7)	NA	NA	NA	NA	84.2 (239)
Total	4414.1 (N=14518)	4414.1 (14518)	NA	3350.6 (10100)	471.0 (2067)	332.8 (1380)	173.3 (582)	86.4 (389)	120.5 (333)	4108.5 (13704)	185.1 (481)	84.2 (239)

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_M.SAS. Data version: V27. User: [redacted] 2014-07-21 13:19.

Table 6 Pediatric (<18 years old) exposure to quetiapine by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<13**	**13-17**	**<18**
By indication											
Peds Schizophrenia[a]	100.2 (N=220)	58.1 (126)	42.1 (94)	58.5 (131)	13.7 (29)	20.7 (42)	5.8 (13)	1.5 (5)	1.2 (2)	99.0 (218)	100.2 (220)
Peds BP mania/mixed	104.5 (N=381)	62.4 (207)	42.0 (174)	82.6 (277)	14.6 (66)	0.5 (4)	4.2 (17)	2.6 (17)	46.9 (152)	57.5 (229)	104.5 (381)
By age group											
Pediatric <13	48.1 (N=154)	30.5 (86)	17.6 (68)	39.5 (119)	7.6 (28)	NA	0.6 (3)	0.5 (4)	NA	NA	NA
Pediatric 13-17	156.5 (N=447)	90.0 (247)	66.5 (200)	101.6 (289)	20.7 (67)	21.2 (46)	9.4 (27)	3.6 (18)	NA	NA	NA
Pediatric <18	204.6 (N=601)	120.5 (333)	84.1 (268)	141.0 (408)	28.3 (95)	21.2 (46)	10.0 (30)	4.1 (22)	NA	NA	NA
Total	**204.6 (N=601)**	**120.5 (333)**	**84.1 (268)**	**141.0 (408)**	**28.3 (95)**	**21.2 (46)**	**10.0 (30)**	**4.1 (22)**	**48.1 (154)**	**156.5 (447)**	**204.6 (601)**

a Includes schizoaffective disorders.
b Inlcudes races of 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Note: Patient's age is given at the start of the clinical trial.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ped.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 7 Female pediatric (<18 years old) exposure to quetiapine by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<13**	**13-17**	**<18**
By indication											
Peds Schizophrenia[a]	42.1 (N=94)	NA	42.1 (94)	26.2 (61)	5.6 (11)	7.9 (17)	1.6 (4)	0.7 (1)	NA	42.1 (94)	42.1 (94)
Peds BP mania/mixed	42.0 (N=174)	NA	42.0 (174)	30.2 (122)	8.0 (35)	0.1 (1)	2.6 (8)	1.2 (8)	17.6 (68)	24.4 (106)	42.0 (174)
By age group											
Pediatric <13	17.6 (N=68)	NA	17.6 (68)	13.3 (49)	4.0 (16)	NA	0.1 (1)	0.2 (2)	NA	NA	NA
Pediatric 13-17	66.5 (N=200)	NA	66.5 (200)	43.1 (134)	9.6 (30)	8.0 (18)	4.1 (11)	1.7 (7)	NA	NA	NA
Pediatric <18	84.1 (N=268)	NA	84.1 (268)	56.4 (183)	13.6 (46)	8.0 (18)	4.2 (12)	1.9 (9)	NA	NA	NA
Total	**84.1 (N=268)**	**NA**	**84.1 (268)**	**56.4 (183)**	**13.6 (46)**	**8.0 (18)**	**4.2 (12)**	**1.9 (9)**	**17.6 (68)**	**66.5 (200)**	**84.1 (268)**

a Includes schizoaffective disorders.
b Inlcudes races of 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Note: Patient's age is given at the start of the clinical trial.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ped_F.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 8 Male Pediatric (<18 years old) exposure to quetiapine by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
Population grouping	Total exposure in patient years	M	F	White	Black	Asian	Hispanic	Other[b]	<13	13-17	<18
By indication											
Peds Schizophrenia[a]	58.1 (N=126)	58.1 (126)	NA	32.3 (70)	8.1 (18)	12.8 (25)	4.1 (9)	0.8 (4)	1.2 (2)	56.9 (124)	58.1 (126)
Peds BP mania/mixed	62.4 (N=207)	62.4 (207)	NA	52.4 (155)	6.6 (31)	0.4 (3)	1.7 (9)	1.4 (9)	29.3 (84)	33.1 (123)	62.4 (207)
By age group											
Pediatric <13	30.5 (N=86)	30.5 (86)	NA	26.1 (70)	3.6 (12)	NA	0.5 (2)	0.3 (2)	NA	NA	NA
Pediatric 13-17	90.0 (N=247)	90.0 (247)	NA	58.5 (155)	11.1 (37)	13.2 (28)	5.3 (16)	1.9 (11)	NA	NA	NA
Pediatric <18	120.5 (N=333)	120.5 (333)	NA	84.6 (225)	14.7 (49)	13.2 (28)	5.8 (18)	2.2 (13)	NA	NA	NA

Table 8 Male Pediatric (<18 years old) exposure to quetiapine by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<13**	**13-17**	**<18**
Total	**120.5 (N=333)**	**120.5 (333)**	**NA**	**84.6 (225)**	**14.7 (49)**	**13.2 (28)**	**5.8 (18)**	**2.2 (13)**	**30.5 (86)**	**90.0 (247)**	**120.5 (333)**

a Includes schizoaffective disorders.
b Inlcudes races of 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Note: Patient's age is given at the start of the clinical trial.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ped_M.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 9 Exposure to Seroquel XR by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**	**18-65**	**>65**	**>74**
						By indication						
Peds Schizophrenia[a]	0.0 (N=1)	NA	0.0 (1)	0.0 (1)	NA	NA	NA	NA	0.0 (1)	NA	NA	NA
Schizophrenia[a]	348.1 (N=2430)	214.4 (1532)	133.7 (898)	239.0 (1399)	48.7 (477)	52.2 (466)	3.5 (43)	4.7 (45)	NA	348.1 (2430)	NA	NA

Table 9 Exposure to Seroquel XR by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**	**18-65**	**>65**	**>74**
Bipolar depression	35.4 (N=284)	14.4 (117)	21.1 (167)	11.7 (101)	3.5 (28)	19.8 (149)	NA	0.5 (6)	NA	35.4 (284)	NA	NA
BP mania/mixed	45.4 (N=581)	28.3 (351)	17.1 (230)	25.0 (302)	4.3 (116)	15.5 (152)	NA	0.6 (11)	NA	45.4 (581)	NA	NA
Peds BP mania/mixed	12.5 (N=92)	6.4 (45)	6.2 (47)	8.8 (65)	2.0 (14)	0.5 (4)	0.1 (1)	1.2 (8)	12.5 (92)	NA	NA	NA
MDD	820.1 (N=3796)	283.0 (1355)	537.2 (2441)	696.1 (3153)	89.5 (454)	9.8 (66)	18.7 (94)	6.1 (29)	NA	795.0 (3629)	25.2 (167)	4.9 (36)
GAD	612.5 (N=3226)	213.2 (1129)	399.3 (2097)	523.1 (2759)	45.3 (262)	30.1 (118)	9.9 (55)	4.1 (32)	NA	577.3 (3002)	35.1 (224)	5.4 (37)
Mixed	0.7 (N=65)	0.5 (44)	0.2 (21)	0.4 (35)	0.2 (16)	0.0 (1)	0.1 (12)	0.0 (1)	NA	0.7 (65)	NA	NA
Other[b]	13.3 (N=355)	7.3 (239)	6.0 (116)	9.5 (167)	2.2 (108)	0.0 (2)	1.4 (73)	0.1 (5)	NA	6.1 (288)	7.2 (67)	6.2 (56)
By age group												
Pediatric <18	12.6 (N=93)	6.4 (45)	6.2 (48)	8.8 (66)	2.0 (14)	0.5 (4)	0.1 (1)	1.2 (8)	12.6 (93)	NA	NA	NA
Adult 18-65	1808.0 (N=10279)	740.9 (4631)	1067.2 (5648)	1437.4 (7460)	193.3 (1459)	127.4 (954)	33.7 (277)	16.1 (129)	NA	1808.0 (10279)	NA	NA

Table 9 Exposure to Seroquel XR by indication and demographic characteristics: all studies

		Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
Population grouping	**Total exposure in patient years**	**M**	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**	**18-65**	**>65**	**>74**
Elderly >65	67.5 (N=458)	20.1 (136)	47.3 (322)	67.2 (456)	0.3 (2)	NA	NA	NA	NA	NA	67.5 (458)	NA
Elderly >74	16.4 (N=129)	5.0 (40)	11.4 (89)	16.4 (129)	NA	NA	NA	NA	NA	NA	NA	16.4 (129)
Total	**1888.1 (N=10830)**	**767.4 (4812)**	**1120.7 (6018)**	**1513.5 (7982)**	**195.6 (1475)**	**127.9 (958)**	**33.8 (278)**	**17.3 (137)**	**12.6 (93)**	**1808.0 (10279)**	**67.5 (458)**	**16.4 (129)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other and Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only extended release quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_XR.SAS. Data version: V27. User: [redacted] 2014-07-21 13:18.

Table 10 Quetiapine exposure by indication and age group relative to duration of treatment: all studies

Population grouping	Quetiapine exposure in patient years by duration of exposure								
	>=1 d	>=2 wk	>=1 mo	>=3 mo	>=6 mo	>=9 mo	>=12 mo	>=24 mo	>=36 mo
By indication									
Schizophrenia[a] (n)[b]	3593.5 (10055)	3564.2 (8488)	3492.9 (7255)	2795.7 (2924)	2304.3 (1548)	2078.7 (1179)	1786.9 (855)	912.2 (288)	559.0 (140)
Bipolar depression (n)[b]	557.7 (2242)	552.4 (1950)	538.1 (1708)	333.2 (433)	297.1 (339)	230.7 (234)	101.1 (91)	NA	NA
BP mania/mixed[b] (n)[b]	2368.0 (7117)	2352.8 (6187)	2302.3 (5322)	1974.7 (3346)	1236.1 (1375)	788.6 (637)	580.3 (394)	116.1 (52)	3.1 (1)
MDD (n)[b]	820.1 (3796)	812.9 (3350)	788.9 (2943)	518.3 (955)	300.6 (341)	219.3 (213)	125.6 (107)	NA	NA
GAD (n)[b]	612.5 (3226)	605.7 (2802)	587.2 (2490)	285.2 (633)	127.1 (178)	55.5 (59)	17.2 (16)	NA	NA
Mixed (n)b	0.9 (86)	NA	NA	NA	NA	NA	NA	NA	NA
Other[c] (n)[b]	430.9 (1453)	422.5 (997)	412.0 (811)	321.6 (291)	266.2 (153)	250.3 (127)	228.6 (103)	171.8 (66)	12.9 (4)
Peds Schizophrenia[d] (n)[b]	100.2 (220)	100.0 (213)	99.2 (200)	94.0 (163)	76.6 (120)	9.2 (7)	7.7 (5)	NA	NA
Peds BP mania/mixed (n)[b]	104.5 (381)	103.0 (324)	100.3 (278)	82.1 (157)	62.0 (107)	3.7 (3)	2.7 (2)	NA	NA
By age group									
Pediatric <13 (n)[b]	48.1 (154)	47.4 (130)	46.6 (115)	40.7 (76)	31.2 (52)	3.9 (3)	3.9 (3)	NA	NA
Pediatric 13-17 (n)[b]	156.5 (447)	155.6 (407)	152.9 (363)	135.4 (244)	107.3 (175)	9.0 (7)	6.5 (4)	NA	NA
Pediatric <18 (n)[b]	204.6 (601)	203.0 (537)	199.5 (478)	176.1 (320)	138.5 (227)	12.9 (10)	10.4 (7)	NA	NA
Adult 18-65 (n)[b]	7864.6 (26510)	7793.2 (22403)	7611.9 (19285)	5871.2 (8220)	4249.9 (3767)	3362.2 (2316)	2599.7 (1456)	1022.6 (338)	563.7 (142)

Elderly >65 (n)[b]	519.0 (1465)	517.4 (1371)	509.6 (1244)	357.5 (362)	281.4 (167)	260.9 (133)	240.0 (110)	177.4 (68)	11.3 (3)
Elderly >74 (n)[b]	287.6 (826)	286.6 (769)	281.7 (687)	194.0 (187)	151.5 (79)	146.6 (71)	136.9 (60)	110.4 (43)	3.1 (1)
Total (n)[b]	**8588.3 (28576)**	**8513.5 (24311)**	**8321.0 (21007)**	**6404.8 (8902)**	**4669.8 (4161)**	**3636.1 (2459)**	**2850.1 (1573)**	**1200.1 (406)**	**575.0 (145)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dur.SAS. Data version: V27. User: [redacted]. 2014-07-21 13:20.

Table 11 Quetiapine exposure by indication and age group relative to mean daily dose: all studies

	Quetiapine exposure in patient years by mean daily dose									**Other**	
Population grouping	**<100**	**100 to 199**	**200 to 299**	**300 to 399**	**400 to 499**	**500 to 599**	**600 to 699**	**700 to 799**	**>799**	**Mean of mean daily dose(mg)**	**Mean maximum dose (mg)**
By indication											
Schizophrenia[a]	59.4 (494)	142.1 (643)	403.2 (1276)	607.5 (1851)	666.5 (1584)	728.1 (1867)	402.6 (903)	514.6 (1182)	69.6 (255)	453.1 (10055)	552.4 (10055)
Bipolar depression	0.4 (57)	1.0 (67)	362.4 (1338)	1.9 (54)	9.6 (100)	182.2 (625)	0.1 (1)	NA	NA	354.3 (2242)	408.0 (2242)
BP mania/mixed[b]	0.5 (34)	18.3 (528)	104.3 (658)	647.6 (1793)	553.1 (1334)	512.9 (1351)	237.8 (615)	262.4 (712)	31.1 (91)	456.4 (7116)	547.7 (7116)
MDD	154.4 (763)	373.2 (1778)	291.7 (1251)	0.8 (3)	NA	NA	0.1 (1)	NA	NA	167.4 (3796)	204.9 (3796)

GAD	157.2 (968)	290.8 (1482)	164.5 (776)	NA	NA	NA	NA	NA	NA	146.9 (3226)	178.2 (3226)
Mixed	0.3 (26)	0.3 (28)	0.2 (15)	0.2 (17)	NA	NA	NA	NA	NA	149.6 (86)	163.4 (86)
Other[c]	148.0 (673)	145.9 (569)	66.7 (109)	31.5 (52)	17.9 (18)	18.5 (29)	1.8 (2)	0.6 (1)	NA	137.7 (1453)	190.6 (1453)
Peds Schizophrenia[d]	0.0 (1)	0.0 (1)	1.8 (8)	10.3 (33)	13.2 (26)	18.9 (40)	27.6 (52)	28.3 (59)	NA	575.8 (220)	736.8 (220)
Peds BP mania/mixed	0.0 (4)	6.8 (59)	9.0 (59)	8.8 (41)	18.0 (81)	26.5 (67)	19.8 (40)	15.5 (30)	NA	417.4 (381)	576.8 (381)
By age group											
Pediatric	(0)	NA	(0)	NA	NA	NA	NA	NA	NA	188.7 (0)	216.7 (0)
Pediatric <13	0.0 (2)	1.8 (13)	3.5 (21)	4.8 (19)	7.1 (36)	12.9 (29)	9.4 (17)	8.7 (17)	NA	451.7 (154)	623.1 (154)
Pediatric 13-17	0.0 (3)	5.1 (47)	7.3 (46)	14.3 (55)	24.1 (71)	32.6 (78)	38.0 (75)	35.1 (72)	NA	483.6 (447)	639.6 (447)
Pediatric <18	0.0 (5)	6.8 (60)	10.8 (67)	19.1 (74)	31.2 (107)	45.5 (107)	47.4 (92)	43.8 (89)	NA	475.4 (601)	635.4 (601)
Adult 18-65	373.8 (2473)	803.6 (4520)	1302.5 (5217)	1238.3 (3702)	1211.4 (3005)	1426.9 (3851)	637.6 (1512)	770.6 (1885)	100.0 (344)	365.0 (26509)	441.3 (26509)
Elderly >65	146.4 (542)	167.9 (575)	90.5 (206)	51.1 (68)	35.8 (31)	14.8 (21)	4.7 (10)	7.0 (10)	0.8 (2)	166.0 (1465)	212.8 (1465)
Elderly >74	101.0 (413)	104.9 (324)	46.8 (59)	18.3 (19)	13.7 (9)	NA	NA	2.9 (2)	NA	129.2 (826)	168.0 (826)

Total	**520.2 (3020)**	**978.4 (5155)**	**1403.8 (5490)**	**1308.5 (3844)**	**1278.3 (3143)**	**1487.1 (3979)**	**689.8 (1614)**	**821.4 (1984)**	**100.8 (346)**	**357.2 (28575)**	**433.7 (28575)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_meandose.SAS. Data version: V27. User: [redacted]. 2014-07-21 13:21.

1.1.2 All OL and OLE trials

Table 12 Exposure to quetiapine by indication and demographic characteristics: all OL and OLE except longterm withdrawal studies

Population grouping	Total exposure in patient years	Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
		M	F	White	Black	Asian	Hispanic	Other[b]	<18	18-65	>65	>74
By indication												
Peds Schizophrenia[a]	9.2 (N=10)	3.2 (4)	6.0 (6)	2.9 (5)	6.0 (4)	0.2 (1)	NA	NA	9.2 (10)	NA	NA	NA
Schizophrenia[a]	2840.8 (N=6010)	1806.1 (3838)	1034.6 (2172)	2018.6 (3891)	399.8 (897)	251.9 (717)	118.1 (284)	52.4 (221)	NA	2807.7 (5944)	33.1 (66)	7.3 (18)
BP mania/mixed	68.0 (N=435)	51.2 (282)	16.8 (153)	46.9 (259)	0.6 (9)	17.2 (154)	1.9 (4)	1.5 (9)	NA	64.7 (433)	3.3 (2)	NA
Peds BP mania/mixed	4.6 (N=29)	4.2 (16)	0.4 (13)	4.1 (14)	0.5 (14)	NA	NA	0.0 (1)	4.6 (29)	NA	NA	NA

Other[b]	352.4 (N=754)	142.2 (394)	210.1 (360)	307.6 (622)	29.6 (83)	0.1 (4)	9.5 (34)	5.6 (11)	NA	47.9 (268)	304.5 (486)	204.7 (363)
By age group												
Pediatric <18	13.8 (N=39)	7.3 (20)	6.5 (19)	7.0 (19)	6.5 (18)	0.2 (1)	NA	0.0 (1)	13.8 (39)	NA	NA	NA
Adult 18-65	2920.3 (N=6645)	1873.6 (4309)	1046.7 (2336)	2071.3 (4302)	402.5 (940)	265.4 (855)	121.6 (307)	59.5 (241)	NA	2920.3 (6645)	NA	NA
Elderly >65	340.9 (N=554)	126.0 (205)	214.8 (349)	301.8 (470)	27.5 (49)	3.8 (20)	7.8 (15)	NA	NA	NA	340.9 (554)	NA
Elderly >74	211.9 (N=381)	63.4 (117)	148.6 (264)	190.8 (344)	16.2 (26)	0.0 (1)	4.9 (10)	NA	NA	NA	NA	211.9 (381)
Total	**3275.0 (N=7238)**	**2006.9 (4534)**	**1268.0 (2704)**	**2380.1 (4791)**	**436.5 (1007)**	**269.4 (876)**	**129.5 (322)**	**59.6 (242)**	**13.8 (39)**	**2920.3 (6645)**	**340.9 (554)**	**211.9 (381)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ol.SAS. Data version: V27. User: [redacted] 2014-07-21 13:19.

Table 13 Exposure to quetiapine by indication and demographic characteristics: all OL and OLE except long-term withdrawal studies, adults

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**									
		Sex		**Race**					**Age group**		
		M	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**18-65**	**>65**	**>74**
By indication											

Schizophrenia[a]	2840.8 (N=6010)	1806.1 (3838)	1034.6 (2172)	2018.6 (3891)	399.8 (897)	251.9 (717)	118.1 (284)	52.4 (221)	2807.7 (5944)	33.1 (66)	7.3 (18)
BP mania/mixed	68.0 (N=435)	51.2 (282)	16.8 (153)	46.9 (259)	0.6 (9)	17.2 (154)	1.9 (4)	1.5 (9)	64.7 (433)	3.3 (2)	NA
Other[b]	352.4 (N=754)	142.2 (394)	210.1 (360)	307.6 (622)	29.6 (83)	0.1 (4)	9.5 (34)	5.6 (11)	47.9 (268)	304.5 (486)	204.7 (363)
By age group											
Adult 18-65	2920.3 (N=6645)	1873.6 (4309)	1046.7 (2336)	2071.3 (4302)	402.5 (940)	265.4 (855)	121.6 (307)	59.5 (241)	2920.3 (6645)	NA	NA
Elderly >65	340.9 (N=554)	126.0 (205)	214.8 (349)	301.8 (470)	27.5 (49)	3.8 (20)	7.8 (15)	NA	NA	340.9 (554)	NA
Elderly >74	211.9 (N=381)	63.4 (117)	148.6 (264)	190.8 (344)	16.2 (26)	0.0 (1)	4.9 (10)	NA	NA	NA	211.9 (381)
Total	**3261.2 (N=7199)**	**1999.6 (4514)**	**1261.6 (2685)**	**2373.1 (4772)**	**430.0 (989)**	**269.2 (875)**	**129.5 (322)**	**59.5 (241)**	**2920.3 (6645)**	**340.9 (554)**	**211.9 (381)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ol_adult.SAS. Data version: V27. User: [redacted] 2014-07-21 13:19.

Table 14 Pedriatric (<18 years old) exposure to quetiapine by indication and demographic characteristics: all OL and OLE except longterm withdrawal studies

Population grouping	Total exposure in patient years	Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
		M	F	White	Black	Asian	hispanic	Other[b]	<13	13-17	<18
By indication											
Peds Schizophrenia[a]	9.2 (N=10)	3.2 (4)	6.0 (6)	2.9 (5)	6.0 (4)	0.2 (1)	NA	NA	1.2 (2)	8.0 (8)	9.2 (10)
Peds BP mania/mixed	4.6 (N=29)	4.2 (16)	0.4 (13)	4.1 (14)	0.5 (14)	NA	NA	0.0 (1)	3.2 (14)	1.4 (15)	4.6 (29)
By age group											
Pediatric <13	4.4 (N=16)	4.1 (10)	0.2 (6)	3.0 (9)	1.4 (7)	NA	NA	NA	NA	NA	NA
Pediatric 13-17	9.4 (N=23)	3.2 (10)	6.2 (13)	4.0 (10)	5.1 (11)	0.2 (1)	NA	0.0 (1)	NA	NA	NA
Pediatric <18	13.8 (N=39)	7.3 (20)	6.5 (19)	7.0 (19)	6.5 (18)	0.2 (1)	NA	0.0 (1)	NA	NA	NA
Total	**13.8 (N=39)**	**7.3 (20)**	**6.5 (19)**	**7.0 (19)**	**6.5 (18)**	**0.2 (1)**	**NA**	**0.0 (1)**	**4.4 (16)**	**9.4 (23)**	**13.8 (39)**

a Includes schizoaffective disorders.
b Inlcudes races of 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Note: Patient's age is given at the start of the clinical trial.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ol_ped.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 15 Quetiapine exposure by indication and age group relative to duration of treatment: all OL and OLE except longterm withdrawal studies

Population grouping	Quetiapine exposure in patient years by duration of exosure								
	>=1 d	>=2 wk	>=1 mo	>=3 mo	>=6 mo	>=9 mo	>=12 mo	>=24 mo	>=36 mo
By indication									
Schizophrenia[a]	2840.8	2827.4	2748.6	2423.9	2045.7	1874.9	1638.2	805.8	440.0
(n)[b]	(6010)	(5360)	(4177)	(2371)	(1334)	(1056)	(795)	(263)	(111)
BP mania/mixed[b]	68.0	67.0	64.6	28.4	25.6	24.3	24.3	10.5	NA
(n)[b]	(435)	(382)	(339)	(22)	(15)	(13)	(13)	(4)	
Other[c]	352.4	350.3	343.2	286.7	265.5	249.7	228.1	171.7	12.9
(n)[b]	(754)	(605)	(474)	(206)	(153)	(127)	(103)	(66)	(4)
Peds Schizophrenia[d]	9.2	9.1	9.1	8.9	8.4	8.4	7.7	NA	NA
(n)[b]	(10)	(8)	(8)	(7)	(6)	(6)	(5)		
Peds BP mania/mixed	4.6	3.7	3.7	3.7	3.7	3.7	2.7	NA	NA
(n)[b]	(29)	(3)	(3)	(3)	(3)	(3)	(2)		
By age group									
Pediatric <13	4.4	3.9	3.9	3.9	3.9	3.9	3.9	NA	NA
(n)[b]	(16)	(3)	(3)	(3)	(3)	(3)	(3)		
Pediatric 13-17	9.4	8.9	8.9	8.7	8.3	8.3	6.5	NA	NA
(n)[b]	(23)	(8)	(8)	(7)	(6)	(6)	(4)		
Pediatric <18	13.8	12.8	12.8	12.6	12.2	12.2	10.4	NA	NA
(n)[b]	(39)	(11)	(11)	(10)	(9)	(9)	(7)		
Adult 18-65	2920.3	2904.4	2818.2	2457.9	2083.8	1908.9	1666.8	820.7	441.6
(n)[b]	(6645)	(5823)	(4503)	(2385)	(1362)	(1077)	(810)	(269)	(112)

Elderly >65	340.9	340.4	338.2	281.0	252.9	240.1	223.8	167.3	11.3
(n)[b]	(554)	(524)	(487)	(214)	(140)	(119)	(101)	(64)	(3)
Elderly >74	211.9	211.6	209.9	163.3	149.2	144.3	135.4	110.4	3.1
(n)[b]	(381)	(361)	(332)	(114)	(77)	(69)	(59)	(43)	(1)
Total	**3275.0**	**3257.6**	**3169.2**	**2751.6**	**2348.9**	**2161.1**	**1901.0**	**988.0**	**452.9**
(n)[b]	**(7238)**	**(6358)**	**(5001)**	**(2609)**	**(1511)**	**(1205)**	**(918)**	**(333)**	**(115)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dur_ol.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 16 Quetiapine exposure by indication and age group relative to duration of treatment: all OL and OLE except longterm withdrawal studies, adults

Population grouping	Quetiapine exposure in patient years by duration of exosure								
	>=1 d	**>=2 wk**	**>=1 mo**	**>=3 mo**	**>=6 mo**	**>=9 mo**	**>=12 mo**	**>=24 mo**	**>=36 mo**
By indication									
Schizophrenia[a]	2840.8	2827.4	2748.6	2423.9	2045.7	1874.9	1638.2	805.8	440.0
(n)[b]	(6010)	(5360)	(4177)	(2371)	(1334)	(1056)	(795)	(263)	(111)
BP mania/mixed[b]	68.0	67.0	64.6	28.4	25.6	24.3	24.3	10.5	NA
(n)[b]	(435)	(382)	(339)	(22)	(15)	(13)	(13)	(4)	
Other[c]	352.4	350.3	343.2	286.7	265.5	249.7	228.1	171.7	12.9
(n)[b]	(754)	(605)	(474)	(206)	(153)	(127)	(103)	(66)	(4)
By age group									

Adult 18-65	2920.3	2904.4	2818.2	2457.9	2083.8	1908.9	1666.8	820.7	441.6
(n)[b]	(6645)	(5823)	(4503)	(2385)	(1362)	(1077)	(810)	(269)	(112)
Elderly >65	340.9	340.4	338.2	281.0	252.9	240.1	223.8	167.3	11.3
(n)[b]	(554)	(524)	(487)	(214)	(140)	(119)	(101)	(64)	(3)
Elderly >74	211.9	211.6	209.9	163.3	149.2	144.3	135.4	110.4	3.1
(n)[b]	(381)	(361)	(332)	(114)	(77)	(69)	(59)	(43)	(1)
Total	**3261.2**	**3244.7**	**3156.4**	**2738.9**	**2336.8**	**2148.9**	**1890.6**	**988.0**	**452.9**
(n)[b]	**(7199)**	**(6347)**	**(4990)**	**(2599)**	**(1502)**	**(1196)**	**(911)**	**(333)**	**(115)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dur_ol_adults.SAS. Data version: V27. User: [redacted] 2014-07-21 13:21.

Table 17 Quetiapine exposure by indication and age group relative to duration of treatment: all OL and OLE except longterm withdrawal studies, pediatrics

Population grouping	Quetiapine exposure in patient years by duration of exosure						
	>=1 d	**>=2 wk**	**>=1 mo**	**>=3 mo**	**>=6 mo**	**>=9 mo**	**>=12 mo**
				By indication			
Peds Schizophrenia[d]	9.2	9.1	9.1	8.9	8.4	8.4	7.7
(n)[b]	(10)	(8)	(8)	(7)	(6)	(6)	(5)
Peds BP mania/mixed	4.6	3.7	3.7	3.7	3.7	3.7	2.7
(n)[b]	(29)	(3)	(3)	(3)	(3)	(3)	(2)
				By age group			

Pediatric <13	4.4	3.9	3.9	3.9	3.9	3.9	3.9
(n)[b]	(16)	(3)	(3)	(3)	(3)	(3)	(3)
Pediatric 13-17	9.4	8.9	8.9	8.7	8.3	8.3	6.5
(n)[b]	(23)	(8)	(8)	(7)	(6)	(6)	(4)
Pediatric <18	13.8	12.8	12.8	12.6	12.2	12.2	10.4
(n)[b]	(39)	(11)	(11)	(10)	(9)	(9)	(7)
Total	**13.8**	**12.8**	**12.8**	**12.6**	**12.2**	**12.2**	**10.4**
(n)[b]	**(39)**	**(11)**	**(11)**	**(10)**	**(9)**	**(9)**	**(7)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dur_ol_ped.SAS. Data version: V27. User: [redacted] 2014-07-21 13:21.

Table 18 Quetiapine exposure by indication and age group relative to mean daily dose: all OL and OLE except longterm withdrawal studies

Population grouping	**Quetiapine exposure in patient years by mean daily dose**									**Other**	
	<100	**100 to 199**	**200 to 299**	**300 to 399**	**400 to 499**	**500 to 599**	**600 to 699**	**700 to 799**	**>799**	**Mean of mean daily dose(mg)**	**Mean maximum dose (mg)**
By indication											
Schizophrenia[a]	44.0	123.2	316.3	482.2	539.0	559.7	336.9	401.5	37.9	459.1	572.9
	(254)	(371)	(689)	(1013)	(1169)	(1042)	(707)	(516)	(249)	(6010)	(6010)
BP mania/mixed[b]	0.0	0.1	0.4	3.1	10.2	30.6	7.6	15.3	0.7	590.8	669.7
	(3)	(3)	(17)	(15)	(76)	(138)	(43)	(132)	(8)	(435)	(435)

Other[c]	110.1 (392)	109.8 (198)	63.6 (93)	30.7 (39)	17.9 (15)	17.9 (14)	1.7 (2)	0.6 (1)	NA	134.2 (754)	196.4 (754)
Peds Schizophrenia[d]	NA	NA	0.2 (2)	1.2 (2)	NA	2.1 (2)	5.7 (4)	NA	NA	504.4 (10)	685.0 (10)
Peds BP mania/mixed	NA	NA	0.0 (2)	0.1 (3)	1.7 (22)	1.3 (1)	1.4 (1)	NA	NA	426.9 (29)	760.3 (29)
By age group											
Pediatric <13	NA	NA	NA	1.3 (5)	0.3 (9)	1.3 (1)	1.4 (1)	NA	NA	436.2 (16)	768.8 (16)
Pediatric 13-17	NA	NA	0.3 (4)	NA	1.4 (13)	2.1 (2)	5.7 (4)	NA	NA	454.1 (23)	721.7 (23)
Pediatric <18	NA	NA	0.3 (4)	1.3 (5)	1.7 (22)	3.4 (3)	7.1 (5)	NA	NA	446.8 (39)	741.0 (39)
Adult 18-65	51.8 (392)	129.4 (389)	316.2 (740)	484.4 (1037)	539.5 (1244)	601.5 (1189)	344.7 (750)	414.1 (647)	38.7 (257)	457.1 (6645)	567.4 (6645)
Elderly >65	102.4 (257)	103.6 (183)	64.1 (59)	31.6 (30)	27.6 (16)	6.7 (5)	1.5 (2)	3.2 (2)	NA	145.1 (554)	202.3 (554)
Elderly >74	66.9 (200)	72.4 (130)	41.8 (31)	16.3 (12)	12.0 (7)	NA	NA	2.6 (1)	NA	123.7 (381)	174.7 (381)
Total	**154.1 (649)**	**233.0 (572)**	**380.6 (803)**	**517.3 (1072)**	**568.8 (1282)**	**611.6 (1197)**	**353.3 (757)**	**417.4 (649)**	**38.7 (257)**	**433.1 (7238)**	**540.4 (7238)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_meandose_ol.SAS. Data version: V27. User: [redacted] 2014-07-21 13:21.

Table 19 Quetiapine exposure by indication and age group relative to mean daily dose: all OL and OLE except longterm withdrawal studies, adults

Population grouping	Quetiapine exposure in patient years by mean daily dose									Other	
	<100	100 to 199	200 to 299	300 to 399	400 to 499	500 to 599	600 to 699	700 to 799	>799	Mean of mean daily dose(mg)	Mean maximum dose (mg)
By indication											
Schizophrenia[a]	44.0	123.2	316.3	482.2	539.0	559.7	336.9	401.5	37.9	459.1	572.9
	(254)	(371)	(689)	(1013)	(1169)	(1042)	(707)	(516)	(249)	(6010)	(6010)
BP mania/mixed[b]	0.0	0.1	0.4	3.1	10.2	30.6	7.6	15.3	0.7	590.8	669.7
	(3)	(3)	(17)	(15)	(76)	(138)	(43)	(132)	(8)	(435)	(435)
Other[c]	110.1	109.8	63.6	30.7	17.9	17.9	1.7	0.6	NA	134.2	196.4
	(392)	(198)	(93)	(39)	(15)	(14)	(2)	(1)		(754)	(754)
By age group											
Adult 18-65	51.8	129.4	316.2	484.4	539.5	601.5	344.7	414.1	38.7	457.1	567.4
	(392)	(389)	(740)	(1037)	(1244)	(1189)	(750)	(647)	(257)	(6645)	(6645)
Elderly >65	102.4	103.6	64.1	31.6	27.6	6.7	1.5	3.2	NA	145.1	202.3
	(257)	(183)	(59)	(30)	(16)	(5)	(2)	(2)		(554)	(554)

Elderly >74	66.9 (200)	72.4 (130)	41.8 (31)	16.3 (12)	12.0 (7)	NA	NA	2.6 (1)	NA	123.7 (381)	174.7 (381)
Total	**154.1 (649)**	**233.0 (572)**	**380.3 (799)**	**516.0 (1067)**	**567.1 (1260)**	**608.2 (1194)**	**346.3 (752)**	**417.4 (649)**	**38.7 (257)**	**433.1 (7199)**	**539.3 (7199)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_meandose_ol_adults.SAS. Data version: V27. User: [redacted] 2014-07-21 13:22.

Table 20 Quetiapine exposure by indication and age group relative to mean daily dose: all OL and OLE except longterm withdrawal studies, pediatrics

Population grouping	Quetiapine exposure in patient years by mean daily dose									Other	
	<100	**100 to 199**	**200 to 299**	**300 to 399**	**400 to 499**	**500 to 599**	**600 to 699**	**700 to 799**	**>799**	**Mean of mean daily dose(mg)**	**Mean maximum dose (mg)**
By indication											
Peds Schizophrenia[d]	NA	NA	0.2 (2)	1.2 (2)	NA	2.1 (2)	5.7 (4)	NA	NA	504.4 (10)	685.0 (10)
Peds BP mania/mixed	NA	NA	0.0 (2)	0.1 (3)	1.7 (22)	1.3 (1)	1.4 (1)	NA	NA	426.9 (29)	760.3 (29)
By age group											
Pediatric <13	NA	NA	NA	1.3 (5)	0.3 (9)	1.3 (1)	1.4 (1)	NA	NA	436.2 (16)	768.8 (16)

Pediatric 13-17	NA	NA	0.3 (4)	NA	1.4 (13)	2.1 (2)	5.7 (4)	NA	NA	454.1 (23)	721.7 (23)
Pediatric <18	NA	NA	0.3 (4)	1.3 (5)	1.7 (22)	3.4 (3)	7.1 (5)	NA	NA	446.8 (39)	741.0 (39)
Total	**NA**	**NA**	**0.3 (4)**	**1.3 (5)**	**1.7 (22)**	**3.4 (3)**	**7.1 (5)**	**NA**	**NA**	**446.8 (39)**	**741.0 (39)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_meandose_ol_peds.SAS. Data version: V27. User: [redacted] 2014-07-21 13:22.

