AstraZeneca

Addendum to the Clinical Overview

Medicinal Product(s)	Ticagrelor
Date	16 January 2015

Ticagrelor (BRILIQUE™/POSSIA™/BRILINTA™)

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Approved by: [redacted]

16th January 2015
Date

EXECUTIVE SUMMARY

- **Introduction:** This Addendum to the Clinical Overview for ticagrelor addresses the current benefit-risk profile on the basis of safety and efficacy/effectiveness data received and evaluated by AstraZeneca since the granting of the marketing approval (ie, between 03 December 2010 and 08 November 2014). It is intended to support a licence renewal for this product.

- **Medicinal product:** Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines and is a selective and reversibly binding adenosine diphosphate (ADP) receptor antagonist acting on the $P2Y_{12}$ ADP-receptor that can prevent ADP-mediated platelet activation and aggregation. Ticagrelor has an additional mechanism of action, increasing local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter-1 (ENT-1).

  - Ticagrelor is indicated for prevention of thrombotic events (cardiovascular [CV] death, myocardial infarction [MI], and stroke) in patients with acute coronary syndromes (ACS) (unstable angina [UA], non-ST-segment elevation MI [NSTEMI] or ST-segment elevation MI [STEMI]), including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).

  - Ticagrelor treatment should be initiated with a single, 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Patients taking ticagrelor should also take acetylsalicylic acid (ASA) daily, unless specifically contraindicated. Following an initial dose of ASA, ticagrelor should be used with a maintenance dose of ASA of 75 mg to 150 mg.

- **Estimated cumulative exposure of clinical trial subjects:** Approximately 71107 patients and/or healthy volunteers have been enrolled into the clinical development programme through 08 November 2014, of which approximately 40254 have received ticagrelor.

- **Estimated reporting period and cumulative patient exposure from post-approval (marketing) experience:** During the reporting period (ie, from December 2010 up to 08 November 2014), the global post-marketing exposure was estimated to be approximately 648000 patient-years. Since the reporting period includes data since the first launch of ticagrelor, this exposure also equals the estimated cumulative global post-marketing exposure.

- **Marketing approval(s):** Ticagrelor was first approved for marketing in the European Union on 03 December 2010. On 20 July 2011, ticagrelor was also

approved by the United States (US) Food and Drug Administration. As of 08 November 2014, ticagrelor was approved in more than 100 countries.

- **Summary of overall benefit-risk balance:** The benefits of treatment with ticagrelor have been weighed against safety experience, both from the clinical programme and post-marketing experience. The safety data received during the reporting period do not indicate a change in the positive benefit-risk profile of ticagrelor.

- **Actions taken or proposed for safety reasons:** No significant actions related to safety were taken or proposed during the reporting period that had the potential to affect the positive benefit-risk profile of ticagrelor.

- **Significant changes to the SmPC:** Safety-related updates were made regarding hypersensitivity reactions, interaction with cyclosporine, use in patients with severe renal impairment, concomitant use of ticagrelor with grapefruit juice, dizziness, and fatal intracranial bleedings.

- **Conclusions and expert statement:** ACS is a serious, life-threatening medical condition that contributes substantially to morbidity and mortality worldwide. Compared with clopidogrel, ticagrelor prevents more major adverse cardiac events after ACS, most notably reducing CV mortality, without adding any clinically important safety concerns. A comprehensive review of clinical studies and post-marketing experience reveals that no new information that alters the overall positive benefit-risk profile for ticagrelor has become available during the reporting period. It is the opinion of AstraZeneca that the efficacy and safety information in the current ticagrelor SmPC accurately reflects the known benefit-risk profile for ticagrelor. However, AstraZeneca proposes a minor update to the current SmPC with the renewal application.

  - The updated benefit-risk evaluation has been addressed adequately (taking account of the consolidated version of the file and all relevant new information).
  - Regulatory authorities have been kept informed of any additional data considered significant to the assessment of the benefit-risk balance of ticagrelor.
  - The ticagrelor proposed product information is up-to-date with current scientific knowledge (including the conclusions of assessments and recommendations made publicly available by regulatory authorities).
  - The current ticagrelor Risk Management Plan (version 8.0) is up-to-date and no updated version is included with the renewal application.
  - It is concluded that the product can be safely renewed for an unlimited period.

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LIST OF ABBREVIATIONS

The following abbreviations are used in this Addendum to the Clinical Overview.

Abbreviation or special term	Explanation
ACS	Acute coronary syndromes
ADR	Adverse drug reaction
ADP	Adenosine diphosphate
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARR	Absolute risk reduction
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATLANTIC	Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (Study D5130L00006)
AUC	Area under the concentration versus time curve
AUC_{τ}	Area under the concentration versus time curve during a dosing interval
AV	Atrioventricular
BID	Twice daily
CABG	Coronary artery by-pass graft
CAD	Coronary artery disease
CBFV	Coronary blood flow velocity
CDS	Core Data Sheet
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
CTA	Clinical Trial Authorisation
CV	Cardiovascular
CYP	Cytochrome P450
DAPT	Dual antiplatelet therapy
DIBD	Development International Birth Date

Abbreviation or special term	Explanation
DUS	Drug utilisation study
EMA	European Medicines Agency
ENT-1	Equilibrative nucleoside transporter-1
EU	European Union
EUCLID	Examining Use of tiCagreLor In paD (Study D5135C00001)
FDA	Food and Drug Administration
GI	Gastrointestinal
HR	Hazard ratio
IBD	International Birth Date
ICH	Intra-cranial haemorrhage
IPA	Inhibition of platelet aggregation
KAU	Knowledge and Understanding
KM	Kaplan-Meier
LD	Loading dose
MD	Maintenance dose
MedDRA	Medical Dictionary for Regulatory Activities
MAH	Marketing Authorisation Holder
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drug
NSTE	Non-ST-segment elevation
NSTEMI	Non-ST-segment elevation myocardial infarction
OD	Once daily
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PEGASUS	PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome - Thrombolysis In Myocardial Infarction Study Group (Study D5132C00001)
PHILO	PHase the International study of ticagreLor and clinical Outcomes in Asian ACS patients (Study D5130C00027)
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PLATO	PLATelet inhibition and Patient Outcomes (Study D5130C05262)

Abbreviation or special term	Explanation
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
RRR	Relative risk reduction
SAE	Serious adverse event
SCD	Sickle cell anaemia
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOCRATES	Acute Stroke Or Transient IsChaemic Attack TReated with Aspirin or Ticagrelor and Patient OutcomES (Study D5134C00001)
STEMI	ST-segment elevation myocardial infarction
THEMIS	Effect of Ticagrelor on Health outcomes in diabEtes Mellitus patients Intervention Study (Study D513BC00001)
TIMI	Thrombolysis in Myocardial Infarction
t_{max}	Time to maximum concentration
UA	Unstable angina
ULN	Upper limit of normal
US	United States

1. INTRODUCTION

This Addendum to the Clinical Overview prepared by AstraZeneca addresses the current benefit-risk profile for ticagrelor (BRILIQUE™/POSSIA™/BRILINTA™[1]), on the basis of the safety and efficacy/effectiveness information received and evaluated by AstraZeneca from worldwide sources since the granting of the marketing approval (ie, between 03 December 2010 and 08 November 2014. This document is intended to support a licence renewal for this product with unlimited validity.