1.1.3 All randomized double-blind trials

Table 21 Exposure to quetiapine by indication and demographic characteristics: all randomized double blind studies

Population grouping	Total exposure in patient years	Exposure in patient years by demographic characteristic (n)										
		Sex		Race					Age group			
		M	F	White	Black	Asian	Hispanic	Other[b]	<18	18-65	>65	>74
By indication												
Peds Schizophrenia[a]	16.3 (N=148)	10.0 (88)	6.3 (60)	9.7 (89)	1.7 (16)	3.3 (29)	1.1 (9)	0.4 (5)	16.3 (148)	NA	NA	NA
Schizophrenia[a]	673.4 (N=5610)	446.0 (3799)	227.4 (1811)	464.1 (3653)	102.2 (1023)	70.4 (628)	20.5 (170)	16.1 (136)	NA	671.1 (5604)	2.3 (6)	0.0 (1)

Bipolar depression	557.7 (N=2242)	233.5 (924)	324.2 (1318)	389.0 (1550)	76.7 (294)	60.0 (258)	24.1 (82)	8.0 (58)	NA	557.7 (2242)	NA	NA
BP mania/mixed	669.7 (N=1937)	311.0 (970)	358.7 (967)	523.3 (1394)	44.1 (263)	48.8 (146)	34.8 (64)	18.7 (70)	NA	654.6 (1906)	15.0 (31)	1.6 (4)
Peds BP mania/mixed	23.4 (N=285)	12.4 (150)	10.9 (135)	17.2 (214)	3.5 (42)	0.5 (4)	0.7 (12)	1.4 (13)	23.4 (285)	NA	NA	NA
MDD	391.0 (N=2333)	129.5 (818)	261.5 (1515)	323.9 (1905)	49.3 (311)	6.9 (54)	8.2 (45)	2.7 (18)	NA	365.8 (2167)	25.2 (166)	4.9 (36)
GAD	323.8 (N=2217)	111.2 (757)	212.5 (1460)	279.9 (1923)	29.4 (203)	6.6 (32)	4.7 (35)	3.2 (24)	NA	288.6 (1993)	35.1 (224)	5.4 (37)
Mixed	0.9 (N=86)	0.7 (61)	0.3 (25)	0.5 (48)	0.2 (20)	0.0 (1)	0.2 (16)	0.0 (1)	NA	0.9 (86)	NA	NA
Other[b]	77.3 (N=799)	23.9 (358)	53.4 (441)	64.4 (538)	7.4 (134)	0.7 (25)	4.5 (91)	0.2 (11)	NA	6.2 (286)	71.1 (513)	61.1 (439)
By age group												
Pediatric <18	39.7 (N=433)	22.4 (238)	17.2 (195)	27.0 (303)	5.2 (58)	3.8 (33)	1.8 (21)	1.9 (18)	39.7 (433)	NA	NA	NA
Adult 18-65	2545.0 (N=14284)	1211.8 (7421)	1333.1 (6863)	1906.1 (10133)	303.8 (2209)	192.6 (1139)	94.1 (486)	48.4 (317)	NA	2545.0 (14284)	NA	NA
Elderly >65	148.8 (N=940)	43.9 (266)	104.8 (674)	138.9 (878)	5.6 (39)	0.8 (5)	2.8 (17)	0.5 (1)	NA	NA	148.8 (940)	NA
Elderly >74	72.9 (N=517)	18.9 (137)	54.0 (380)	65.7 (470)	4.0 (28)	0.6 (3)	2.6 (16)	NA	NA	NA	NA	72.9 (517)
Total	**2733.4 (N=15657)**	**1278.2 (7925)**	**1455.2 (7732)**	**2072.0 (11314)**	**314.7 (2306)**	**197.2 (1177)**	**98.8 (524)**	**50.8 (336)**	**39.7 (433)**	**2545.0 (14284)**	**148.8 (940)**	**72.9 (517)**

a Includes schizoaffective disorders.

b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_rnd.SAS. Data version: V27. User: [redacted] 2014-07-21 23:32.

Table 22 Exposure to quetiapine by indication and demographic characteristics: all randomized double blind studies, adults

Population grouping	Total exposure in patient years	Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
		M	F	White	Black	Asian	Hispanic	Other[b]	18-65	>65	>74
By indication											
Schizophrenia[a]	673.4 (N=5610)	446.0 (3799)	227.4 (1811)	464.1 (3653)	102.2 (1023)	70.4 (628)	20.5 (170)	16.1 (136)	671.1 (5604)	2.3 (6)	0.0 (1)
Bipolar depression	557.7 (N=2242)	233.5 (924)	324.2 (1318)	389.0 (1550)	76.7 (294)	60.0 (258)	24.1 (82)	8.0 (58)	557.7 (2242)	NA	NA
BP mania/mixed	669.7 (N=1937)	311.0 (970)	358.7 (967)	523.3 (1394)	44.1 (263)	48.8 (146)	34.8 (64)	18.7 (70)	654.6 (1906)	15.0 (31)	1.6 (4)
MDD	391.0 (N=2333)	129.5 (818)	261.5 (1515)	323.9 (1905)	49.3 (311)	6.9 (54)	8.2 (45)	2.7 (18)	365.8 (2167)	25.2 (166)	4.9 (36)
GAD	323.8 (N=2217)	111.2 (757)	212.5 (1460)	279.9 (1923)	29.4 (203)	6.6 (32)	4.7 (35)	3.2 (24)	288.6 (1993)	35.1 (224)	5.4 (37)
Mixed	0.9 (N=86)	0.7 (61)	0.3 (25)	0.5 (48)	0.2 (20)	0.0 (1)	0.2 (16)	0.0 (1)	0.9 (86)	NA	NA
Other[b]	77.3 (N=799)	23.9 (358)	53.4 (441)	64.4 (538)	7.4 (134)	0.7 (25)	4.5 (91)	0.2 (11)	6.2 (286)	71.1 (513)	61.1 (439)

By age group											
Adult 18-65	2545.0 (N=14284)	1211.8 (7421)	1333.1 (6863)	1906.1 (10133)	303.8 (2209)	192.6 (1139)	94.1 (486)	48.4 (317)	2545.0 (14284)	NA	NA
Elderly >65	148.8 (N=940)	43.9 (266)	104.8 (674)	138.9 (878)	5.6 (39)	0.8 (5)	2.8 (17)	0.5 (1)	NA	148.8 (940)	NA
Elderly >74	72.9 (N=517)	18.9 (137)	54.0 (380)	65.7 (470)	4.0 (28)	0.6 (3)	2.6 (16)	NA	NA	NA	72.9 (517)
Total	**2693.7 (N=15224)**	**1255.7 (7687)**	**1438.0 (7537)**	**2045.1 (11011)**	**309.4 (2248)**	**193.4 (1144)**	**96.9 (503)**	**48.9 (318)**	**2545.0 (14284)**	**148.8 (940)**	**72.9 (517)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_rnd_adult.SAS. Data version: V27. User: [redacted] 2014-07-21 23:46.

Table 23 Exposure to quetiapine by indication and demographic characteristics: all randomized double blind studies, pediatrics

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**							
		Sex		**Race**					**Age group**
		M	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**
By indication									
Peds Schizophrenia[a]	16.3 (N=148)	10.0 (88)	6.3 (60)	9.7 (89)	1.7 (16)	3.3 (29)	1.1 (9)	0.4 (5)	16.3 (148)
Peds BP mania/mixed	23.4 (N=285)	12.4 (150)	10.9 (135)	17.2 (214)	3.5 (42)	0.5 (4)	0.7 (12)	1.4 (13)	23.4 (285)

By age group									
Pediatric <18	39.7 (N=433)	22.4 (238)	17.2 (195)	27.0 (303)	5.2 (58)	3.8 (33)	1.8 (21)	1.9 (18)	39.7 (433)
Total	**39.7 (N=433)**	**22.4 (238)**	**17.2 (195)**	**27.0 (303)**	**5.2 (58)**	**3.8 (33)**	**1.8 (21)**	**1.9 (18)**	**39.7 (433)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_rnd_ped.SAS. Data version: V27. User: [redacted] 2014-07-21 23:53.

Table 24 Quetiapine exposure by indication and age group relative to duration of treatment: all randomized double blind studies

Population grouping	Quetiapine exposure in patient years by duration of exosure								
	>=1 d	**>=2 wk**	**>=1 mo**	**>=3 mo**	**>=6 mo**	**>=9 mo**	**>=12 mo**	**dur8**	**dur9**
By indication									
Schizophrenia[a] (n)[b]	673.4 (5610)	653.3 (4532)	604.5 (3656)	160.9 (247)	123.6 (145)	93.7 (96)	30.1 (29)	NA	NA
Bipolar depression (n)[b]	557.7 (2242)	552.4 (1950)	538.1 (1708)	333.2 (433)	297.1 (339)	230.7 (234)	101.1 (91)	NA	NA
BP mania/mixed[b] (n)[b]	669.7 (1937)	663.9 (1581)	644.3 (1244)	547.4 (708)	463.8 (478)	356.4 (300)	260.0 (188)	NA	NA
MDD (n)[b]	391.0 (2333)	386.7 (2083)	374.1 (1864)	163.8 (276)	120.3 (162)	70.7 (81)	3.0 (3)	NA	NA
GAD (n)[b]	323.8 (2217)	319.1 (1939)	305.3 (1709)	48.8 (106)	25.8 (41)	3.9 (5)	NA	NA	NA

Mixed (n)[b]	0.9 (86)	NA	NA	NA	NA	NA	NA	NA	NA
Other[c] (n)[b]	77.3 (799)	71.6 (489)	67.7 (425)	NA	NA	NA	NA	NA	NA
Peds Schizophrenia[d] (n)[b]	16.3 (148)	16.2 (143)	15.0 (124)	NA	NA	NA	NA	NA	NA
Peds BP mania/mixed (n)[b]	23.4 (285)	22.7 (255)	12.0 (82)	NA	NA	NA	NA	NA	NA
By age group									
Pediatric <13 (n)[b]	8.4 (110)	8.1 (100)	3.4 (23)	NA	NA	NA	NA	NA	NA
Pediatric 13-17 (n)[b]	31.3 (323)	30.8 (298)	23.6 (183)	NA	NA	NA	NA	NA	NA
Pediatric <18 (n)[b]	39.7 (433)	38.9 (398)	27.0 (206)	NA	NA	NA	NA	NA	NA
Adult 18-65 (n)[b]	2545.0 (14284)	2499.2 (11687)	2392.4 (9818)	1239.4 (1755)	1015.8 (1150)	743.6 (706)	386.1 (305)	NA	NA
Elderly >65 (n)[b]	148.8 (940)	147.8 (887)	141.6 (788)	14.7 (15)	14.7 (15)	11.8 (10)	8.2 (6)	NA	NA
Elderly >74 (n)[b]	72.9 (517)	72.3 (482)	68.2 (416)	1.1 (1)	1.1 (1)	1.1 (1)	1.1 (1)	NA	NA
Total **(n)[b]**	**2733.4** **(15657)**	**2685.9** **(12972)**	**2561.1** **(10812)**	**1254.2** **(1770)**	**1030.6** **(1165)**	**755.3** **(716)**	**394.2** **(311)**	**NA**	**NA**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dur_rnd.SAS. Data version: V27. User: [redacted] 2014-07-21 13:21.

Table 25 Quetiapine exposure by indication and age group relative to duration of treatment: all randomized double blind studies, adults

Population grouping	Quetiapine exposure in patient years by duration of exosure								
	>=1 d	>=2 wk	>=1 mo	>=3 mo	>=6 mo	>=9 mo	>=12 mo	dur8	dur9
					By indication				
Schizophrenia[a]	672.6	653.3	604.5	160.9	123.6	93.7	30.1	NA	NA
(n)[b]	(5584)	(4532)	(3656)	(247)	(145)	(96)	(29)		
Bipolar depression	557.7	552.4	538.1	333.2	297.1	230.7	101.1	NA	NA
(n)[b]	(2242)	(1950)	(1708)	(433)	(339)	(234)	(91)		
BP mania/mixed[b]	669.5	663.9	644.3	547.4	463.8	356.4	260.0	NA	NA
(n)[b]	(1933)	(1581)	(1244)	(708)	(478)	(300)	(188)		
MDD	391.0	386.7	374.1	163.8	120.3	70.7	3.0	NA	NA
(n)[b]	(2333)	(2083)	(1864)	(276)	(162)	(81)	(3)		
GAD	323.8	319.1	305.3	48.8	25.8	3.9	NA	NA	NA
(n)[b]	(2217)	(1939)	(1709)	(106)	(41)	(5)			
Mixed	0.9	NA	NA	NA	NA	NA	NA	NA	NA
(n)[b]	(86)								
Other[c]	77.2	71.6	67.7	NA	NA	NA	NA	NA	NA
(n)[b]	(781)	(489)	(425)						

By age group									
Adult 18-65	2543.9	2499.2	2392.4	1239.4	1015.8	743.6	386.1	NA	NA
(n)[b]	(14236)	(11687)	(9818)	(1755)	(1150)	(706)	(305)		
Elderly >65	148.8	147.8	141.6	14.7	14.7	11.8	8.2	NA	NA
(n)[b]	(940)	(887)	(788)	(15)	(15)	(10)	(6)		
Elderly >74	72.9	72.3	68.2	1.1	1.1	1.1	1.1	NA	NA
(n)[b]	(517)	(482)	(416)	(1)	(1)	(1)	(1)		
Total	**2692.7**	**2647.0**	**2534.0**	**1254.2**	**1030.6**	**755.3**	**394.2**	**NA**	**NA**
(n)[b]	**(15176)**	**(12574)**	**(10606)**	**(1770)**	**(1165)**	**(716)**	**(311)**		

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dur_rnd_adults.SAS. Data version: V27. User: [redacted] 2014-07-21 13:21.

Table 26 Quetiapine exposure by indication and age group relative to duration of treatment: all randomized double blind studies, pediatrics

Population grouping	Quetiapine exposure in patient years by duration of exposure						
	>=1 d	>=2 wk	>=1 mo	dur4	dur5	dur6	dur7
By indication							
Peds Schizophrenia[d]	16.3	16.2	15.0	NA	NA	NA	NA
(n)[b]	(148)	(143)	(124)				
Peds BP mania/mixed	23.4	22.7	12.0	NA	NA	NA	NA
(n)[b]	(285)	(255)	(82)				
By age group							
Pediatric <13	8.4	8.1	3.4	NA	NA	NA	NA
(n)[b]	(110)	(100)	(23)				
Pediatric 13-17	31.3	30.8	23.6	NA	NA	NA	NA
(n)[b]	(323)	(298)	(183)				
Pediatric <18	39.7	38.9	27.0	NA	NA	NA	NA
(n)[b]	(433)	(398)	(206)				
Total	**39.7**	**38.9**	**27.0**	**NA**	**NA**	**NA**	**NA**
(n)[b]	**(433)**	**(398)**	**(206)**				

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dur_rnd_ped.SAS. Data version: V27. User: [redacted] 2014-07-21 13:21.

Table 27 Quetiapine exposure by indication and age group relative to mean daily dose: all randomized double blind studies, all

Population grouping	Quetiapine exposure in patient years by mean daily dose									Other	
	<100	100 to 199	200 to 299	300 to 399	400 to 499	500 to 599	600 to 699	700 to 799	>799	Mean of mean daily dose(mg)	Mean of maximum dose(mg)
By indication											
Schizophrenia[a]	47.0 (456)	17.8 (315)	100.9 (724)	88.5 (932)	105.0 (915)	156.7 (1001)	52.1 (433)	56.8 (534)	44.0 (258)	445.1 (5568)	511.4 (5568)
Bipolar depression	0.4 (57)	1.0 (67)	362.4 (1338)	1.9 (54)	9.6 (100)	182.2 (625)	0.1 (1)	NA	NA	354.3 (2242)	408.0 (2242)
BP mania/mixed[b]	0.1 (16)	6.8 (178)	16.0 (114)	58.2 (216)	261.3 (524)	85.8 (287)	140.9 (330)	53.5 (169)	47.2 (103)	474.6 (1937)	531.3 (1937)
MDD	64.7 (362)	183.3 (1167)	86.7 (683)	56.2 (121)	NA	NA	NA	NA	NA	174.3 (2333)	192.8 (2333)
GAD	81.4 (605)	151.5 (1036)	77.7 (528)	13.1 (48)	NA	NA	NA	NA	NA	151.4 (2217)	169.6 (2217)
Mixed	0.3 (26)	0.3 (28)	0.2 (15)	0.2 (17)	NA	NA	NA	NA	NA	149.6 (86)	163.4 (86)
Other[c]	37.8 (331)	35.6 (409)	2.8 (22)	0.5 (19)	0.0 (3)	0.5 (15)	NA	NA	NA	140.4 (799)	185.2 (799)
Peds Schizophrenia[d]	0.0 (1)	0.0 (1)	0.1 (3)	8.0 (71)	NA	0.4 (5)	1.6 (15)	6.3 (52)	NA	524.8 (148)	615.2 (148)
Peds BP mania/mixed	0.0 (3)	6.7 (58)	6.2 (49)	5.2 (87)	3.2 (55)	2.1 (33)	NA	NA	NA	331.8 (285)	436.3 (285)

By age group											
Pediatric <13	0.0 (1)	1.8 (13)	1.9 (16)	2.3 (39)	1.4 (25)	1.0 (16)	NA	NA	NA	360.2 (110)	473.5 (110)
Pediatric 13-17	0.0 (3)	5.0 (46)	4.4 (36)	10.8 (119)	1.8 (30)	1.4 (22)	1.6 (15)	6.3 (52)	NA	410.6 (323)	505.6 (323)
Pediatric <18	0.0 (4)	6.7 (59)	6.2 (52)	13.1 (158)	3.2 (55)	2.5 (38)	1.6 (15)	6.3 (52)	NA	397.8 (433)	497.4 (433)
Adult 18-65	186.3 (1513)	331.8 (2771)	623.5 (3281)	216.8 (1403)	370.0 (1533)	421.3 (1922)	190.7 (759)	110.0 (702)	89.9 (358)	345.2 (14242)	393.3 (14242)
Elderly >65	45.4 (340)	64.6 (429)	23.3 (143)	1.9 (4)	5.9 (9)	3.9 (6)	2.3 (5)	0.2 (1)	1.3 (3)	152.5 (940)	189.1 (940)
Elderly >74	34.5 (262)	32.2 (220)	4.9 (32)	NA	1.1 (2)	NA	NA	0.2 (1)	NA	126.5 (517)	156.1 (517)
Total	**231.7 (1857)**	**403.1 (3259)**	**653.0 (3476)**	**231.8 (1565)**	**379.1 (1597)**	**427.6 (1966)**	**194.6 (779)**	**116.5 (755)**	**91.2 (361)**	**335.0 (15615)**	**383.9 (15615)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_meandose_rnd2.SAS. Data version: V27. User: [redacted] 2014-07-21 13:22.

Table 28 Quetiapine exposure by indication and age group relative to mean daily dose: all randomized double blind studies, adults

Population grouping	Quetiapine exposure in patient years by mean daily dose									Other	
	<100	100 to 199	200 to 299	300 to 399	400 to 499	500 to 599	600 to 699	700 to 799	>799	Mean of mean daily dose(mg)	Mean of maximum dose(mg)
By indication											
Schizophrenia[a]	47.0 (456)	17.8 (315)	100.9 (724)	88.5 (932)	105.0 (915)	156.7 (1001)	52.1 (433)	56.8 (534)	44.0 (258)	445.1 (5568)	511.4 (5568)
Bipolar depression	0.4 (57)	1.0 (67)	362.4 (1338)	1.9 (54)	9.6 (100)	182.2 (625)	0.1 (1)	NA	NA	354.3 (2242)	408.0 (2242)
BP mania/mixed[b]	0.1 (16)	6.8 (178)	16.0 (114)	58.2 (216)	261.3 (524)	85.8 (287)	140.9 (330)	53.5 (169)	47.2 (103)	474.6 (1937)	531.3 (1937)
MDD	64.7 (362)	183.3 (1167)	86.7 (683)	56.2 (121)	NA	NA	NA	NA	NA	174.3 (2333)	192.8 (2333)
GAD	81.4 (605)	151.5 (1036)	77.7 (528)	13.1 (48)	NA	NA	NA	NA	NA	151.4 (2217)	169.6 (2217)
Mixed	0.3 (26)	0.3 (28)	0.2 (15)	0.2 (17)	NA	NA	NA	NA	NA	149.6 (86)	163.4 (86)
Other[c]	37.8 (331)	35.6 (409)	2.8 (22)	0.5 (19)	0.0 (3)	0.5 (15)	NA	NA	NA	140.4 (799)	185.2 (799)
By age group											
Adult 18-65	186.3 (1513)	331.8 (2771)	623.5 (3281)	216.8 (1403)	370.0 (1533)	421.3 (1922)	190.7 (759)	110.0 (702)	89.9 (358)	345.2 (14242)	393.3 (14242)

Elderly >65	45.4 (340)	64.6 (429)	23.3 (143)	1.9 (4)	5.9 (9)	3.9 (6)	2.3 (5)	0.2 (1)	1.3 (3)	152.5 (940)	189.1 (940)
Elderly >74	34.5 (262)	32.2 (220)	4.9 (32)	NA	1.1 (2)	NA	NA	0.2 (1)	NA	126.5 (517)	156.1 (517)
Total	**231.7 (1853)**	**396.4 (3200)**	**646.8 (3424)**	**218.7 (1407)**	**375.9 (1542)**	**425.2 (1928)**	**193.0 (764)**	**110.2 (703)**	**91.2 (361)**	**333.2 (15182)**	**380.7 (15182)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_meandose_rnd2.SAS. Data version: V27. User: [redacted] 2014-07-21 13:22.

Table 29 Quetiapine exposure by indication and age group relative to mean daily dose: all randomized double blind studies, pediatrics

Population grouping	Quetiapine exposure in patient years by mean daily dose									Other	
	<100	**100 to 199**	**200 to 299**	**300 to 399**	**400 to 499**	**500 to 599**	**600 to 699**	**700 to 799**	**level9**	**Mean of mean daily dose(mg)**	**Mean of maximum dose(mg)**
By indication											
Peds Schizophrenia[d]	0.0 (1)	0.0 (1)	0.1 (3)	8.0 (71)	NA	0.4 (5)	1.6 (15)	6.3 (52)	NA	524.8 (148)	615.2 (148)
Peds BP mania/mixed	0.0 (3)	6.7 (58)	6.2 (49)	5.2 (87)	3.2 (55)	2.1 (33)	NA	NA	NA	331.8 (285)	436.3 (285)
By age group											

Pediatric <13	0.0	1.8	1.9	2.3	1.4	1.0	NA	NA	NA	360.2	473.5
	(1)	(13)	(16)	(39)	(25)	(16)				(110)	(110)
Pediatric 13-17	0.0	5.0	4.4	10.8	1.8	1.4	1.6	6.3	NA	410.6	505.6
	(3)	(46)	(36)	(119)	(30)	(22)	(15)	(52)		(323)	(323)
Pediatric <18	0.0	6.7	6.2	13.1	3.2	2.5	1.6	6.3	NA	397.8	497.4
	(4)	(59)	(52)	(158)	(55)	(38)	(15)	(52)		(433)	(433)
Total	**0.0**	**6.7**	**6.2**	**13.1**	**3.2**	**2.5**	**1.6**	**6.3**	**NA**	**397.8**	**497.4**
	(4)	**(59)**	**(52)**	**(158)**	**(55)**	**(38)**	**(15)**	**(52)**		**(433)**	**(433)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_meandose_rnd2.SAS. Data version: V27. User: [redacted] 2014-07-21 13:22.

1.1.4 Placebo-controlled trials

Table 30 Exposure to Seroquel IR by indication and demographic characteristics: all placebo-controlled trials

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**										
		Sex		**Race**					**Age group**			
		M	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**	**18-65**	**>65**	**>74**
						By indication						
Peds Schizophrenia[a]	16.2 (N=147)	9.9 (87)	6.3 (60)	9.7 (89)	1.7 (16)	3.3 (29)	1.1 (9)	0.3 (4)	16.2 (147)	NA	NA	NA
Schizophrenia[a]	73.2 (N=924)	52.3 (664)	20.9 (260)	43.2 (530)	19.3 (266)	5.4 (56)	3.5 (52)	1.6 (20)	NA	73.2 (924)	NA	NA

Bipolar depression	221.8 (N=1712)	92.2 (702)	129.6 (1010)	165.0 (1274)	28.9 (234)	11.2 (84)	10.6 (70)	6.1 (50)	NA	221.8 (1712)	NA	NA
BP mania/mixed	71.6 (N=581)	39.5 (315)	32.1 (266)	51.6 (429)	2.4 (34)	13.4 (75)	0.9 (10)	3.4 (33)	NA	70.1 (570)	1.5 (11)	0.5 (2)
Peds BP mania/mixed	10.8 (N=193)	6.0 (105)	4.8 (88)	8.4 (149)	1.6 (28)	0.0 (0)	0.6 (11)	0.2 (5)	10.8 (193)	NA	NA	NA
MDD	0.0 (N=0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	NA	0.0 (0)	0.0 (0)	0.0 (0)
GAD	0.0 (N=0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	NA	0.0 (0)	0.0 (0)	0.0 (0)
Other[b]	55.9 (N=370)	14.5 (98)	41.3 (272)	46.6 (306)	5.6 (38)	0.6 (3)	3.0 (18)	0.1 (5)	NA	1.0 (11)	54.8 (359)	47.8 (314)
By age group												
Pediatric <13	4.9 (N=85)	2.8 (46)	2.1 (39)	4.0 (70)	0.7 (12)	NA	0.1 (2)	0.0 (1)	NA	NA	NA	NA
Pediatric 13-17	22.1 (N=255)	13.2 (146)	9.0 (109)	14.1 (168)	2.5 (32)	3.3 (29)	1.6 (18)	0.6 (8)	NA	NA	NA	NA
Pediatric <18	27.0 (N=340)	15.9 (192)	11.1 (148)	18.1 (238)	3.2 (44)	3.3 (29)	1.7 (20)	0.6 (9)	27.0 (340)	NA	NA	NA
Adult 18-65	366.2 (N=3217)	184.3 (1687)	181.9 (1530)	258.8 (2225)	51.0 (537)	29.9 (214)	15.3 (133)	11.2 (108)	NA	366.2 (3217)	NA	NA
Elderly >65	56.4 (N=370)	14.3 (92)	42.1 (278)	47.7 (314)	5.2 (35)	0.7 (4)	2.8 (17)	NA	NA	NA	56.4 (370)	NA
Elderly >74	48.2 (N=316)	11.7 (75)	36.5 (241)	41.1 (270)	3.9 (27)	0.6 (3)	2.6 (16)	NA	NA	NA	NA	48.2 (316)

Total	**449.5 (N=3927)**	**214.5 (1971)**	**235.0 (1956)**	**324.6 (2777)**	**59.4 (616)**	**33.9 (247)**	**19.8 (170)**	**11.8 (117)**	**27.0 (340)**	**366.2 (3217)**	**56.4 (370)**	**48.2 (316)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only immediate release quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_pla_ctrl_IR.SAS. Data version: V27. User: [redacted] 2014-08-18 14:27.

Table 31 Exposure to Seroquel XR by indication and demographic characteristics: all placebo-controlled trials

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**										
		Sex		**Race**					**Age group**			
		M	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**	**18-65**	**>65**	**>74**
						By indication						
Peds Schizophrenia[a]	0.0 (N=0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	NA	NA	NA
Schizophrenia[a]	83.7 (N=951)	57.3 (670)	26.4 (281)	39.9 (462)	25.7 (307)	14.2 (134)	2.1 (24)	1.8 (24)	NA	83.7 (951)	NA	NA
Bipolar depression	35.4 (N=284)	14.4 (117)	21.1 (167)	11.7 (101)	3.5 (28)	19.8 (149)	0.0 (0)	0.5 (6)	NA	35.4 (284)	NA	NA
BP mania/mixed	7.7 (N=151)	4.7 (92)	3.0 (59)	3.6 (72)	3.7 (72)	0.1 (1)	0.0 (0)	0.3 (6)	NA	7.7 (151)	0.0 (0)	0.0 (0)
Peds BP mania/mixed	12.5 (N=92)	6.4 (45)	6.2 (47)	8.8 (65)	2.0 (14)	0.5 (4)	0.1 (1)	1.2 (8)	12.5 (92)	NA	NA	NA
MDD	212.2 (N=1942)	73.8 (683)	138.3 (1259)	170.0 (1566)	30.7 (278)	6.2 (52)	3.7 (32)	1.6 (14)	NA	187.0 (1776)	25.2 (166)	4.9 (36)

GAD	260.6 (N=2001)	87.6 (686)	172.9 (1315)	226.4 (1740)	24.9 (190)	2.3 (16)	4.0 (32)	3.0 (23)	NA	225.4 (1777)	35.1 (224)	5.4 (37)
Other[b]	2.3 (N=126)	1.4 (82)	0.8 (44)	0.3 (20)	0.8 (41)	0.0 (0)	1.2 (65)	0.0 (0)	NA	2.3 (126)	0.0 (0)	0.0 (0)
By age group												
Pediatric <13	3.5 (N=25)	1.8 (12)	1.8 (13)	2.3 (17)	0.7 (5)	NA	0.0 (0)	0.5 (3)	NA	NA	NA	NA
Pediatric 13-17	9.0 (N=67)	4.6 (33)	4.4 (34)	6.5 (48)	1.2 (9)	0.5 (4)	0.1 (1)	0.8 (5)	NA	NA	NA	NA
Pediatric <18	12.5 (N=92)	6.4 (45)	6.2 (47)	8.8 (65)	2.0 (14)	0.5 (4)	0.1 (1)	1.2 (8)	12.5 (92)	NA	NA	NA
Adult 18-65	541.5 (N=5065)	221.6 (2217)	319.9 (2848)	391.8 (3573)	89.0 (914)	42.5 (352)	11.0 (153)	7.2 (73)	NA	541.5 (5065)	NA	NA
Elderly >65	60.3 (N=390)	17.6 (113)	42.7 (277)	60.0 (388)	0.3 (2)	0.0 (0)	0.0 (0)	NA	NA	NA	60.3 (390)	NA
Elderly >74	10.2 (N=73)	2.7 (20)	7.5 (53)	10.2 (73)	0.0 (0)	0.0 (0)	0.0 (0)	NA	NA	NA	NA	10.2 (73)
Total	**614.3 (N=5547)**	**245.6 (2375)**	**368.8 (3172)**	**460.6 (4026)**	**91.3 (930)**	**43.0 (356)**	**11.1 (154)**	**8.4 (81)**	**12.5 (92)**	**541.5 (5065)**	**60.3 (390)**	**10.2 (73)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only immediate release quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_pla_ctrl_XR.SAS. Data version: V27. User: [redacted] 2014-08-18 14:27.

Table 32 Adult exposure to quetiapine by indication and demographic characteristics (all placebo-controlled trials)

Population grouping	Total exposure in patient years	Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
		M	F	White	Black	Asian	Hispanic	Other[b]	18-65	>65	>74
By indication											
Schizophrenia[a]	156.9 (N=1875)[b]	109.6 (1334)	47.3 (541)	83.1 (992)	45.0 (573)	19.6 (190)	5.6 (76)	3.5 (44)	156.9 (1875)	NA	NA
Bipolar depression	257.3 (N=1996)[b]	106.6 (819)	150.7 (1177)	176.7 (1375)	32.4 (262)	31.0 (233)	10.6 (70)	6.6 (56)	257.3 (1996)	NA	NA
BP mania/mixed	79.3 (N=732)[b]	44.2 (407)	35.1 (325)	55.1 (501)	6.1 (106)	13.4 (76)	0.9 (10)	3.7 (39)	77.8 (721)	1.5 (11)	0.5 (2)
MDD	212.2 (N=1942)[b]	73.8 (683)	138.3 (1259)	170.0 (1566)	30.7 (278)	6.2 (52)	3.7 (32)	1.6 (14)	187.0 (1776)	25.2 (166)	4.9 (36)
GAD	260.6 (N=2001)[b]	87.6 (686)	172.9 (1315)	226.4 (1740)	24.9 (190)	2.3 (16)	4.0 (32)	3.0 (23)	225.4 (1777)	35.1 (224)	5.4 (37)
Other[c]	58.2 (N=496)[b]	16.0 (180)	42.2 (316)	46.9 (326)	6.3 (79)	0.6 (3)	4.2 (83)	0.1 (5)	3.3 (137)	54.8 (359)	47.8 (314)
By age group											
Adult 18-65	907.7 (N=8282)[b]	405.9 (3904)	501.8 (4378)	650.6 (5798)	140.0 (1451)	72.4 (566)	26.3 (286)	18.4 (181)	907.7 (8282)	NA	NA
Elderly >65	116.7 (N=760)[b]	31.9 (205)	84.8 (555)	107.7 (702)	5.5 (37)	0.7 (4)	2.8 (17)	NA	NA	116.7 (760)	NA

Elderly >74	58.5 (N=389)[b]	14.4 (95)	44.1 (294)	51.3 (343)	3.9 (27)	0.6 (3)	2.6 (16)	NA	NA	NA	58.5 (389)
Total	**1024.3 (N=9042)[b]**	**437.8 (4109)**	**586.5 (4933)**	**758.2 (6500)**	**145.5 (1488)**	**73.1 (570)**	**29.1 (303)**	**18.4 (181)**	**907.7 (8282)**	**116.7 (760)**	**58.5 (389)**

a Or schizoaffective disorders.
b Patients from studies included in the quetiapine integrated clinical-study safety database.
c Including dementia-related psychoses.
b Inlcudes 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_adult_pla_ctrl.SAS. Data version: V27. User: [redacted] 2014-07-21 13:19.

Table 33 Adult exposure to quetiapine by indication and demographic characteristics in Females (all placebo-controlled trials)

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**									
		Sex		**Race**					**Age group**		
		m	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**18-65**	**>65**	**>74**
					By indication						
Schizophrenia[a]	47.3 (N=541)[b]	NA	47.3 (541)	26.5 (299)	13.2 (162)	5.4 (51)	1.1 (15)	1.1 (14)	47.3 (541)	NA	NA
Bipolar depression	150.7 (N=1177)[b]	NA	150.7 (1177)	100.4 (792)	21.7 (173)	18.2 (135)	7.0 (48)	3.4 (29)	150.7 (1177)	NA	NA
BP mania/mixed	35.1 (N=325)[b]	NA	35.1 (325)	26.0 (229)	2.7 (45)	4.3 (28)	0.6 (7)	1.5 (16)	33.9 (316)	1.2 (9)	0.5 (2)
MDD	138.3 (N=1259)[b]	NA	138.3 (1259)	111.6 (1020)	18.7 (173)	3.9 (31)	2.8 (23)	1.4 (12)	121.0 (1143)	17.4 (116)	3.3 (24)

GAD	172.9 (N=1315)[b]	NA	172.9 (1315)	150.9 (1151)	16.7 (125)	1.3 (9)	2.0 (15)	2.1 (15)	147.6 (1154)	25.3 (161)	4.2 (29)
Other[c]	42.2 (N=316)[b]	NA	42.2 (316)	35.2 (235)	3.5 (31)	0.2 (1)	3.3 (49)	NA	1.3 (47)	40.9 (269)	36.1 (239)
By age group											
Adult 18-65	501.8 (N=4378)[b]	NA	501.8 (4378)	371.9 (3213)	73.1 (684)	33.0 (253)	14.4 (142)	9.5 (86)	501.8 (4378)	NA	NA
Elderly >65	84.8 (N=555)[b]	NA	84.8 (555)	78.6 (513)	3.4 (25)	0.3 (2)	2.4 (15)	NA	NA	84.8 (555)	NA
Elderly >74	44.1 (N=294)[b]	NA	44.1 (294)	38.7 (258)	3.0 (21)	0.2 (1)	2.2 (14)	NA	NA	NA	44.1 (294)
Total	**586.5 (N=4933)[b]**	**NA**	**586.5 (4933)**	**450.5 (3726)**	**76.5 (709)**	**33.3 (255)**	**16.8 (157)**	**9.5 (86)**	**501.8 (4378)**	**84.8 (555)**	**44.1 (294)**

a Or schizoaffective disorders.
b Patients from studies included in the quetiapine integrated clinical-study safety database.
c Including dementia-related psychoses.
b Inlcudes 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_adult_pla_ctrl_F.SAS. Data version: V27. User: [redacted] 2014-07-21 13:19.

Table 34 Adult exposure to quetiapine by indication and demographic characteristics in Males (all placebo-controlled trials)

Population grouping	Total exposure in patient years	Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
		M	f	White	Black	Asian	Hispanic	Other[b]	18-65	>65	>74
By indication											
Schizophrenia[a]	109.6 (N=1334)[b]	109.6 (1334)	NA	56.6 (693)	31.9 (411)	14.3 (139)	4.5 (61)	2.3 (30)	109.6 (1334)	NA	NA
Bipolar depression	106.6 (N=819)[b]	106.6 (819)	NA	76.3 (583)	10.7 (89)	12.7 (98)	3.6 (22)	3.2 (27)	106.6 (819)	NA	NA
BP mania/mixed	44.2 (N=407)[b]	44.2 (407)	NA	29.2 (272)	3.4 (61)	9.1 (48)	0.3 (3)	2.2 (23)	43.9 (405)	0.3 (2)	NA
MDD	73.8 (N=683)[b]	73.8 (683)	NA	58.4 (546)	12.0 (105)	2.3 (21)	0.9 (9)	0.2 (2)	66.0 (633)	7.8 (50)	1.6 (12)
GAD	87.6 (N=686)[b]	87.6 (686)	NA	75.5 (589)	8.2 (65)	1.0 (7)	2.0 (17)	0.9 (8)	77.8 (623)	9.8 (63)	1.1 (8)
Other[c]	16.0 (N=180)[b]	16.0 (180)	NA	11.7 (91)	2.8 (48)	0.4 (2)	0.9 (34)	0.1 (5)	2.0 (90)	14.0 (90)	11.7 (75)
By age group											
Adult 18-65	405.9 (N=3904)[b]	405.9 (3904)	NA	278.7 (2585)	66.9 (767)	39.4 (313)	11.9 (144)	8.9 (95)	405.9 (3904)	NA	NA
Elderly >65	31.9 (N=205)[b]	31.9 (205)	NA	29.0 (189)	2.0 (12)	0.4 (2)	0.4 (2)	NA	NA	31.9 (205)	NA

Elderly >74	14.4 (N=95)[b]	14.4 (95)	NA	12.7 (85)	0.9 (6)	0.4 (2)	0.4 (2)	NA	NA	NA	14.4 (95)
Total	**437.8 (N=4109)[b]**	**437.8 (4109)**	**NA**	**307.7 (2774)**	**69.0 (779)**	**39.8 (315)**	**12.3 (146)**	**8.9 (95)**	**405.9 (3904)**	**31.9 (205)**	**14.4 (95)**

a Or schizoaffective disorders.
b Patients from studies included in the quetiapine integrated clinical-study safety database.
c Including dementia-related psychoses.
b Inlcudes 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_adult_pla_ctrl_M.SAS. Data version: V27. User: [redacted] 2014-07-21 13:19.

Table 35 Pediatric (<18-years-old) exposure to quetiapine by indication and demographic characteristics (all placebo-controlled trials)

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**									
		Sex		**Race**					**Age group**		
		M	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<13**	**13-17**	**<18**
					By indication						
Peds Schizophrenia[a]	16.2 (N=147)	9.9 (87)	6.3 (60)	9.7 (89)	1.7 (16)	3.3 (29)	1.1 (9)	0.3 (4)	NA	16.2 (147)	16.2 (147)
Peds BP mania/mixed	23.4 (N=285)	12.4 (150)	10.9 (135)	17.2 (214)	3.5 (42)	0.5 (4)	0.7 (12)	1.4 (13)	8.4 (110)	15.0 (175)	23.4 (285)
					By age group						
Pediatric <13	8.4 (N=110)	4.5 (58)	3.9 (52)	6.3 (87)	1.5 (17)	NA	0.1 (2)	0.5 (4)	NA	NA	NA

Pediatric 13-17	31.2 (N=322)	17.8 (179)	13.4 (143)	20.6 (216)	3.7 (41)	3.8 (33)	1.7 (19)	1.3 (13)	NA	NA	NA
Pediatric <18	39.5 (N=432)	22.3 (237)	17.2 (195)	27.0 (303)	5.2 (58)	3.8 (33)	1.8 (21)	1.8 (17)	NA	NA	NA
Total	**39.5 (N=432)**	**22.3 (237)**	**17.2 (195)**	**27.0 (303)**	**5.2 (58)**	**3.8 (33)**	**1.8 (21)**	**1.8 (17)**	**8.4 (110)**	**31.2 (322)**	**39.5 (432)**

a Includes schizoaffective disorders.
b Inlcudes races of 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Note: Patient's age is given at the start of the clinical trial.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ped_pla_ctrl.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 36 Female Pediatric (<18 years old) exposure to quetiapine by indication and demographic characteristics (all placebo-controlled trials)

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**									
		Sex		**Race**					**Age group**		
		m	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<13**	**13-17**	**<18**
By indication											
Peds Schizophrenia[a]	6.3 (N=60)	NA	6.3 (60)	4.0 (39)	0.6 (6)	1.3 (12)	0.2 (2)	0.1 (1)	NA	6.3 (60)	6.3 (60)
Peds BP mania/mixed	10.9 (N=135)	NA	10.9 (135)	7.6 (98)	2.3 (25)	0.1 (1)	0.3 (5)	0.7 (6)	3.9 (52)	7.1 (83)	10.9 (135)
By age group											

Pediatric <13	3.9 (N=52)	NA	3.9 (52)	2.6 (37)	1.0 (12)	NA	0.1 (1)	0.2 (2)	NA	NA	NA
Pediatric 13-17	13.4 (N=143)	NA	13.4 (143)	9.0 (100)	1.9 (19)	1.4 (13)	0.5 (6)	0.7 (5)	NA	NA	NA
Pediatric <18	17.2 (N=195)	NA	17.2 (195)	11.6 (137)	2.9 (31)	1.4 (13)	0.5 (7)	0.8 (7)	NA	NA	NA
Total	**17.2 (N=195)**	**NA**	**17.2 (195)**	**11.6 (137)**	**2.9 (31)**	**1.4 (13)**	**0.5 (7)**	**0.8 (7)**	**3.9 (52)**	**13.4 (143)**	**17.2 (195)**

a Includes schizoaffective disorders.
b Inlcudes races of 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Note: Patient's age is given at the start of the clinical trial.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ped_pla_ctrl_F.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 37 Male pediatric (<18 years old) exposure to quetiapine by indication and demographic characteristics (all placebo-controlled trials)

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**									
		Sex		**Race**					**Age group**		
		M	**f**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<13**	**13-17**	**<18**
					By indication						
Peds Schizophrenia[a]	9.9 (N=87)	9.9 (87)	NA	5.7 (50)	1.1 (10)	2.0 (17)	0.9 (7)	0.2 (3)	NA	9.9 (87)	9.9 (87)
Peds BP mania/mixed	12.4 (N=150)	12.4 (150)	NA	9.6 (116)	1.3 (17)	0.4 (3)	0.4 (7)	0.8 (7)	4.5 (58)	7.9 (92)	12.4 (150)

By age group											
Pediatric <13	4.5 (N=58)	4.5 (58)	NA	3.7 (50)	0.4 (5)	NA	0.1 (1)	0.3 (2)	NA	NA	NA
Pediatric 13-17	17.8 (N=179)	17.8 (179)	NA	11.6 (116)	1.9 (22)	2.4 (20)	1.2 (13)	0.6 (8)	NA	NA	NA
Pediatric <18	22.3 (N=237)	22.3 (237)	NA	15.3 (166)	2.3 (27)	2.4 (20)	1.3 (14)	0.9 (10)	NA	NA	NA
Total	**22.3 (N=237)**	**22.3 (237)**	**NA**	**15.3 (166)**	**2.3 (27)**	**2.4 (20)**	**1.3 (14)**	**0.9 (10)**	**4.5 (58)**	**17.8 (179)**	**22.3 (237)**

a Includes schizoaffective disorders.
b Inlcudes races of 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Note: Patient's age is given at the start of the clinical trial.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ped_pla_ctrl_M.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 38 Quetiapine exposure by indication and age group relative to duration of treatment (all placebo-controlled trials)

Population grouping	**Quetiapine exposure in patient years by duration of exposure**								
	>=1 d	**>=2 wk**	**>=1 mo**	**>=3 mo**	**>=6 mo**	**>=9 mo**	**>=12 mo**	**>=24 mo**	**>=36 mo**
By indication									
Schizophrenia[a] (n)[b]	156.9 (1875)	149.7 (1498)	128.6 (1120)	NA	NA	NA	NA	NA	NA
Bipolar depression (n)[b]	257.3 (1996)	252.2 (1719)	239.2 (1501)	0.3 (1)	NA	NA	NA	NA	NA

BP mania/mixed[b] (n)[b]	79.3 (732)	76.8 (580)	62.3 (326)	1.8 (7)	NA	NA	NA	NA	NA
MDD (n)[b]	212.2 (1942)	208.2 (1710)	196.9 (1514)	NA	NA	NA	NA	NA	NA
GAD (n)[b]	260.6 (2001)	256.0 (1729)	244.4 (1532)	0.5 (2)	NA	NA	NA	NA	NA
Other[c] (n)[b]	58.2 (496)	55.5 (344)	52.2 (290)	NA	NA	NA	NA	NA	NA
Peds Schizophrenia[d] (n)[b]	16.2 (147)	16.1 (142)	14.9 (123)	NA	NA	NA	NA	NA	NA
Peds BP mania/mixed (n)[b]	23.4 (285)	22.7 (255)	12.0 (82)	NA	NA	NA	NA	NA	NA
By age group									
Pediatric <13 (n)[b]	8.4 (110)	8.1 (100)	3.4 (23)	NA	NA	NA	NA	NA	NA
Pediatric 13-17 (n)[b]	31.2 (322)	30.7 (297)	23.5 (182)	NA	NA	NA	NA	NA	NA
Pediatric <18 (n)[b]	39.5 (432)	38.8 (397)	26.9 (205)	NA	NA	NA	NA	NA	NA
Adult 18-65 (n)[b]	907.7 (8282)	882.3 (6861)	813.0 (5650)	2.6 (10)	NA	NA	NA	NA	NA
Elderly >65 (n)[b]	116.7 (760)	115.9 (719)	110.5 (633)	NA	NA	NA	NA	NA	NA
Elderly >74 (n)[b]	58.5 (389)	58.0 (362)	54.5 (305)	NA	NA	NA	NA	NA	NA

Total (n)[b]	**1063.9 (9474)**	**1037.1 (7977)**	**950.4 (6488)**	**2.6 (10)**	**NA**	**NA**	**NA**	**NA**	**NA**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dur_pla_ctrl.SAS. Data version: V27. User: [redacted] 2014-07-21 13:21.

Table 39 Quetiapine exposure by indication and age group relative to mean daily dose (all placebo-controlled trials)

Population grouping	**Quetiapine exposure in patient years by mean daily dose**									**Other**	
	<100	**100 to 199**	**200 to 299**	**300 to 399**	**400 to 499**	**500 to 599**	**600 to 699**	**700 to 799**	**>799**	**Mean of mean daily dose(mg)**	**Mean maximum dose (mg)**
By indication											
Schizophrenia[a]	3.6 (85)	6.0 (112)	19.0 (246)	43.0 (495)	6.7 (118)	38.4 (407)	5.2 (70)	34.9 (342)	NA	456.5 (1875)	512.4 (1875)
Bipolar depression	0.4 (55)	1.0 (62)	146.8 (1099)	1.9 (54)	9.6 (100)	97.5 (625)	0.1 (1)	NA	NA	360.0 (1996)	421.8 (1996)
BP mania/mixed[b]	0.1 (15)	1.4 (33)	7.7 (91)	18.8 (141)	9.5 (103)	15.3 (152)	10.6 (93)	15.9 (103)	0.1 (1)	475.8 (732)	578.0 (732)
MDD	21.0 (267)	114.7 (1009)	76.5 (666)	NA	NA	NA	NA	NA	NA	173.7 (1942)	194.1 (1942)
GAD	65.2 (551)	120.7 (930)	74.7 (520)	NA	NA	NA	NA	NA	NA	150.1 (2001)	169.9 (2001)

Other[c]	29.2 (201)	27.9 (289)	1.1 (6)	NA	NA	NA	NA	NA	NA	132.6 (496)	169.1 (496)
Peds Schizophrenia[d]	0.0 (1)	0.0 (1)	0.1 (3)	8.0 (71)	NA	0.2 (4)	1.6 (15)	6.3 (52)	NA	524.7 (147)	614.3 (147)
Peds BP mania/mixed	0.0 (3)	6.7 (58)	6.2 (49)	5.2 (87)	3.2 (55)	2.1 (33)	NA	NA	NA	331.8 (285)	436.3 (285)
By age group											
Pediatric <13	0.0 (1)	1.8 (13)	1.9 (16)	2.3 (39)	1.4 (25)	1.0 (16)	NA	NA	NA	360.2 (110)	473.5 (110)
Pediatric 13-17	0.0 (3)	5.0 (46)	4.4 (36)	10.8 (119)	1.8 (30)	1.3 (21)	1.6 (15)	6.3 (52)	NA	410.2 (322)	504.8 (322)
Pediatric <18	0.0 (4)	6.7 (59)	6.2 (52)	13.1 (158)	3.2 (55)	2.4 (37)	1.6 (15)	6.3 (52)	NA	397.5 (432)	496.8 (432)
Adult 18-65	82.9 (913)	213.9 (2067)	304.3 (2503)	63.6 (689)	25.4 (319)	151.1 (1183)	15.8 (163)	50.6 (444)	0.1 (1)	303.4 (8282)	348.3 (8282)
Elderly >65	36.6 (261)	57.8 (368)	21.4 (125)	0.1 (1)	0.3 (2)	0.1 (1)	0.1 (1)	0.2 (1)	NA	149.1 (760)	186.8 (760)
Elderly >74	27.8 (195)	26.9 (173)	3.5 (20)	NA	NA	NA	NA	0.2 (1)	NA	129.1 (389)	158.1 (389)
Total	**119.5 (1178)**	**278.4 (2494)**	**331.9 (2680)**	**76.8 (848)**	**28.9 (376)**	**153.6 (1221)**	**17.5 (179)**	**57.1 (497)**	**0.1 (1)**	**295.3 (9474)**	**342.1 (9474)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_meandose_pla_ctrl.SAS. Data version: V27. User: [redacted] 2014-07-21 13:22.

Table 40 Adult exposure to quetiapine by indication and demographic characteristics (all placebo-controlled monotherapy trials)

Population grouping	Total exposure in patient years	Exposure in patient years by demographic characteristic (n)									
		Sex		Race					Age group		
		M	F	White	Black	Asian	Hispanic	Other[b]	18-65	>65	>74
By indication											
Schizophrenia[a]	156.9 (N=1875)[b]	109.6 (1334)	47.3 (541)	83.1 (992)	45.0 (573)	19.6 (190)	5.6 (76)	3.5 (44)	156.9 (1875)	NA	NA
Bipolar depression	257.3 (N=1996)[b]	106.6 (819)	150.7 (1177)	176.7 (1375)	32.4 (262)	31.0 (233)	10.6 (70)	6.6 (56)	257.3 (1996)	NA	NA
BP mania/mixed	43.4 (N=360)[b]	22.5 (190)	20.9 (170)	25.8 (207)	3.7 (72)	12.8 (70)	0.5 (2)	0.6 (9)	42.3 (353)	1.1 (7)	0.5 (2)
MDD	148.8 (N=1315)[b]	55.8 (502)	93.0 (813)	110.2 (973)	28.2 (254)	6.0 (50)	3.3 (28)	1.1 (10)	123.7 (1149)	25.2 (166)	4.9 (36)
GAD	260.6 (N=2001)[b]	87.6 (686)	172.9 (1315)	226.4 (1740)	24.9 (190)	2.3 (16)	4.0 (32)	3.0 (23)	225.4 (1777)	35.1 (224)	5.4 (37)
Other[c]	58.2 (N=496)[b]	16.0 (180)	42.2 (316)	46.9 (326)	6.3 (79)	0.6 (3)	4.2 (83)	0.1 (5)	3.3 (137)	54.8 (359)	47.8 (314)

By age group											
Adult 18-65	808.9 (N=7287)[b]	366.3 (3507)	442.6 (3780)	561.9 (4915)	135.1 (1393)	71.6 (558)	25.4 (274)	14.8 (147)	808.9 (7287)	NA	NA
Elderly >65	116.2 (N=756)[b]	31.8 (204)	84.4 (552)	107.2 (698)	5.5 (37)	0.7 (4)	2.8 (17)	NA	NA	116.2 (756)	NA
Elderly >74	58.5 (N=389)[b]	14.4 (95)	44.1 (294)	51.3 (343)	3.9 (27)	0.6 (3)	2.6 (16)	NA	NA	NA	58.5 (389)
Total	**925.1 (N=8043)[b]**	**398.1 (3711)**	**527.0 (4332)**	**669.1 (5613)**	**140.6 (1430)**	**72.3 (562)**	**28.2 (291)**	**14.8 (147)**	**808.9 (7287)**	**116.2 (756)**	**58.5 (389)**

a Or schizoaffective disorders.
b Patients from studies included in the quetiapine integrated clinical-study safety database.
c Including dementia-related psychoses.
b Inlcudes 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_adult_pla_mono.SAS. Data version: V27. User: [redacted] 2014-07-21 13:19.

Table 41 Pedriatric (<18 years old) exposure to quetiapine by indication and demographic characteristics (all placebo-controlled monotherapy trials)

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**									
		Sex		**Race**					**Age group**		
		M	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<13**	**13-17**	**<18**
By indication											
Peds Schizophrenia[a]	16.2 (N=147)	9.9 (87)	6.3 (60)	9.7 (89)	1.7 (16)	3.3 (29)	1.1 (9)	0.3 (4)	NA	16.2 (147)	16.2 (147)

Peds BP mania/mixed	23.4 (N=285)	12.4 (150)	10.9 (135)	17.2 (214)	3.5 (42)	0.5 (4)	0.7 (12)	1.4 (13)	8.4 (110)	15.0 (175)	23.4 (285)
By age group											
Pediatric <13	8.4 (N=110)	4.5 (58)	3.9 (52)	6.3 (87)	1.5 (17)	NA	0.1 (2)	0.5 (4)	NA	NA	NA
Pediatric 13-17	31.2 (N=322)	17.8 (179)	13.4 (143)	20.6 (216)	3.7 (41)	3.8 (33)	1.7 (19)	1.3 (13)	NA	NA	NA
Pediatric <18	39.5 (N=432)	22.3 (237)	17.2 (195)	27.0 (303)	5.2 (58)	3.8 (33)	1.8 (21)	1.8 (17)	NA	NA	NA
Total	**39.5 (N=432)**	**22.3 (237)**	**17.2 (195)**	**27.0 (303)**	**5.2 (58)**	**3.8 (33)**	**1.8 (21)**	**1.8 (17)**	**8.4 (110)**	**31.2 (322)**	**39.5 (432)**

a Includes schizoaffective disorders.
b Inlcudes races of 'Mixed, Other' and 'Not specified'.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Note: Patient's age is given at the start of the clinical trial.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_ped_pla_mono.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 42 Exposure to quetiapine by indication and demographic characteristics: all placebo-controlled monotherapy studies

Population grouping	**Total exposure in patient years**	**Exposure in patient years by demographic characteristic (n)**										
		Sex		**Race**					**Age group**			
		M	**F**	**White**	**Black**	**Asian**	**Hispanic**	**Other[b]**	**<18**	**18-65**	**>65**	**>74**
By indication												

Schizophrenia[a]	173.1 (N=2022)	119.5 (1421)	53.6 (601)	92.8 (1081)	46.7 (589)	22.9 (219)	6.8 (85)	3.8 (48)	16.2 (147)	156.9 (1875)	NA	NA
Bipolar depression	257.3 (N=1996)	106.6 (819)	150.7 (1177)	176.7 (1375)	32.4 (262)	31.0 (233)	10.6 (70)	6.6 (56)	NA	257.3 (1996)	NA	NA
BP mania/mixed	66.7 (N=645)	34.9 (340)	31.8 (305)	43.0 (421)	7.3 (114)	13.3 (74)	1.2 (14)	2.0 (22)	23.4 (285)	42.3 (353)	1.1 (7)	0.5 (2)
MDD	148.8 (N=1315)	55.8 (502)	93.0 (813)	110.2 (973)	28.2 (254)	6.0 (50)	3.3 (28)	1.1 (10)	NA	123.7 (1149)	25.2 (166)	4.9 (36)
GAD	260.6 (N=2001)	87.6 (686)	172.9 (1315)	226.4 (1740)	24.9 (190)	2.3 (16)	4.0 (32)	3.0 (23)	NA	225.4 (1777)	35.1 (224)	5.4 (37)
Other[b]	58.2 (N=496)	16.0 (180)	42.2 (316)	46.9 (326)	6.3 (79)	0.6 (3)	4.2 (83)	0.1 (5)	NA	3.3 (137)	54.8 (359)	47.8 (314)
By age group												
Pediatric <13	8.4 (N=110)	4.5 (58)	3.9 (52)	6.3 (87)	1.5 (17)	NA	0.1 (2)	0.5 (4)	NA	NA	NA	NA
Pediatric 13-17	31.2 (N=322)	17.8 (179)	13.4 (143)	20.6 (216)	3.7 (41)	3.8 (33)	1.7 (19)	1.3 (13)	NA	NA	NA	NA
Pediatric <18	39.5 (N=432)	22.3 (237)	17.2 (195)	27.0 (303)	5.2 (58)	3.8 (33)	1.8 (21)	1.8 (17)	39.5 (432)	NA	NA	NA
Adult 18-65	808.9 (N=7287)	366.3 (3507)	442.6 (3780)	561.9 (4915)	135.1 (1393)	71.6 (558)	25.4 (274)	14.8 (147)	NA	808.9 (7287)	NA	NA
Elderly >65	116.2 (N=756)	31.8 (204)	84.4 (552)	107.2 (698)	5.5 (37)	0.7 (4)	2.8 (17)	NA	NA	NA	116.2 (756)	NA
Elderly >74	58.5 (N=389)	14.4 (95)	44.1 (294)	51.3 (343)	3.9 (27)	0.6 (3)	2.6 (16)	NA	NA	NA	NA	58.5 (389)

Total	**964.6 (N=8475)**	**420.4 (3948)**	**544.3 (4527)**	**696.1 (5916)**	**145.8 (1488)**	**76.0 (595)**	**30.0 (312)**	**16.6 (164)**	**39.5 (432)**	**808.9 (7287)**	**116.2 (756)**	**58.5 (389)**

a Includes schizoaffective disorders.
b Including dementia-related psychoses.
c Inlcudes races of 'Mixed, Other' and 'Not specified'.
Note: Patient years calculated as days of total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dem_pla_mono.SAS. Data version: V27. User: [redacted] 2014-07-21 13:20.

Table 43 Quetiapine exposure by indication and age group relative to duration of treatment (all placebo-controlled monotherapy trials)

Population grouping	**Quetiapine exposure in patient years by duration of exposure**								
	>=1 d	**>=2 wk**	**>=1 mo**	**>=3 mo**	**>=6 mo**	**>=9 mo**	**>=12 mo**	**>=24 mo**	**>=36 mo**
				By indication					
Schizophrenia[a]	156.9	149.7	128.6	NA	NA	NA	NA	NA	NA
(n)[b]	(1875)	(1498)	(1120)						
Bipolar depression	257.3	252.2	239.2	0.3	NA	NA	NA	NA	NA
(n)[b]	(1996)	(1719)	(1501)	(1)					
BP mania/mixed[b]	43.4	42.4	33.6	NA	NA	NA	NA	NA	NA
(n)[b]	(360)	(309)	(156)						
MDD	148.8	145.7	137.5	NA	NA	NA	NA	NA	NA
(n)[b]	(1315)	(1142)	(1000)						
GAD	260.6	256.0	244.4	0.5	NA	NA	NA	NA	NA
(n)[b]	(2001)	(1729)	(1532)	(2)					
Other[c]	58.2	55.5	52.2	NA	NA	NA	NA	NA	NA
(n)[b]	(496)	(344)	(290)						

Peds Schizophrenia[d] (n)[b]	16.2 (147)	16.1 (142)	14.9 (123)	NA	NA	NA	NA	NA	NA
Peds BP mania/mixed (n)[b]	23.4 (285)	22.7 (255)	12.0 (82)	NA	NA	NA	NA	NA	NA
By age group									
Pediatric <13 (n)[b]	8.4 (110)	8.1 (100)	3.4 (23)	NA	NA	NA	NA	NA	NA
Pediatric 13-17 (n)[b]	31.2 (322)	30.7 (297)	23.5 (182)	NA	NA	NA	NA	NA	NA
Pediatric <18 (n)[b]	39.5 (432)	38.8 (397)	26.9 (205)	NA	NA	NA	NA	NA	NA
Adult 18-65 (n)[b]	808.9 (7287)	786.0 (6026)	725.4 (4970)	0.8 (3)	NA	NA	NA	NA	NA
Elderly >65 (n)[b]	116.2 (756)	115.5 (715)	110.1 (629)	NA	NA	NA	NA	NA	NA
Elderly >74 (n)[b]	58.5 (389)	58.0 (362)	54.5 (305)	NA	NA	NA	NA	NA	NA
Total (n)[b]	**964.6 (8475)**	**940.3 (7138)**	**862.4 (5804)**	**0.8 (3)**	**NA**	**NA**	**NA**	**NA**	**NA**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_dur_pla_mono.SAS. Data version: V27. User: [redacted] 2014-07-21 13:21.

Table 44 Quetiapine exposure by indication and age group relative to mean daily dose (all placebo-controlled monotherapy trials)

Population grouping	Quetiapine exposure in patient years by mean daily dose									Other	
	<100	100 to 199	200 to 299	300 to 399	400 to 499	500 to 599	600 to 699	700 to 799	>799	Mean of mean daily dose(mg)	Mean maximum dose (mg)
By indication											
Schizophrenia[a]	3.6 (85)	6.0 (112)	19.0 (246)	43.0 (495)	6.7 (118)	38.4 (407)	5.2 (70)	34.9 (342)	NA	456.5 (1875)	512.4 (1875)
Bipolar depression	0.4 (55)	1.0 (62)	146.8 (1099)	1.9 (54)	9.6 (100)	97.5 (625)	0.1 (1)	NA	NA	360.0 (1996)	421.8 (1996)
BP mania/mixed[b]	NA	0.2 (3)	2.6 (16)	2.9 (26)	4.5 (57)	10.2 (103)	8.2 (62)	14.7 (92)	0.1 (1)	573.4 (360)	677.5 (360)
MDD	20.9 (245)	81.7 (690)	46.3 (380)	NA	NA	NA	NA	NA	NA	160.5 (1315)	182.6 (1315)
GAD	65.2 (551)	120.7 (930)	74.7 (520)	NA	NA	NA	NA	NA	NA	150.1 (2001)	169.9 (2001)
Other[c]	29.2 (201)	27.9 (289)	1.1 (6)	NA	NA	NA	NA	NA	NA	132.6 (496)	169.1 (496)
Peds Schizophrenia[d]	0.0 (1)	0.0 (1)	0.1 (3)	8.0 (71)	NA	0.2 (4)	1.6 (15)	6.3 (52)	NA	524.7 (147)	614.3 (147)
Peds BP mania/mixed	0.0 (3)	6.7 (58)	6.2 (49)	5.2 (87)	3.2 (55)	2.1 (33)	NA	NA	NA	331.8 (285)	436.3 (285)
By age group											

Pediatric <13	0.0 (1)	1.8 (13)	1.9 (16)	2.3 (39)	1.4 (25)	1.0 (16)	NA	NA	NA	360.2 (110)	473.5 (110)
Pediatric 13-17	0.0 (3)	5.0 (46)	4.4 (36)	10.8 (119)	1.8 (30)	1.3 (21)	1.6 (15)	6.3 (52)	NA	410.2 (322)	504.8 (322)
Pediatric <18	0.0 (4)	6.7 (59)	6.2 (52)	13.1 (158)	3.2 (55)	2.4 (37)	1.6 (15)	6.3 (52)	NA	397.5 (432)	496.8 (432)
Adult 18-65	82.7 (876)	179.7 (1718)	269.2 (2144)	47.8 (575)	20.5 (273)	146.1 (1135)	13.4 (132)	49.4 (433)	0.1 (1)	308.2 (7287)	352.7 (7287)
Elderly >65	36.6 (261)	57.8 (368)	21.2 (123)	NA	0.3 (2)	NA	0.1 (1)	0.2 (1)	NA	148.0 (756)	185.4 (756)
Elderly >74	27.8 (195)	26.9 (173)	3.5 (20)	NA	NA	NA	NA	0.2 (1)	NA	129.1 (389)	158.1 (389)
Total	**119.4 (1141)**	**244.2 (2145)**	**296.6 (2319)**	**61.0 (733)**	**24.0 (330)**	**148.5 (1172)**	**15.1 (148)**	**55.9 (486)**	**0.1 (1)**	**298.5 (8475)**	**345.1 (8475)**

a Or schizoaffective disorders (pediatric studies excluded).
b Pediatric studies excluded.
c Including dementia-related psychoses.
d Or schizoaffective disorders.
BP Bipolar depression. GAD Generalized anxiety disorder. MDD Major depressive disorder.
Note: Patient years calculated as total exposure/365.25. Only quetiapine-treated patients are included.
Pgm: SESOD...\Reg-Def_PRMP Jun 2014_Exp_all_by_meandose_pla_mono.SAS. Data version: V27. User: [redacted] 2014-07-21 13:22.

1.1.5 By pool

Table 45 Number of patients and exposure by pool

Pool	Treatment	Number of patients	Exposure
All studies	Chlorpromazine	541	66.59
	Duloxetine	149	15.96
	Escitalopram	365	49.19
	Haloperidol	1033	180.58
	Lithium	622	189.84
	Mosapramine	90	10.44
	Olanzapine	168	71.18
	Paroxetine	336	43.51
	Placebo	7016	1283.16
	Quetiapine	28576	8587.92
	Risperidone	1383	721.39
All placebo-controlled trials	Placebo	4992	578.84
	Quetiapine	9474	1063.86
All relapse prevention trials	Placebo	2016	704.27
	Quetiapine	2043	1025.95
All OLE trials with placebo-controlled part 1	Placebo	259	84.89
	Quetiapine	537	237.74
All OL trials	Olanzapine	168	71.18
	Quetiapine	16826	5853.66
	Risperidone	842	655.2
All OL trials with relapse prevention part	Quetiapine	9208	2427.5

Note: Part 2 of studies 5077IL/0049, 50, 52, 53, 54 and 72 corresponds to open label extension study 5077IL/0051
Note: Part 2 of studies 5077IL/0056, 63, 64 and 65 corresponds to open label extension study 5077IL/0057
Note: Part 2 of studies D1441C00112 and D1441C00149 corresponds to open label extension study D1441C00150
Note: Treatment from placebo-controlled part presented for part All OLE trials with placebo-controlled part 1
Note: Patient years calculated as total exposure/365.25.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\Exp_by_pool_DB27.SAS. Data version: V27. User: [redacted] 2014-07-21 13:22.

1.2 Clinical studies

1.2.1 Clinical studies supporting SEROQUEL XR use in patients with MDD

Table 46 Clinical studies supporting SEROQUEL XR use in patients with MDD

Study ID	Study design (Phase III)	Study drug and dosage (mg/day) (fixed unless otherwise noted)		Duration of treatment
Short-term monotherapy		**Treatment**	**No. exposed**	
D1448C 00001	Multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	QTP XR 50 QTP XR 150 QTP XR 300 Placebo once daily	181 176 179 181	6 weeks active tx[a] plus 2 weeks monitoring[b]
D1448C 00002	Multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled, active-controlled	QTP XR 150 QTP XR 300 DUL 60 Placebo once daily	152 152 149 157	6 weeks active tx[a] plus 2 weeks monitoring[c]
D1448C 00003	Multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	QTP XR 150 or 300 [d] Placebo once daily[d]	152 155	8 weeks active tx[a] plus 2 weeks monitoring[b]
D1448C 00004	Multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled, active-controlled	QTP XR 150 or 300[d] ESC 10 or 20[d] Placebo once daily	157 156 155	8 weeks active tx[a] plus 2 weeks monitoring[c]
D1448C 00014 (elderly)	Multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	Flexible dosing: QTP XR 50 to 300 Placebo once daily	 166 172	9 weeks active tx[a] plus 2 weeks monitoring[b]
Short-term adjunct to ongoing antidepressant				
D1448C 00006	Multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	QTP XR 150[e] QTP XR 300[e] Placebo once daily[e]	150 148 148	6 weeks active tx[f] plus 2 weeks monitoring[b]
D1448C 00007	Multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled	QTP XR 150 QTP XR 300 Placebo once daily	167 163 161	6 weeks active tx[f]
Longer-term maintenance				
D1448C 00005	Multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled w/ 4 periods: enrollment, open-label run-in, open-label stabilization, and randomized withdrawal	Flexible dosing: QTP XR 50, 150, or 300[g] QTP XR 50, 150, or 300 Placebo once daily in randomized phase	 1876 open-label QTP 391 randomized phase 385 randomized phase	4 to 6 weeks open-label tx[a]; 12 to 18 weeks stabilization; up to 52 weeks double blind tx with QTP or placebo

[a] Treatment preceded by washout period of ≤28 days.
[b] Refers to 2-week monitoring of discontinuation symptoms after abrupt discontinuation.
[c] Refers to 2-week monitoring of discontinuation symptoms after abrupt discontinuation for QTP XR 150 mg group and dose decrease to 150 mg daily for QTP XR 300 mg group (first 7 days of follow-up period).
[d] Modified fixed dose: patients with inadequate response after 2 weeks of treatment were given the same treatment at double the starting dose (QTP XR 150 mg) for the remainder of the trial.
[e] As an adjunct to amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine.
[f] Treatment preceded by washout period of ≤14 days.
[g] QTP 300-mg dose not given during open-label run-in period.

DUL Duloxetine. ESC Escitalopram. QTP XR Quetiapine extended release. tx Treatment. w/ with.

1.2.2 Human safety database of patients with bipolar depression treated with SEROQUEL

Table 47 Clinical studies supporting SEROQUEL use in bipolar depression

Study ID	Study design	Study drug and dosage (mg/day) (fixed unless otherwise noted)		Duration of treatment
Short term: bipolar disorder w/ acute depressive episode		**Treatment**	**No. exposed**	
5077US/0049[a]	Multicenter, double-blind, randomized, parallel-group, placebo-controlled, double-dummy	QTP 300/QTP 600 Placebo once day	179/180 180	56 days (8 weeks)
D1447C 000135[a]	Multicenter, double-blind, randomized, parallel-group, placebo-controlled	QTP 300/QTP 600 Placebo once day	171/168 168	56 days (8 weeks)
Short-term with continuation phase: bipolar disorder w/ acute depressive episode				
D1447C 00001[b]	Multicenter, double-blind, randomized, parallel-group, placebo-controlled, double-dummy	QTP 300/QTP 600 Placebo once day Lithium 600 to1800 bid	260/267 131 136	56 days (8 weeks)
D1447C 00134 [b]	Multicenter, double-blind, randomized, parallel-group, placebo-controlled, double-dummy	QTP 300/QTP 600 Placebo once day PAR 20	243/244 124 121	56 days (8 weeks)
Longer-term (recurrence prevention): bipolar disorder w/ acute depressive episode				
D1447C 00001[b]	Continuation phase: prevention of mood episode recurrence	QTP 300/QTP 600 Placebo once day Switched to QTP 300 (nonrandomized)	80/84 165 63 from acute placebo 74 from acute lithium	Up to 52 weeks
D1447C 00134[b]	Continuation phase: prevention of mood episode recurrence	QTP 300./QTP 600 Placebo once day Switched to QTP 300 (nonrandomized)	61/66 129 60 from acute placebo 50 from acute PAR	Up to 52 weeks

[a] US only (BOLDER studies).
[b] International including Europe, Americas, Asia, South Africa, and Australia (EMBOLDEN studies).
PAR Paroxetine. QTP Quetiapine

1.2.3 Human safety database of patients with bipolar disorder treated with SEROQUEL for recurrence prevention

Table 48 Longer-term clinical studies supporting SEROQUEL use for recurrence prevention in patients with bipolar disorder

Study ID	Study design	Study drug and dosage (mg/day) (fixed unless otherwise noted)		Duration of treatment
Longer-term (recurrence prevention): bipolar disorder		**Treatment**	**No. exposed**	
D1447C 00144	Multicenter, randomized, parallel-group, double-blind, double dummy placebo-controlled w/ 3 phases: enrollment, open-label stabilization, and randomized treatment	Flexible: QTP 300 to 800 (divided doses) Lithium 600 to 1800[a] Placebo	 2428 open-label QTP 404 randomized phase 404 randomized phase 418 randomized phase	4 to 24 weeks of open-label QTP treatment; up to 104 weeks of treatment with QTP, placebo, or lithium
Longer-term, adjunct (recurrence prevention): bipolar I disorder & most recent episode manic, depressed, or mixed[b]				
D1447C 00127	Multicenter, double-blind, randomized, parallel-group, placebo-controlled w/ open-label stabilization run-in phase	QTP 400 to 800 (2 divided doses) Placebo Adjunct lithium (LI) or valproate (VAL)[c]	1938 open-label QTP 310 w/ LI or VAL[d] 313 w/ LI or VAL[d]	12 to 36 weeks of open-label QTP treatment; up to 104 weeks of double-blind treatment with QTP or placebo

Table 48 Longer-term clinical studies supporting SEROQUEL use for recurrence prevention in patients with bipolar disorder

Study ID	Study design	Study drug and dosage (mg/day) (fixed unless otherwise noted)		Duration of treatment
D1447C 00126	Multicenter, double-blind, randomized, parallel-group, placebo-controlled w/ open-label stabilization run-in phase	QTP 400 to 800 (2 divided doses) Placebo Adjunct lithium or valproate[c]	1433 open-label QTP 336 w/ LI or VAL[d] 367 w/ LI or VAL[d]	12 to 36 weeks of open-label QTP treatment; up to 104 weeks of double-blind treatment with QTP or placebo

[a] Target trough serum concentrations of 0.6 mEq/L to 1.2 mEq/L.
[b] With or without psychotic features.
[c] Target trough serum concentrations: lithium, 0.5 to 1.2 mEq/L; valproate, 50 to125 µg/ml.
[d] Randomized treatment phase.