Ticagrelor was first approved for marketing by the European Commission on 03 December 2010. The ticagrelor International Birth Date (IBD) is 31 December 2010.

Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines and a selective and reversibly binding adenosine diphosphate (ADP) receptor antagonist acting on the $P2Y_{12}$ ADP-receptor that can prevent ADP-mediated platelet activation and aggregation (platelet aggregation inhibitors excl. Heparin, ATC code B01AC24). Ticagrelor has an additional mechanism of action, increasing local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter-1 (ENT-1).

As described in the ticagrelor Summary of Product Characteristics (SmPC), ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) (unstable angina [UA], non-ST-segment elevation myocardial infarction [NSTEMI] or ST-segment elevation myocardial infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

Each film-coated tablet of ticagrelor contains 90 mg of the active ingredient. Ticagrelor treatment should be initiated with a single, 180 mg loading dose (LD) (2 tablets of 90 mg) and then continued at 90 mg twice daily (BID). Patients taking ticagrelor should also take ASA daily, unless specifically contraindicated. Following an initial dose of ASA, ticagrelor should be used with a maintenance dose (MD) of ASA of 75 mg to 150 mg.

The inclusion of any information relating to an important potential risk or missing information within this Addendum to the Clinical Overview should not be taken to imply that a causal association with the use of ticagrelor has been established.

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[1] BRILIQUE™/POSSIA™/BRILINTA™ are trademarks of the AstraZeneca group of companies.

2. HISTORY OF PHARMACOVIGILANCE SYSTEM INSPECTIONS

A history of pharmacovigilance system inspections that have occurred during the reporting period is presented in Appendix 4. The findings from these inspections have not had any impact on the overall benefit/risk balance of the medicinal product.

3. WORLDWIDE MARKETING APPROVAL STATUS

Ticagrelor was first approved for marketing in the European Union (EU) by the European Commission on 03 December 2010. On 20 July 2011 ticagrelor was also approved in the United States (US) by the Food and Drug Administration (FDA). As of 08 November 2014, ticagrelor was approved in more than 100 countries for the prevention of atherothrombotic events in adult patients with ACS (UA, NSTEMI, or STEMI).

The approved indications are consistent with the current ticagrelor Core Data Sheet (CDS). The marketed tablet strength of ticagrelor is 90 mg. During the reporting period Marketing Authorisation in Albania, Belarus and Macedonia was withdrawn for commercial reasons. Per European Commission Decision (dated 28 March 2013) the marketing authorisation of a duplex procedure (trademark Possia™, EU/1/10/656/001-006) has also been withdrawn on request of the Marketing Authorisation Holder (MAH) for commercial reasons.

Ticagrelor is registered under the trademarks Brilinta™, Brilique™, and Possia™. An overview of the current worldwide marketing authorisation status of ticagrelor is presented in Appendix 1.

4. ACTIONS TAKEN FOR SAFETY REASONS

No significant actions related to safety were taken during the period that had the potential to affect the positive benefit-risk profile of ticagrelor. However, the following activities have been reported in this section in the Periodic Safety Update Reports (PSURs) and Periodic Benefit-Risk Evaluation Reports (PBRERs) submitted during the reporting period:

Risk Evaluation and Mitigation Strategy in the US

As part of the US approval process, the FDA agreed to a Risk Evaluation and Mitigation Strategy (REMS) program. As part of the REMS, AstraZeneca conducted educational outreach to physicians and professional organisations to describe the risks associated with ticagrelor, particularly the increased risk of bleeding and that the daily maintenance dose of aspirin, co-administered with ticagrelor, should not exceed 100 mg. In addition, within the US, ticagrelor was dispensed with a Medication Guide that provides to patients the most important information about the medication. The Medication Guide was distributed each time a patient filled their prescription. Ticagrelor was released from the requirement of the REMS on 30 October 2013.

Post-marketing studies required in China

In China, marketing authorisation for ticagrelor was granted with the requirement of conducting 2 post-marketing studies: a pharmacokinetic (PK)/pharmacodynamic (PD) study to understand the dose/effect relationship of ticagrelor in Chinese patients with stable coronary heart disease and a large-sample-size Phase 4 study to further evaluate the safety of ticagrelor in clinical practice, with special attention given to "Major/Life-threatening Bleeding." See also Appendix 5.

Concerns raised after submission of Clinical Trial Authorizations applications for a paediatric study

AstraZeneca submitted applications for Clinical Trial Authorisations (CTAs) in 6 markets for Study D5136C00001, the first paediatric study of ticagrelor. On 02 August 2012, the US FDA placed the IND for this study (IND 112,336) on full clinical hold. AstraZeneca received similar concerns from other authorities (eg, Germany) while the CTA was approved by others (eg, Hungary and France). See Section 11.2.3.6 for further information.

5. SIGNIFICANT CHANGES TO THE SMPC

The proposed SmPC is presented in Appendix 6. In addition to minor typographical changes, AstraZeneca proposes to amend Section 5.1 of the SmPC to accurately reflect the outcomes of study D5130C00067. A detailed justification for this proposed change is presented in Appendix 7.

Table 1 summarises the significant changes that were made (and approved) to the SmPC during the reporting period.

Table 1 Summary of changes made to the SmPC during the reporting period

Procedure number	Description of changes made
WS/292	Update of Sections 4.3 and 4.8 to add safety information regarding hypersensitivity, including angiooedema. Minor corrections in Sections 4.8, 5.1, and 5.2.
II/0017	Update of Sections 4.4 and 4.5 regarding drug-drug interaction between ticagrelor and cyclosporine. Update of Section 5.2 to correct the statement regarding patients with severe renal impairment.

Table 1 Summary of changes made to the SmPC during the reporting period

Procedure number	Description of changes made
II/0018	Implementation of assessment of PSUR4. Update of Sections 4.5 and 4.7 to add warnings regarding concomitant use of ticagrelor with grapefruit juice (Section 4.5) and dizziness in ACS patients taking ticagrelor (Section 4.7). Update to Section 4.8 to add information regarding fatal intracranial bleedings in the post-marketing experience.
II/0021	Update to Sections 4.2 and 5.2 to add information about the bioequivalence of crushed tablets mixed with water and administered orally or via nasogastric tube compared to whole tablets. Update to Sections 4.4 and 4.5 to delete dexamethasone from the list of strong CYP3A inducers with the potential to decrease the exposure and efficacy of ticagrelor.
II/0022	Update to Section 5.1 to add information about an additional mechanism of action (adenosine pathway).

ACS Acute coronary syndromes; CYP Cytochrome P450; PSUR Periodic Safety Update Report; SmPC Summary of Product Characteristics.

AstraZeneca's reference for safety information is the CDS. The CDS contains material relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product (providing the medical and scientific information AstraZeneca believes is necessary for the safe and effective use of the product) and it serves as the master document for regular implementation of material changes in national or local authorised product information.

During the reporting period, the ticagrelor CDS was updated from the version dated 25 August 2010 to versions dated 12 December 2011, 26 April 2012, 01 June 2012, 26 March 2013, and to the current version, dated 03 March 2014.

A copy of the ticagrelor CDS in effect at the end of the reporting period is presented in Appendix 2. An annotated version of this CDS is also included in Appendix 2 highlighting the changes compared with the version of the CDS that was in effect at the beginning of the reporting period.

No changes were made to the CDS during the reporting period that have not yet been implemented in the registered SmPC. For the purpose of this Addendum to the Clinical Overview, the current SmPC, dated 24 July 2014 (date of Committee for Medicinal Products for Human Use [CHMP] positive opinion), is the reference for both the benefit and risk sections.

6. ESTIMATED EXPOSURE

6.1 Cumulative subject exposure in clinical trials

Estimates of overall cumulative subject exposure are provided in Table 2, based on actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials. Approximately 71107 patients and/or healthy volunteers have been enrolled into the clinical development programme through 08 November 2014, of which approximately 40254 have received ticagrelor.

Table 2 Estimated cumulative subject exposure from clinical trials

Treatment	Number of subjects[a]
Ticagrelor	40254
Acetylsalicylic acid[b]	25267
Clopidogrel	17237
Placebo	9122
Other comparators	496

a Cumulative numbers from initiation of the first clinical trial up to 08 November 2014.
b Includes both treatment as a comparator and as background therapy.

Cumulative summary tabulations of exposure to ticagrelor from completed clinical trials by age/sex and by racial group are presented in Table 3 and Table 4, respectively.

Table 3 Estimated cumulative subject exposure to ticagrelor from completed clinical trials by age and sex

	Number of subjects[a]		
Age range (years)	Male	Female	Total
18 to 65	6893	1711	8604
66 to 75	2216	1168	3384
>75	947	759	1706
Missing	1	0	1
Total	10057	3638	13695

a Data from completed clinical trials as of 08 November 2014.

Table 4 Estimated cumulative subject exposure to ticagrelor from completed clinical trials by racial group

Racial group	Number of subjects[a]
White	11844
Asian	1154
Black or African American	353
Other	342
Native Hawaiian or Other Pacific Islander	1
American Indian or Alaska Native	1
Total	13695

a Data from completed clinical trials as of 08 November 2014.

6.2 Cumulative and reporting period patient exposure from marketing experience

The market exposure for ticagrelor is estimated based on monthly ex-factory sales and volume from the local marketing company in each country. These data represent all ticagrelor tablets sold and shipped from AstraZeneca to various distribution channels (wholesalers, pharmacies, etc). The sales volume is provided as the number of tablets distributed.

The estimated periodic market exposure is an approximation based on the assumption that each patient took two 90-mg ticagrelor tablets per day (ie, 730 tablets per patient-year).

The current methodology does not distinguish between sales that are related to initial prescription purchases versus those related to refill purchases. Therefore, it is not possible to estimate the number of patients exposed to ticagrelor. More detailed patient-level data (eg, gender, ethnicity, age category, off-label use, specific special populations etc) are not available.

It should be noted that exposure during the reporting period includes data from first launch and thus equates to the cumulative exposure for ticagrelor. During the reporting period (ie, from December 2010 up to and including October 2014), the cumulative global post-marketing exposure for ticagrelor was estimated to be approximately 648000 patient-years. Approximately 59% of the worldwide distribution of ticagrelor tablets was in Europe, 20% was in North America (US and Canada) and 21% was in the rest of the world. The major countries for ticagrelor tablet delivery were the US (approximately 115000 patient-years), Germany (approximately 107000 patient-years), and Italy (approximately 52000 patient-years).

7. DATA IN SUMMARY TABULATIONS

7.1 Reference information

The Medical Dictionary for Regulatory Activities (MedDRA), version 17.1, has been used for coding adverse events (AEs). The summary tabulations are arranged in the internationally agreed order by primary MedDRA System Organ Class (SOC), and refer to the Preferred Term (PT) level.

7.2 Summary tabulations of serious adverse events from clinical trials

A cumulative summary tabulation of serious adverse events (SAEs) from AstraZeneca interventional clinical trials that have been reported during the ticagrelor clinical development programme, from the Development International Birth Date (DIBD) to the data lock point (08 November 2014), organised by SOC, is presented in Appendix 3.

7.3 Summary tabulations from post-marketing data sources

Cumulative and interval summary tabulations of adverse reactions (ie, AEs considered as "possibly related") that have been reported from marketed experience with ticagrelor, from the IBD to the data lock point, organised by SOC, are presented in Appendix 3.

8. SUMMARIES OF SIGNIFICANT SAFETY AND EFFICACY FINDINGS FROM CLINICAL TRIALS AND NON-INTERVENTIONAL STUDIES

8.1 Completed clinical trials

There were no clinically important emerging safety findings obtained from clinical trials completed during the reporting period. The following clinical trials have been completed during the reporting period:

8.1.1 Study D5130C00065

Study D5130C00065 was a PK and PD study of ticagrelor compared with clopidogrel in Japanese and other Asian patients with stable coronary heart disease. In prior studies, exposure with ticagrelor 90 mg BID was 1.3- to 1.5-fold higher in Asian patients compared with Western patients; these differences were not considered clinically relevant. In this study, the exposure to ticagrelor in Japanese patients was consistent with that observed in Asian patients in prior studies. Inhibition of platelet aggregation in Japanese and other Asian patients in Study D5130C00065 was greater with ticagrelor 90 mg BID than with ticagrelor

45 mg BID or clopidogrel 75 mg once daily (OD). The safety profile of ticagrelor in this study was consistent with its established safety profile.

8.1.2 Study D5130C00067

Study D5130C00067 assessed the effect of ticagrelor on adenosine-induced coronary blood flow velocity and dyspnoea in healthy volunteers. Blood flow velocity was measured by ultrasound during stepwise increase in adenosine infusion rate. Ticagrelor increased the adenosine-induced coronary blood flow velocity response compared with placebo. Theophylline inhibited this response, confirming that an adenosine-mediated mechanism was operating. In parallel, dyspnoea occurrence and severity (reported on the Borg scale) were augmented by ticagrelor and reversed by theophylline, suggesting that adenosine may mediate the dyspnoea reported by some patients taking ticagrelor.