LI Lithium. QTP Quetiapine. VAL Valproate.

1.2.4 Clinical studies supporting SEROQUEL XR use in patients with depressive or manic episodes in bipolar disorder

Table 49 Clinical studies supporting SEROQUEL XR use in patients with depressive or manic episodes in bipolar disorder

Study ID	Study design (Phase III)	Study drug and dosage (mg/day) (fixed unless otherwise noted)[a]		Duration of treatment
Short-term monotherapy		**Treatment**	**No. exposed**	
D144CC 00002	Multicenter, double-blind, randomized, parallel-group, placebo-controlled in patients with bipolar disorder I or bipolar disorder II with acute depressive episode	QTP XR 300 in pm Placebo once daily in pm	137 140	8 weeks
D144CC 00004	Multicenter, randomized, parallel-group, double blind placebo-controlled in patients with bipolar I disorder with an acute manic episode	Flexible: QTP XR 400 to 800 in pm Placebo once daily in pm	 151 160	3 weeks
Short-term adjunct therapy with or without lithium (Phase IV)				
D144AC 00003	Multicenter, double-blind, randomized, placebo-controlled, Phase IV study of the safety and efficacy of lithium versus placebo as an add on to SEROQUEL XR™ (Quetiapine Fumarate) in adult patients with acute mania	Flexible: Open label QTP XR 300 to 800 in pm Placebo or lithium (600-1800mg) twice daily	356 open-label QTP XR 173 (adjunct lithium) 183 (placebo)	6 weeks

QTP XR Quetiapine extended release.

1.2.5 Clinical efficacy studies supporting SEROQUEL XR use in patients with schizophrenia

Table 50 Clinical efficacy studies supporting SEROQUEL XR use in patients with schizophrenia

Study ID	Study design	Study drug and dosage (mg/day) (fixed unless otherwise noted)[a]		Duration of treatment
Short-term (acute schizophrenia)		**Treatment**	**No. exposed**	
D1444C 00132	Multicenter, placebo-controlled, double-blind, double-dummy, randomized, parallel-group study (IR treatment arm included to demonstrate assay sensitivity and provide guidance for XR-IR comparability)	QTP XR 400 in pm[a] QTP XR 600 in pm[a] QTP XR 800 in pm[a] QTP IR 400 bid Placebo bid	113 113 121 123 118	6 weeks
D1444C 00133	Multicenter, placebo-controlled, double-blind, double-dummy, randomized, parallel-group study (IR treatment arm included to demonstrate assay sensitivity and provide guidance for XR-IR comparability)	QTP XR 400 in pm[a] QTP XR 600 in pm[a] QTP XR 800 in pm[a] QTP IR 800 bid Placebo bid	112 101 110 108 111	6 weeks
5077IL/ 0041	Multicenter, placebo-controlled, double-blind, double-dummy, randomized, parallel-group study (IR treatment arm included to demonstrate assay sensitivity and provide guidance for XR-IR comparability)	QTP XR 300 in am[b] QTP XR 600 in am[b] QTP XR 800 in am[b] QTP IR 300 bid QTP IR 600 bid Placebo bid	91 92 89 90 86 84	6 weeks
Switching study				
D1444C 00146	Multicenter, double-blind, double-dummy, randomized, parallel-group study to demonstrate continued efficacy/safety after random switch from treatment w/ QTP IR to an equivalent total daily dose of QTP XR or continued treatment w/ QTP IR after 4-week run-in period with QTP IR	QTP IR QTP 400: XR/IR QTP 600: XR/IR QTP 800: XR/IR	497 run-in 153/76 117/58 61/32	Run-in: 4 weeks Double-blind: 6 weeks
Longer-term (relapse prevention)				
D1444C 00004	Multicenter, randomized, double-blind, parallel group, placebo-controlled with 16-week open-label stabilization period	Flexible: QTP XR 400 to 800 QTP XR 400/600/800 Placebo	 327 (open-label) 94 103	1 year or until relapse[c]

[a] Morning dose was placebo.
[b] Evening dose was placebo.
[c] The protocol-specified interim analysis in Study 00004, performed by an independent drug safety monitoring board (DSMB) after 45 reported relapses, showed that quetiapine XR significantly prolonged time to relapse compared with placebo. Based on these results and the recommendation of the DSMB, the study was terminated. Patients were followed for up to 9 months.

QTP IR Quetiapine immediate release. QTP XR Quetiapine extended release

1.2.6 Phase III elderly-specific clinical studies supporting SEROQUEL/SEROQUEL XR use in elderly patients

Table 51 Phase III elderly-specific clinical studies supporting SEROQUEL/SEROQUEL XR use in elderly patients

Study ID	Study design (Phase III)	Study drug and dosage (mg/day)		Duration of treatment
Short-term monotherapy		**Treatment**	**No. exposed**	
D1448C 00015	Multicenter, randomized, double-blind, parallel-group, placebo-controlled; 2-week post-treatment follow-up period; elderly patients (>65 yr) with GAD	Flexible dosing: QTP XR 50 to 300	223 (13% >75 yr)	9 weeks active treatment plus 2 weeks monitoring
D1448C 00014	Multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled; elderly patients (>65 yr) with MDD	Flexible dosing: QTP XR 50 to 300	166 (18% >75 yr)	9 weeks active treatment plus 2 weeks monitoring
D1446L 00002[a]	Multicenter, double-blind, randomized, placebo-controlled; elderly patients (>55 yr) with agitation associated with Alzheimer's or vascular dementia	Fixed dosing: QTP 100 QTP 200	 122 (≥65 yr) 114 (≥65 yr)	10 weeks
5077IL 0115	Exploratory, multicenter, double-blind, double-dummy, randomized, controlled, parallel group; elderly patients (≥65 yr) with Alzheimer's disease and symptoms of psychosis/agitation	Flexible dosing: QTP/QTP XR 50 to 300 (25 mg QTP on day 1)	 32/68	6 weeks
Combination short- and longer-term active-controlled				
5077IL 0039	Multicenter, double-blind, randomized, controlled, with screening phase and OLE treatment phase; elderly patients (residents) (>65 yr) with Alzheimer's dementia/psychoses	Flexible dosing: QTP 25 to 600 or 800 (depending on phase) (median: 96.0)	124	10 weeks double-blind treatment, plus 12 weeks OLE

[a] Also known as 5077US/0046.
GAD Generalised anxiety disorder. MDD Major depressive disorder. OLE Open-label extension. QTP Quetiapine. XR Extended release.

1.2.7 Clinical studies supporting SEROQUEL/SEROQUEL XR use in pediatric patients

Table 52 Clinical studies supporting SEROQUEL/SEROQUEL XR use in pediatric patients

Study ID	Study design	Study drug and dosage (mg/day) (fixed unless otherwise noted)		Duration of treatment
Pharmacokinetics (Phase I)		**Treatment**	**No. exposed**	
5077IL/ 0038	Open-label, rising multiple-dose, pharmacokinetics and tolerability in pediatric patients with selected psychiatric disorders	QTP 50 to 800 (rising dose)	10	21 days plus 6 extra if needed to tolerate dose escalation
D1441C 00028	Multicenter, open-label in-patient, steady-state pharmacokinetics, safety, and tolerability in pediatric patients with selected psychiatric disorders	QTP 50 to 800 in 2 divided doses (dose escalation over 11 days)	27	13 days
Short-term (Phase IIIb)				
D1441C 00112	Placebo-controlled monotherapy in adolescents (13 to 17 yrs) with schizophrenia[a]	QTP 400 QTP 800 Placebo (2 to 3 divided doses)	73 74 75	6 weeks

Table 52 Clinical studies supporting SEROQUEL/SEROQUEL XR use in pediatric patients

Study ID	Study design	Study drug and dosage (mg/day) (fixed unless otherwise noted)		Duration of treatment
D1441C 00149	Placebo-controlled monotherapy in pediatric patients (10 to 17 yrs) with bipolar I mania[a]	QTP 400 QTP 600 Placebo (2 to 3 divided doses)	95 98 90	3 weeks
D144AC 00001	Multicenter, double-blind, randomized, parallel-group, placebo-controlled efficacy and safety in children and adolescent with bipolar depression	QTP XR 50 to 150 by Day 3, up to 300 per patient response (1 dose in evening)	192 with bipolar depression	8 weeks
Longer-term (6-month)				
D1441C 00150	Multicenter, single-arm, flexible-dose open-label extension for Studies 00112 and 00149 (placebo-controlled studies)	QTP 50 to 400 by Day 5, up to 800 per patient response (2 to 3 divided doses)	175 with schizophrenia 205 with bipolar I mania	26 weeks

QTP Quetiapine.

1.2.8 Clinical studies supporting SEROQUEL XR use in patients with GAD

Table 53 Clinical studies supporting SEROQUEL XR use in patients with GAD

Study ID	Study design (Phase III)	Study drug and dosage (mg/day) (fixed unless otherwise noted)[a]		Duration of treatment
Short-term monotherapy		**Treatment**	**No. exposed**	
D1448C 00009	Multicenter, randomized, double-blind, parallel-group, placebo-controlled; 2-week post-treatment follow-up period	QTP XR 50 QTP XR 150 QTP XR 300 Placebo once daily	232 238 238 234	8 weeks active tx plus 2 weeks monitoring
D1448C 00010	Multicenter, randomized, double-blind, parallel-group, placebo-controlled, active-controlled; 2-week post-treatment follow-up period	QTP XR 150 QTP XR 300 ESC 10 Placebo once daily	217 206 209 214	8 weeks active tx plus 2 weeks monitoring
D1448C 00011	Multicenter, randomized, double-blind, parallel-group, placebo-controlled, active-controlled; 2-week post-treatment follow-up period	QTP XR 50 QTP XR 150 PAR 20 Placebo once daily	220 218 215 217	8 weeks active tx plus 2 weeks monitoring
D1448C 00015 (elderly)	Multicenter, randomized, double-blind, parallel-group, placebo-controlled; 2-week post-treatment follow-up period	Flexible: QTP XR 50 to 300 Placebo once a day	 223 227	9 weeks active tx plus 2 weeks monitoring
Short-term adjunct to SSRI or SNRI with or without benzodiazepine				
D1441L 00016	Multicenter, randomized, double-blind, parallel-group, placebo-controlled with single-blind, placebo run-in	QTP XR 150 or 300 Placebo	209 200	1 week run-in, 8 weeks double-blind treatment, plus 2-weeks follow-up
Longer-term maintenance monotherapy				
D1448C 00012	Multicenter, double-blind, parallel-group, placebo-controlled, randomized withdrawal with open-label run-in and stabilization periods	Flexible: QTP XR 50, 150, or 300 QTP XR 50, 150, or 300 Placebo once a day	 1224open-label QTP 216 randomized phase 216 randomized phase	4 to 8 weeks open-label run-in with QTP XR; 12 to 18 weeks open-label stabilization with QTP XR; up to 52 weeks double-blind treatment with QTP XR or placebo

[a] Studies 0009 to 0012: dosing initiated at 50 mg in evening x 2 days, then 150 mg x 2 days, then 300 mg as appropriate for randomization group assignments; Study 12: investigators were to attempt to stabilize the patient at 150 mg then titrate up or down as appropriate; Study 0015: dosing initiated at 50 mg in evening x 3 days, then increased to 100 mg qd x 3 days, up to 150 mg on Day 8; increasing by 50 mg increments up to a maximum of 300 mg by Day 22

ESC Escitalopram. PAR Paroxetine. QTP XR Quetiapine extended release. SNRI Serotonin-norepinephrine reuptake inhibitor.

1.3 Clinical data ~~pertaining to identified and potential risks~~

1.3.1 All trials

1.3.1.1 Laboratory data

Table 54 Incidence of each laboratory risk (All trials)

	QTP			
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
ALT, 3*ULN	20912	290 (1.4)	6802.0	4.3
AST, 3*ULN	20968	132 (0.6)	6884.9	1.9
Cholesterol, >=6.21 mmol/L	15905	1644 (10.3)	4343.9	37.8
LDL, fasting >=4.2 mmol/L	12508	896 (7.2)	3986.1	22.5
GGT, 3*ULN	1529	37 (2.4)	825.2	4.5
Glucose[e], fasting >=7 mmol/L	9140	265 (2.9)	2759.5	9.6
Glucose[e], random >=11.1 mmol/L	4375	52 (1.2)	1217.7	4.3
Triglycerides, >=2.26 mmol/L	14459	2708 (18.7)	3676.7	73.7
TSH, >5 mIU/L	20634	1049 (5.1)	6817.3	15.4
T3 Free, 0.8*LLN	14501	58 (0.4)	3967.0	1.5
T4 Free, 0.8*LLN	18733	472 (2.5)	6177.0	7.6
T4 Total, 0.8*LLN	2373	105 (4.4)	1084.8	9.7
Prolactin, males >20 ng/mL, females >30 ng/mL	14244	714 (5.0)	4224.8	16.9
HDL, <=1.04 mmol/L	13563	2069 (15.3)	3660.8	56.5

a Number of patients with a normal (defnied as not clinical important) baseline and at least one assesment post baseline.
b Number of patients with event. Event defined as first shift from baseline.
c Exposure in patient years censored at first shift
d 100 x total number of patients with event/total patient years of censored exposure.
e Only patients with diabetes status normal at baseline included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\lab_incid_all.SAS. Data version: V27. User: [redacted] 2014-07-16 0:30.

Table 55 Incidence of each laboratory risk, age <18 years (All trials)

	QTP			
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
ALT, 3*ULN	550	4 (0.7)	195.1	2.1
AST, 3*ULN	551	2 (0.4)	195.5	1.0
Cholesterol, >=6.21 mmol/L	510	10 (2.0)	178.1	5.6
LDL, fasting >=4.2 mmol/L	453	7 (1.5)	161.2	4.3
GGT, 3*ULN	0	0	NA	NA
Glucose[e], fasting >=7 mmol/L	398	4 (1.0)	133.2	3.0
Glucose[e], random >=11.1 mmol/L	72	0 (0.0)	17.6	0.0
Triglycerides, >=2.26 mmol/L	487	83 (17.0)	158.3	52.4
TSH, >5 mIU/L	466	28 (6.0)	177.1	15.8
T3 Free, 0.8*LLN	44	0 (0.0)	6.3	0.0
T4 Free, 0.8*LLN	476	12 (2.5)	177.2	6.8
T4 Total, 0.8*LLN	432	23 (5.3)	165.9	13.9
Prolactin, males >20 ng/mL, females >30 ng/mL	373	52 (13.9)	130.0	40.0
HDL, <=1.04 mmol/L	422	106 (25.1)	135.0	78.5

a Number of patients with a normal (defnied as not clinical important) baseline and at least one assesment post baseline.
b Number of patients with event. Event defined as first shift from baseline.
c Exposure in patient years censored at first shift
d 100 x total number of patients with event/total patient years of censored exposure.
e Only patients with diabetes status normal at baseline included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\lab_incid_all_age17.SAS. Data version: V27. User: [redacted] 2014-07-16 0:31.

Table 56 Incidence of each laboratory risk, age >65 years (All trials)

	QTP			
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
ALT, 3*ULN	962	9 (0.9)	391.2	2.3
AST, 3*ULN	964	8 (0.8)	391.2	2.0
Cholesterol, >=6.21 mmol/L	592	70 (11.8)	116.1	60.3
LDL, fasting >=4.2 mmol/L	489	57 (11.7)	103.9	54.9
GGT, 3*ULN	28	0 (0.0)	7.7	0.0
Glucose[e], fasting >=7 mmol/L	378	16 (4.2)	67.5	23.7
Glucose[e], random >=11.1 mmol/L	450	20 (4.4)	289.8	6.9
Triglycerides, >=2.26 mmol/L	639	62 (9.7)	118.4	52.4
TSH, >5 mIU/L	1194	72 (6.0)	433.2	16.6
T3 Free, 0.8*LLN	496	3 (0.6)	98.9	3.0
T4 Free, 0.8*LLN	1202	52 (4.3)	418.9	12.4
T4 Total, 0.8*LLN	13	1 (7.7)	6.8	14.8
Prolactin, males >20 ng/mL, females >30 ng/mL	459	14 (3.1)	100.8	13.9
HDL, <=1.04 mmol/L	510	43 (8.4)	105.0	41.0

a Number of patients with a normal (defnied as not clinical important) baseline and at least one assesment post baseline.
b Number of patients with event. Event defined as first shift from baseline.
c Exposure in patient years censored at first shift
d 100 x total number of patients with event/total patient years of censored exposure.
e Only patients with diabetes status normal at baseline included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Pgm: PRMP Jun 2014\...\lab_incid_all_age66.SAS. Data version: V27. User: [redacted] 2014-07-16 0:31
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Table 57 Incidence of each laboratory risk, age 18-65 years (All trials)

	QTP			
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
ALT, 3*ULN	19400	277 (1.4)	6215.7	4.5
AST, 3*ULN	19453	122 (0.6)	6298.2	1.9
Cholesterol, >=6.21 mmol/L	14803	1564 (10.6)	4049.7	38.6
LDL, fasting >=4.2 mmol/L	11566	832 (7.2)	3721.0	22.4
GGT, 3*ULN	1501	37 (2.5)	817.5	4.5
Glucose[e], fasting >=7 mmol/L	8364	245 (2.9)	2558.7	9.6
Glucose[e], random >=11.1 mmol/L	3853	32 (0.8)	910.3	3.5
Triglycerides, >=2.26 mmol/L	13333	2563 (19.2)	3400.0	75.4
TSH, >5 mIU/L	18974	949 (5.0)	6207.0	15.3
T3 Free, 0.8*LLN	13961	55 (0.4)	3861.8	1.4
T4 Free, 0.8*LLN	17055	408 (2.4)	5580.9	7.3
T4 Total, 0.8*LLN	1928	81 (4.2)	912.1	8.9
Prolactin, males >20 ng/mL, females >30 ng/mL	13412	648 (4.8)	3994.1	16.2
HDL, <=1.04 mmol/L	12631	1920 (15.2)	3420.8	56.1

a Number of patients with a normal (defnied as not clinical important) baseline and at least one assesment post baseline.
b Number of patients with event. Event defined as first shift from baseline.
c Exposure in patient years censored at first shift
d 100 x total number of patients with event/total patient years of censored exposure.
e Only patients with diabetes status normal at baseline included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\lab_incid_all_age1865.SAS. Data version: V27. User: [redacted] 2014-07-16 0:38.

Table 58 Incidence of each laboratory risk for patients with at least 6 months exposure to Seroquel (All trials)

	QTP			
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
ALT, 3*ULN	3403	46 (1.4)	3854.9	2153.4
AST, 3*ULN	3415	32 (0.9)	3884.8	2177.3
Cholesterol, >=6.21 mmol/L	2285	315 (13.8)	2062.5	920.0
LDL, fasting >=4.2 mmol/L	2132	212 (9.9)	2010.2	944.2
GGT, 3*ULN	433	10 (2.3)	589.5	373.0
Glucose[e], fasting >=7 mmol/L	1327	55 (4.1)	1204.1	540.6
Glucose[e], random >=11.1 mmol/L	441	13 (2.9)	683.9	463.4
Triglycerides, >=2.26 mmol/L	1953	508 (26.0)	1683.7	707.2
TSH, >5 mIU/L	3393	272 (8.0)	3830.7	2134.2
T3 Free, 0.8*LLN	1954	14 (0.7)	1757.5	780.5
T4 Free, 0.8*LLN	3131	120 (3.8)	3472.1	1906.6
T4 Total, 0.8*LLN	624	32 (5.1)	750.6	438.6
Prolactin, males >20 ng/mL, females >30 ng/mL	2200	128 (5.8)	2080.5	980.5
HDL, <=1.04 mmol/L	1987	430 (21.6)	1713.2	719.7

a Number of patients with a normal (defnied as not clinical important) baseline and at least one assesment 6 months post baseline.
b Number of patients with event. Event defined as first shift from baseline, after 6 months exposure.
c Exposure in patient years censored at first shift
d Exposure in patient-years, censored at first event after 6 months exposure. Only exposure after 6 months of treatment is included.
e Only patients with diabetes status normal at baseline included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\lab_incid_all_lt.SAS. Data version: V27. User: [redacted] 2014-07-16 0:39.

Table 59 Incidence of shift for neutrophils, all age (all trials)

Laboratory test	Treatment	Patients with event n (%)[a]	Total patients[b]	Exposure[c]
Neutropenia 1.0*10**9 <= cells/L and <1.5*10**9 cells/L	QTP	651 (2.62)	24834	7965.4
Neutropenia 0.5*10**9 <= cells/L and <1.0*10**9 cells/L	QTP	118 (0.48)	24834	8115.4
Agranulocytosis < 0.5*10**9 cells/L	QTP	22 (0.09)	24834	8156.7

a Number of patients with event. Event defined as first shift from baseline.
b Number of patients with a normal (defined as not clinical important) baseline and at least one assessment post baseline.
c Exposure in patient-years, censored at first shift.
d 100 x total number of patients with event/total patient years of censored exposure.
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\neuts_incid.SAS. Data version: V27. User: [redacted] 2014-07-16 0:43.

Table 60 Incidence of shift for Neutrophils, age <18 years (all trials)

Laboratory test	Treatment	Patients with event n (%)[a]	Total patients[b]	Exposure[c]
Neutropenia 1.0*10**9 <= cells/L and <1.5*10**9 cells/L	QTP	43 (7.83)	549	180.9
Neutropenia 0.5*10**9 <= cells/L and <1.0*10**9 cells/L	QTP	5 (0.91)	549	195.0
Agranulocytosis < 0.5*10**9 cells/L	QTP	1 (0.18)	549	195.7

a Number of patients with event. Event defined as first shift from baseline.
b Number of patients with a normal (defined as not clinical important) baseline and at least one assessment post baseline.
c Exposure in patient-years, censored at first shift.
d 100 x total number of patients with event/total patient years of censored exposure.
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\neuts_incid.SAS. Data version: V27. User: [redacted] 2014-07-16 0:43.

Table 61 Incidence of shift for Neutrophils, age >65 years (all trials)

Laboratory test	Treatment	Patients with event n (%)[a]	Total patients[b]	Exposure[c]
Neutropenia 1.0*10**9 <= cells/L and <1.5*10**9 cells/L	QTP	24 (1.82)	1319	488.4
Neutropenia 0.5*10**9 <= cells/L and <1.0*10**9 cells/L	QTP	2 (0.15)	1319	494.5
Agranulocytosis < 0.5*10**9 cells/L	QTP	1 (0.08)	1319	496.9

a Number of patients with event. Event defined as first shift from baseline.
b Number of patients with a normal (defined as not clinical important) baseline and at least one assessment post baseline.
c Exposure in patient-years, censored at first shift.
d 100 x total number of patients with event/total patient years of censored exposure.
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\neuts_incid.SAS. Data version: V27. User: [redacted] 2014-07-16 0:44.

Table 62 Incidence of shift for Neutrophils, age 18-65 years (all trials)

Laboratory test	Treatment	Patients with event n (%)[a]	Total patients[b]	Exposure[c]
Neutropenia 1.0*10**9 <= cells/L and <1.5*10**9 cells/L	QTP	584 (2.54)	22966	7296.2
Neutropenia 0.5*10**9 <= cells/L and <1.0*10**9 cells/L	QTP	111 (0.48)	22966	7425.9
Agranulocytosis < 0.5*10**9 cells/L	QTP	20 (0.09)	22966	7464.1

a Number of patients with event. Event defined as first shift from baseline.
b Number of patients with a normal (defined as not clinical important) baseline and at least one assessment post baseline.
c Exposure in patient-years, censored at first shift.
d 100 x total number of patients with event/total patient years of censored exposure.
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\neuts_incid.SAS. Data version: V27. User: [redacted] 2014-07-16 0:44.

Table 63 Incidence of shift for Neutrophils for patients with at least 6 months exposure to Seroquel, all age (all trials)

Laboratory test	Treatment	Patients with event n (%)[a]	Total patients[b]	Exposure[c]
Neutropenia 1.0*10**9 <= cells/L and <1.5*10**9 cells/L	QTP	97 (2.57)	3778	4373.0
Neutropenia 0.5*10**9 <= cells/L and <1.0*10**9 cells/L	QTP	17 (0.45)	3778	4410.0
Agranulocytosis < 0.5*10**9 cells/L	QTP	2 (0.05)	3778	4420.0

a Number of patients with event. Event defined as first shift from baseline.
b Number of patients with a normal (defined as not clinical important) baseline and at least one assessment post baseline.
c Exposure in patient-years, censored at first shift.
d Exposure in patient-years, censored at first shift after 6 months exposure. Only exposure after 6 months of treatment is included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\neuts_incid.SAS. Data version: V27. User: [redacted] 2014-07-16 0:44.

1.3.1.2 Adverse event data

All events

Table 64 Seriousness, outcomes, and severity of each adverse event risk - all trials

Risk Adverse event group[a] N=28576	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Anaphylactic reaction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
EPS	2764 (9.67)	35 (1.27)	16 (0.58)	1807 (65.38)	152 (5.50)	805 (29.12)	0 (0.00)	1750 (63.31)	875 (31.66)	137 (4.96)
Hepatitis	10 (0.03)	1 (10.00)	1 (10.00)	4 (40.00)	1 (10.00)	5 (50.00)	0 (0.00)	7 (70.00)	2 (20.00)	1 (10.00)
Hyperglycemia and Diabetes mellitus	225 (0.79)	16 (7.11)	15 (6.67)	75 (33.33)	5 (2.22)	144 (64.00)	1 (0.44)	125 (55.56)	81 (36.00)	18 (8.00)
Hypothyroidism	198 (0.69)	3 (1.52)	1 (0.51)	57 (28.79)	9 (4.55)	132 (66.67)	0 (0.00)	138 (69.70)	52 (26.26)	8 (4.04)
Jaundice	17 (0.06)	1 (5.88)	1 (5.88)	7 (41.18)	5 (29.41)	5 (29.41)	0 (0.00)	10 (58.82)	2 (11.76)	1 (5.88)
Neuroleptic Malignant Syndrome	4 (0.01)	3 (75.00)	2 (50.00)	2 (50.00)	1 (25.00)	1 (25.00)	0 (0.00)	1 (25.00)	0 (0.00)	3 (75.00)
Neutropenia	124 (0.43)	5 (4.03)	1 (0.81)	83 (66.94)	5 (4.03)	36 (29.03)	0 (0.00)	73 (58.87)	41 (33.06)	10 (8.06)
Seizure	79 (0.28)	32 (40.51)	21 (26.58)	66 (83.54)	8 (10.13)	5 (6.33)	0 (0.00)	14 (17.72)	35 (44.30)	30 (37.97)
Somnolence	11925 (41.73)	18 (0.15)	13 (0.11)	8751 (73.38)	296 (2.48)	2875 (24.11)	3 (0.03)	5810 (48.72)	4932 (41.36)	1183 (9.92)
Stevens-Johnson syndrome and other serious skin reactions	3 (0.01)	0 (0.00)	0 (0.00)	2 (66.67)	0 (0.00)	1 (33.33)	0 (0.00)	2 (66.67)	1 (33.33)	0 (0.00)

Syncope and orthostatic hypotension	883 (3.09)	45 (5.10)	31 (3.51)	759 (85.96)	48 (5.44)	76 (8.61)	0 (0.00)	516 (58.44)	288 (32.62)	79 (8.95)
Cerebrovascular Adverse Events	67 (0.23)	31 (46.27)	26 (38.81)	43 (64.18)	1 (1.49)	15 (22.39)	8 (11.94)	19 (28.36)	20 (29.85)	27 (40.30)
Abuse Misuse	20 (0.07)	4 (20.00)	4 (20.00)	18 (90.00)	0 (0.00)	2 (10.00)	0 (0.00)	5 (25.00)	9 (45.00)	6 (30.00)
Aggression/agitation	1937 (6.78)	99 (5.11)	76 (3.92)	1281 (66.13)	232 (11.98)	423 (21.84)	1 (0.05)	650 (33.56)	920 (47.50)	367 (18.95)
Agranulocytosis	1 (0.00)	1 (100.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)
Hyperprolactinemia	20 (0.07)	0 (0.00)	0 (0.00)	7 (35.00)	2 (10.00)	11 (55.00)	0 (0.00)	10 (50.00)	5 (25.00)	3 (15.00)
QT prolongation and Torsade de Pointes	30 (0.10)	2 (6.67)	2 (6.67)	18 (60.00)	1 (3.33)	11 (36.67)	0 (0.00)	22 (73.33)	7 (23.33)	0 (0.00)
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	15 (0.05)	5 (33.33)	4 (26.67)	10 (66.67)	2 (13.33)	2 (13.33)	1 (6.67)	4 (26.67)	7 (46.67)	3 (20.00)
Suicide	297 (1.04)	164 (55.22)	139 (46.80)	245 (82.49)	6 (2.02)	35 (11.78)	11 (3.70)	81 (27.27)	81 (27.27)	135 (45.45)
Pancreatitis	12 (0.04)	7 (58.33)	7 (58.33)	7 (58.33)	1 (8.33)	4 (33.33)	0 (0.00)	3 (25.00)	5 (41.67)	4 (33.33)
Dysphagia	134 (0.47)	4 (2.99)	2 (1.49)	83 (61.94)	23 (17.16)	26 (19.40)	2 (1.49)	73 (54.48)	50 (37.31)	11 (8.21)
Tardive dyskinesia	57 (0.20)	1 (1.75)	1 (1.75)	18 (31.58)	7 (12.28)	32 (56.14)	0 (0.00)	37 (64.91)	16 (28.07)	4 (7.02)
Pneumonia	152 (0.53)	76 (50.00)	59 (38.82)	108 (71.05)	8 (5.26)	13 (8.55)	23 (15.13)	20 (13.16)	80 (52.63)	51 (33.55)
Accidental injury	571 (2.00)	54 (9.46)	46 (8.06)	474 (83.01)	5 (0.88)	90 (15.76)	2 (0.35)	299 (52.36)	212 (37.13)	60 (10.51)
Metabolic syndrome	5 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (100.00)	0 (0.00)	1 (20.00)	3 (60.00)	1 (20.00)
Ischemic heart disease	77 (0.27)	22 (28.57)	18 (23.38)	57 (74.03)	2 (2.60)	13 (16.88)	5 (6.49)	32 (41.56)	23 (29.87)	22 (28.57)

Venous thromboembolism/Embolic venous	23 (0.08)	17 (73.91)	14 (60.87)	14 (60.87)	0 (0.00)	7 (30.43)	2 (8.70)	3 (13.04)	5 (21.74)	15 (65.22)
Intestinal obstruction/ileus	25 (0.09)	15 (60.00)	13 (52.00)	17 (68.00)	3 (12.00)	4 (16.00)	1 (4.00)	3 (12.00)	10 (40.00)	12 (48.00)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Note: 6 adverse events have no information on intensity and are therefore not considered.
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Table 65 Seriousness, outcomes, and severity of each adverse event risk, age <18 years - all trials

Risk Adverse event group[a] N=601	**Adverse event n (%)**	**Serious adverse event n (%)**	**Hospitalized n (%)**	**Recovered n (%)**	**Recover status unknown n (%)**	**Not recovered n (%)**	**Death n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Anaphylactic reaction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
EPS	65 (10.82)	2 (3.08)	2 (3.08)	48 (73.85)	0 (0.00)	17 (26.15)	0 (0.00)	35 (53.85)	26 (40.00)	4 (6.15)
Hepatitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperglycemia and Diabetes mellitus	6 (1.00)	1 (16.67)	1 (16.67)	0 (0.00)	0 (0.00)	6 (100.00)	0 (0.00)	2 (33.33)	2 (33.33)	2 (33.33)
Hypothyroidism	8 (1.33)	0 (0.00)	0 (0.00)	3 (37.50)	3 (37.50)	2 (25.00)	0 (0.00)	5 (62.50)	3 (37.50)	0 (0.00)
Jaundice	1 (0.17)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)
Neuroleptic Malignant Syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Neutropenia	8 (1.33)	1 (12.50)	0 (0.00)	6 (75.00)	0 (0.00)	2 (25.00)	0 (0.00)	2 (25.00)	4 (50.00)	2 (25.00)
Seizure	1 (0.17)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)

Somnolence	304 (50.58)	0 (0.00)	0 (0.00)	193 (63.49)	0 (0.00)	111 (36.51)	0 (0.00)	160 (52.63)	129 (42.43)	15 (4.93)
Stevens-Johnson syndrome and other serious skin reactions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Syncope and orthostatic hypotension	13 (2.16)	2 (15.38)	0 (0.00)	13 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	6 (46.15)	5 (38.46)	2 (15.38)
Cerebrovascular Adverse Events	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Abuse Misuse	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Aggression/agitation	84 (13.98)	11 (13.10)	11 (13.10)	57 (67.86)	0 (0.00)	27 (32.14)	0 (0.00)	26 (30.95)	40 (47.62)	18 (21.43)
Agranulocytosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperprolactinemia	5 (0.83)	0 (0.00)	0 (0.00)	3 (60.00)	0 (0.00)	2 (40.00)	0 (0.00)	4 (80.00)	1 (20.00)	0 (0.00)
QT prolongation and Torsade de Pointes	14 (2.33)	0 (0.00)	0 (0.00)	8 (57.14)	1 (7.14)	5 (35.71)	0 (0.00)	11 (78.57)	2 (14.29)	0 (0.00)
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Suicide	9 (1.50)	2 (22.22)	2 (22.22)	8 (88.89)	0 (0.00)	1 (11.11)	0 (0.00)	5 (55.56)	2 (22.22)	2 (22.22)
Pancreatitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Dysphagia	1 (0.17)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)
Tardive dyskinesia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Pneumonia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Accidental injury	12 (2.00)	0 (0.00)	0 (0.00)	10 (83.33)	0 (0.00)	2 (16.67)	0 (0.00)	7 (58.33)	5 (41.67)	0 (0.00)
Metabolic syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Ischemic heart disease	2 (0.33)	0 (0.00)	0 (0.00)	2 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	1 (50.00)
Venous thromboembolism/Embolic venous	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Intestinal obstruction/ileus	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are exclude
Note: 1 adverse event has no information on intensity and is therefore not considered.
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Table 66 Seriousness, outcomes, and severity of each adverse event risk, age 18-65 years - all trials

Risk Adverse event group[a] N=26510	**Adverse event n (%)**	**Serious adverse event n (%)**	**Hospitalized n (%)**	**Recovered n (%)**	**Recover status unknown n (%)**	**Not recovered n (%)**	**Death n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Anaphylactic reaction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
EPS	2578 (9.72)	30 (1.16)	12 (0.47)	1684 (65.32)	149 (5.78)	745 (28.90)	0 (0.00)	1642 (63.69)	810 (31.42)	124 (4.81)
Hepatitis	10 (0.04)	1 (10.00)	1 (10.00)	4 (40.00)	1 (10.00)	5 (50.00)	0 (0.00)	7 (70.00)	2 (20.00)	1 (10.00)
Hyperglycemia and Diabetes mellitus	203 (0.77)	13 (6.40)	12 (5.91)	67 (33.00)	5 (2.46)	131 (64.53)	0 (0.00)	113 (55.67)	74 (36.45)	15 (7.39)
Hypothyroidism	172 (0.65)	3 (1.74)	1 (0.58)	47 (27.33)	6 (3.49)	119 (69.19)	0 (0.00)	122 (70.93)	42 (24.42)	8 (4.65)
Jaundice	16 (0.06)	1 (6.25)	1 (6.25)	6 (37.50)	5 (31.25)	5 (31.25)	0 (0.00)	9 (56.25)	2 (12.50)	1 (6.25)

Neuroleptic Malignant Syndrome	4 (0.02)	3 (75.00)	2 (50.00)	2 (50.00)	1 (25.00)	1 (25.00)	0 (0.00)	1 (25.00)	0 (0.00)	3 (75.00)
Neutropenia	114 (0.43)	4 (3.51)	1 (0.88)	77 (67.54)	5 (4.39)	32 (28.07)	0 (0.00)	70 (61.40)	36 (31.58)	8 (7.02)
Seizure	65 (0.25)	28 (43.08)	18 (27.69)	54 (83.08)	8 (12.31)	3 (4.62)	0 (0.00)	11 (16.92)	26 (40.00)	28 (43.08)
Somnolence	11180 (42.17)	13 (0.12)	8 (0.07)	8198 (73.33)	290 (2.59)	2689 (24.05)	3 (0.03)	5401 (48.31)	4644 (41.54)	1135 (10.15)
Stevens-Johnson syndrome and other serious skin reactions	3 (0.01)	0 (0.00)	0 (0.00)	2 (66.67)	0 (0.00)	1 (33.33)	0 (0.00)	2 (66.67)	1 (33.33)	0 (0.00)
Syncope and orthostatic hypotension	790 (2.98)	27 (3.42)	17 (2.15)	675 (85.44)	44 (5.57)	71 (8.99)	0 (0.00)	466 (58.99)	259 (32.78)	65 (8.23)
Cerebrovascular Adverse Events	37 (0.14)	14 (37.84)	13 (35.14)	23 (62.16)	1 (2.70)	9 (24.32)	4 (10.81)	12 (32.43)	11 (29.73)	14 (37.84)
Abuse Misuse	20 (0.08)	4 (20.00)	4 (20.00)	18 (90.00)	0 (0.00)	2 (10.00)	0 (0.00)	5 (25.00)	9 (45.00)	6 (30.00)
Aggression/agitation	1741 (6.57)	75 (4.31)	53 (3.04)	1139 (65.42)	228 (13.10)	373 (21.42)	1 (0.06)	599 (34.41)	824 (47.33)	318 (18.27)
Agranulocytosis	1 (0.00)	1 (100.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)
Hyperprolactinemia	15 (0.06)	0 (0.00)	0 (0.00)	4 (26.67)	2 (13.33)	9 (60.00)	0 (0.00)	6 (40.00)	4 (26.67)	3 (20.00)
QT prolongation and Torsade de Pointes	12 (0.05)	1 (8.33)	1 (8.33)	7 (58.33)	0 (0.00)	5 (41.67)	0 (0.00)	8 (66.67)	4 (33.33)	0 (0.00)
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	13 (0.05)	4 (30.77)	3 (23.08)	9 (69.23)	2 (15.38)	2 (15.38)	0 (0.00)	4 (30.77)	6 (46.15)	2 (15.38)
Suicide	283 (1.07)	159 (56.18)	134 (47.35)	232 (81.98)	6 (2.12)	34 (12.01)	11 (3.89)	76 (26.86)	77 (27.21)	130 (45.94)
Pancreatitis	9 (0.03)	6 (66.67)	6 (66.67)	6 (66.67)	1 (11.11)	2 (22.22)	0 (0.00)	2 (22.22)	4 (44.44)	3 (33.33)
Dysphagia	121 (0.46)	3 (2.48)	2 (1.65)	77 (63.64)	23 (19.01)	20 (16.53)	1 (0.83)	67 (55.37)	44 (36.36)	10 (8.26)
Tardive dyskinesia	51 (0.19)	1 (1.96)	1 (1.96)	17 (33.33)	7 (13.73)	27 (52.94)	0 (0.00)	34 (66.67)	14 (27.45)	3 (5.88)

Pneumonia	92 (0.35)	38 (41.30)	33 (35.87)	73 (79.35)	6 (6.52)	7 (7.61)	6 (6.52)	10 (10.87)	60 (65.22)	22 (23.91)
Accidental injury	295 (1.11)	27 (9.15)	21 (7.12)	240 (81.36)	2 (0.68)	51 (17.29)	2 (0.68)	125 (42.37)	134 (45.42)	36 (12.20)
Metabolic syndrome	5 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (100.00)	0 (0.00)	1 (20.00)	3 (60.00)	1 (20.00)
Ischemic heart disease	63 (0.24)	16 (25.40)	14 (22.22)	49 (77.78)	2 (3.17)	11 (17.46)	1 (1.59)	26 (41.27)	21 (33.33)	16 (25.40)
Venous thromboembolism/Embolic venous	16 (0.06)	12 (75.00)	10 (62.50)	11 (68.75)	0 (0.00)	5 (31.25)	0 (0.00)	2 (12.50)	5 (31.25)	9 (56.25)
Intestinal obstruction/ileus	19 (0.07)	11 (57.89)	9 (47.37)	12 (63.16)	3 (15.79)	3 (15.79)	1 (5.26)	1 (5.26)	8 (42.11)	10 (52.63)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are exclude
Note: 3 adverse events have no information on intensity and are therefore not considered.
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Table 67 Seriousness, outcomes, and severity of each adverse event risk, age >=66 years - all trials

Risk Adverse event group[a] N=1465	**Adverse event n (%)**	**Serious adverse event n (%)**	**Hospitalized n (%)**	**Recovered n (%)**	**Recover status unknown n (%)**	**Not recovered n (%)**	**Death n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Anaphylactic reaction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
EPS	121 (8.26)	3 (2.48)	2 (1.65)	75 (61.98)	3 (2.48)	43 (35.54)	0 (0.00)	73 (60.33)	39 (32.23)	9 (7.44)
Hepatitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperglycemia and Diabetes mellitus	16 (1.09)	2 (12.50)	2 (12.50)	8 (50.00)	0 (0.00)	7 (43.75)	1 (6.25)	10 (62.50)	5 (31.25)	1 (6.25)

Hypothyroidism	18 (1.23)	0 (0.00)	0 (0.00)	7 (38.89)	0 (0.00)	11 (61.11)	0 (0.00)	11 (61.11)	7 (38.89)	0 (0.00)
Jaundice	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Neuroleptic Malignant Syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Neutropenia	2 (0.14)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (100.00)	0 (0.00)	1 (50.00)	1 (50.00)	0 (0.00)
Seizure	13 (0.89)	4 (30.77)	3 (23.08)	12 (92.31)	0 (0.00)	1 (7.69)	0 (0.00)	3 (23.08)	8 (61.54)	2 (15.38)
Somnolence	441 (30.10)	5 (1.13)	5 (1.13)	360 (81.63)	6 (1.36)	75 (17.01)	0 (0.00)	249 (56.46)	159 (36.05)	33 (7.48)
Stevens-Johnson syndrome and other serious skin reactions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Syncope and orthostatic hypotension	80 (5.46)	16 (20.00)	14 (17.50)	71 (88.75)	4 (5.00)	5 (6.25)	0 (0.00)	44 (55.00)	24 (30.00)	12 (15.00)
Cerebrovascular Adverse Events	30 (2.05)	17 (56.67)	13 (43.33)	20 (66.67)	0 (0.00)	6 (20.00)	4 (13.33)	7 (23.33)	9 (30.00)	13 (43.33)
Abuse Misuse	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Aggression/agitation	112 (7.65)	13 (11.61)	12 (10.71)	85 (75.89)	4 (3.57)	23 (20.54)	0 (0.00)	25 (22.32)	56 (50.00)	31 (27.68)
Agranulocytosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperprolactinemia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
QT prolongation and Torsade de Pointes	4 (0.27)	1 (25.00)	1 (25.00)	3 (75.00)	0 (0.00)	1 (25.00)	0 (0.00)	3 (75.00)	1 (25.00)	0 (0.00)
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	2 (0.14)	1 (50.00)	1 (50.00)	1 (50.00)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	1 (50.00)	1 (50.00)
Suicide	5 (0.34)	3 (60.00)	3 (60.00)	5 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (40.00)	3 (60.00)
Pancreatitis	3 (0.20)	1 (33.33)	1 (33.33)	1 (33.33)	0 (0.00)	2 (66.67)	0 (0.00)	1 (33.33)	1 (33.33)	1 (33.33)

Dysphagia	12 (0.82)	1 (8.33)	0 (0.00)	6 (50.00)	0 (0.00)	5 (41.67)	1 (8.33)	5 (41.67)	6 (50.00)	1 (8.33)
Tardive dyskinesia	6 (0.41)	0 (0.00)	0 (0.00)	1 (16.67)	0 (0.00)	5 (83.33)	0 (0.00)	3 (50.00)	2 (33.33)	1 (16.67)
Pneumonia	60 (4.10)	38 (63.33)	26 (43.33)	35 (58.33)	2 (3.33)	6 (10.00)	17 (28.33)	10 (16.67)	20 (33.33)	29 (48.33)
Accidental injury	264 (18.02)	27 (10.23)	25 (9.47)	224 (84.85)	3 (1.14)	37 (14.02)	0 (0.00)	167 (63.26)	73 (27.65)	24 (9.09)
Metabolic syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ischemic heart disease	12 (0.82)	6 (50.00)	4 (33.33)	6 (50.00)	0 (0.00)	2 (16.67)	4 (33.33)	5 (41.67)	2 (16.67)	5 (41.67)
Venous thromboembolism/Embolic venous	7 (0.48)	5 (71.43)	4 (57.14)	3 (42.86)	0 (0.00)	2 (28.57)	2 (28.57)	1 (14.29)	0 (0.00)	6 (85.71)
Intestinal obstruction/ileus	6 (0.41)	4 (66.67)	4 (66.67)	5 (83.33)	0 (0.00)	1 (16.67)	0 (0.00)	2 (33.33)	2 (33.33)	2 (33.33)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are exclude
Note: 2 adverse events have no information on intensity and are therefore not considered.
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Table 68 Seriousness, outcomes, and severity of each adverse event risk, occuring after 6 months of exposure on Quetiapine - all trials

Risk Adverse event group[a] N=4161	**Adverse event n (%)**	**Serious adverse event n (%)**	**Hospitalized n (%)**	**Recovered n (%)**	**Recover status unknown n (%)**	**Not recovered n (%)**	**Death n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Anaphylactic reaction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

EPS	204 (4.90)	7 (3.43)	3 (1.47)	100 (49.02)	12 (5.88)	92 (45.10)	0 (0.00)	138 (67.65)	58 (28.43)	8 (3.92)
Hepatitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperglycemia and Diabetes mellitus	50 (1.20)	6 (12.00)	6 (12.00)	16 (32.00)	0 (0.00)	33 (66.00)	1 (2.00)	25 (50.00)	18 (36.00)	7 (14.00)
Hypothyroidism	47 (1.13)	0 (0.00)	0 (0.00)	13 (27.66)	0 (0.00)	34 (72.34)	0 (0.00)	28 (59.57)	16 (34.04)	3 (6.38)
Jaundice	3 (0.07)	0 (0.00)	0 (0.00)	3 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (100.00)	0 (0.00)	0 (0.00)
Neuroleptic Malignant Syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Neutropenia	22 (0.53)	1 (4.55)	1 (4.55)	16 (72.73)	1 (4.55)	5 (22.73)	0 (0.00)	11 (50.00)	11 (50.00)	0 (0.00)
Seizure	18 (0.43)	3 (16.67)	3 (16.67)	14 (77.78)	2 (11.11)	2 (11.11)	0 (0.00)	6 (33.33)	8 (44.44)	4 (22.22)
Somnolence	347 (8.34)	7 (2.02)	4 (1.15)	218 (62.82)	29 (8.36)	98 (28.24)	2 (0.58)	230 (66.28)	104 (29.97)	13 (3.75)
Stevens-Johnson syndrome and other serious skin reactions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Syncope and orthostatic hypotension	66 (1.59)	9 (13.64)	9 (13.64)	54 (81.82)	5 (7.58)	7 (10.61)	0 (0.00)	39 (59.09)	26 (39.39)	1 (1.52)
Cerebrovascular Adverse Events	16 (0.38)	7 (43.75)	6 (37.50)	8 (50.00)	1 (6.25)	5 (31.25)	2 (12.50)	5 (31.25)	5 (31.25)	6 (37.50)
Abuse Misuse	5 (0.12)	2 (40.00)	2 (40.00)	5 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (20.00)	3 (60.00)	1 (20.00)
Aggression/agitation	139 (3.34)	11 (7.91)	10 (7.19)	78 (56.12)	24 (17.27)	37 (26.62)	0 (0.00)	50 (35.97)	68 (48.92)	21 (15.11)
Agranulocytosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperprolactinemia	7 (0.17)	0 (0.00)	0 (0.00)	0 (0.00)	2 (28.57)	5 (71.43)	0 (0.00)	3 (42.86)	2 (28.57)	2 (28.57)
QT prolongation and Torsade de Pointes	7 (0.17)	0 (0.00)	0 (0.00)	4 (57.14)	0 (0.00)	3 (42.86)	0 (0.00)	7 (100.00)	0 (0.00)	0 (0.00)

Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	5 (0.12)	2 (40.00)	2 (40.00)	2 (40.00)	1 (20.00)	1 (20.00)	1 (20.00)	1 (20.00)	2 (40.00)	2 (40.00)
Suicide	44 (1.06)	30 (68.18)	26 (59.09)	32 (72.73)	2 (4.55)	7 (15.91)	3 (6.82)	10 (22.73)	11 (25.00)	23 (52.27)
Pancreatitis	3 (0.07)	2 (66.67)	2 (66.67)	2 (66.67)	0 (0.00)	1 (33.33)	0 (0.00)	0 (0.00)	1 (33.33)	2 (66.67)
Dysphagia	18 (0.43)	2 (11.11)	1 (5.56)	11 (61.11)	1 (5.56)	5 (27.78)	1 (5.56)	6 (33.33)	11 (61.11)	1 (5.56)
Tardive dyskinesia	6 (0.14)	0 (0.00)	0 (0.00)	0 (0.00)	1 (16.67)	5 (83.33)	0 (0.00)	6 (100.00)	0 (0.00)	0 (0.00)
Pneumonia	49 (1.18)	28 (57.14)	24 (48.98)	33 (67.35)	5 (10.20)	1 (2.04)	10 (20.41)	4 (8.16)	29 (59.18)	16 (32.65)
Accidental injury	102 (2.45)	13 (12.75)	12 (11.76)	81 (79.41)	2 (1.96)	19 (18.63)	0 (0.00)	42 (41.18)	48 (47.06)	12 (11.76)
Metabolic syndrome	3 (0.07)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (100.00)	0 (0.00)	1 (33.33)	2 (66.67)	0 (0.00)
Ischemic heart disease	13 (0.31)	3 (23.08)	3 (23.08)	7 (53.85)	1 (7.69)	3 (23.08)	2 (15.38)	6 (46.15)	3 (23.08)	4 (30.77)
Venous thromboembolism/Embolic venous	7 (0.17)	6 (85.71)	4 (57.14)	3 (42.86)	0 (0.00)	2 (28.57)	2 (28.57)	1 (14.29)	1 (14.29)	5 (71.43)
Intestinal obstruction/ileus	7 (0.17)	4 (57.14)	4 (57.14)	4 (57.14)	0 (0.00)	3 (42.86)	0 (0.00)	2 (28.57)	2 (28.57)	3 (42.86)

a Any type of adverse event in the group. . Only new, recurrent or events with change in intensity are included. Events ongoing at 6 months of treatment are not included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 69 Incidence of each adverse event risk, all age (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Incidence density[e]
Anaphylactic reaction	QTP	0 (0)	28576	0.00	8587.9	0.0
	Pla	0 (0)	7016	0.00	1283.2	0.0
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	1033	0.00	180.6	0.0
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1383	0.00	721.4	0.0
EPS	QTP	2764 (35)	28576	9.67	7715.3	35.8
	Pla	305 (1)	7016	4.35	1249.1	24.4
	Chl	143 (0)	541	26.43	54.9	260.5
	Dul	14 (0)	149	9.40	14.9	93.9
	Esc	27 (0)	365	7.40	46.8	57.7
	Hal	480 (32)	1033	46.47	112.0	428.5
	Li	61 (1)	622	9.81	176.5	34.6
	Mos	48 (1)	90	53.33	6.2	776.1
	Olz	11 (1)	168	6.55	68.8	16.0
	Par	22 (0)	336	6.55	41.2	53.4
	Ri	311 (2)	1383	22.49	594.1	52.3
Hepatitis	QTP	10 (1)	28576	0.03	8586.3	0.1
	Pla	1 (1)	7016	0.01	1283.2	0.1
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0

	Hal	0 (0)	1033	0.00	180.6	0.0
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	1 (0)	1383	0.07	719.5	0.1
Hyperglycemia and Diabetes mellitus	QTP	225 (16)	28576	0.79	8529.0	2.6
	Pla	35 (3)	7016	0.50	1280.2	2.7
	Chl	2 (0)	541	0.37	66.5	3.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	3 (0)	365	0.82	48.9	6.1
	Hal	3 (0)	1033	0.29	179.9	1.7
	Li	8 (0)	622	1.29	188.7	4.2
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	33 (4)	1383	2.39	700.6	4.7
Hypothyroidism	QTP	198 (3)	28576	0.69	8506.8	2.3
	Pla	18 (0)	7016	0.26	1280.6	1.4
	Chl	2 (0)	541	0.37	66.4	3.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	2 (0)	1033	0.19	180.5	1.1
	Li	16 (0)	622	2.57	184.6	8.7
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	6 (1)	1383	0.43	720.8	0.8
Jaundice	QTP	17 (1)	28576	0.06	8586.1	0.2

	Pla	1 (0)	7016	0.01	1283.0	0.1
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	1 (0)	1033	0.10	180.6	0.6
	Li	1 (0)	622	0.16	189.7	0.5
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	1 (0)	1383	0.07	720.8	0.1
Neuroleptic Malignant Syndrome	QTP	4 (3)	28576	0.01	8587.9	0.0
	Pla	0 (0)	7016	0.00	1283.2	0.0
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	3 (2)	1033	0.29	180.6	1.7
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	1 (1)	90	1.11	10.4	9.6
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1383	0.00	721.4	0.0
Neutropenia	QTP	124 (5)	28576	0.43	8545.9	1.5
	Pla	5 (0)	7016	0.07	1282.7	0.4
	Chl	1 (0)	541	0.18	66.5	1.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	1 (0)	365	0.27	49.2	2.0
	Hal	5 (2)	1033	0.48	180.1	2.8
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0

	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	13 (1)	1383	0.94	718.7	1.8
Seizure	QTP	79 (32)	28576	0.28	8563.9	0.9
	Pla	11 (7)	7016	0.16	1282.5	0.9
	Chl	4 (1)	541	0.74	66.5	6.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	5 (2)	1033	0.48	179.5	2.8
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	1 (0)	90	1.11	10.4	9.6
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	5 (2)	1383	0.36	720.8	0.7
Somnolence	QTP	11925 (18)	28576	41.73	5391.1	221.2
	Pla	815 (0)	7016	11.62	1182.2	68.9
	Chl	68 (0)	541	12.57	59.2	114.9
	Dul	56 (0)	149	37.58	10.7	521.5
	Esc	114 (0)	365	31.23	36.8	309.5
	Hal	155 (4)	1033	15.00	155.0	100.0
	Li	36 (0)	622	5.79	183.2	19.7
	Mos	15 (0)	90	16.67	9.0	167.1
	Olz	15 (0)	168	8.93	67.5	22.2
	Par	71 (0)	336	21.13	36.7	193.3
	Ri	288 (0)	1383	20.82	557.2	51.7
Stevens-Johnson syndrome and other serious skin reactions	QTP	3 (0)	28576	0.01	8585.6	0.0
	Pla	0 (0)	7016	0.00	1283.2	0.0
	Chl	0 (0)	541	0.00	66.6	0.0

	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	1033	0.00	180.6	0.0
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1383	0.00	721.4	0.0
Syncope and orthostatic hypotension	QTP	883 (45)	28576	3.09	8347.4	10.6
	Pla	67 (2)	7016	0.95	1276.8	5.2
	Chl	71 (4)	541	13.12	60.9	116.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	2 (0)	365	0.55	49.1	4.1
	Hal	24 (1)	1033	2.32	178.9	13.4
	Li	2 (1)	622	0.32	189.7	1.1
	Mos	3 (0)	90	3.33	10.1	29.6
	Olz	1 (0)	168	0.60	71.1	1.4
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	18 (2)	1383	1.30	713.0	2.5
Cerebrovascular Adverse Events	QTP	67 (31)	28576	0.23	8562.1	0.8
	Pla	10 (4)	7016	0.14	1282.7	0.8
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	3 (2)	1033	0.29	180.6	1.7
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0

	Par	0 (0)	336	0.00	43.5	0.0
	Ri	2 (1)	1383	0.14	719.1	0.3
Abuse Misuse	QTP	20 (4)	28576	0.07	8582.7	0.2
	Pla	2 (0)	7016	0.03	1283.2	0.2
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	1033	0.00	180.6	0.0
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	1 (0)	1383	0.07	720.0	0.1
Aggression/agitation	QTP	1937 (99)	28576	6.78	8134.6	23.8
	Pla	281 (10)	7016	4.01	1262.8	22.3
	Chl	59 (0)	541	10.91	61.9	95.4
	Dul	3 (1)	149	2.01	16.0	18.8
	Esc	24 (0)	365	6.58	48.0	50.0
	Hal	103 (7)	1033	9.97	171.0	60.3
	Li	5 (0)	622	0.80	189.1	2.6
	Mos	33 (0)	90	36.67	7.9	417.5
	Olz	7 (0)	168	4.17	69.5	10.1
	Par	6 (0)	336	1.79	43.2	13.9
	Ri	60 (7)	1383	4.34	697.2	8.6
Agranulocytosis	QTP	1 (1)	28576	0.00	8587.9	0.0
	Pla	0 (0)	7016	0.00	1283.2	0.0
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	1033	0.00	180.6	0.0

	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1383	0.00	721.4	0.0
Hyperprolactinemia	QTP	20 (0)	28576	0.07	8582.7	0.2
	Pla	6 (0)	7016	0.09	1282.8	0.5
	Chl	1 (0)	541	0.18	66.5	1.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	1033	0.00	180.6	0.0
	Li	1 (0)	622	0.16	189.8	0.5
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	1 (0)	336	0.30	43.5	2.3
	Ri	14 (0)	1383	1.01	717.6	2.0
QT prolongation and Torsade de Pointes	QTP	30 (2)	28576	0.10	8571.9	0.3
	Pla	2 (0)	7016	0.03	1283.2	0.2
	Chl	4 (0)	541	0.74	66.4	6.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	1 (0)	1033	0.10	180.6	0.6
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1383	0.00	721.4	0.0

Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	QTP	15 (5)	28576	0.05	8582.7	0.2
	Pla	2 (0)	7016	0.03	1283.2	0.2
	Chl	2 (0)	541	0.37	66.5	3.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	2 (0)	1033	0.19	180.5	1.1
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1383	0.00	721.4	0.0
Suicide	QTP	297 (164)	28576	1.04	8526.3	3.5
	Pla	58 (28)	7016	0.83	1281.9	4.5
	Chl	3 (2)	541	0.55	66.6	4.5
	Dul	1 (0)	149	0.67	16.0	6.3
	Esc	2 (1)	365	0.55	49.1	4.1
	Hal	14 (7)	1033	1.36	178.4	7.8
	Li	4 (1)	622	0.64	189.8	2.1
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	2 (0)	336	0.60	43.4	4.6
	Ri	31 (24)	1383	2.24	706.0	4.4
Pancreatitis	QTP	12 (7)	28576	0.04	8586.2	0.1
	Pla	3 (3)	7016	0.04	1283.1	0.2
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0

	Hal	0 (0)	1033	0.00	180.6	0.0
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	2 (1)	1383	0.14	719.5	0.3
Dysphagia	QTP	134 (4)	28576	0.47	8550.6	1.6
	Pla	12 (0)	7016	0.17	1282.1	0.9
	Chl	7 (0)	541	1.29	66.1	10.6
	Dul	2 (0)	149	1.34	15.7	12.8
	Esc	1 (0)	365	0.27	49.2	2.0
	Hal	20 (0)	1033	1.94	179.6	11.1
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	9 (0)	90	10.00	10.1	88.9
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	3 (0)	1383	0.22	719.6	0.4
Tardive dyskinesia	QTP	57 (1)	28576	0.20	8553.0	0.7
	Pla	2 (0)	7016	0.03	1282.9	0.2
	Chl	3 (0)	541	0.55	66.4	4.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	3 (0)	1033	0.29	180.4	1.7
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	1 (0)	168	0.60	70.9	1.4
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	8 (0)	1383	0.58	714.3	1.1
Pneumonia	QTP	152 (76)	28576	0.53	8539.2	1.8
	Pla	16 (8)	7016	0.23	1280.2	1.2

	Chl	3 (2)	541	0.55	66.3	4.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	1 (1)	365	0.27	49.2	2.0
	Hal	10 (3)	1033	0.97	180.2	5.5
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	2 (0)	168	1.19	71.1	2.8
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	11 (7)	1383	0.80	717.3	1.5
Accidental injury	QTP	571 (54)	28576	2.00	8384.5	6.8
	Pla	124 (7)	7016	1.77	1269.2	9.8
	Chl	7 (2)	541	1.29	66.2	10.6
	Dul	1 (0)	149	0.67	16.0	6.3
	Esc	5 (0)	365	1.37	48.8	10.2
	Hal	58 (1)	1033	5.61	175.2	33.1
	Li	2 (0)	622	0.32	189.8	1.1
	Mos	1 (0)	90	1.11	10.4	9.6
	Olz	2 (0)	168	1.19	70.4	2.8
	Par	3 (0)	336	0.89	43.2	6.9
	Ri	28 (3)	1383	2.02	707.3	4.0
Metabolic syndrome	QTP	5 (0)	28576	0.02	8587.2	0.1
	Pla	0 (0)	7016	0.00	1283.2	0.0
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	1033	0.00	180.6	0.0
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0

	Ri	0 (0)	1383	0.00	721.4	0.0
Ischemic heart disease	QTP	77 (22)	28576	0.27	8554.2	0.9
	Pla	18 (8)	7016	0.26	1282.2	1.4
	Chl	1 (0)	541	0.18	66.6	1.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	5 (2)	1033	0.48	180.5	2.8
	Li	1 (0)	622	0.16	189.8	0.5
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	1 (0)	168	0.60	71.2	1.4
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	5 (3)	1383	0.36	718.5	0.7
Venous thromboembolism/Embolic venous	QTP	23 (17)	28576	0.08	8576.5	0.3
	Pla	4 (2)	7016	0.06	1281.9	0.3
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	1 (1)	1033	0.10	180.6	0.6
	Li	0 (0)	622	0.00	189.8	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	2 (2)	1383	0.14	720.4	0.3
Intestinal obstruction/ileus	QTP	25 (15)	28576	0.09	8578.6	0.3
	Pla	1 (1)	7016	0.01	1283.2	0.1
	Chl	1 (0)	541	0.18	66.6	1.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0

Hal	0 (0)	1033	0.00	180.6	0.0
Li	0 (0)	622	0.00	189.8	0.0
Mos	0 (0)	90	0.00	10.4	0.0
Olz	0 (0)	168	0.00	71.2	0.0
Par	0 (0)	336	0.00	43.5	0.0
Ri	0 (0)	1383	0.00	721.4	0.0

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event.
e 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T26_ae_inc_all.SAS. Data version: V27. User: [redacted] 2014-08-22 13:52.

Table 70 Incidence of each adverse event risk, age <18 years (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Incidence density[e]
Anaphylactic reaction	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
EPS	QTP	65 (2)	601	10.82	185.4	35.1
	Pla	5 (0)	265	1.89	26.3	19.0
	Mos	1 (0)	1	100.00	0.0	36525.0
Hepatitis	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Hyperglycemia and Diabetes mellitus	QTP	6 (1)	601	1.00	203.2	3.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Hypothyroidism	QTP	8 (0)	601	1.33	200.0	4.0
	Pla	1 (0)	265	0.38	26.6	3.8
	Mos	0 (0)	1	0.00	0.0	0.0

Jaundice	QTP	1 (0)	601	0.17	204.1	0.5
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Neuroleptic Malignant Syndrome	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Neutropenia	QTP	8 (1)	601	1.33	201.6	4.0
	Pla	3 (0)	265	1.13	26.6	11.3
	Mos	0 (0)	1	0.00	0.0	0.0
Seizure	QTP	1 (0)	601	0.17	204.6	0.5
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Somnolence	QTP	304 (0)	601	50.58	100.4	302.7
	Pla	44 (0)	265	16.60	24.3	181.3
	Mos	0 (0)	1	0.00	0.0	0.0
Stevens-Johnson syndrome and other serious skin reactions	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Syncope and orthostatic hypotension	QTP	13 (2)	601	2.16	202.0	6.4
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Cerebrovascular Adverse Events	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Abuse Misuse	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Aggression/agitation	QTP	84 (11)	601	13.98	184.1	45.6
	Pla	28 (2)	265	10.57	24.2	115.5

	Mos	0 (0)	1	0.00	0.0	0.0
Agranulocytosis	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Hyperprolactinemia	QTP	5 (0)	601	0.83	202.8	2.5
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
QT prolongation and Torsade de Pointes	QTP	14 (0)	601	2.33	198.4	7.1
	Pla	1 (0)	265	0.38	26.6	3.8
	Mos	0 (0)	1	0.00	0.0	0.0
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Suicide	QTP	9 (2)	601	1.50	203.5	4.4
	Pla	1 (0)	265	0.38	26.5	3.8
	Mos	0 (0)	1	0.00	0.0	0.0
Pancreatitis	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Dysphagia	QTP	1 (0)	601	0.17	204.4	0.5
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Tardive dyskinesia	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Pneumonia	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Accidental injury	QTP	12 (0)	601	2.00	201.5	6.0

	Pla	3 (0)	265	1.13	26.5	11.3
	Mos	0 (0)	1	0.00	0.0	0.0
Metabolic syndrome	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Ischemic heart disease	QTP	2 (0)	601	0.33	204.6	1.0
	Pla	1 (0)	265	0.38	26.6	3.8
	Mos	0 (0)	1	0.00	0.0	0.0
Venous thromboembolism/Embolic venous	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0
Intestinal obstruction/ileus	QTP	0 (0)	601	0.00	204.6	0.0
	Pla	0 (0)	265	0.00	26.6	0.0
	Mos	0 (0)	1	0.00	0.0	0.0

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event.
e 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T26_ae_inc_all_age17.SAS. Data version: V27. User: [redacted] 2014-08-22 13:50.

Table 71 Incidence of each adverse event risk, age 18-65 years (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Incidence density[e]
Anaphylactic reaction	QTP	0 (0)	26510	0.00	7864.3	0.0
	Pla	0 (0)	6099	0.00	1151.5	0.0
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0

	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1368	0.00	717.5	0.0
EPS	QTP	2578 (30)	26510	9.72	7049.6	36.6
	Pla	273 (1)	6099	4.48	1120.5	24.4
	Chl	143 (0)	541	26.43	54.9	260.5
	Dul	14 (0)	149	9.40	14.9	93.9
	Esc	27 (0)	365	7.40	46.8	57.7
	Hal	434 (29)	841	51.61	89.8	483.6
	Li	57 (1)	612	9.31	174.9	32.6
	Mos	47 (1)	89	52.81	6.2	760.3
	Olz	11 (1)	168	6.55	68.8	16.0
	Par	22 (0)	336	6.55	41.2	53.4
	Ri	310 (2)	1368	22.66	590.2	52.5
Hepatitis	QTP	10 (1)	26510	0.04	7862.6	0.1
	Pla	1 (1)	6099	0.02	1151.5	0.1
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	1 (0)	1368	0.07	715.6	0.1
Hyperglycemia and Diabetes mellitus	QTP	203 (13)	26510	0.77	7808.0	2.6
	Pla	32 (3)	6099	0.52	1148.7	2.8

	Chl	2 (0)	541	0.37	66.5	3.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	3 (0)	365	0.82	48.9	6.1
	Hal	3 (0)	841	0.36	154.0	1.9
	Li	8 (0)	612	1.31	186.2	4.3
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	33 (4)	1368	2.41	696.6	4.7
Hypothyroidism	QTP	172 (3)	26510	0.65	7793.8	2.2
	Pla	15 (0)	6099	0.25	1148.9	1.3
	Chl	2 (0)	541	0.37	66.4	3.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	1 (0)	841	0.12	154.7	0.6
	Li	16 (0)	612	2.61	182.1	8.8
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	6 (1)	1368	0.44	716.9	0.8
Jaundice	QTP	16 (1)	26510	0.06	7863.0	0.2
	Pla	1 (0)	6099	0.02	1151.3	0.1
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	1 (0)	612	0.16	187.2	0.5
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0

	Ri	1 (0)	1368	0.07	716.9	0.1
Neuroleptic Malignant Syndrome	QTP	4 (3)	26510	0.02	7864.3	0.1
	Pla	0 (0)	6099	0.00	1151.5	0.0
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	3 (2)	841	0.36	154.7	1.9
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	1 (1)	89	1.12	10.4	9.6
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1368	0.00	717.5	0.0
Neutropenia	QTP	114 (4)	26510	0.43	7825.6	1.5
	Pla	2 (0)	6099	0.03	1151.0	0.2
	Chl	1 (0)	541	0.18	66.5	1.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	1 (0)	365	0.27	49.2	2.0
	Hal	5 (2)	841	0.59	154.2	3.2
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	13 (1)	1368	0.95	714.8	1.8
Seizure	QTP	65 (28)	26510	0.25	7847.6	0.8
	Pla	10 (6)	6099	0.16	1150.8	0.9
	Chl	4 (1)	541	0.74	66.5	6.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	5 (2)	841	0.59	153.6	3.3

	Li	0 (0)	612	0.00	187.3	0.0
	Mos	1 (0)	89	1.12	10.4	9.6
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	5 (2)	1368	0.37	716.9	0.7
Somnolence	QTP	11180 (13)	26510	42.17	4914.9	227.5
	Pla	705 (0)	6099	11.56	1061.6	66.4
	Chl	68 (0)	541	12.57	59.2	114.9
	Dul	56 (0)	149	37.58	10.7	521.5
	Esc	114 (0)	365	31.23	36.8	309.5
	Hal	97 (1)	841	11.53	133.3	72.7
	Li	35 (0)	612	5.72	180.8	19.4
	Mos	15 (0)	89	16.85	9.0	167.2
	Olz	15 (0)	168	8.93	67.5	22.2
	Par	71 (0)	336	21.13	36.7	193.3
	Ri	287 (0)	1368	20.98	553.6	51.8
Stevens-Johnson syndrome and other serious skin reactions	QTP	3 (0)	26510	0.01	7862.0	0.0
	Pla	0 (0)	6099	0.00	1151.5	0.0
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1368	0.00	717.5	0.0
Syncope and orthostatic hypotension	QTP	790 (27)	26510	2.98	7655.7	10.3

	Pla	54 (2)	6099	0.89	1146.2	4.7
	Chl	71 (4)	541	13.12	60.9	116.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	2 (0)	365	0.55	49.1	4.1
	Hal	14 (1)	841	1.66	153.8	9.1
	Li	2 (1)	612	0.33	187.2	1.1
	Mos	3 (0)	89	3.37	10.1	29.6
	Olz	1 (0)	168	0.60	71.1	1.4
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	17 (1)	1368	1.24	709.3	2.4
Cerebrovascular Adverse Events	QTP	37 (14)	26510	0.14	7853.3	0.5
	Pla	5 (3)	6099	0.08	1151.2	0.4
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	1 (0)	841	0.12	154.7	0.6
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	2 (1)	1368	0.15	715.2	0.3
Abuse Misuse	QTP	20 (4)	26510	0.08	7859.1	0.3
	Pla	2 (0)	6099	0.03	1151.5	0.2
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0

	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	1 (0)	1368	0.07	716.0	0.1
Aggression/agitation	QTP	1741 (75)	26510	6.57	7475.2	23.3
	Pla	220 (7)	6099	3.61	1136.0	19.4
	Chl	59 (0)	541	10.91	61.9	95.4
	Dul	3 (1)	149	2.01	16.0	18.8
	Esc	24 (0)	365	6.58	48.0	50.0
	Hal	87 (7)	841	10.34	146.2	59.5
	Li	5 (0)	612	0.82	186.6	2.7
	Mos	33 (0)	89	37.08	7.9	417.6
	Olz	7 (0)	168	4.17	69.5	10.1
	Par	6 (0)	336	1.79	43.2	13.9
	Ri	60 (7)	1368	4.39	693.3	8.7
Agranulocytosis	QTP	1 (1)	26510	0.00	7864.3	0.0
	Pla	0 (0)	6099	0.00	1151.5	0.0
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1368	0.00	717.5	0.0
Hyperprolactinemia	QTP	15 (0)	26510	0.06	7860.9	0.2
	Pla	6 (0)	6099	0.10	1151.2	0.5
	Chl	1 (0)	541	0.18	66.5	1.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0

	Hal	0 (0)	841	0.00	154.7	0.0
	Li	1 (0)	612	0.16	187.3	0.5
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	1 (0)	336	0.30	43.5	2.3
	Ri	14 (0)	1368	1.02	713.6	2.0
QT prolongation and Torsade de Pointes	QTP	12 (1)	26510	0.05	7857.2	0.2
	Pla	1 (0)	6099	0.02	1151.5	0.1
	Chl	4 (0)	541	0.74	66.4	6.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1368	0.00	717.5	0.0
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	QTP	13 (4)	26510	0.05	7861.8	0.2
	Pla	1 (0)	6099	0.02	1151.5	0.1
	Chl	2 (0)	541	0.37	66.5	3.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	2 (0)	841	0.24	154.6	1.3
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0

	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1368	0.00	717.5	0.0
Suicide	QTP	283 (159)	26510	1.07	7806.7	3.6
	Pla	55 (26)	6099	0.90	1150.3	4.8
	Chl	3 (2)	541	0.55	66.6	4.5
	Dul	1 (0)	149	0.67	16.0	6.3
	Esc	2 (1)	365	0.55	49.1	4.1
	Hal	13 (7)	841	1.55	152.6	8.5
	Li	4 (1)	612	0.65	187.3	2.1
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	2 (0)	336	0.60	43.4	4.6
	Ri	31 (24)	1368	2.27	702.1	4.4
Pancreatitis	QTP	9 (6)	26510	0.03	7862.8	0.1
	Pla	3 (3)	6099	0.05	1151.5	0.3
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	2 (1)	1368	0.15	715.6	0.3
Dysphagia	QTP	121 (3)	26510	0.46	7828.8	1.5
	Pla	6 (0)	6099	0.10	1150.7	0.5
	Chl	7 (0)	541	1.29	66.1	10.6
	Dul	2 (0)	149	1.34	15.7	12.8
	Esc	1 (0)	365	0.27	49.2	2.0
	Hal	17 (0)	841	2.02	153.9	11.0

	Li	0 (0)	612	0.00	187.3	0.0
	Mos	9 (0)	89	10.11	10.1	88.9
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	3 (0)	1368	0.22	715.6	0.4
Tardive dyskinesia	QTP	51 (1)	26510	0.19	7833.9	0.7
	Pla	2 (0)	6099	0.03	1151.2	0.2
	Chl	3 (0)	541	0.55	66.4	4.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	3 (0)	841	0.36	154.5	1.9
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	1 (0)	168	0.60	70.9	1.4
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	8 (0)	1368	0.58	710.4	1.1
Pneumonia	QTP	92 (38)	26510	0.35	7828.9	1.2
	Pla	9 (3)	6099	0.15	1148.6	0.8
	Chl	3 (2)	541	0.55	66.3	4.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	1 (1)	365	0.27	49.2	2.0
	Hal	4 (1)	841	0.48	154.5	2.6
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	2 (0)	168	1.19	71.1	2.8
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	11 (7)	1368	0.80	713.4	1.5
Accidental injury	QTP	295 (27)	26510	1.11	7754.8	3.8
	Pla	54 (6)	6099	0.89	1142.5	4.7
	Chl	7 (2)	541	1.29	66.2	10.6

	Dul	1 (0)	149	0.67	16.0	6.3
	Esc	5 (0)	365	1.37	48.8	10.2
	Hal	5 (1)	841	0.59	153.4	3.3
	Li	2 (0)	612	0.33	187.3	1.1
	Mos	1 (0)	89	1.12	10.4	9.6
	Olz	2 (0)	168	1.19	70.4	2.8
	Par	3 (0)	336	0.89	43.2	6.9
	Ri	28 (3)	1368	2.05	703.3	4.0
Metabolic syndrome	QTP	5 (0)	26510	0.02	7863.6	0.1
	Pla	0 (0)	6099	0.00	1151.5	0.0
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1368	0.00	717.5	0.0
Ischemic heart disease	QTP	63 (16)	26510	0.24	7832.6	0.8
	Pla	12 (5)	6099	0.20	1150.6	1.0
	Chl	1 (0)	541	0.18	66.6	1.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	1 (1)	841	0.12	154.7	0.6
	Li	1 (0)	612	0.16	187.3	0.5
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	1 (0)	168	0.60	71.2	1.4
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	5 (3)	1368	0.37	714.6	0.7

Venous thromboembolism/Embolic venous	QTP	16 (12)	26510	0.06	7858.2	0.2
	Pla	4 (2)	6099	0.07	1150.2	0.3
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	2 (2)	1368	0.15	716.5	0.3
Intestinal obstruction/ileus	QTP	19 (11)	26510	0.07	7858.3	0.2
	Pla	0 (0)	6099	0.00	1151.5	0.0
	Chl	1 (0)	541	0.18	66.6	1.5
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	0 (0)	841	0.00	154.7	0.0
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	89	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	0 (0)	1368	0.00	717.5	0.0

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event.
e 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T26_ae_inc_all_age1865.SAS. Data version: V27. User: [redacted] 2014-08-22 13:49.