8.1.3 Study D5130C00073

Study D5130C00073 was an open-label, crossover study of the effect of ticagrelor on the PK of venlafaxine and vice versa in 25 healthy volunteers. The study evaluated the potential for drug-drug interactions via cytochrome P450 (CYP) 2D6-mediated metabolism. Venlafaxine had no effect on the exposure of ticagrelor or its metabolite AR-C124910XX. Ticagrelor had no effect on the overall exposure (area under the concentration-time curve during a dosing interval [AUC_τ]) of venlafaxine. However, the maximum plasma concentration (C_{max}) of venlafaxine was 22% higher when co-administered with ticagrelor. Ticagrelor had no effect on the exposure of O-desmethylvenlafaxine. Collectively, these results indicate that ticagrelor has no effect on CYP2D6-mediated metabolism.

8.1.4 Study D5130C00074

Study D5130C00074 was a single-centre, crossover study to investigate the potential PK interaction of 600 mg of cyclosporine and 180 mg ticagrelor in 26 healthy male volunteers. The mean area under the concentration versus time curve (AUC) and C_{max} for ticagrelor were approximately 2.8-fold and 2.3-fold higher, respectively, in the presence of cyclosporine. The geometric mean AUC for the ticagrelor active metabolite AR-C124910XX was 32% higher and C_{max} was 15% lower in the presence of cyclosporine. The time to maximum concentration (t_{max}) and half-life were similar between treatments for both ticagrelor and AR-C124910XX. Generally, all PK parameters for cyclosporine were similar when cyclosporine was given alone or when co-administered with ticagrelor. It was concluded that co-administration of cyclosporine increased the AUC and C_{max} of ticagrelor, and increased the AUC and decreased the C_{max} of AR-C124910ZXX. Ticagrelor had no effect on the exposure of cyclosporine.

8.1.5 Study D5133C00001

Study D5133C00001 was designed to assess the PK of ticagrelor and its active metabolite AR-C124910XX, and the safety and tolerability of ticagrelor following administration of a single, oral 90-mg dose in 12 healthy male Japanese volunteers. There were no AEs or SAEs observed in the study. Thus, the single 90-mg dose of ticagrelor was well tolerated in healthy male Japanese subjects.

8.1.6 Study D5130C00027 (PHILO)

Study D5130C00027 (PHILO) was a double-blind, randomised comparison of ticagrelor and clopidogrel assessing safety and prevention of vascular events in 801 Japanese/Asian patients with ACS. PLATO-defined total major bleeding (primary safety endpoint) did not differ significantly between treatment groups; combined (major +minor) bleeding events were significantly higher in the ticagrelor group. Overall, bleeding and other safety results were consistent with the results from the 18624 patients who participated in PLATO (study D5130C05262) and with the established safety profile of ticagrelor. Clinical efficacy data were limited in PHILO because of the small number of reported cardiovascular (CV) events (myocardial infarction [MI], stroke, and CV death); numerically more events were observed with ticagrelor than clopidogrel. AstraZeneca concluded that the benefit-risk for Japanese patients does not differ from other ACS populations.

8.1.7 Study D5130L00012

Study D5130L00012 (Hispanic-American patients) was a multi-centre, randomised, open-label, multiple-dose, crossover study of the onset and maintenance of antiplatelet effect in Hispanic patients with stable coronary artery disease (CAD). Ticagrelor was compared with clopidogrel, with chronic low-dose ASA (75 mg to 100 mg) as background therapy. Forty patients were randomised to receive either ticagrelor (180 mg LD followed by a 90 mg BID MD for 7 to 9 days) or clopidogrel (600 mg LD followed by a 75 mg OD MD for 7 to 9 days). After a 10- to 14-day washout period, patients crossed over therapy. Compared with clopidogrel, platelet reactivity (as measured by VerifyNow™) was decreased to a greater extent with ticagrelor, both after the loading dose and throughout the maintenance doses. Ticagrelor was well tolerated and safety findings were consistent with its established AE profile.

8.1.8 Study D5130L00013

Study D5130L00013 (African-American patients) was a multi-centre, randomised, open-label, multiple-dose, crossover study of the onset and maintenance of antiplatelet effect in African American patients with stable CAD. Ticagrelor was compared with clopidogrel, with chronic low-dose ASA as background therapy. Patients were randomised to receive either ticagrelor (180 mg LD followed by a 90 mg BID MD for 7 to 9 days) or clopidogrel (600 mg LD followed by a 75 mg OD MD for 7–9 days). After a 10- to 14-day washout period, patients crossed over therapy. Of the 34 patients randomised to treatment, 50% had diabetes mellitus. In the full cohort, as well as in the diabetic and non-diabetic subgroups, platelet reactivity was lower with ticagrelor treatment than with clopidogrel at all post-dose time points. Ticagrelor was well tolerated and safety findings were consistent with its established AE profile.

8.1.9 Study D5130C00076

Study D5130C00076 (nasogastric tube) was an open-label, crossover study in 36 healthy subjects. Plasma levels of ticagrelor and the active metabolite AR-C124910XX were measured following single-dose ticagrelor 90 mg administered in random sequence as follows: swallowed intact tablet, crushed tablet suspended in 200 mL water, and crushed tablet suspended in water via nasogastric tube. Each dose was separated by a 7-day washout period.

The results showed that bioequivalence between crushed and intact tablets is maintained. Median t_{max} was 1 hour for crushed tablets compared with 2 hours for intact tablets. There were no deaths, SAEs, or AEs leading to discontinuation of the investigational product reported.

8.1.10 Study D5130L00006 (ATLANTIC)

Study D5130L00006 (ATLANTIC) was a double-blind, randomised comparison of pre-hospital and in-hospital initiation of ticagrelor therapy in 1862 patients with STEMI who were planned to undergo PCI. The study did not meet any of its co-primary endpoints: Thrombolysis in Myocardial Infarction (TIMI) Flow Grade 3 of MI Culprit Vessel at initial angiography or ST-segment elevation resolution ≥70% pre-PCI. The time difference between the groups for active loading dose was 31 minutes. The study was not powered to assess outcomes, but there was no difference with regard to the pre-specified composite of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis at 30 days. There was a lower incidence of definite stent thrombosis in the pre-hospital group, and no difference with regard to bleeding between pre-hospital and in-hospital loading. Numerically, but not statistically significant, more deaths were observed in the pre-hospital group. This numerical imbalance in deaths occurred during the first day. The most common causes of death were cardiogenic shock, cardiac arrest or cardiac rupture rather than bleeding or ischaemic events. The numerical difference was not related to ticagrelor therapy or time of initiation, but it may have occurred due to a slight imbalance in randomisation of more severely diseased patients or by chance alone. In this study in patients with acute STEMI, pre-hospital administration of ticagrelor did not improve pre-PCI coronary reperfusion, but had no adverse effect on bleedings.

8.2 Ongoing clinical trials

No clinically important safety information has emerged from the 4 ongoing studies described below or from any other ongoing clinical trials during the reporting period.

The following 4 major clinical studies in patients with atherosclerotic disease and at high risk for CV events are in progress.