Table 72 Incidence of each adverse event risk, age >=66 years (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Incidence density[e]
Anaphylactic reaction	QTP	0 (0)	1465	0.00	519.0	0.0
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
EPS	QTP	121 (3)	1465	8.26	480.4	25.2
	Pla	27 (0)	652	4.14	102.3	26.4
	Hal	46 (3)	192	23.96	22.3	206.7
	Li	4 (0)	10	40.00	1.6	251.9
	Ri	1 (0)	15	6.67	3.9	25.7
Hepatitis	QTP	0 (0)	1465	0.00	519.0	0.0
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Hyperglycemia and Diabetes mellitus	QTP	16 (2)	1465	1.09	517.8	3.1
	Pla	3 (0)	652	0.46	104.9	2.9
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Hypothyroidism	QTP	18 (0)	1465	1.23	513.0	3.5
	Pla	2 (0)	652	0.31	105.1	1.9
	Hal	1 (0)	192	0.52	25.7	3.9
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Jaundice	QTP	0 (0)	1465	0.00	519.0	0.0

	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	1 (0)	192	0.52	25.8	3.9
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Neuroleptic Malignant Syndrome	QTP	0 (0)	1465	0.00	519.0	0.0
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Neutropenia	QTP	2 (0)	1465	0.14	518.8	0.4
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Seizure	QTP	13 (4)	1465	0.89	511.6	2.5
	Pla	1 (1)	652	0.15	105.1	1.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Somnolence	QTP	441 (5)	1465	30.10	375.8	117.3
	Pla	66 (0)	652	10.12	96.3	68.5
	Hal	58 (3)	192	30.21	21.7	267.1
	Li	1 (0)	10	10.00	2.3	42.7
	Ri	1 (0)	15	6.67	3.6	27.8
Stevens-Johnson syndrome and other serious skin reactions	QTP	0 (0)	1465	0.00	519.0	0.0
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0

	Ri	0 (0)	15	0.00	3.9	0.0
Syncope and orthostatic hypotension	QTP	80 (16)	1465	5.46	489.7	16.3
	Pla	13 (0)	652	1.99	104.0	12.5
	Hal	10 (0)	192	5.21	25.1	39.9
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	1 (1)	15	6.67	3.7	27.1
Cerebrovascular Adverse Events	QTP	30 (17)	1465	2.05	504.1	6.0
	Pla	5 (1)	652	0.77	104.9	4.8
	Hal	2 (2)	192	1.04	25.9	7.7
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Abuse Misuse	QTP	0 (0)	1465	0.00	519.0	0.0
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Aggression/agitation	QTP	112 (13)	1465	7.65	475.3	23.6
	Pla	33 (1)	652	5.06	102.5	32.2
	Hal	16 (0)	192	8.33	24.7	64.7
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Agranulocytosis	QTP	0 (0)	1465	0.00	519.0	0.0
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Hyperprolactinemia	QTP	0 (0)	1465	0.00	519.0	0.0
	Pla	0 (0)	652	0.00	105.1	0.0

	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
QT prolongation and Torsade de Pointes	QTP	4 (1)	1465	0.27	516.3	0.8
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	1 (0)	192	0.52	25.9	3.9
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	QTP	2 (1)	1465	0.14	516.3	0.4
	Pla	1 (0)	652	0.15	105.1	1.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Suicide	QTP	5 (3)	1465	0.34	516.1	1.0
	Pla	2 (2)	652	0.31	105.1	1.9
	Hal	1 (0)	192	0.52	25.9	3.9
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Pancreatitis	QTP	3 (1)	1465	0.20	518.7	0.6
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Dysphagia	QTP	12 (1)	1465	0.82	517.4	2.3
	Pla	6 (0)	652	0.92	104.8	5.7
	Hal	3 (0)	192	1.56	25.7	11.7

	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Tardive dyskinesia	QTP	6 (0)	1465	0.41	514.5	1.2
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Pneumonia	QTP	60 (38)	1465	4.10	505.7	11.9
	Pla	7 (5)	652	1.07	105.0	6.7
	Hal	6 (2)	192	3.13	25.7	23.4
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Accidental injury	QTP	264 (27)	1465	18.02	428.2	61.7
	Pla	67 (1)	652	10.28	100.2	66.8
	Hal	53 (0)	192	27.60	21.8	243.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Metabolic syndrome	QTP	0 (0)	1465	0.00	519.0	0.0
	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Ischemic heart disease	QTP	12 (6)	1465	0.82	516.9	2.3
	Pla	5 (3)	652	0.77	105.0	4.8
	Hal	4 (1)	192	2.08	25.8	15.5
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Venous thromboembolism/Embolic venous	QTP	7 (5)	1465	0.48	513.7	1.4

	Pla	0 (0)	652	0.00	105.1	0.0
	Hal	1 (1)	192	0.52	25.9	3.9
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0
Intestinal obstruction/ileus	QTP	6 (4)	1465	0.41	515.6	1.2
	Pla	1 (1)	652	0.15	105.1	1.0
	Hal	0 (0)	192	0.00	25.9	0.0
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event.
e 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T26_ae_inc_all_age66.SAS. Data version: V27. User: [redacted] 2014-08-22 13:48.

Table 73 Incidence of adverse events occuring after 6 months of exposure on Quetiapine (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Exposure after 6 months[e]
Anaphylactic reaction	QTP	0 (0)	4161	0.00	4669.8	2589.3
EPS	QTP	204 (7)	4161	4.90	4526.3	2445.8
Hepatitis	QTP	0 (0)	4161	0.00	4669.8	2589.3
Hyperglycemia and Diabetes mellitus	QTP	50 (6)	4161	1.20	4650.0	2569.5
Hypothyroidism	QTP	47 (0)	4161	1.13	4640.1	2559.6
Jaundice	QTP	3 (0)	4161	0.07	4669.4	2588.9
Neuroleptic Malignant Syndrome	QTP	0 (0)	4161	0.00	4669.8	2589.3
Neutropenia	QTP	22 (1)	4161	0.53	4661.2	2580.7
Seizure	QTP	18 (3)	4161	0.43	4661.0	2580.5

Somnolence	QTP	347 (7)	4161	8.34	4410.8	2330.3
Stevens-Johnson syndrome and other serious skin reactions	QTP	0 (0)	4161	0.00	4669.8	2589.3
Syncope and orthostatic hypotension	QTP	66 (9)	4161	1.59	4614.4	2533.9
Cerebrovascular Adverse Events	QTP	16 (7)	4161	0.38	4662.3	2581.8
Abuse Misuse	QTP	5 (2)	4161	0.12	4668.1	2587.6
Aggression/agitation	QTP	139 (11)	4161	3.34	4577.7	2497.2
Agranulocytosis	QTP	0 (0)	4161	0.00	4669.8	2589.3
Hyperprolactinemia	QTP	7 (0)	4161	0.17	4666.5	2586.0
QT prolongation and Torsade de Pointes	QTP	7 (0)	4161	0.17	4664.3	2583.8
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	QTP	5 (2)	4161	0.12	4667.7	2587.2
Suicide	QTP	44 (30)	4161	1.06	4644.7	2564.2
Pancreatitis	QTP	3 (2)	4161	0.07	4669.5	2589.0
Dysphagia	QTP	18 (2)	4161	0.43	4659.0	2578.5
Tardive dyskinesia	QTP	6 (0)	4161	0.14	4665.1	2584.6
Pneumonia	QTP	49 (28)	4161	1.18	4641.8	2561.3
Accidental injury	QTP	102 (13)	4161	2.45	4595.9	2515.4
Metabolic syndrome	QTP	3 (0)	4161	0.07	4669.5	2589.0
Ischemic heart disease	QTP	13 (3)	4161	0.31	4658.3	2577.8
Venous thromboembolism/Embolic venous	QTP	7 (6)	4161	0.17	4664.1	2583.6
Intestinal obstruction/ileus	QTP	7 (4)	4161	0.17	4664.2	2583.7

a Any type of adverse event in the group. Only new, recurrent or events with change in intensity are included. Events ongoing at 6 months of treatment are not included.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event after 6 months exposure.
e Exposure in patient-years, censored at first event after 6 months exposure. Only exposure after 6 months of treatment is included.

Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Mania and hypomania

Table 74 Seriousness, outcomes, and severity of treatment emergent mania and hypomania AEs - all trials

Risk Adverse event group[a] N=2095	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
AEs of mania or hypomania	31 (1.48)	12 (38.71)	12 (38.71)	23 (74.19)	0 (0.00)	8 (25.81)	0 (0.00)	6 (19.35)	12 (38.71)	13 (41.94)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: Included trials: D144CC00002, D1447C00001, D1447C00134, D1447C00135 and 5077US/0049.
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Table 75 Seriousness, outcomes, and severity of treatment emergent mania and hypomania AEs occuring after 6 months of exposure on Quetiapine - all trials

Risk Adverse event group[a] N=339	Adverse event[a] n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
AEs of mania or hypomania	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

a Any type of adverse event in the group. Events ongoing at 6 months of treatment are not included.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: Included trials: D144CC00002, D1447C00001, D1447C00134, D1447C00135 and 5077US/0049.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\TE_mania_ae_all_lt.SAS. Version: V27. User: [redacted] 2014-08-22 13:58.

Table 76 Treatment emergent mania and hypomania AEs (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Incidence density[e]
AEs of mania or hypomania	QTP	31 (12)	2095	1.48	536.5	5.8
	Pla	12 (5)	1024	1.17	219.0	5.5
	Li	1 (1)	136	0.74	18.0	5.5
	Par	4 (3)	121	3.31	15.1	26.5

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event.
e 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Included trials: D144CC00002, D1447C00001, D1447C00134, D1447C00135 and 5077US/0049.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\TE_mania_ae_inc_all.SAS. Data version: V27. User: [redacted] 2014-08-22 13:58.

Table 77 Treatment emergent mania and hypomania AEs occuring after 6 months of exposure on Quetiapine (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Exposure after 6 months[e]
Any[b]	QTP	0 (0)	339	0.00	297.1	127.6

a Any type of adverse event in the group. Only new, recurrent or events with change in intensity are included. Events ongoing at 6 months of treatment are not included.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event after 6 months exposure.
e Exposure in patient-years, censored at first event after 6 months exposure. Only exposure after 6 months of treatment is included.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Included trials: D144CC00002, D1447C00001, D1447C00134, D1447C00135 and 5077US/0049.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\TE_mania_ae_inc_all_lt.SAS. Data version: V27. User: [redacted] 2014-08-22 13:58.

Cerebrovascular

Table 78 Seriousness, outcomes, and severity of each adverse event risk, age > 65 years - all trials

Risk Adverse event group[a] N=1465	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Cerebrovascular Adverse Events	30 (2.05)	17 (56.67)	13 (43.33)	20 (66.67)	0 (0.00)	6 (20.00)	4 (13.33)	7 (23.33)	9 (30.00)	13 (43.33)

a Any type of adverse event in the group.
QTP Quetiapine.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: 1 adverse event has no information on intensity and is therefore not considered.
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Table 79 Seriousness, outcomes, and severity of each adverse event risk, age <66 years - all trials

Risk Adverse event group[a] N=27111	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Cerebrovascular Adverse Events	37 (0.14)	14 (37.84)	13 (35.14)	23 (62.16)	1 (2.70)	9 (24.32)	4 (10.81)	12 (32.43)	11 (29.73)	14 (37.84)

a Any type of adverse event in the group.
QTP Quetiapine.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\CVA_ae_all_ageunder66.SAS. Version: V27. User: [redacted] 2014-07-15 23:39.

Table 80 Seriousness, outcomes, and severity of each adverse event risk, occurring after 6 months of exposure on Quetiapine, age > 65 - all trials

Risk Adverse event group[a] N=167	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Cerebrovascular Adverse Events	10 (5.99)	3 (30.00)	2 (20.00)	6 (60.00)	0 (0.00)	4 (40.00)	0 (0.00)	4 (40.00)	4 (40.00)	2 (20.00)

a Any type of adverse event in the group. . Only new, recurrent or events with change in intensity are included. Events ongoing at 6 months of treatment are not included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\CVA_ae_all_lt_ageover65.SAS. Version: V27. User: [redacted] 2014-07-15 23:40.

Table 81 Seriousness, outcomes, and severity of each adverse event risk, occurring after 6 months of exposure on Quetiapine, age<66 - all trials

Risk Adverse event group[a] N=3994	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Cerebrovascular Adverse Events	6 (0.15)	4 (66.67)	4 (66.67)	2 (33.33)	1 (16.67)	1 (16.67)	2 (33.33)	1 (16.67)	1 (16.67)	4 (66.67)

a Any type of adverse event in the group. . Only new, recurrent or events with change in intensity are included. Events ongoing at 6 months of treatment are not included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\CVA_ae_all_lt_ageunder66.SAS. Version: V27. User: [redacted] 2014-07-15 23:39.

Table 82 Incidence of each adverse event risk, age > 65 years (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Incidence density[e]
Cerebrovascular Adverse Events	QTP	30 (17)	1465	2.05	504.1	6.0
	Pla	5 (1)	652	0.77	104.9	4.8
	Hal	2 (2)	192	1.04	25.9	7.7
	Li	0 (0)	10	0.00	2.5	0.0
	Ri	0 (0)	15	0.00	3.9	0.0

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event.
e 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\CVA_ae_inc_all_ageover65.SAS. Data version: V27. User: [redacted] 2014-07-15 23:40.

Table 83 Incidence of each adverse event risk, age <66 years (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Incidence density[e]
Cerebrovascular Adverse Events	QTP	37 (14)	27111	0.14	8057.9	0.5
	Pla	5 (3)	6364	0.08	1177.8	0.4
	Chl	0 (0)	541	0.00	66.6	0.0
	Dul	0 (0)	149	0.00	16.0	0.0
	Esc	0 (0)	365	0.00	49.2	0.0
	Hal	1 (0)	841	0.12	154.7	0.6
	Li	0 (0)	612	0.00	187.3	0.0
	Mos	0 (0)	90	0.00	10.4	0.0
	Olz	0 (0)	168	0.00	71.2	0.0
	Par	0 (0)	336	0.00	43.5	0.0
	Ri	2 (1)	1368	0.15	715.2	0.3

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event.
e 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\CVA_ae_inc_all_ageunder66.SAS. Data version: V27. User: [redacted] 2014-07-15 23:39.

Table 84 Incidence of adverse events occuring after 6 months of exposure on Quetiapine, age > 65 (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Exposure after 6 months[e]
Cerebrovascular Adverse Events	QTP	10 (3)	167	5.99	274.0	190.5

a Any type of adverse event in the group. Only new, recurrent or events with change in intensity are included. Events ongoing at 6 months of treatment are not included.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event after 6 months exposure.
e Exposure in patient-years, censored at first event after 6 months exposure. Only exposure after 6 months of treatment is included.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\CVA_ae_inc_all_lt_ageover65.SAS. Data version: V27. User: [redacted] 2014-07-15 23:40.

Table 85 Incidence of adverse events occuring after 6 months of exposure on Quetiapine, age <66 (all trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Incidence rate[c]	Exposure[d]	Exposure after 6 months[e]
Cerebrovascular Adverse Events	QTP	6 (4)	3994	0.15	4388.4	2391.4

a Any type of adverse event in the group. Only new, recurrent or events with change in intensity are included. Events ongoing at 6 months of treatment are not included.
b Patients must have received at least one dose of trial medication.
c 100 x total number of patients with event/total number of patients.
d Exposure in patient-years, censored at first event after 6 months exposure.
e Exposure in patient-years, censored at first event after 6 months exposure. Only exposure after 6 months of treatment is included.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\CVA_ae_inc_all_lt_ageunder66.SAS. Data version: V27. User: [redacted] 2014-07-15 23:40.

1.3.1.3 Metabolic risk factors

Table 86 Incidence of shifts in metabolic risk factors to end of treatment (All trials)

		QTP			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
Shift from < 3 metabolic risk factors at baseline to >=3 post baseline	All	7750	989 (12.8)	2518.8	39.3
	18 to 65 years	7436	939 (12.6)	2453.6	38.3
	> 65 years	314	50 (15.9)	65.3	76.6

a Number of patients, age >= 18, with a normal (defnied as < 3 risk factors) baseline. Patient must have all 5 risk assessments at baseline and post baseline.
b Number of patients with event. Event defined as >= 3 risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_all.SAS. Data version: V27. User: [redacted] 2014-07-16 2:06.

Table 87 Incidence of shifts in metabolic risk factors to end of treatment (All trials). Patients with >= 3 shifts

		QTP			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
BMI >= 30 at EOT	All	583	195 (33.4)	234.0	83.4
	18 to 65 years	542	187 (34.5)	226.1	82.7
	> 65 years	41	8 (19.5)	7.8	102.2

GLUC >= 100(CF)/140(RF/NF) mg/dL at EOT	All	846	457 (54.0)	324.5	140.8
	18 to 65 years	811	439 (54.1)	318.3	137.9
	> 65 years	35	18 (51.4)	6.2	289.9
HDL < 40(M)/50(F) mg/dL at EOT	All	691	387 (56.0)	247.2	156.6
	18 to 65 years	654	369 (56.4)	240.3	153.6
	> 65 years	37	18 (48.6)	6.9	260.7
Supine BP >=130(SBP)/85(DBP) at EOT	All	562	144 (25.6)	234.3	61.5
	18 to 65 years	552	138 (25.0)	232.5	59.4
	> 65 years	10	6 (60.0)	1.8	334.6
TRIGL >= 150 mg/dL at EOT	All	652	505 (77.5)	241.6	209.0
	18 to 65 years	615	476 (77.4)	234.7	202.8
	> 65 years	37	29 (78.4)	6.9	419.5

a Number of patients, age >= 18, with a normal (defined as < 3 risk factors) baseline and >= 3 risk factors at end of treatment. Patient must have all 5 risk assessments at baseline and post baseline.
Additionally the patient must have a normal baseline per risk factor
b Number of patients with event. Event defined as shift in risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fasting, RF Random fasting, NF Non fasting, F Female, M Male
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_all_byRF.SAS. Data version: V27. User: [redacted] 2014-07-16 2:06.

Table 88 Incidence of shifts in metabolic risk factors to end of treatment (All trials)

		QTP			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
BMI >= 30 at EOT	All	16559	988 (6.0)	5305.3	18.6
	18 to 65 years	15746	963 (6.1)	4955.6	19.4
	> 65 years	813	25 (3.1)	349.7	7.1
GLUC >= 100(CF)/140(RF/NF) mg/dL at EOT	All	12732	1929 (15.2)	4250.8	45.4
	18 to 65 years	11987	1789 (14.9)	3909.7	45.8

	> 65 years	745	140 (18.8)	341.1	41.0
HDL < 40(M)/50(F) mg/dL at EOT	All	8523	1559 (18.3)	2687.0	58.0
	18 to 65 years	8177	1508 (18.4)	2612.3	57.7
	> 65 years	346	51 (14.7)	74.7	68.3
Supine BP >=130(SBP)/85(DBP) at EOT	All	15136	1159 (7.7)	4271.4	27.1
	18 to 65 years	14668	1096 (7.5)	4079.4	26.9
	> 65 years	468	63 (13.5)	191.9	32.8
TRIGL >= 150 mg/dL at EOT	All	7249	1782 (24.6)	2262.7	78.8
	18 to 65 years	6844	1697 (24.8)	2183.1	77.7
	> 65 years	405	85 (21.0)	79.6	106.8

a Number of patients, age >= 18. The patient must have a normal baseline and an EOT assessment per risk factor.
b Number of patients with event. Event defined as shift in risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_all_byRF_notMetSynd.SAS. Data version: V27. User: [redacted] 2014-07-16 2:06.

Table 89 Incidence of shifts in metabolic risk factors to end of treatment (All trials) by number of risks at baseline

		QTP			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
Shift from 0 metabolic risk factors at baseline to >=3 post baseline	All	2411	47 (1.9)	752.5	6.2
	18 to 65 years	2375	46 (1.9)	744.8	6.2
	> 65 years	36	1 (2.8)	7.7	13.0
Shift from 1 metabolic risk factors at baseline to >=3 post baseline	All	2937	273 (9.3)	950.4	28.7
	18 to 65 years	2793	265 (9.5)	920.1	28.8
	> 65 years	144	8 (5.6)	30.4	26.3
Shift from 2 metabolic risk factors at baseline to >=3 post baseline	All	2402	669 (27.9)	815.9	82.0

	18 to 65 years	2268	628 (27.7)	788.7	79.6
	> 65 years	134	41 (30.6)	27.2	150.7

a Number of patients, age >= 18, with a normal (defnied as < 3 risk factors) baseline. Patient must have all 5 risk assessments at baseline and post baseline.
b Number of patients with event. Event defined as >= 3 risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_all_NbrRfSplit.SAS. Data version: V27. User: [redacted] 2014-07-16 2:06.

Table 90 Incidence of shifts in metabolic risk factors to end of treatment, patients with at least 6 months exposure (All trials)

		QTP			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Exposure after 6m[c]**
Shift from < 3 metabolic risk factors at baseline to >=3 post baseline	All	1366	234 (17.1)	1220.1	537.1
	18 to 65 years	1354	233 (17.2)	1209.3	532.3
	> 65 years	12	1 (8.3)	10.8	4.8

a Number of patients, age >= 18, with a normal (defnied as < 3 risk factors) baseline. Patient must have all 5 risk assessments at baseline and post baseline.
b Number of patients with event. Event defined as >= 3 risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Note: Patient must have at least 6 months exposure, but risk factor may have occured at any time previously.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_lt.SAS. Data version: V27. User: [redacted] 2014-07-16 2:06.

Table 91 Incidence of shifts in metabolic risk factors to end of treatment, patients with at least 6 months exposure (All trials) and >= 3 shifts

		QTP			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Exposure after 6m[c]**
BMI >= 30 at EOT	All	151	69 (45.7)	137.4	61.9
	18 to 65 years	150	68 (45.3)	136.9	61.9
	> 65 years	1	1 (100.0)	0.5	0.0

GLUC >= 100(CF)/140(RF/NF) mg/dL at EOT	All	207	119 (57.5)	188.0	84.5
	18 to 65 years	207	119 (57.5)	188.0	84.5
	> 65 years	0	0	0	0
HDL < 40(M)/50(F) mg/dL at EOT	All	154	93 (60.4)	132.1	55.1
	18 to 65 years	153	93 (60.8)	131.6	55.1
	> 65 years	1	0 (0.0)	0.5	0.0
Supine BP >=130(SBP)/85(DBP) at EOT	All	151	45 (29.8)	141.5	66.0
	18 to 65 years	151	45 (29.8)	141.5	66.0
	> 65 years	0	0	0	0
TRIGL >= 150 mg/dL at EOT	All	143	113 (79.0)	135.9	64.4
	18 to 65 years	142	112 (78.9)	135.4	64.4

a Number of patients, age >= 18, with a normal (defnied as < 3 risk factors) baseline and >= 3 risk factors at end of treatment. Patient must have all 5 risk assessments at baseline and post baseline.
Additionally the patient must have a normal baseline per risk factor
b Number of patients with event. Event defined as shift in risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Note: Patient must have at least 6 months exposure, but risk factor may have occured at any time previously.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_lt_byRF.SAS. Data version: V27. User: [redacted] 2014-07-16 2:06.

Table 92 Incidence of shifts in metabolic risk factors to end of treatment, patients with at least 6 months exposure (All trials)

		QTP			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Exposure after 6m[c]**
BMI >= 30 at EOT	All	2514	299 (11.9)	2898.4	1641.4
	18 to 65 years	2378	292 (12.3)	2662.4	1473.4
	> 65 years	136	7 (5.1)	236.0	168.0
GLUC >= 100(CF)/140(RF/NF) mg/dL at EOT	All	2154	413 (19.2)	2277.7	1200.7
	18 to 65 years	2032	392 (19.3)	2063.9	1047.9

	> 65 years	122	21 (17.2)	213.8	152.8
HDL < 40(M)/50(F) mg/dL at EOT	All	1453	309 (21.3)	1323.3	596.8
	18 to 65 years	1438	307 (21.3)	1308.3	589.3
	> 65 years	15	2 (13.3)	15.0	7.5
Supine BP >=130(SBP)/85(DBP) at EOT	All	2001	228 (11.4)	2174.9	1174.4
	18 to 65 years	1937	219 (11.3)	2065.0	1096.5
	> 65 years	64	9 (14.1)	109.9	77.9
TRIGL >= 150 mg/dL at EOT	All	1167	313 (26.8)	1057.8	474.3
	18 to 65 years	1153	309 (26.8)	1045.0	468.5
	> 65 years	14	4 (28.6)	12.8	5.8

a Number of patients, age >= 18. The patient must have a normal baseline and an EOT assessment per risk factor
b Number of patients with event. Event defined as shift in risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Note: Patient must have at least 6 months exposure, but risk factor may have occured at any time previously.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_lt_byRF_notMetSynd.SAS. Data version: V27. User: [redacted] 2014-07-16 2:07.

Table 93 Incidence of shifts in metabolic risk factors to end of treatment, patients with at least 6 months exposure (All trials) by number of risks at baseline

		QTP			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Exposure after 6m[c]**
Shift from 0 metabolic risk factors at baseline to >=3 post baseline	All	399	18 (4.5)	338.8	139.3
	18 to 65 years	398	18 (4.5)	337.8	138.8
	> 65 years	1	0 (0.0)	0.9	0.4
Shift from 1 metabolic risk factors at baseline to >=3 post baseline	All	511	68 (13.3)	460.8	205.3
	18 to 65 years	505	68 (13.5)	455.8	203.3
	> 65 years	6	0 (0.0)	5.0	2.0

Shift from 2 metabolic risk factors at baseline to >=3 post baseline	All	456	148 (32.5)	420.5	192.5
	18 to 65 years	451	147 (32.6)	415.6	190.1
	> 65 years	5	1 (20.0)	4.9	2.4

a Number of patients, age >= 18, with a normal (defnied as < 3 risk factors) baseline. Patient must have all 5 risk assessments at baseline and post baseline.
b Number of patients with event. Event defined as >= 3 risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Note: Patient must have at least 6 months exposure, but risk factor may have occured at any time previously.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_lt_NbrRfSplit.SAS. Data version: V27. User: [redacted] 2014-07-16 2:07.

1.3.1.4 Weight

Table 94 Mean (SD) change from baseline to end of treatment in weight (all trials)

		QTP N=28576	Pla N=7016	Chl N=541	Dul N=149	Esc N=365	Hal N=1033	Li N=622	Mos N=90	Olz N=168	Par N=336	Ri N=1383
Patients[a]		25103	6589	507	149	360	760	610	86	168	324	996
Baseline	Mean (SD)	78.0 (20.6)	78.7 (21.0)	68.4 (14.8)	84.8 (19.5)	76.4 (19.3)	71.2 (16.5)	72.5 (18.7)	60.6 (12.1)	71.6 (14.4)	77.2 (20.5)	86.5 (21.6)
End of treatment	Mean (SD)	79.6 (20.8)	78.4 (21.1)	69.9 (15.0)	84.6 (19.9)	76.5 (19.3)	71.1 (16.0)	72.0 (18.7)	60.3 (12.0)	75.5 (15.5)	77.3 (20.3)	87.8 (20.9)
Change	Mean (SD)	1.5 (4.9)	-0.3 (3.4)	1.5 (5.6)	-0.2 (2.7)	0.1 (2.0)	0.0 (4.0)	-0.5 (3.4)	-0.2 (2.5)	4.0 (6.0)	0.1 (2.3)	1.3 (7.5)
	Median	1.0	0.0	1.0	0.0	0.0	0.0	0.0	-0.5	3.2	0.0	1.0
	Min to max	-95.0 to 100.0	-72.9 to 78.8	-12.0 to 89.2	-7.7 to 19.0	-6.4 to 8.1	-32.4 to 25.2	-23.0 to 13.0	-8.0 to 10.0	-17.6 to 23.1	-12.0 to 8.0	-119.5 to 38.0

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
QTP Quetiapine. Pla Placebo. Chl Chlorpromazine. Dul Duloxetine. Esc Escitalopram. Hal Haloperidol. Li Lithium. Mos Mosapramine. Olz Olanzapine. Par Paroxetine. Ri Risperidone.
Note: the placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_WEIGHT_CH_ALL.SAS. Data version: V27. User: [redacted] 2014-07-16 0:52.

Table 95 Mean (SD) change from baseline to end of treatment in weight, age <=17 (all trials)

		QTP N=601	Pla N=265	Mos N=1
Patients[a]		571	265	1
Baseline	Mean (SD)	61.9 (18.7)	63.0 (19.7)	51.5
End of treatment	Mean (SD)	65.7 (19.7)	63.4 (20.0)	50.5
Change	Mean (SD)	3.8 (6.9)	0.3 (2.4)	-1.0
	Median	2.0	0.0	-1.0
	Min to max	-18.0 to 100.0	-12.0 to 11.0	-1.0

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
QTP Quetiapine. Pla Placebo. Mos Mosapramine.
Note: the placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_WEIGHT_CH_ALL_AGE17.SAS. Data version: V27. User: [redacted] 2014-07-16 0:52.

Table 96 Mean (SD) change from baseline to end of treatment in weight, age 18 to 65 (all trials)

		QTP N=26510	Pla N=6099	Chl N=541	Dul N=149	Esc N=365	Hal N=841	Li N=612	Mos N=89	Olz N=168	Par N=336	Ri N=1368
Patients[a]		23253	5702	507	149	360	644	601	85	168	324	996
Baseline	Mean (SD)	79.0 (20.6)	80.3 (21.2)	68.4 (14.8)	84.8 (19.5)	76.4 (19.3)	72.4 (16.6)	72.5 (18.8)	60.7 (12.2)	71.6 (14.4)	77.2 (20.5)	86.5 (21.6)
End of treatment	Mean (SD)	80.6 (20.8)	80.0 (21.2)	69.9 (15.0)	84.6 (19.9)	76.5 (19.3)	72.4 (16.0)	72.1 (18.8)	60.5 (12.1)	75.5 (15.5)	77.3 (20.3)	87.8 (20.9)
Change	Mean (SD)	1.5 (4.9)	-0.3 (3.6)	1.5 (5.6)	-0.2 (2.7)	0.1 (2.0)	0.0 (4.0)	-0.5 (3.5)	-0.2 (2.5)	4.0 (6.0)	0.1 (2.3)	1.3 (7.5)
	Median	1.0	0.0	1.0	0.0	0.0	0.0	0.0	-0.5	3.2	0.0	1.0
	Min to max	-95.0 to 78.9	-72.9 to 78.8	-12.0 to 89.2	-7.7 to 19.0	-6.4 to 8.1	-32.4 to 25.2	-23.0 to 13.0	-8.0 to 10.0	-17.6 to 23.1	-12.0 to 8.0	-119.5 to 38.0

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
QTP Quetiapine. Pla Placebo. Chl Chlorpromazine. Dul Duloxetine. Esc Escitalopram. Hal Haloperidol. Li Lithium. Mos Mosapramine. Olz Olanzapine. Par Paroxetine. Ri Risperidone.
Note: the placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_WEIGHT_CH_ALL_AGE1865.SAS. Data version: V27. User: [redacted] 2014-07-16 0:52.

Table 97 Mean (SD) change from baseline to end of treatment in weight, age >=66 (all trials)

		QTP N=1465	Pla N=652	Hal N=192	Li N=10	Ri N=15
Patients[a]		1279	622	116	9	0
Baseline	Mean (SD)	67.2 (14.4)	70.1 (14.5)	64.4 (14.7)	69.2 (12.0)	NA
End of treatment	Mean (SD)	67.5 (14.6)	69.9 (14.6)	63.9 (14.7)	68.5 (11.9)	NA
Change	Mean (SD)	0.3 (3.8)	-0.1 (2.0)	-0.4 (3.9)	-0.7 (1.4)	NA
	Median	0.2	0.0	-0.4	-0.1	NA
	Min to max	-23.7 to 20.0	-10.9 to 11.4	-19.1 to 14.5	-4.0 to 1.0	NA

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
QTP Quetiapine. Pla Placebo. Hal Haloperidol. Li Lithium. Ri Risperidone.
Note: the placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_WEIGHT_CH_ALL_AGE66.SAS. Data version: V27. User: [redacted] 2014-07-16 0:52.

Table 98 Mean (SD) change from baseline to end of treatment in weight for patients with at least 6 months exposure to Seroquel - (all trials)

		QTP N=4161
Patients[a]		4048
Baseline	Mean (SD)	78.5 (20.5)
End of treatment	Mean (SD)	81.5 (21.2)
Change	Mean (SD)	3.0 (7.8)
	Median	2.0
	Min to max	-39.0 to 46.7

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
QTP Quetiapine.
Note: the placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_WEIGHT_CH_ALL_LT.SAS. Data version: V27. User: [redacted] 2014-07-16 0:52.

Table 99 Mean (SD) change from baseline to end of treatment in weight for patients with at least 6 months exposure to Seroquel, age <=17 (all trials)

		QTP N=227
Patients[a]		227
Baseline	Mean (SD)	60.6 (17.3)
End of treatment	Mean (SD)	66.4 (19.0)
Change	Mean (SD)	5.8 (6.9)
	Median	5.0
	Min to max	-18.0 to 29.0

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
QTP Quetiapine.
Note: the placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_WEIGHT_CH_ALL_LT_AGE17.SAS. Data version: V27. User: [redacted] 2014-07-16 0:52.

Table 100 Mean (SD) change from baseline to end of treatment in weight for patients with at least 6 months exposure to Seroquel, age 18 to 65 - (all trials)

		QTP N=3767
Patients[a]		3660
Baseline	Mean (SD)	80.1 (20.2)
End of treatment	Mean (SD)	83.0 (21.0)
Change	Mean (SD)	2.9 (7.8)
	Median	2.0
	Min to max	-39.0 to 46.7

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
QTP Quetiapine.
Note: the placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_WEIGHT_CH_ALL_LT_AGE1865.SAS. Data version: V27. User: [redacted] 2014-07-16 0:53.

Table 101 Mean (SD) change from baseline to end of treatment in weight for patients with at least 6 months exposure to Seroquel, age >=66 - (all trials)

		QTP N=167
Patients[a]		161
Baseline	Mean (SD)	68.1 (15.5)
End of treatment	Mean (SD)	68.3 (16.5)
Change	Mean (SD)	0.3 (7.5)
	Median	0.0
	Min to max	-23.7 to 20.0

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
QTP Quetiapine.
Note: the placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_WEIGHT_CH_ALL_LT_AGE66.SAS. Data version: V27. User: [redacted] 2014-07-16 0:53.

Table 102 Incidence of weight gain >= 7% increase (all trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	Incidence density[c]
QTP	4615 (18.4)	25103	6288.9	73.4
Pla	260 (3.9)	6589	1231.5	21.1
Chl	79 (15.6)	507	60.5	130.6
Dul	2 (1.3)	149	15.7	12.7
Esc	12 (3.3)	360	48.2	24.9
Hal	62 (8.2)	760	130.4	47.5
Li	50 (8.2)	610	175.6	28.5
Mos	5 (5.8)	86	10.1	49.7
Olz	84 (50.0)	168	51.5	163.2
Par	15 (4.6)	324	41.7	36.0
Ri	280 (28.1)	996	489.1	57.3

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
b Exposure in patient-years, censored at first event.
c 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_all.SAS. Data version: V27. User: [redacted] 2014-07-16 0:53.

Table 103 Incidence of weight gain >= 7% increase, age <=17 (all trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	Incidence density[c]
QTP	253 (44.3)	571	121.6	208.0
Pla	20 (7.5)	265	25.6	78.2
Mos	0 (0.0)	1	0.0	0.0

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
b Exposure in patient-years, censored at first event.
c 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_all_age17.SAS. Data version: V27. User: [redacted] 2014-07-16 0:53.

Table 104 Incidence of weight gain >= 7% increase, age 18 to 65 (all trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	Incidence density[c]
QTP	4222 (18.2)	23253	5761.1	73.3
Pla	228 (4.0)	5702	1105.1	20.6
Chl	79 (15.6)	507	60.5	130.6
Dul	2 (1.3)	149	15.7	12.7
Esc	12 (3.3)	360	48.2	24.9
Hal	51 (7.9)	644	112.5	45.3
Li	50 (8.3)	601	173.2	28.9
Mos	5 (5.9)	85	10.1	49.7
Olz	84 (50.0)	168	51.5	163.2
Par	15 (4.6)	324	41.7	36.0
Ri	280 (28.1)	996	489.1	57.3

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
b Exposure in patient-years, censored at first event.
c 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_all_age1865.SAS. Data version: V27. User: [redacted] 2014-07-16 0:53.

Table 105 Incidence of weight gain >= 7% increase, age >=66 (all trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	Incidence density[c]
QTP	140 (10.9)	1279	406.2	34.5
Pla	12 (1.9)	622	100.8	11.9
Hal	11 (9.5)	116	17.9	61.3
Li	0 (0.0)	9	2.4	0.0

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
b Exposure in patient-years, censored at first event.
c 100 x total number of patients with event/total patient years of censored exposure.
Note: Patients with multiple events are counted only once.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_all_age66.SAS. Data version: V27. User: [redacted] 2014-07-16 0:53.

Table 106 Incidence of weight gain >= 7% increase for patients with at least 6 months exposure to Seroquel, age <=17 (all trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	Exposure after 6 months[c]
QTP	128 (58.4)	219	125.7	16.2

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value 6 months post baseline.
b Exposure in patient-years, censored at first event after 6 months exposure.
c Exposure in patient-years, censored at first event after 6 months exposure. Only exposure after 6 months of treatment is included.
Note: Patients with multiple events are counted only once.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_all_lt_age17_v2.SAS. Data version: V27. User: [redacted] 2014-07-16 0:53.

Table 107 Incidence of weight gain >= 7% increase for patients with at least 6 months exposure to Seroquel, age 18 to 65 (all trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	Exposure after 6 months[c]
QTP	1341 (39.1)	3426	3106.3	1393.3

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value 6 months post baseline.
b Exposure in patient-years, censored at first event after 6 months exposure.
c Exposure in patient-years, censored at first event after 6 months exposure. Only exposure after 6 months of treatment is included.
Note: Patients with multiple events are counted only once.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_all_lt_age1865_v2.SAS. Data version: V27. User: [redacted] 2014-07-16 0:54.

Table 108 Incidence of weight gain >= 7% increase for patients with at least 6 months exposure to Seroquel, age >=66 (all trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	Exposure after 6 months[c]
QTP	56 (36.1)	155	213.9	136.4

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value 6 months post baseline.
b Exposure in patient-years, censored at first event after 6 months exposure.
c Exposure in patient-years, censored at first event after 6 months exposure. Only exposure after 6 months of treatment is included.
Note: Patients with multiple events are counted only once.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_all_lt_age66_v2.SAS. Data version: V27. User: [redacted] 2014-07-16 0:54.

Table 109 Incidence of weight gain >= 7% increase for patients with at least 6 months exposure to Seroquel (all trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	Exposure after 6 months[c]
QTP	1525 (40.1)	3800	3445.9	1545.9

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value 6 months post baseline.
b Exposure in patient-years, censored at first event after 6 months exposure.
c Exposure in patient-years, censored at first event after 6 months exposure. Only exposure after 6 months of treatment is included.
Note: Patients with multiple events are counted only once.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_all_lt_v2.SAS. Data version: V27. User: [redacted] 2014-07-16 0:53.

1.3.2 Placebo-controlled trials

1.3.2.1 Laboratory data

Table 110 Incidence of each laboratory risk (Placebo-controlled trials)

	QTP				PLA				QTP vs PLA		
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**N**	**n (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**MH relative risk[d]**	**95% CI Lower**	**95% CI Upper**
ALT, 3*ULN	7850	69 (0.9)	938.1	6.68	4100	33 (0.8)	501.4	6.22	1.07	0.69	1.66
AST, 3*ULN	7864	34 (0.4)	940.7	3.30	4109	24 (0.6)	502.1	4.38	0.75	0.43	1.30
Cholesterol, >=6.21 mmol/L	6353	563 (8.9)	747.5	74.41	3288	215 (6.5)	401.6	52.39	1.42	1.21	1.67
LDL, fasting >=4.2 mmol/L	5003	291 (5.8)	630.0	44.29	2692	137 (5.1)	345.5	39.01	1.14	0.92	1.40
GGT, 3*ULN	139	5 (3.6)	19.5	25.59	137	7 (5.1)	22.1	31.66	0.81	0.26	2.55
Glucose[e], fasting >=7 mmol/L	3725	75 (2.0)	469.9	16.74	1934	29 (1.5)	246.3	11.43	1.46	0.94	2.28
Glucose[e], random >=11.1 mmol/L	1754	16 (0.9)	184.7	9.16	1054	5 (0.5)	114.5	4.06	2.26	0.81	6.30
Triglycerides, >=2.26 mmol/L	6178	920 (14.9)	727.8	127.65	3169	299 (9.4)	389.2	75.29	1.70	1.48	1.94
TSH, >5 mIU/L	7749	247 (3.2)	938.3	28.21	4066	108 (2.7)	505.0	20.53	1.37	1.09	1.73
T3 Free, 0.8*LLN	5842	11 (0.2)	713.2	1.49	2837	1 (0.0)	362.0	0.36	4.16	0.59	29.43
T4 Free, 0.8*LLN	7387	54 (0.7)	907.2	5.94	3826	4 (0.1)	487.4	0.77	7.73	2.71	22.04
T4 Total, 0.8*LLN	1097	37 (3.4)	120.9	34.41	651	4 (0.6)	66.4	4.96	6.94	2.37	20.33

Table 110 Incidence of each laboratory risk (Placebo-controlled trials)

	QTP				PLA				QTP vs PLA		
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**N**	**n (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**MH relative risk[d]**	**95% CI Lower**	**95% CI Upper**
Prolactin, males >20 ng/mL, females >30 ng/mL	5652	207 (3.7)	687.9	26.77	2783	70 (2.5)	346.3	21.09	1.27	0.96	1.68
HDL, <=1.04 mmol/L	5688	657 (11.6)	680.8	96.87	2844	287 (10.1)	353.7	81.90	1.18	1.02	1.37

a Number of patients with a normal (defnied as not clinical important) baseline and at least one assesment post baseline.
b Number of patients with event. Event defined as first shift from baseline.
c Exposure in patient years censored at first shift
d Mantel-Haenzel incidence rate and relative risk estimates are adjusted for study and exposure time.
e Only patients with diabetes status normal at baseline included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
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Table 111 Incidence of each laboratory risk, age <18 years (Placebo-controlled trials)

	QTP				PLA				QTP vs PLA		
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**N**	**n (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**MH relative risk[d]**	**95% CI Lower**	**95% CI Upper**
ALT, 3*ULN	391	1 (0.3)	36.6	3.71	234	0 (0.0)	24.9	0.00	NA	NA	NA

Table 111 Incidence of each laboratory risk, age <18 years (Placebo-controlled trials)

	QTP				PLA				QTP vs PLA		
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**N**	**n (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**MH relative risk[d]**	**95% CI Lower**	**95% CI Upper**
AST, 3*ULN	392	1 (0.3)	36.7	2.15	234	0 (0.0)	24.9	0.00	NA	NA	NA
Cholesterol, >=6.21 mmol/L	389	7 (1.8)	36.4	16.98	232	3 (1.3)	24.7	13.13	1.29	0.33	5.12
LDL, fasting >=4.2 mmol/L	329	5 (1.5)	32.1	14.23	198	3 (1.5)	22.1	12.93	1.10	0.25	4.77
GGT, 3*ULN	0	0	NA	NA	0	0	NA	NA	NA	NA	NA
Glucose[e], fasting >=7 mmol/L	280	1 (0.4)	27.2	3.14	158	0 (0.0)	18.0	0.00	NA	NA	NA
Glucose[e], random >=11.1 mmol/L	59	0 (0.0)	4.4	0.00	36	0 (0.0)	3.0	0.00	NA	NA	NA
Triglycerides, >=2.26 mmol/L	369	42 (11.4)	34.5	116.84	213	7 (3.3)	22.7	32.48	3.60	1.60	8.10
TSH, >5 mIU/L	328	10 (3.0)	29.3	33.93	173	4 (2.3)	15.8	25.75	1.32	0.41	4.24
T3 Free, 0.8*LLN	44	0 (0.0)	6.3	0.00	38	0 (0.0)	5.2	0.00	NA	NA	NA
T4 Free, 0.8*LLN	341	4 (1.2)	30.4	13.39	180	0 (0.0)	16.5	0.00	NA	NA	NA
T4 Total, 0.8*LLN	297	8 (2.7)	24.1	33.16	142	0 (0.0)	11.3	0.00	NA	NA	NA
Prolactin, males >20 ng/mL, females >30 ng/mL	245	26 (10.6)	18.5	144.44	111	3 (2.7)	8.2	36.49	3.96	1.20	13.05
HDL, <=1.04 mmol/L	323	45 (13.9)	28.9	156.65	185	25 (13.5)	19.6	132.05	1.19	0.72	1.97

a Number of patients with a normal (defnied as not clinical important) baseline and at least one assesment post baseline.
b Number of patients with event. Event defined as first shift from baseline.
c Exposure in patient years censored at first shift
d Mantel-Haenzel incidence rate and relative risk estimates are adjusted for study and exposure time.
e Only patients with diabetes status normal at baseline included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
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Table 112 Incidence of each laboratory risk, age >65 years (Placebo-controlled trials)

	QTP				PLA				QTP vs PLA		
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**N**	**n (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**MH relative risk[d]**	**95% CI Lower**	**95% CI Upper**
ALT, 3*ULN	560	4 (0.7)	89.5	4.74	439	2 (0.5)	68.7	2.73	1.74	0.31	9.72
AST, 3*ULN	561	3 (0.5)	89.7	3.41	439	2 (0.5)	68.7	2.73	1.25	0.20	7.70
Cholesterol, >=6.21 mmol/L	430	51 (11.9)	69.9	71.24	336	39 (11.6)	53.2	68.99	1.03	0.67	1.58
LDL, fasting >=4.2 mmol/L	423	47 (11.1)	70.0	66.56	341	25 (7.3)	54.6	43.09	1.54	0.94	2.53
GGT, 3*ULN	0	0	NA	NA	0	0	NA	NA	NA	NA	NA
Glucose[e], fasting >=7 mmol/L	288	11 (3.8)	45.7	23.92	217	6 (2.8)	33.9	19.82	1.21	0.44	3.35
Glucose[e], random >=11.1 mmol/L	118	4 (3.4)	19.0	22.26	112	4 (3.6)	18.0	22.30	1.00	0.25	3.99
Triglycerides, >=2.26 mmol/L	481	48 (10.0)	76.8	64.84	373	25 (6.7)	58.5	42.05	1.54	0.94	2.53
TSH, >5 mIU/L	629	24 (3.8)	100.8	22.67	517	19 (3.7)	81.1	21.34	1.06	0.57	1.99

Table 112 Incidence of each laboratory risk, age >65 years (Placebo-controlled trials)

	QTP				PLA				QTP vs PLA		
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**N**	**n (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**MH relative risk[d]**	**95% CI Lower**	**95% CI Upper**
T3 Free, 0.8*LLN	327	1 (0.3)	52.8	1.88	331	0 (0.0)	53.0	0.00	NA	NA	NA
T4 Free, 0.8*LLN	659	9 (1.4)	105.9	10.04	537	1 (0.2)	85.6	1.09	9.24	1.17	72.97
T4 Total, 0.8*LLN	9	1 (11.1)	1.3	17.93	8	0 (0.0)	0.6	0.00	NA	NA	NA
Prolactin, males >20 ng/mL, females >30 ng/mL	320	8 (2.5)	51.4	15.75	321	8 (2.5)	51.0	16.44	0.96	0.36	2.57
HDL, <=1.04 mmol/L	442	41 (9.3)	71.0	51.38	352	24 (6.8)	56.2	43.98	1.17	0.70	1.96

a Number of patients with a normal (defnied as not clinical important) baseline and at least one assesment post baseline.
b Number of patients with event. Event defined as first shift from baseline.
c Exposure in patient years censored at first shift
d Mantel-Haenzel incidence rate and relative risk estimates are adjusted for study and exposure time.
e Only patients with diabetes status normal at baseline included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
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Table 113 Incidence of each laboratory risk, age 18-65 years (Placebo-controlled trials)

	QTP				PLA				QTP vs PLA		
Laboratory parameter	**N[a]**	**n[b] (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**N**	**n (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**MH relative risk[d]**	**95% CI Lower**	**95% CI Upper**
ALT, 3*ULN	6899	64 (0.9)	811.9	7.13	3427	31 (0.9)	407.8	7.08	1.01	0.64	1.58
AST, 3*ULN	6911	30 (0.4)	814.3	3.34	3436	22 (0.6)	408.5	4.87	0.69	0.38	1.23
Cholesterol, >=6.21 mmol/L	5534	505 (9.1)	641.2	78.87	2720	173 (6.4)	323.8	52.78	1.49	1.25	1.79
LDL, fasting >=4.2 mmol/L	4251	239 (5.6)	527.9	42.66	2153	109 (5.1)	268.9	40.25	1.06	0.84	1.34
GGT, 3*ULN	139	5 (3.6)	19.5	25.59	137	7 (5.1)	22.1	31.66	0.81	0.26	2.55
Glucose[e], fasting >=7 mmol/L	3157	63 (2.0)	397.1	16.97	1559	23 (1.5)	194.4	11.14	1.52	0.93	2.49
Glucose[e], random >=11.1 mmol/L	1577	12 (0.8)	161.3	7.37	906	1 (0.1)	93.5	1.10	6.67	0.85	52.44
Triglycerides, >=2.26 mmol/L	5328	830 (15.6)	616.5	138.76	2583	267 (10.3)	308.0	83.73	1.66	1.44	1.91
TSH, >5 mIU/L	6792	213 (3.1)	808.1	28.95	3376	85 (2.5)	408.1	19.99	1.45	1.12	1.88
T3 Free, 0.8*LLN	5471	10 (0.2)	654.1	1.46	2468	1 (0.0)	303.7	0.41	3.54	0.48	25.96
T4 Free, 0.8*LLN	6387	41 (0.6)	770.9	4.86	3109	3 (0.1)	385.3	0.73	6.64	1.95	22.55
T4 Total, 0.8*LLN	791	28 (3.5)	95.5	33.91	501	4 (0.8)	54.6	6.22	5.45	1.86	15.96
Prolactin, males >20 ng/mL, females >30 ng/mL	5087	173 (3.4)	618.0	24.71	2351	59 (2.5)	287.1	21.32	1.16	0.85	1.58
HDL, <=1.04 mmol/L	4923	571 (11.6)	580.9	100.98	2307	238 (10.3)	277.9	85.18	1.19	1.01	1.39

a Number of patients with a normal (defnied as not clinical important) baseline and at least one assesment post baseline.
b Number of patients with event. Event defined as first shift from baseline.
c Exposure in patient years censored at first shift
d Mantel-Haenzel incidence rate and relative risk estimates are adjusted for study and exposure time.
e Only patients with diabetes status normal at baseline included
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
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Table 114 Incidence of shift for Neutrophils, all ages (all placebo-controlled trials)

Laboratory parameter	Treatment	Patients with event n (%)[a]	Total patients[b]	Exposure[c]	MH incidence rate per 100 pt-yrs[d]	MH relative risk QTP vs Pla[e]	95% CI Lower	95% CI Upper
Neutropenia 1.0*10**9 <= cells/L and <1.5*10**9 cells/L	QTP	134 (1.59)	8434	1005.9	13.4	1.31	0.95	1.81
	Pla	56 (1.25)	4490	548.1	10.2			
Neutropenia 0.5*10**9 <= cells/L and <1.0*10**9 cells/L	QTP	19 (0.23)	8434	1009.3	2.1	1.20	0.54	2.65
	Pla	10 (0.22)	4490	549.8	1.7			
Agranulocytosis < 0.5*10**9 cells/L	QTP	4 (0.05)	8434	1009.8	0.4	2.76	0.26	28.89
	Pla	1 (0.02)	4490	549.9	0.1			

a Number of patients with event. Event defined as first shift from baseline.
b Number of patients with a normal (defined as not clinical important) baseline and at least one assessment post baseline.
c Exposure in patient-years, censored at first shift.
d Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
e Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134.
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Table 115 Incidence of shift for Neutrophils, age <18 years (all placebo-controlled trials)

Laboratory parameter	Treatment	Patients with event n (%)[a]	Total patients[b]	Exposure[c]	MH incidence rate per 100 pt-yrs[d]	MH relative risk QTP vs Pla[e]	95% CI Lower	95% CI Upper
Neutropenia 1.0*10**9 <= cells/L and <1.5*10**9 cells/L	QTP	15 (3.89)	386	36.3	37.2	0.75	0.34	1.62
	Pla	12 (5.11)	235	24.6	49.8			
Neutropenia 0.5*10**9 <= cells/L and <1.0*10**9 cells/L	QTP	1 (0.26)	386	36.5	3.8	0.23	0.03	1.94
	Pla	4 (1.70)	235	24.9	16.4			
Agranulocytosis < 0.5*10**9 cells/L	QTP	0 (0.00)	386	36.5	0.0	NA	NA	NA
	Pla	1 (0.43)	235	24.9	3.3			

a Number of patients with event. Event defined as first shift from baseline.
b Number of patients with a normal (defined as not clinical important) baseline and at least one assessment post baseline.
c Exposure in patient-years, censored at first shift.
d Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
e Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134.
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Table 116 Incidence of shift for Neutrophils, age >65 years (all placebo-controlled trials)

Laboratory parameter	Treatment	Patients with event n (%)[a]	Total patients[b]	Exposure[c]	MH incidence rate per 100 pt-yrs[d]	MH relative risk QTP vs Pla[e]	95% CI Lower	95% CI Upper
Neutropenia 1.0*10**9 <= cells/L and <1.5*10**9 cells/L	QTP	6 (0.89)	673	107.9	6.1	2.30	0.47	11.28
	Pla	2 (0.36)	559	88.7	2.6			
Neutropenia 0.5*10**9 <= cells/L and <1.0*10**9 cells/L	QTP	0 (0.00)	673	108.1	0.0	NA	NA	NA
	Pla	1 (0.18)	559	88.7	1.0			
Agranulocytosis < 0.5*10**9 cells/L	QTP	0 (0.00)	673	108.1	0.0	NA	NA	NA
	Pla	0 (0.00)	559	88.7	0.0			

a Number of patients with event. Event defined as first shift from baseline.
b Number of patients with a normal (defined as not clinical important) baseline and at least one assessment post baseline.
c Exposure in patient-years, censored at first shift.
d Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
e Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134.
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Table 117 Incidence of shift for Neutrophils, age 18-65 years (all placebo-controlled trials)

Laboratory parameter	Treatment	Patients with event n (%)[a]	Total patients[b]	Exposure[c]	MH incidence rate per 100 pt-yrs[d]	MH relative risk QTP vs Pla[e]	95% CI Lower	95% CI Upper
Neutropenia 1.0*10**9 <= cells/L and <1.5*10**9 cells/L	QTP	113 (1.53)	7375	861.7	13.4	1.41	0.98	2.03
	Pla	42 (1.14)	3696	434.8	9.5			
Neutropenia 0.5*10**9 <= cells/L and <1.0*10**9 cells/L	QTP	18 (0.24)	7375	864.7	2.3	2.18	0.79	6.04
	Pla	5 (0.14)	3696	436.2	1.1			
Agranulocytosis < 0.5*10**9 cells/L	QTP	4 (0.05)	7375	865.2	0.5	NA	NA	NA
	Pla	0 (0.00)	3696	436.3	0.0			

a Number of patients with event. Event defined as first shift from baseline.
b Number of patients with a normal (defined as not clinical important) baseline and at least one assessment post baseline.
c Exposure in patient-years, censored at first shift.
d Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
e Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Shifts are from normal baseline to clinically important value at anytime post baseline.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134.
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1.3.2.2 Adverse event data

All events

Table 118 Seriousness, outcomes, and severity of each adverse event risk - all placebo-controlled trials

Risk Adverse event group[a] N=9474	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Anaphylactic reaction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
EPS	657 (6.93)	2 (0.30)	1 (0.15)	486 (73.97)	0 (0.00)	171 (26.03)	0 (0.00)	420 (63.93)	213 (32.42)	24 (3.65)
Hepatitis	1 (0.01)	1 (100.00)	1 (100.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)
Hyperglycemia and Diabetes mellitus	44 (0.46)	1 (2.27)	1 (2.27)	18 (40.91)	0 (0.00)	26 (59.09)	0 (0.00)	30 (68.18)	13 (29.55)	1 (2.27)
Hypothyroidism	28 (0.30)	0 (0.00)	0 (0.00)	7 (25.00)	0 (0.00)	21 (75.00)	0 (0.00)	17 (60.71)	10 (35.71)	1 (3.57)
Jaundice	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Neuroleptic Malignant Syndrome	1 (0.01)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)
Neutropenia	10 (0.11)	0 (0.00)	0 (0.00)	4 (40.00)	1 (10.00)	5 (50.00)	0 (0.00)	5 (50.00)	4 (40.00)	1 (10.00)
Seizure	13 (0.14)	5 (38.46)	3 (23.08)	13 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (23.08)	4 (30.77)	6 (46.15)
Somnolence	4187 (44.19)	0 (0.00)	0 (0.00)	3109 (74.25)	5 (0.12)	1073 (25.63)	0 (0.00)	1982 (47.34)	1743 (41.63)	462 (11.03)
Stevens-Johnson syndrome and other serious skin reactions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Syncope and orthostatic hypotension	319 (3.37)	14 (4.39)	6 (1.88)	298 (93.42)	0 (0.00)	21 (6.58)	0 (0.00)	184 (57.68)	99 (31.03)	36 (11.29)

Cerebrovascular Adverse Events	12 (0.13)	3 (25.00)	3 (25.00)	6 (50.00)	0 (0.00)	4 (33.33)	2 (16.67)	4 (33.33)	3 (25.00)	5 (41.67)
Abuse Misuse	7 (0.07)	0 (0.00)	0 (0.00)	6 (85.71)	0 (0.00)	1 (14.29)	0 (0.00)	2 (28.57)	2 (28.57)	3 (42.86)
Aggression/agitation	471 (4.97)	14 (2.97)	14 (2.97)	362 (76.86)	1 (0.21)	107 (22.72)	1 (0.21)	161 (34.18)	220 (46.71)	90 (19.11)
Agranulocytosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperprolactinemia	1 (0.01)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)
QT prolongation and Torsade de Pointes	6 (0.06)	0 (0.00)	0 (0.00)	3 (50.00)	0 (0.00)	3 (50.00)	0 (0.00)	5 (83.33)	1 (16.67)	0 (0.00)
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	2 (0.02)	0 (0.00)	0 (0.00)	2 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (50.00)	1 (50.00)	0 (0.00)
Suicide	76 (0.80)	38 (50.00)	33 (43.42)	67 (88.16)	0 (0.00)	9 (11.84)	0 (0.00)	22 (28.95)	20 (26.32)	34 (44.74)
Pancreatitis	1 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)
Dysphagia	38 (0.40)	0 (0.00)	0 (0.00)	30 (78.95)	0 (0.00)	8 (21.05)	0 (0.00)	22 (57.89)	14 (36.84)	2 (5.26)
Tardive dyskinesia	8 (0.08)	0 (0.00)	0 (0.00)	4 (50.00)	0 (0.00)	4 (50.00)	0 (0.00)	8 (100.00)	0 (0.00)	0 (0.00)
Pneumonia	28 (0.30)	14 (50.00)	8 (28.57)	20 (71.43)	0 (0.00)	2 (7.14)	6 (21.43)	5 (17.86)	13 (46.43)	10 (35.71)
Accidental injury	167 (1.76)	11 (6.59)	9 (5.39)	132 (79.04)	1 (0.60)	34 (20.36)	0 (0.00)	101 (60.48)	52 (31.14)	14 (8.38)
Metabolic syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ischemic heart disease	12 (0.13)	4 (33.33)	2 (16.67)	9 (75.00)	0 (0.00)	1 (8.33)	2 (16.67)	6 (50.00)	1 (8.33)	5 (41.67)
Venous thromboembolism/Embolic venous	4 (0.04)	2 (50.00)	1 (25.00)	2 (50.00)	0 (0.00)	2 (50.00)	0 (0.00)	0 (0.00)	3 (75.00)	1 (25.00)
Intestinal obstruction/ileus	3 (0.03)	1 (33.33)	1 (33.33)	2 (66.67)	0 (0.00)	1 (33.33)	0 (0.00)	0 (0.00)	1 (33.33)	2 (66.67)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 119 Seriousness, outcomes, and severity of each adverse event risk, age <18 years - all placebo-controlled trials

Risk Adverse event group[a] N=432	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Anaphylactic reaction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
EPS	28 (6.48)	1 (3.57)	1 (3.57)	17 (60.71)	0 (0.00)	11 (39.29)	0 (0.00)	19 (67.86)	8 (28.57)	1 (3.57)
Hepatitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperglycemia and Diabetes mellitus	3 (0.69)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (100.00)	0 (0.00)	2 (66.67)	1 (33.33)	0 (0.00)
Hypothyroidism	2 (0.46)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)	2 (100.00)	0 (0.00)
Jaundice	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Neuroleptic Malignant Syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Neutropenia	1 (0.23)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)
Seizure	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Somnolence	193 (44.68)	0 (0.00)	0 (0.00)	115 (59.59)	0 (0.00)	78 (40.41)	0 (0.00)	103 (53.37)	80 (41.45)	10 (5.18)

Stevens-Johnson syndrome and other serious skin reactions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Syncope and orthostatic hypotension	9 (2.08)	1 (11.11)	0 (0.00)	9 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (44.44)	4 (44.44)	1 (11.11)
Cerebrovascular Adverse Events	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Abuse Misuse	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Aggression/agitation	39 (9.03)	5 (12.82)	5 (12.82)	30 (76.92)	0 (0.00)	9 (23.08)	0 (0.00)	11 (28.21)	22 (56.41)	6 (15.38)
Agranulocytosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperprolactinemia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
QT prolongation and Torsade de Pointes	3 (0.69)	0 (0.00)	0 (0.00)	1 (33.33)	0 (0.00)	2 (66.67)	0 (0.00)	3 (100.00)	0 (0.00)	0 (0.00)
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Suicide	5 (1.16)	1 (20.00)	1 (20.00)	4 (80.00)	0 (0.00)	1 (20.00)	0 (0.00)	3 (60.00)	1 (20.00)	1 (20.00)
Pancreatitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Dysphagia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Tardive dyskinesia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Pneumonia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Accidental injury	4 (0.93)	0 (0.00)	0 (0.00)	3 (75.00)	0 (0.00)	1 (25.00)	0 (0.00)	2 (50.00)	2 (50.00)	0 (0.00)
Metabolic syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ischemic heart disease	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Venous thromboembolism/Embolic venous	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Intestinal obstruction/ileus	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.
Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 120 Seriousness, outcomes, and severity of each adverse event risk, age 18-65 years - all placebo-controlled trials

Risk Adverse event group[a] N=8282	**Adverse event n (%)**	**Serious adverse event n (%)**	**Hospitalized n (%)**	**Recovered n (%)**	**Recover status unknown n (%)**	**Not recovered n (%)**	**Death n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Anaphylactic reaction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
EPS	579 (6.99)	1 (0.17)	0 (0.00)	432 (74.61)	0 (0.00)	147 (25.39)	0 (0.00)	367 (63.39)	189 (32.64)	23 (3.97)
Hepatitis	1 (0.01)	1 (100.00)	1 (100.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)
Hyperglycemia and Diabetes mellitus	33 (0.40)	1 (3.03)	1 (3.03)	14 (42.42)	0 (0.00)	19 (57.58)	0 (0.00)	22 (66.67)	10 (30.30)	1 (3.03)
Hypothyroidism	21 (0.25)	0 (0.00)	0 (0.00)	6 (28.57)	0 (0.00)	15 (71.43)	0 (0.00)	14 (66.67)	6 (28.57)	1 (4.76)
Jaundice	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Neuroleptic Malignant Syndrome	1 (0.01)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)
Neutropenia	9 (0.11)	0 (0.00)	0 (0.00)	4 (44.44)	1 (11.11)	4 (44.44)	0 (0.00)	4 (44.44)	4 (44.44)	1 (11.11)
Seizure	7 (0.08)	4 (57.14)	3 (42.86)	7 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (28.57)	5 (71.43)
Somnolence	3758 (45.38)	0 (0.00)	0 (0.00)	2784 (74.08)	5 (0.13)	969 (25.78)	0 (0.00)	1748 (46.51)	1578 (41.99)	432 (11.50)
Stevens-Johnson syndrome and other serious skin reactions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Syncope and orthostatic hypotension	284 (3.43)	8 (2.82)	3 (1.06)	265 (93.31)	0 (0.00)	19 (6.69)	0 (0.00)	169 (59.51)	86 (30.28)	29 (10.21)
Cerebrovascular Adverse Events	7 (0.08)	0 (0.00)	0 (0.00)	3 (42.86)	0 (0.00)	4 (57.14)	0 (0.00)	3 (42.86)	2 (28.57)	2 (28.57)
Abuse Misuse	7 (0.08)	0 (0.00)	0 (0.00)	6 (85.71)	0 (0.00)	1 (14.29)	0 (0.00)	2 (28.57)	2 (28.57)	3 (42.86)
Aggression/agitation	406 (4.90)	6 (1.48)	6 (1.48)	309 (76.11)	1 (0.25)	95 (23.40)	1 (0.25)	137 (33.74)	191 (47.04)	78 (19.21)
Agranulocytosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperprolactinemia	1 (0.01)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)
QT prolongation and Torsade de Pointes	2 (0.02)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	1 (50.00)	0 (0.00)	2 (100.00)	0 (0.00)	0 (0.00)
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	2 (0.02)	0 (0.00)	0 (0.00)	2 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (50.00)	1 (50.00)	0 (0.00)
Suicide	70 (0.85)	36 (51.43)	31 (44.29)	62 (88.57)	0 (0.00)	8 (11.43)	0 (0.00)	19 (27.14)	19 (27.14)	32 (45.71)
Pancreatitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Dysphagia	33 (0.40)	0 (0.00)	0 (0.00)	28 (84.85)	0 (0.00)	5 (15.15)	0 (0.00)	19 (57.58)	12 (36.36)	2 (6.06)
Tardive dyskinesia	6 (0.07)	0 (0.00)	0 (0.00)	3 (50.00)	0 (0.00)	3 (50.00)	0 (0.00)	6 (100.00)	0 (0.00)	0 (0.00)

Pneumonia	14 (0.17)	5 (35.71)	5 (35.71)	13 (92.86)	0 (0.00)	1 (7.14)	0 (0.00)	3 (21.43)	8 (57.14)	3 (21.43)
Accidental injury	63 (0.76)	5 (7.94)	4 (6.35)	47 (74.60)	0 (0.00)	16 (25.40)	0 (0.00)	26 (41.27)	31 (49.21)	6 (9.52)
Metabolic syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ischemic heart disease	6 (0.07)	2 (33.33)	2 (33.33)	5 (83.33)	0 (0.00)	1 (16.67)	0 (0.00)	3 (50.00)	0 (0.00)	3 (50.00)
Venous thromboembolism/Embolic venous	4 (0.05)	2 (50.00)	1 (25.00)	2 (50.00)	0 (0.00)	2 (50.00)	0 (0.00)	0 (0.00)	3 (75.00)	1 (25.00)
Intestinal obstruction/ileus	3 (0.04)	1 (33.33)	1 (33.33)	2 (66.67)	0 (0.00)	1 (33.33)	0 (0.00)	0 (0.00)	1 (33.33)	2 (66.67)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.
Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 121 Seriousness, outcomes, and severity of each adverse event risk, age >=66 years - all placebo-controlled trials