8.2.1 Study D5132C00001 (PEGASUS)

Study D5132C00001 (PEGASUS) is a randomised, double-blind, placebo-controlled, parallel group, multinational study to assess the prevention of thrombotic events with ticagrelor on a background of ASA therapy in patients with a history of MI. The ticagrelor dosing regimens are 90 mg BID and 60 mg BID. First patient in occurred in October 2010. The study is fully recruited and 21162 patients have been randomised. The study is long term and event-driven. Estimated date of last patient completed is Q4 2014.

8.2.2 Study D5134C00001 (SOCRATES)

Study D5134C00001 (SOCRATES) is a randomised, double-blind, multinational study to assess the prevention of major vascular events with ticagrelor compared with ASA in patients with acute ischaemic stroke or transient ischaemic attack. The ticagrelor dosing regimen is a 180-mg LD followed by 90 mg BID. Planned enrolment is approximately 9600 patients. First patient in occurred in Q1 2014. Treatment duration is 3 months. The estimated date of last patient completed is Q3 2015.

8.2.3 Study D5135C00001 (EUCLID)

Study D5135C00001 (EUCLID) is a randomised, double-blind, parallel group, multicentre Phase 3b study to compare ticagrelor with clopidogrel treatment on the risk of CV death, MI and ischaemic stroke in patients with established peripheral artery disease. The dosing regimens are ticagrelor 90 mg BID or clopidogrel 75 mg OD. First patient in occurred in December 2012. The study is fully recruited, and 13887 patients have been randomised. The estimated date of last patient completed is Q1 2016.

8.2.4 Study D513B00001 (THEMIS)

Study D513B00001 (THEMIS) is a multinational, randomised, double-blind, placebo-controlled study to evaluate the effect of ticagrelor 90 mg BID on the incidence of CV death, MI or stroke, in patients with type 2 diabetes mellitus and coronary atherosclerosis, but no prior MI or stroke. The ticagrelor dosing regimen is 90 mg BID. Planned enrolment is approximately 17000 patients. First patient in occurred in Q1 2014. The study is long term and event driven. The estimated date of last patient completed is Q3 2017.

8.3 Long-term follow-up

At present, patients completing ticagrelor trials are not subject to long-term follow-up.

8.4 Other therapeutic use of medicinal product

AstraZeneca is not aware of any clinically important safety findings from programmes that follow a specific protocol with solicited reporting.

8.5 New safety data related to fixed-combination therapies

This section is not applicable because ticagrelor is not available as a fixed-combination product.

8.6 Findings from non-interventional studies

There is no relevant safety information that has become available to AstraZeneca during the reporting period regarding non-interventional studies.

8.7 Lack of efficacy in controlled clinical trials

Any data indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), did not reflect a significant risk to the treated population.

8.8 Milestones for post-approval studies

For the drug utilisation study (DUS) (D5130N00010), the 4th annual report will be submitted in December 2014. No other milestones have been reached. A tabular summary of the post-approval studies is presented in Appendix 5.

9. LITERATURE

9.1 Clinical pharmacology publications

During the reporting period several publications have been generated from clinical pharmacology studies. The following publications are available from AstraZeneca studies.

9.1.1 Publications on the pharmacokinetics, metabolism and tolerability of ticagrelor:

- Pharmacokinetics, pharmacodynamics, tolerability and safety of single ascending doses of ticagrelor, a reversibly binding oral $P2Y_{12}$ receptor antagonist, in healthy subjects (Teng and Butler 2010). Study no: D5130C05169 and D5130C05171
- Absorption, distribution, metabolism and excretion of ticagrelor in healthy subjects. (Teng et al 2010). Study no: D5130C00013
- Pharmacokinetics, pharmacodynamics, safety and tolerability of multiple ascending doses of ticagrelor in healthy volunteers (Teng and Butler 2010). Study no: D5130C05239
- Single-dose ticagrelor does not prolong the QT interval in healthy subjects (Butler et al 2010). Study no: D5130C00037
- Safety, tolerability, pharmacokinetics and pharmacodynamics of high, single, ascending doses of ticagrelor in healthy volunteers (Teng and Butler 2013d). Study no: D5130C00049
  - **AstraZeneca comment**: These publications, which have made the PK, PD, and early tolerability data from AstraZeneca clinical pharmacology studies available to the scientific community, reflect what is available in the clinical reports previously submitted. This information is reflected in the SmPC.

9.1.2 Publications on pharmacokinetics in special populations

- Pharmacokinetics, pharmacodynamics, and safety of ticagrelor in volunteers with mild hepatic impairment (Butler and Teng 2011b). Study no: D5130C00016

  - **AstraZeneca comment:** As ticagrelor undergoes extensive hepatic elimination, the effect of mild hepatic impairment on its PK profile was assessed in a single centre, non-randomised, open label, and parallel group study. A single oral ticagrelor 90-mg dose was administered to subjects with and without hepatic impairment. C_{max} and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment than in matched healthy subjects. As this increased exposure was not associated with clinically relevant changes in PD or tolerability, dose adjustments are not necessary in these patients.

- Pharmacokinetics, pharmacodynamics, and safety of ticagrelor in volunteers with severe renal impairment (Butler and Teng 2012a). Study no: D5130C00015

  - **AstraZeneca comment:** In patients with severe renal impairment (creatinine clearance <30 mL/min), the C_{max} and AUC of ticagrelor were 20% lower and the C_{max} and AUC of AR-C124910XX were 17% higher than in patients with normal renal function. This suggests that renal impairment may have a limited effect on the systemic exposure to these compounds; these effects were not considered to be clinically relevant. Dose adjustments are therefore not necessary in patients with renal impairment.

- Evaluation and characterization of the effects of ticagrelor on serum and urinary uric acid in healthy volunteers (Butler and Teng 2012b). Study no: D5130C00050

  - **AstraZeneca comment:** In this placebo-controlled, randomised cross-over study, 24 healthy male subjects received ticagrelor 90 mg BID for 5 days. Serum uric acid levels were significantly increased compared to placebo but rapidly returned to baseline levels following cessation of ticagrelor dosing. Urinary uric acid excretion was higher following ticagrelor versus placebo on both days. However, no uric acid-related AEs were observed. These data suggest that serum uric acid elevations following ticagrelor treatment are modest, reversible and unlikely to cause clinically relevant hyperuricaemia.

- Effect of age and gender on the pharmacokinetics and pharmacodynamics of a single ticagrelor dose in healthy subjects (Teng et al 2012b). Study no: D5130C00014

  - **AstraZeneca comment:** In this study evaluating a single ticagrelor dose of 200 mg in healthy subjects, AUC and C_{max} were 42% and 63% higher

in patients aged ≥65 years than in younger patients and 37% and 52% higher in females than in males, respectively. The mean half-life was similar across all age groups but was 22% longer in females than in males. Similarly, greater exposure to ticagrelor and AR-C124910XX was observed in patients with ACS aged ≥75 years than in younger patients and in women compared with men. However, these differences are not considered clinically relevant and no dose adjustments are required based on age or gender.