Risk Adverse event group[a] N=760	**Adverse event n (%)**	**Serious adverse event n (%)**	**Hospitalized n (%)**	**Recovered n (%)**	**Recover status unknown n (%)**	**Not recovered n (%)**	**Death n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Anaphylactic reaction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
EPS	50 (6.58)	0 (0.00)	0 (0.00)	37 (74.00)	0 (0.00)	13 (26.00)	0 (0.00)	34 (68.00)	16 (32.00)	0 (0.00)
Hepatitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Hyperglycemia and Diabetes mellitus	8 (1.05)	0 (0.00)	0 (0.00)	4 (50.00)	0 (0.00)	4 (50.00)	0 (0.00)	6 (75.00)	2 (25.00)	0 (0.00)
Hypothyroidism	5 (0.66)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (100.00)	0 (0.00)	3 (60.00)	2 (40.00)	0 (0.00)
Jaundice	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Neuroleptic Malignant Syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Neutropenia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Seizure	6 (0.79)	1 (16.67)	0 (0.00)	6 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (50.00)	2 (33.33)	1 (16.67)
Somnolence	236 (31.05)	0 (0.00)	0 (0.00)	210 (88.98)	0 (0.00)	26 (11.02)	0 (0.00)	131 (55.51)	85 (36.02)	20 (8.47)
Stevens-Johnson syndrome and other serious skin reactions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Syncope and orthostatic hypotension	26 (3.42)	5 (19.23)	3 (11.54)	24 (92.31)	0 (0.00)	2 (7.69)	0 (0.00)	11 (42.31)	9 (34.62)	6 (23.08)
Cerebrovascular Adverse Events	5 (0.66)	3 (60.00)	3 (60.00)	3 (60.00)	0 (0.00)	0 (0.00)	2 (40.00)	1 (20.00)	1 (20.00)	3 (60.00)
Abuse Misuse	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Aggression/agitation	26 (3.42)	3 (11.54)	3 (11.54)	23 (88.46)	0 (0.00)	3 (11.54)	0 (0.00)	13 (50.00)	7 (26.92)	6 (23.08)
Agranulocytosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hyperprolactinemia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
QT prolongation and Torsade de Pointes	1 (0.13)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Suicide	1 (0.13)	1 (100.00)	1 (100.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)

Pancreatitis	1 (0.13)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)
Dysphagia	5 (0.66)	0 (0.00)	0 (0.00)	2 (40.00)	0 (0.00)	3 (60.00)	0 (0.00)	3 (60.00)	2 (40.00)	0 (0.00)
Tardive dyskinesia	2 (0.26)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	1 (50.00)	0 (0.00)	2 (100.00)	0 (0.00)	0 (0.00)
Pneumonia	14 (1.84)	9 (64.29)	3 (21.43)	7 (50.00)	0 (0.00)	1 (7.14)	6 (42.86)	2 (14.29)	5 (35.71)	7 (50.00)
Accidental injury	100 (13.16)	6 (6.00)	5 (5.00)	82 (82.00)	1 (1.00)	17 (17.00)	0 (0.00)	73 (73.00)	19 (19.00)	8 (8.00)
Metabolic syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ischemic heart disease	6 (0.79)	2 (33.33)	0 (0.00)	4 (66.67)	0 (0.00)	0 (0.00)	2 (33.33)	3 (50.00)	1 (16.67)	2 (33.33)
Venous thromboembolism/Embolic venous	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Intestinal obstruction/ileus	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 122 Incidence of each adverse event risk, all age (all placebo-controlled trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Exposure[c]	Incidence rate[d]	MH incidence rate per 100 pt-yrs[e]	MH relative risk[f] QTP vs Pla	95% CI Lower	95% CI Upper
Anaphylactic reaction	QTP	0 (0)	9474	1063.9	0.00	0.0	NA	NA	NA

	Pla	0 (0)	4992	578.8	0.00	0.0			
EPS	QTP	657 (2)	9474	1011.8	6.93	64.2	1.43	1.23	1.67
	Pla	247 (1)	4992	560.4	4.95	44.8			
Hepatitis	QTP	1 (1)	9474	1063.9	0.01	0.0	NA	NA	NA
	Pla	0 (0)	4992	578.8	0.00	0.0			
Hyperglycemia and Diabetes mellitus	QTP	44 (1)	9474	1062.2	0.46	4.5	1.05	0.63	1.76
	Pla	24 (1)	4992	577.7	0.48	4.3			
Hypothyroidism	QTP	28 (0)	9474	1063.3	0.30	3.4	1.96	0.97	3.98
	Pla	11 (0)	4992	578.6	0.22	1.7			
Jaundice	QTP	0 (0)	9474	1063.9	0.00	0.0	NA	NA	NA
	Pla	0 (0)	4992	578.8	0.00	0.0			
Neuroleptic Malignant Syndrome	QTP	1 (0)	9474	1063.9	0.01	0.1	NA	NA	NA
	Pla	0 (0)	4992	578.8	0.00	0.0			
Neutropenia	QTP	10 (0)	9474	1063.4	0.11	1.1	1.91	0.58	6.28
	Pla	4 (0)	4992	578.8	0.08	0.6			
Seizure	QTP	13 (5)	9474	1063.6	0.14	1.3	0.86	0.34	2.16
	Pla	8 (6)	4992	578.8	0.16	1.6			
Somnolence	QTP	4187 (0)	9474	654.2	44.19	726.9	5.00	4.62	5.41
	Pla	732 (0)	4992	507.6	14.66	145.4			

Stevens-Johnson syndrome and other serious skin reactions	QTP	0 (0)	9474	1063.9	0.00	0.0	NA	NA	NA
	Pla	0 (0)	4992	578.8	0.00	0.0			
Syncope and orthostatic hypotension	QTP	319 (14)	9474	1043.5	3.37	27.9	2.38	1.80	3.15
	Pla	61 (2)	4992	574.5	1.22	11.7			
Cerebrovascular Adverse Events	QTP	12 (3)	9474	1063.4	0.13	1.2	0.69	0.29	1.63
	Pla	10 (4)	4992	578.4	0.20	1.7			
Abuse Misuse	QTP	7 (0)	9474	1063.8	0.07	0.6	4.51	0.46	44.10
	Pla	1 (0)	4992	578.8	0.02	0.1			
Aggression/agitation	QTP	471 (14)	9474	1036.8	4.97	43.9	0.97	0.83	1.13
	Pla	248 (9)	4992	564.0	4.97	45.4			
Agranulocytosis	QTP	0 (0)	9474	1063.9	0.00	0.0	NA	NA	NA
	Pla	0 (0)	4992	578.8	0.00	0.0			
Hyperprolactinemia	QTP	1 (0)	9474	1063.9	0.01	0.1	0.30	0.03	3.55
	Pla	2 (0)	4992	578.8	0.04	0.3			
QT prolongation and Torsade de Pointes	QTP	6 (0)	9474	1063.8	0.06	0.7	1.90	0.38	9.62
	Pla	2 (0)	4992	578.8	0.04	0.3			

Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	QTP	2 (0)	9474	1063.7	0.02	0.2	1.09	0.09	13.70
	Pla	1 (0)	4992	578.8	0.02	0.1			
Suicide	QTP	76 (38)	9474	1062.2	0.80	6.5	0.91	0.61	1.37
	Pla	38 (17)	4992	578.0	0.76	7.1			
Pancreatitis	QTP	1 (0)	9474	1063.9	0.01	0.1	0.44	0.04	4.87
	Pla	2 (2)	4992	578.8	0.04	0.3			
Dysphagia	QTP	38 (0)	9474	1061.2	0.40	3.7	2.49	1.15	5.39
	Pla	8 (0)	4992	578.6	0.16	1.5			
Tardive dyskinesia	QTP	8 (0)	9474	1063.7	0.08	0.5	2.13	0.26	17.34
	Pla	1 (0)	4992	578.8	0.02	0.2			
Pneumonia	QTP	28 (14)	9474	1063.2	0.30	2.7	1.16	0.59	2.27
	Pla	13 (7)	4992	578.5	0.26	2.4			
Accidental injury	QTP	167 (11)	9474	1051.6	1.76	17.8	1.03	0.80	1.33
	Pla	103 (5)	4992	572.1	2.06	17.2			
Metabolic syndrome	QTP	0 (0)	9474	1063.9	0.00	0.0	NA	NA	NA
	Pla	0 (0)	4992	578.8	0.00	0.0			
Ischemic heart disease	QTP	12 (4)	9474	1063.8	0.13	1.0	0.45	0.20	1.01
	Pla	13 (6)	4992	578.5	0.26	2.3			

Venous thromboembolism/Embolic venous	QTP	4 (2)	9474	1063.6	0.04	0.3	0.99	0.18	5.62
	Pla	2 (1)	4992	578.8	0.04	0.3			
Intestinal obstruction/ileus	QTP	3 (1)	9474	1063.7	0.03	0.3	1.23	0.13	12.01
	Pla	1 (1)	4992	578.8	0.02	0.2			

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c Exposure in patient-years, censored at first event.
d 100 x total number of patients with event/total patient.
e Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
f Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 123 Incidence of each adverse event risk, age <18 years (all placebo-controlled trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Exposure[c]	Incidence rate[d]	MH incidence rate per 100 pt-yrs[e]	MH relative risk[f] QTP vs Pla	95% CI Lower	95% CI Upper
Anaphylactic reaction	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
EPS	QTP	28 (1)	432	37.9	6.48	63.0	2.79	1.08	7.23
	Pla	5 (0)	265	26.3	1.89	22.5			

Hepatitis	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Hyperglycemia and Diabetes mellitus	QTP	3 (0)	432	39.5	0.69	7.7	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Hypothyroidism	QTP	2 (0)	432	39.5	0.46	4.2	0.95	0.09	10.43
	Pla	1 (0)	265	26.6	0.38	4.4			
Jaundice	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Neuroleptic Malignant Syndrome	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Neutropenia	QTP	1 (0)	432	39.5	0.23	2.1	0.22	0.02	2.65
	Pla	3 (0)	265	26.6	1.13	9.4			
Seizure	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Somnolence	QTP	193 (0)	432	27.0	44.68	685.5	3.65	2.62	5.07
	Pla	44 (0)	265	24.3	16.60	187.9			
Stevens-Johnson syndrome and other serious skin reactions	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			

Syncope and orthostatic hypotension	QTP	9 (1)	432	39.2	2.08	20.5	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Cerebrovascular Adverse Events	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Abuse Misuse	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Aggression/agitation	QTP	39 (5)	432	37.5	9.03	90.9	0.72	0.44	1.18
	Pla	28 (2)	265	24.2	10.57	125.7			
Agranulocytosis	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Hyperprolactinemia	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
QT prolongation and Torsade de Pointes	QTP	3 (0)	432	39.5	0.69	6.3	1.42	0.15	13.63
	Pla	1 (0)	265	26.6	0.38	4.4			
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Suicide	QTP	5 (1)	432	39.3	1.16	11.9	2.65	0.31	22.33

	Pla	1 (0)	265	26.5	0.38	4.5			
Pancreatitis	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Dysphagia	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Tardive dyskinesia	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Pneumonia	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Accidental injury	QTP	4 (0)	432	39.4	0.93	8.4	0.63	0.14	2.80
	Pla	3 (0)	265	26.5	1.13	13.5			
Metabolic syndrome	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Ischemic heart disease	QTP	0 (0)	432	39.5	0.00	0.0	0.00	NA	NA
	Pla	1 (0)	265	26.6	0.38	4.5			
Venous thromboembolism/Embolic venous	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			
Intestinal obstruction/ileus	QTP	0 (0)	432	39.5	0.00	0.0	NA	NA	NA
	Pla	0 (0)	265	26.6	0.00	0.0			

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c Exposure in patient-years, censored at first event.
d 100 x total number of patients with event/total patient.
e Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
f Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 124 Incidence of each adverse event risk, age 18-65 years (all placebo-controlled trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Exposure[c]	Incidence rate[d]	MH incidence rate per 100 pt-yrs[e]	MH relative risk[f] QTP vs Pla	95% CI Lower	95% CI Upper
Anaphylactic reaction	QTP	0 (0)	8282	907.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	4105	457.9	0.00	0.0			
EPS	QTP	579 (1)	8282	861.4	6.99	67.6	1.38	1.18	1.63
	Pla	216 (1)	4105	442.2	5.26	48.8			
Hepatitis	QTP	1 (1)	8282	907.7	0.01	0.1	NA	NA	NA
	Pla	0 (0)	4105	457.9	0.00	0.0			
Hyperglycemia and Diabetes mellitus	QTP	33 (1)	8282	906.4	0.40	4.0	0.85	0.48	1.51
	Pla	21 (1)	4105	457.0	0.51	4.7			
Hypothyroidism	QTP	21 (0)	8282	907.2	0.25	3.2	2.06	0.90	4.69

	Pla	8 (0)	4105	457.7	0.19	1.6			
Jaundice	QTP	0 (0)	8282	907.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	4105	457.9	0.00	0.0			
Neuroleptic Malignant Syndrome	QTP	1 (0)	8282	907.7	0.01	0.1	NA	NA	NA
	Pla	0 (0)	4105	457.9	0.00	0.0			
Neutropenia	QTP	9 (0)	8282	907.2	0.11	1.3	5.68	0.76	42.53
	Pla	1 (0)	4105	457.9	0.02	0.2			
Seizure	QTP	7 (4)	8282	907.6	0.08	0.7	0.41	0.14	1.24
	Pla	7 (5)	4105	457.9	0.17	1.6			
Somnolence	QTP	3758 (0)	8282	538.7	45.38	819.2	5.23	4.80	5.70
	Pla	623 (0)	4105	396.7	15.18	156.6			
Stevens-Johnson syndrome and other serious skin reactions	QTP	0 (0)	8282	907.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	4105	457.9	0.00	0.0			
Syncope and orthostatic hypotension	QTP	284 (8)	8282	889.2	3.43	29.7	2.56	1.87	3.50
	Pla	48 (2)	4105	454.6	1.17	11.6			
Cerebrovascular Adverse Events	QTP	7 (0)	8282	907.3	0.08	0.8	0.70	0.22	2.27
	Pla	5 (3)	4105	457.7	0.12	1.1			
Abuse Misuse	QTP	7 (0)	8282	907.6	0.08	0.8	4.43	0.46	42.80

	Pla	1 (0)	4105	457.9	0.02	0.2			
Aggression/agitation	QTP	406 (6)	8282	884.4	4.90	45.5	1.05	0.88	1.26
	Pla	189 (6)	4105	447.3	4.60	43.2			
Agranulocytosis	QTP	0 (0)	8282	907.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	4105	457.9	0.00	0.0			
Hyperprolactinemia	QTP	1 (0)	8282	907.7	0.01	0.1	0.30	0.03	3.55
	Pla	2 (0)	4105	457.9	0.05	0.4			
QT prolongation and Torsade de Pointes	QTP	2 (0)	8282	907.7	0.02	0.3	1.57	0.14	18.07
	Pla	1 (0)	4105	457.9	0.02	0.2			
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	QTP	2 (0)	8282	907.5	0.02	0.2	NA	NA	NA
	Pla	0 (0)	4105	457.9	0.00	0.0			
Suicide	QTP	70 (36)	8282	906.2	0.85	7.1	0.86	0.56	1.30
	Pla	36 (16)	4105	457.2	0.88	8.3			
Pancreatitis	QTP	0 (0)	8282	907.7	0.00	0.0	NA	NA	NA
	Pla	2 (2)	4105	457.9	0.05	0.4			
Dysphagia	QTP	33 (0)	8282	905.1	0.40	3.9	8.73	2.07	36.71
	Pla	2 (0)	4105	457.9	0.05	0.4			
Tardive dyskinesia	QTP	6 (0)	8282	907.5	0.07	0.3	1.16	0.14	9.70
	Pla	1 (0)	4105	457.9	0.02	0.3			

Pneumonia	QTP	14 (5)	8282	907.2	0.17	1.6	1.33	0.50	3.57
	Pla	6 (2)	4105	457.6	0.15	1.2			
Accidental injury	QTP	63 (5)	8282	903.7	0.76	7.4	1.07	0.69	1.65
	Pla	33 (4)	4105	456.1	0.80	6.9			
Metabolic syndrome	QTP	0 (0)	8282	907.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	4105	457.9	0.00	0.0			
Ischemic heart disease	QTP	6 (2)	8282	907.6	0.07	0.5	0.33	0.10	1.06
	Pla	7 (3)	4105	457.6	0.17	1.5			
Venous thromboembolism/Embolic venous	QTP	4 (2)	8282	907.4	0.05	0.4	1.00	0.18	5.68
	Pla	2 (1)	4105	457.9	0.05	0.4			
Intestinal obstruction/ileus	QTP	3 (1)	8282	907.5	0.04	0.3	NA	NA	NA
	Pla	0 (0)	4105	457.9	0.00	0.0			

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c Exposure in patient-years, censored at first event.
d 100 x total number of patients with event/total patient.
e Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
f Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 125 Incidence of each adverse event risk, age >=66 years (all placebo-controlled trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Exposure[c]	Incidence rate[d]	MH incidence rate per 100 pt-yrs[e]	MH relative risk[f] QTP vs Pla	95% CI Lower	95% CI Upper
Anaphylactic reaction	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
EPS	QTP	50 (0)	760	112.4	6.58	45.7	1.57	0.97	2.54
	Pla	26 (0)	622	91.9	4.18	29.2			
Hepatitis	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Hyperglycemia and Diabetes mellitus	QTP	8 (0)	760	116.3	1.05	6.2	2.06	0.53	8.08
	Pla	3 (0)	622	94.2	0.48	3.0			
Hypothyroidism	QTP	5 (0)	760	116.5	0.66	4.6	2.30	0.44	12.12
	Pla	2 (0)	622	94.3	0.32	2.0			
Jaundice	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Neuroleptic Malignant Syndrome	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Neutropenia	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA

	Pla	0 (0)	622	94.3	0.00	0.0			
Seizure	QTP	6 (1)	760	116.4	0.79	5.6	3.83	0.53	27.80
	Pla	1 (1)	622	94.3	0.16	1.5			
Somnolence	QTP	236 (0)	760	88.5	31.05	284.0	3.69	2.80	4.87
	Pla	65 (0)	622	86.6	10.45	76.9			
Stevens-Johnson syndrome and other serious skin reactions	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Syncope and orthostatic hypotension	QTP	26 (5)	760	115.1	3.42	19.6	1.21	0.61	2.38
	Pla	13 (0)	622	93.3	2.09	16.3			
Cerebrovascular Adverse Events	QTP	5 (3)	760	116.5	0.66	3.6	0.66	0.19	2.38
	Pla	5 (1)	622	94.1	0.80	5.5			
Abuse Misuse	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Aggression/agitation	QTP	26 (3)	760	114.9	3.42	20.3	0.59	0.34	1.01
	Pla	31 (1)	622	92.4	4.98	34.5			
Agranulocytosis	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Hyperprolactinemia	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			

QT prolongation and Torsade de Pointes	QTP	1 (0)	760	116.6	0.13	1.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Syndrome of inappropriate anti-diuretic hormone (SIADH) and hyponatraemia	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	1 (0)	622	94.3	0.16	0.0			
Suicide	QTP	1 (1)	760	116.7	0.13	1.0	1.04	0.07	16.62
	Pla	1 (1)	622	94.3	0.16	1.0			
Pancreatitis	QTP	1 (0)	760	116.7	0.13	1.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Dysphagia	QTP	5 (0)	760	116.5	0.66	3.6	0.46	0.14	1.57
	Pla	6 (0)	622	94.1	0.96	7.8			
Tardive dyskinesia	QTP	2 (0)	760	116.6	0.26	1.5	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Pneumonia	QTP	14 (9)	760	116.4	1.84	9.9	1.02	0.40	2.59
	Pla	7 (5)	622	94.3	1.13	9.7			
Accidental injury	QTP	100 (6)	760	108.5	13.16	83.0	1.03	0.75	1.42
	Pla	67 (1)	622	89.5	10.77	80.4			
Metabolic syndrome	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Ischemic heart disease	QTP	6 (2)	760	116.6	0.79	4.2	0.71	0.21	2.43

	Pla	5 (3)	622	94.3	0.80	5.9			
Venous thromboembolism/Embolic venous	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	0 (0)	622	94.3	0.00	0.0			
Intestinal obstruction/ileus	QTP	0 (0)	760	116.7	0.00	0.0	NA	NA	NA
	Pla	1 (1)	622	94.3	0.16	1.5			

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c Exposure in patient-years, censored at first event.
d 100 x total number of patients with event/total patient.
e Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
f Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Mania and hypomania

Table 126 Treatment emergent mania and hypomania AEs (all placebo-controlled trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Exposure[c]	Incidence rate[d]	MH incidence rate per 100 pt-yrs[e]	MH relative risk[f] QTP vs Pla	95% CI Lower	95% CI Upper
AEs of mania or hypomania	QTP	27 (11)	1849	237.1	1.46	10.0	1.01	0.47	2.18
	Pla	9 (3)	742	92.4	1.21	9.9			

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c Exposure in patient-years, censored at first event.
d 100 x total number of patients with event/total number of patients.
e Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
f Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Included trials: D144CC00002, D1447C00001, D1447C00134, D1447C00135 and 5077US/0049.
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Table 127 Seriousness, outcomes, and severity of treatment emergent mania and hypomania AEs - all placebo-controlled trials

Risk Adverse event group[a] N=1849	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
AEs of mania or hypomania	27 (1.46)	11 (40.74)	11 (40.74)	20 (74.07)	0 (0.00)	7 (25.93)	0 (0.00)	5 (18.52)	12 (44.44)	10 (37.04)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: Included trials: D144CC00002, D1447C00001, D1447C00134, D1447C00135 and 5077US/0049.
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Cerebrovascular

Table 128 Incidence of each adverse event risk, age > 65 years (all placebo-controlled trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Exposure[c]	Incidence rate[d]	MH incidence rate per 100 pt-yrs[e]	MH relative risk[f] QTP vs Pla	95% CI Lower	95% CI Upper
Cerebrovascular Adverse Events	QTP	5 (3)	760	116.5	0.66	3.6	0.66	0.19	2.38
	Pla	5 (1)	622	94.1	0.80	5.5			

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c Exposure in patient-years, censored at first event.
d 100 x total number of patients with event/total patient.
e Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
f Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 129 Incidence of each adverse event risk, age <66 years (all placebo-controlled trials)

Adverse event group[a]	Treatment	Patients with event	Total patients[b]	Exposure[c]	Incidence rate[d]	MH incidence rate per 100 pt-yrs[e]	MH relative risk[f] QTP vs Pla	95% CI Lower	95% CI Upper
Cerebrovascular Adverse Events	QTP	7 (0)	8714	946.9	0.08	0.8	0.70	0.22	2.27
	Pla	5 (3)	4370	484.2	0.11	1.1			

a Any type of adverse event in the group.
b Patients must have received at least one dose of trial medication.
c Exposure in patient-years, censored at first event.
d 100 x total number of patients with event/total patient.
e Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
f Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
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Table 130 Seriousness, outcomes, and severity of each adverse event risk, age > 65 years - all placebo-controlled trials

Risk Adverse event group[a] (N=760)	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Cerebrovascular Adverse Events	5 (0.66)	3 (60.00)	3 (60.00)	3 (60.00)	0 (0.00)	0 (0.00)	2 (40.00)	1 (20.00)	1 (20.00)	3 (60.00)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 andThe placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\CVA_ae_pla_ctrl_ageover65.SAS. Version: V27. User: [redacted] 2014-07-15 23:40.

Table 131 Seriousness, outcomes, and severity of each adverse event risk, age <66 years - all placebo-controlled trials

Risk Adverse event group[a] (N=8714)	Adverse event n (%)	Serious adverse event n (%)	Hospitalized n (%)	Recovered n (%)	Recover status unknown n (%)	Not recovered n (%)	Death n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Cerebrovascular Adverse Events	7 (0.08)	0 (0.00)	0 (0.00)	3 (42.86)	0 (0.00)	4 (57.14)	0 (0.00)	3 (42.86)	2 (28.57)	2 (28.57)

a Any type of adverse event in the group.
Note: Only QTP patients are included.
Note: Patients with multiple events are counted only once.
Note: Percentages are calculated as (n/(number of adverse events)*100). For the adverse events column percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and the placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\CVA_ae_pla_ctrl_ageunder66.SAS. Version: V27. User: [redacted] 2014-07-15 23:40.

1.3.2.3 Metabolic risk factors

Table 132 Incidence of shifts in metabolic risk factors to end of treatment (Placebo-controlled trials)

		QTP				PLA				QTP vs PLA		
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**N**	**n (%)**	**Exposure[c]**	**MH incidence rate per 100 pt-yrs[d]**	**MH relative risk[d]**	**95% CI Lower**	**95% CI Upper**
Shift from < 3 metabolic risk factors at baseline to >=3 post baseline	All	2999	332 (11.1)	417.0	79.87	1551	136 (8.8)	218.3	61.63	1.30	1.05	1.59
	18 to 65 years	2726	285 (10.5)	371.3	78.54	1316	104 (7.9)	179.9	57.53	1.37	1.08	1.72
	> 65 years	273	47 (17.2)	45.7	86.95	235	32 (13.6)	38.4	84.99	1.02	0.64	1.63

a Number of patients, age >= 18, with a normal (defnied as < 3 risk factors) baseline. Patient must have all 5 risk assessments at baseline and post baseline.
b Number of patients with event. Event defined as >= 3 risk factors at end of treatment.
c Total exposure in patient years.
d Mantel-Haenzel incidence rate and relative risk estimates are adjusted for study and total exposure time.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134. The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
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Table 133 Incidence of shifts in metabolic risk factors to end of treatment (Placebo-controlled trials). Patients with >= 3 shifts.

		QTP				PLA			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
BMI >= 30 at EOT	All	182	41 (22.5)	26.9	152.3	69	9 (13.0)	10.3	87.6
	18 to 65 years	144	34 (23.6)	20.1	169.0	43	9 (20.9)	6.2	146.0
	> 65 years	38	7 (18.4)	6.8	103.0	26	0 (0.0)	4.1	0.0
GLUC >= 100(CF)/140(RF/NF) mg/dL at EOT	All	281	141 (50.2)	39.0	361.7	114	67 (58.8)	15.6	429.4
	18 to 65 years	248	125 (50.4)	33.3	375.5	93	55 (59.1)	12.2	452.0
	> 65 years	33	16 (48.5)	5.7	280.8	21	12 (57.1)	3.4	349.2
HDL < 40(M)/50(F) mg/dL at EOT	All	243	141 (58.0)	33.6	419.0	92	42 (45.7)	12.7	330.7
	18 to 65 years	209	124 (59.3)	27.8	446.5	68	28 (41.2)	8.8	316.6
	> 65 years	34	17 (50.0)	5.9	289.2	24	14 (58.3)	3.9	362.9
Supine BP >=130(SBP)/85(DBP) at EOT	All	162	37 (22.8)	22.2	166.8	62	14 (22.6)	8.8	159.6
	18 to 65 years	152	31 (20.4)	20.4	152.0	54	13 (24.1)	7.4	176.4
	> 65 years	10	6 (60.0)	1.8	334.6	8	1 (12.5)	1.4	71.5
TRIGL >= 150 mg/dL at EOT	All	244	188 (77.0)	34.2	550.3	102	68 (66.7)	13.7	495.7
	18 to 65 years	208	160 (76.9)	27.8	576.2	78	50 (64.1)	9.9	502.5
	> 65 years	36	28 (77.8)	6.4	437.6	24	18 (75.0)	3.8	477.8

a Number of patients, age >= 18, with a normal (defnied as < 3 risk factors) baseline and >= 3 risk factors at end of treatment. Patient must have all 5 risk assessments at baseline and post baseline.
Additionally the patient must have a normal baseline per risk factor
b Number of patients with event. Event defined as shift in risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_pla_ctrl_byRF.SAS. Data version: V27. User: [redacted] 2014-07-16 2:07.

Table 134 Incidence of shifts in metabolic risk factors to end of treatment (Placebo-controlled trials)

		QTP				PLA			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
BMI >= 30 at EOT	All	5597	222 (4.0)	669.3	33.2	2962	72 (2.4)	363.0	19.8
	18 to 65 years	5116	207 (4.0)	594.6	34.8	2576	69 (2.7)	304.7	22.6
	> 65 years	481	15 (3.1)	74.7	20.1	386	3 (0.8)	58.3	5.1
GLUC >= 100(CF)/140(RF/NF) mg/dL at EOT	All	5064	696 (13.7)	660.9	105.3	2840	330 (11.6)	362.7	91.0
	18 to 65 years	4688	616 (13.1)	598.3	103.0	2531	266 (10.5)	312.5	85.1
	> 65 years	376	80 (21.3)	62.6	127.7	309	64 (20.7)	50.2	127.4
HDL < 40(M)/50(F) mg/dL at EOT	All	3475	570 (16.4)	463.2	123.1	1785	252 (14.1)	239.3	105.3
	18 to 65 years	3173	524 (16.5)	412.4	127.1	1523	217 (14.2)	196.2	110.6
	> 65 years	302	46 (15.2)	50.7	90.7	262	35 (13.4)	43.1	81.2
Supine BP >=130(SBP)/85(DBP) at EOT	All	5262	360 (6.8)	591.0	60.9	2692	166 (6.2)	308.8	53.8
	18 to 65 years	5034	317 (6.3)	556.3	57.0	2504	140 (5.6)	280.4	49.9

	> 65 years	228	43 (18.9)	34.7	123.8	188	26 (13.8)	28.4	91.7
TRIGL >= 150 mg/dL at EOT	All	2980	671 (22.5)	407.7	164.6	1635	247 (15.1)	220.8	111.9
	18 to 65 years	2670	601 (22.5)	355.4	169.1	1385	207 (14.9)	180.0	115.0
	> 65 years	310	70 (22.6)	52.3	133.9	250	40 (16.0)	40.7	98.2

a Number of patients, age >= 18. The patient must have a normal baseline and an EOT assessment per risk factor.
b Number of patients with event. Event defined as shift in risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\metabolic_incid_pla_ctrl_byRF_notMetSynd.SAS. Data version: V27. User: [redacted] 2014-07-16 2:07.

Table 135 Incidence of shifts in metabolic risk factors to end of treatment (Placebo-controlled trials) by number of risks at baseline

		QTP				PLA			
Laboratory parameter	**Age group**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**	**N[a]**	**n[b] (%)**	**Exposure[c]**	**Incidence density[d]**
Shift from 0 metabolic risk factors at baseline to >=3 post baseline	All	934	12 (1.3)	130.5	9.2	454	1 (0.2)	64.0	1.6
	18 to 65 years	903	11 (1.2)	125.2	8.8	428	1 (0.2)	59.9	1.7
	> 65 years	31	1 (3.2)	5.3	18.9	26	0 (0.0)	4.1	0.0
Shift from 1 metabolic risk factors at baseline to >=3 post baseline	All	1156	92 (8.0)	158.4	58.1	588	29 (4.9)	83.0	34.9
	18 to 65 years	1034	84 (8.1)	138.2	60.8	482	22 (4.6)	65.6	33.5
	> 65 years	122	8 (6.6)	20.2	39.6	106	7 (6.6)	17.3	40.4
Shift from 2 metabolic risk factors at baseline to >=3 post baseline	All	909	228 (25.1)	128.2	177.9	509	106 (20.8)	71.4	148.5

18 to 65 years	789	190 (24.1)	107.9	176.0	406	81 (20.0)	54.4	148.9
> 65 years	120	38 (31.7)	20.3	187.6	103	25 (24.3)	17.0	147.4

a Number of patients, age >= 18, with a normal (defnied as < 3 risk factors) baseline. Patient must have all 5 risk assessments at baseline and post baseline.
b Number of patients with event. Event defined as >= 3 risk factors at end of treatment.
c Total exposure in patient years.
d 100 x total number of patients with event/total patient years of total exposure.
QTP Quetapine, PLA Placebo, EOT End of treatment, SBP Systolic blood pressure, DBP Diastolic blood pressure
CF Confirmed fastingRF Random fasting, NF Non fasting, F Female, M Male
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1.3.2.4 Weight

Table 136 Mean (SD) change from baseline to end of treatment in weight (all placebo-controlled trials)

		QTP N=9474	Pla N=4992
Patients[a]		8820	4688
Baseline	Mean (SD)	78.4 (21.0)	77.7 (21.2)
End of treatment	Mean (SD)	79.6 (21.1)	77.9 (21.3)
Change	Mean (SD)	1.2 (3.3)	0.2 (3.0)
	Median	1.0	0.0
	Min to max	-56.0 to 78.9	-72.9 to 78.8

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Note: Trial: D1447C00126, D1447C00127, D1444C00004, D1447C00144, D1448C00005 and D1448C00012 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.
Only the acute phase is included for trial D1447C00001 and D1447C00134.
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Table 137 Mean (SD) change from baseline to end of treatment in weight, age <=17 (all placebo-controlled trials)

		QTP N=432	Pla N=265
Patients[a]		432	265
Baseline	Mean (SD)	61.5 (19.0)	63.0 (19.7)
End of treatment	Mean (SD)	63.2 (19.3)	63.4 (20.0)
Change	Mean (SD)	1.7 (2.5)	0.3 (2.4)
	Median	1.0	0.0
	Min to max	-7.0 to 17.0	-12.0 to 11.0

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Note: Trial: D1447C00126, D1447C00127, D1444C00004, D1447C00144, D1448C00005 and D1448C00012 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.
Only the acute phase is included for trial D1447C00001 and D1447C00134.
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Table 138 Mean (SD) change from baseline to end of treatment in weight, age 18 to 65 (all placebo-controlled trials)

		QTP N=8282	Pla N=4105
Patients[a]		7678	3830
Baseline	Mean (SD)	80.3 (21.0)	79.9 (21.5)
End of treatment	Mean (SD)	81.5 (21.0)	80.1 (21.6)
Change	Mean (SD)	1.2 (3.3)	0.2 (3.2)
	Median	1.0	0.0
	Min to max	-56.0 to 78.9	-72.9 to 78.8

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Note: Trial: D1447C00126, D1447C00127, D1444C00004, D1447C00144, D1448C00005 and D1448C00012 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.
Only the acute phase is included for trial D1447C00001 and D1447C00134.
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Table 139 Mean (SD) change from baseline to end of treatment in weight, age >=66 (all placebo-controlled trials)

		QTP N=760	Pla N=622
Patients[a]		710	593
Baseline	Mean (SD)	68.5 (13.9)	69.8 (14.5)
End of treatment	Mean (SD)	69.0 (13.9)	69.7 (14.5)
Change	Mean (SD)	0.5 (2.6)	-0.1 (1.9)
	Median	0.4	0.0
	Min to max	-16.8 to 18.9	-10.9 to 8.6

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Note: Trial: D1447C00126, D1447C00127, D1444C00004, D1447C00144, D1448C00005 and D1448C00012 are excluded due to their initial uncontrolled open label phase prior to the randomised phase.
Only the acute phase is included for trial D1447C00001 and D1447C00134.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_WEIGHT_CH_PLA_CTRL_AGE66.SAS. Data version: V27. User: [redacted] 2014-07-16 0:53.

Table 140 Incidence of weight gain >= 7% increase (all placebo-controlled trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	MH incidence rate per 100 pt-yrs[c]	MH relative risk[d] QTP vs Pla	95% CI Lower	95% CI Upper
QTP	878 (10.0)	8820	985.5	87.9	2.67	2.26	3.14
Pla	178 (3.8)	4688	555.2	33.0			

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
b Exposure in patient-years, censored at first event.
c Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
d Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_pla_ctrl.SAS. Data version: V27. User: [redacted] 2014-07-16 0:54.

Table 141 Incidence of weight gain >= 7% increase, age <=17 (all placebo-controlled trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	MH incidence rate per 100 pt-yrs[c]	MH relative risk[d] QTP vs Pla	95% CI Lower	95% CI Upper
QTP	75 (17.4)	432	36.0	193.8	2.46	1.49	4.07
Pla	20 (7.5)	265	25.6	78.8			

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
b Exposure in patient-years, censored at first event.
c Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
d Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_pla_ctrl_age17.SAS. Data version: V27. User: [redacted] 2014-07-16 0:54.

Table 142 Incidence of weight gain >= 7% increase, age 18 to 65 (all placebo-controlled trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	MH incidence rate per 100 pt-yrs[c]	MH relative risk[d] QTP vs Pla	95% CI Lower	95% CI Upper
QTP	762 (9.9)	7678	839.6	92.2	2.70	2.25	3.23
Pla	148 (3.9)	3830	438.8	34.2			

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
b Exposure in patient-years, censored at first event.
c Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
d Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_pla_ctrl_age1865.SAS. Data version: V27. User: [redacted] 2014-07-16 0:54.

Table 143 Incidence of weight gain >= 7% increase, age >=66 (all placebo-controlled trials)

Treatment	Patients with event n (%)	Total patients[a]	Exposure[b]	MH incidence rate per 100 pt-yrs[c]	MH relative risk[d] QTP vs Pla	95% CI Lower	95% CI Upper
QTP	41 (5.8)	710	109.8	33.1	2.70	1.34	5.45
Pla	10 (1.7)	593	90.6	12.3			

a Patients must have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
b Exposure in patient-years, censored at first event.
c Mantel-Haenszel incidence rate per 100 patient-years adjusted for study.
d Mantel-Haenszel relative risk estimate adjusted for study and exposure time.
Note: Patients with multiple events are counted only once.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001 and D1447C00134.
Pgm: SESOD...\Reg-Def\PRMP Jun 2014\T27_weight_inc_pla_ctrl_age66.SAS. Data version: V27. User: [redacted] 2014-07-16 0:54.

1.3.3 Details of important identified risk in the pediatric population

Increased blood pressure

See Table II-68 in the main document of the EU-RMP.