- Pharmacokinetics and tolerability of single and multiple doses of ticagrelor in healthy Chinese subjects: an open-label, sequential, two-cohort, single-centre study (Li et al 2012). Study no: D5130C00054

  This study investigated 90 mg and 180 mg doses of ticagrelor in healthy Chinese subjects. Following single and multiple doses at both dose levels, ticagrelor was rapidly absorbed. Steady-state concentrations of ticagrelor and the metabolite AR-C124910XX were rapidly established with both dosing regimens. Both ticagrelor parent and its metabolite exhibited linear and predictable PK with single and multiple dosing.

  – **AstraZeneca comment:** Ticagrelor and AR-C124910XX exposure at steady state were found to be slightly higher in Chinese subjects. These results were broadly similar to previous data in Caucasian subjects. Overall, ticagrelor was well tolerated in healthy Chinese subjects. Dose adjustments are not necessary in Chinese patients.

- Pharmacokinetics, pharmacodynamics, and tolerability of single and multiple doses of ticagrelor in Japanese and Caucasian volunteers (Teng and Butler 2014). Study no: D5130C05266 and D5130C05267

  Two studies assessing ticagrelor PK, PD, and tolerability in healthy Japanese and Caucasian volunteers. Single, ascending-dose (SAD) study: Japanese (n=20) and Caucasians (n=20) received single doses of ticagrelor (50, 100, 200, 300, 400 and 600 mg) or placebo. Multiple-ascending dose (MAD) study: Japanese (n=36) and Caucasians (n=36) received a single dose of 100 mg or 300 mg ticagrelor (Day 1), BID 100 mg or 300 mg ticagrelor, or placebo (Days 4 to 9), and single doses of 100 mg or 300 mg ticagrelor (Day 10). The results showed exposure to ticagrelor and its active metabolite, AR-C-124910XX, was generally higher in Japanese than in Caucasian subjects. In the SAD study, AUC values were 33% (ticagrelor) and 55% (AR-C124910XX) greater in Japanese vs Caucasians following 600 mg ticagrelor. In the MAD study, AUC values of ticagrelor and AR-C124910XX following multiple doses of ticagrelor 100 mg and 300 mg were statistically significantly greater (33% to 48 %) in Japanese vs Caucasians. In both groups, mean peak inhibition of platelet aggregation (IPA) was >86% after single doses of ≥100 mg ticagrelor and >84 % after multiple doses. Bleeding times were ≥60 minutes longer

in Japanese than in Caucasians with multiple dosing of 100 mg and 300 mg ticagrelor. Adverse events were similar between groups (mild to moderate intensity).

- **AstraZeneca comment:** The PK and tolerability of ticagrelor were broadly similar in Japanese and Caucasians, although exposure was slightly greater in Japanese volunteers. Ticagrelor was generally well tolerated. Dose adjustments are not necessary in Japanese patients.

9.1.3 Publications on interactions with ticagrelor

- Effect of the CYP3A inhibitors, diltiazem and ketoconazole, on ticagrelor pharmacokinetics in healthy volunteers (Teng and Butler 2013a). Study no: D5130C00022 and D5130C00040

- Effect of rifampicin on the pharmacokinetics and pharmacodynamics of ticagrelor in healthy subjects (Teng et al 2013c). Study no: D5130C00039

  - **AstraZeneca comment:** Ticagrelor is a CYP3A4 substrate and a mild inhibitor of CYP3A4. Therefore, concomitant administration of the strong inhibitor ketokonazole and the moderate inhibitor diltiazem was studied in this interaction study. Co-administration with ketoconazole increased the ticagrelor C_{max} and AUC by 2.4- and 7.3-fold, respectively. Co-administration with diltiazem significantly increased ticagrelor C_{max} and AUC by 69% and 174%, respectively. Co-administration with rifampicin decreased ticagrelor C_{max} and AUC by 73% and 86%, respectively, and half-life was reduced by 67%. In addition, although the maximum IPA was unaffected by co-administration with rifampicin, the loss of ticagrelor-mediated IPA was more rapid. Thus, the SmPC states that co-administration of ticagrelor with strong CYP3A4 inhibitors is contraindicated and may lead to a substantial increase in ticagrelor exposure. In addition, CYP3A4 inducers would be expected to decrease the exposure to ticagrelor and may result in reduced efficacy of ticagrelor.

- Pharmacokinetics interaction study of ticagrelor and cyclosporine in healthy volunteers (Teng et al 2014c). Study no. D5130C000074

  - **AstraZeneca comment**: Like ticagrelor, cyclosporine (a widely used immunosuppressant) is a substrate and a weak inhibitor of CYP3A4, and it is a potent inhibitor of P-glycoprotein and other drug transporters. This single-dose study in healthy volunteers demonstrated that co-administration of cyclosporine increased the exposure (AUC and C_{max}) of ticagrelor, and also increased the AUC and decreased C_{max} of AR-C124910XX. Ticagrelor had no effect on cyclosporine PK. A single ticagrelor dose of 180 mg was used in this study as this is the

recommended loading dose and the highest approved dose of ticagrelor. As both agents have anti-platelet activity, it is important to consider whether such increases in the presence of cyclosporine may affect the safety of ticagrelor. However, co-administration of ticagrelor and cyclosporine was generally well tolerated in the healthy male volunteers who participated in this study.

- The effect of ticagrelor on the metabolism of midazolam in healthy volunteers (Teng and Butler 2013b). Study no: D5130C00017

  - **AstraZeneca comment:** This study assessed the effects of ticagrelor on the PK of oral midazolam and oral versus intravenous midazolam. In addition, the effect of midazolam on ticagrelor PK parameters and the safety and tolerability of ticagrelor /midazolam co-administration were examined. Ticagrelor increased clearance of the model CYP3A substrate, midazolam, in these healthy subjects. Ticagrelor co-administration resulted in a significantly decreased exposure to midazolam and to its minor metabolite 4-OH midazolam (oral midazolam only), and decreased the 4-OH midazolam:midazolam ratio. These results are consistent with in vitro findings and suggest that ticagrelor acts as a weak activator and inhibitor of CYP3A activity. Overall, ticagrelor was well tolerated when administered alone or in combination with a single dose of midazolam.

- Pharmacokinetic interaction studies of co-administration of ticagrelor and atorvastatin or simvastatin in healthy volunteers (Teng et al 2013d). Study no: D5130C00024 and D5130C00025

  - **AstraZeneca comment:** Concomitant use of ticagrelor and statins may increase the C_{max} and AUC of these agents. The PK profiles of atorvastatin (80 mg) and simvastatin (80 mg) during co-administration of ticagrelor (270 mg LD followed by 90 mg BID in the simvastatin study for 7 days) were evaluated in two separate crossover studies. Co-administration increased atorvastatin C_{max} by 23% and AUC by 36%. These increases were considered to be modest and not clinically significant. The magnitude of the interaction between ticagrelor and simvastatin was greater, with the C_{max} and AUC of the statin increasing by 81% and 56%, respectively; plasma concentrations were unaffected. As such, concomitant use of ticagrelor with simvastatin or lovastatin at doses >40 mg is not recommended. Although the doses used in the studies were higher than the approved dose and those used in the PLATO study (180 mg LD, 90 mg BID MD), they are not thought to have influenced the observed PK interaction. However, the extent of the interaction effect on simvastatin could be lower with the usual clinical ticagrelor dose. It is also worth noting that more than 90% of ticagrelor

recipients in the PLATO study received concomitant statins with no safety concerns.

- Effect of ticagrelor on the pharmacokinetics of ethinyl oestradiol and levonorgestrel in healthy volunteers (Butler and Teng 2011a). Study no: D5130C00042

  - **AstraZeneca comment:** Most widely used oral contraceptives include a low-dose oestrogenic compound (eg, ethinylestradiol) combined with a synthetic progestogen (eg, levonorgestrel). As CYP isoenzymes, including CYP3A4, play a role in the oxidative metabolism of ethinylestradiol and hydroxylation of levonorestrogel, potential interactions with ticagrelor were evaluated in young healthy females. In this study 22 healthy female volunteers (on stable ethinyl oestradiol/levonorgestrel) received 90 mg ticagrelor or placebo BID with ethinyl oestradiol/levonorgestrel on cycle Days 1 to 21. The subjects crossed over treatment on Day 1/cycle 2. Pharmacokinetic parameters were evaluated on cycle Day 21, and endogenous hormones assayed on cycle days 1, 7, 14 and 21. Co-administration of ticagrelor had no significant effects on the PK of ethinylestradiol or levonorgestrel, meaning that no clinically relevant effect of ticagrelor on oral contraceptive efficacy or safety is expected.

- Evaluation of the pharmacokinetic interaction between ticagrelor and tolbutamide, a cytochrome P450 2C9 substrate, in healthy volunteers (Teng et al 2013b). Study no: D5130C00051

  - **AstraZeneca comment:** Although ticagrelor has been shown to be a moderate inhibitor of CYP2C9 in vitro, it is considered unlikely to alter CYP2C9-mediated metabolism of products such as warfarin and tolbutamide. This study in healthy volunteers demonstrated that no PK interactions were observed when ticagrelor was co-administered with tolbutamide, suggesting that ticagrelor is not a CYP2C9 inhibitor in vivo and, therefore unlikely to affect CYP2C9-mediated metabolism.

- Lack of clinically significant pharmacological interactions between ticagrelor and enoxaparin or unfractionated heparin in healthy subjects (Teng and Butler 2012). Study no: D5130C00006

  - **AstraZeneca comment:** As heparin and, to a lesser extent, enoxaparin are known to activate platelets, administration with an antiplatelet agent may lead to decreased clinical effectiveness. This study in healthy subjects found that co-administration of ticagrelor with heparin or enoxaparin did not cause any notable changes in the PK of ticagrelor or AR-C124910, or any clinically relevant impact on IPA conferred by

ticagrelor. Importantly, ticagrelor had no clinically relevant effect on the anticoagulant effects of heparin or enoxaparin.

- A pharmacokinetic interaction study of ticagrelor and digoxin in healthy volunteers (Teng and Butler 2013c). Study no: D5130C05265

  - **AstraZeneca Comment**: Ticagrelor is a P-gp substrate and a weak P-gp inhibitor. Concomitant use of ticagrelor and digoxin had no impact on ticagrelor exposure and led to an increased exposure to digoxin (C_{max} and AUC increased by 75% and 28 %, respectively). In the SmPC, appropriate clinical and/or laboratory monitoring is recommended when giving ticagrelor with narrow therapeutic index P-gp-dependent medicinal products such as digoxin. Although no data are currently available, concomitant use of ticagrelor with potent P-gp inhibitors (eg, verapamil and quinidine) may lead to increased exposure to ticagrelor and caution is therefore advised.

- Evaluation of the pharmacokinetic interaction between ticagrelor and venlafaxine, a cytochrome P-450 2D6 substrate, in healthy subjects (Teng et al 2014a). Study no: D5130C00073

  - **AstraZeneca comment**: This study showed that ticagrelor had no clinically relevant effect on CYP2D6-mediated metabolism of venlafaxine. The lack of effect of ticagrelor on the PK of venlafaxine seen in this study contrasts with in vitro evidence suggesting that ticagrelor is an inhibitor of CYP2D6. Thus, the inhibitor effects of ticagrelor on this enzyme are not of sufficient magnitude to be clinically relevant.

- The effect of desmopressin on bleeding time and platelet aggregation in healthy volunteers administered ticagrelor (Teng et al 2014b). Study no: D5130C00026

  - **AstraZeneca Comment**: This study investigated the effect of the vasopressin agonist desmopressin on ticagrelor-induced bleeding time prolongation. Desmopressin has previously been shown to improve primary haemostasis and is widely used as first-line therapy for individuals with bleeding disorders. In this randomised, double-blind, 2-period crossover study, healthy volunteers received ticagrelor (270 mg LD; 180 mg BID) for 5 days. On Day 5, desmopressin (0.3 µg/kg) or saline intravenous infusion were administered. Desmopressin had no significant effect on bleeding time or inhibition of platelet aggregation by ticagrelor, although primary haemostatic activity was significantly increased. Ticagrelor PK parameters were not affected by co-administration with desmopressin. Therefore, desmopressin is unlikely to be an effective therapeutic agent for control of the potential bleeding

events associated with ticagrelor. Co-administration of ticagrelor and desmopressin was generally well tolerated, and the AE profile of ticagrelor was consistent with that observed in other studies.

- Lack of significant food effect on the pharmacokinetics of ticagrelor in healthy volunteers (Teng et al 2012a). Study no: D5130C00033

  - **AstraZeneca comment**: Ingestion of a high-fat meal had no significant effects on the C_{max} of ticagrelor or the AUC of AR-C124910XX in healthy subjects. However, the AUC of ticagrelor was increased by 21% and the C_{max} of AR-C124910XX was decreased by 22% compared with the fasted state. These changes were considered to be of minimal clinical relevance and were similar to data from another study. As such, there are no restrictions regarding the administration of ticagrelor relative to food intake.

- Evaluation of the pharmacokinetics and pharmacodynamics of ticagrelor co-administered with aspirin in healthy volunteers (Teng et al 2013a). Study no: D5130C00005 and D5130C05261

  - **AstraZeneca comment:** These 2 studies in healthy volunteers were conducted early in the development program to explore the potential effects of aspirin on the PK and PD of ticagrelor. Two aspirin doses were assessed: 75 mg OD, (the effective dose range for thrombotic event reduction) and 300 mg OD (close to the 325 mg OD commonly used in the US). The primary objectives were to evaluate ticagrelor PK with and without aspirin, and to compare IPA with ticagrelor plus aspirin vs clopidogrel plus aspirin. Aspirin is not associated with a PK or PD (IPA) effect on ticagrelor. However, aspirin and ticagrelor had an additive effect on IPA. Ticagrelor/aspirin co-administration was well tolerated at all dose combinations.

9.1.4 Publications on adenosine response and pulmonary function

- Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans (Wittfeldt et al 2013). Study no: D5130C00067

  The objective of this study was to determine if ticagrelor augments adenosine-induced coronary blood flow and the sensation of dyspnoea in human subjects. In this double-blind, placebo-controlled study, 40 healthy male subjects were randomised to receive a single dose of ticagrelor (180 mg) or placebo in a crossover fashion. Coronary blood flow velocity (CBFV) was measured by using transthoracic Doppler echocardiography at rest after multiple stepwise adenosine infusions given before and after study drug, and again after the infusion of theophylline. Compared with placebo, ticagrelor significantly increased the AUC of CBFV versus the adenosine dose (p=0.008). There was a significant correlation

between ticagrelor plasma concentrations and increases in the AUC ($p<0.001$). In both treatment groups, the adenosine-induced increase in CBFV was significantly attenuated by theophylline, with no significant differences between subjects receiving ticagrelor or placebo ($p=0.39$). Furthermore, ticagrelor significantly enhanced the sensation of dyspnoea during adenosine infusion, and the effects were diminished by theophylline.

- **AstraZeneca comment**: Ticagrelor enhanced adenosine-induced CBFV and the sensation of dyspnoea in these healthy male subjects via an adenosine-mediated mechanism. This is consistent with the proposed mechanism of action that ticagrelor inhibits cellular uptake of adenosine, in addition to antagonizing the $P2Y_{12}$ receptor.

- Effect of ticagrelor on pulmonary function in healthy elderly volunteers and asthma or chronic obstructive pulmonary disease patients (Butler et al 2013). Study no: D5130C00028 and D5130C00034

In these studies the objective was to determine the effect of ticagrelor on pulmonary function in healthy elderly volunteers and patients with asthma or chronic obstructive pulmonary disease (COPD). Resting pulmonary function parameters, including respiratory rate, minute ventilation, and tidal volume were similar between ticagrelor and placebo in any cohort. Furthermore, bronchospasm (as determined by spirometry and pulse oximetry) was not observed with either ticagrelor or placebo in any cohort. Perception of breathing was generally similar following ticagrelor or placebo. Exercise performance was not affected, and no clinically relevant differences were seen in pulmonary parameters during exercise for ticagrelor or placebo. There was no apparent relationship between plasma concentrations of ticagrelor and its main metabolite and pulmonary function.

- **AstraZeneca comment**: Short-term administration of high doses of ticagrelor did not appear to alter pulmonary function at rest and during exercise in healthy elderly subjects or patients with respiratory impairment (mild-to-moderate COPD). Study limitations include the use of relatively few subjects without documented coronary artery disease. Ticagrelor was generally well tolerated in all cohorts.

9.1.5 Additional studies in healthy subjects

- Grapefruit juice markedly increases the plasma concentrations and antiplatelet effects of ticagrelor in healthy subjects (Holmberg et al 2013).

This randomised, crossover study examined the effects of grapefruit juice on ticagrelor PK. Ten healthy volunteers ingested 200 mL of grapefruit juice or water 3 times daily for 4 days. On Day 3, the volunteers ingested a single 90 mg dose of ticagrelor. Grapefruit juice increased ticagrelor geometric mean C_{max} to 165% (95% CI: 147%-184%) and $AUC_{0\text{-}8h}$ to 221% of control (95% CI: 200%-245%).

The C_{max} and AUC_{0-34h}, but not the AUC_{0-8h}, of the active metabolite C12490XX were decreased significantly ($p<0.05$). Grapefruit juice had a minor effect on ticagrelor elimination half-life prolonging it from 6.7 to 7.2 hours ($p=0.036$). In good correlation with the elevated plasma ticagrelor concentrations, grapefruit juice enhanced the antiplatelet effect of ticagrelor, assessed with the VerifyNow® and Multiplate® methods, and postponed the recovery of platelet reactivity. Grapefruit juice increased ticagrelor exposure by more than 2-fold, leading to an enhanced and prolonged ticagrelor antiplatelet effect. No signs of bleeding were observed in any of the subjects. The authors concluded that the grapefruit juice-ticagrelor interaction seems to be clinically important and indicates the significance of intestinal metabolism on ticagrelor PK.

– **AstraZeneca comment**: The increase in C_{max} and AUC described with concomitant use of 600 mL multiple daily glasses of grapefruit juice for 3 days prior to ticagrelor dosing is similar to what has been seen in the study with a moderate CYP3A4 inhibitor (ie, diltiazem). As the magnitude of exposure increases caused by diltiazem is not considered clinically relevant, and the pattern of grapefruit juice consumption is atypical, it is unlikely that concomitant use of grapefruit juice with ticagrelor will be of clinical relevance.

9.2 Publications from the PLATO study

The first results from the PLATelet inhibition and patient Outcomes (PLATO; study no: D5130C05262) trial were published in 2009 (Wallentin et al 2009). During this reporting period, the PLATO study group has presented and published a long series of predefined and post-hoc analyses to further explore and better understand the effects of ticagrelor. The results have been very consistent with similar results seen in patients with STEMI or non-ST-segment elevation (NSTE)-ACS (Lindholm et al 2014, Steg et al 2010), patients intended to undergo invasive or non-invasive treatment (Cannon et al 2010, James SK et al 2011), patients with or without diabetes mellitus (James S et al 2010a), patients with or without renal dysfunction (James S et al 2010b), elderly or younger patients (Husted et al 2012), male and female patients (Husted et al 2014), non-smokers or smokers (Cornel et al 2012), patients with or without pulmonary disease (Storey et al 2011).

Stent thrombosis, with both bare-metal and drug eluting stents, was reduced with ticagrelor compared with both higher and lower clopidogrel loading doses (Steg et al 2013). The reduction in mortality was shown to be the result of a combination of fewer CV events and fewer bleeding and infection-related deaths (Held et al 2011, Varenhorst et al 2014). The reduction in CV events was consistent both in patients with and without CYP2C19 loss-of-function polymorphism (Wallentin et al 2010). The geographic heterogeneity of effect appeared to be attenuated with a lack of superiority of ticagrelor in North America, which could be explained by chance alone or an interaction with the use of a high dose of aspirin in about half of the patients in North America. This is in accordance with a similar reduction of

efficacy observed in the very small proportion of patients on a high dose of aspirin in the rest of the world (James SK et al 2013, Mahaffey et al 2011). The reduction in event rate with ticagrelor treatment has also been shown to be consistent over time with a reduction in not only the first event but also in the total number of events over the entire treatment period (Kohli et al 2013).

In addition to the findings described above, manuscripts based on the following have been published: results from the ECG sub-study (Armstrong et al 2012, Armstrong et al 2013), Q waves as a prognostic marker (Siha et al 2012), incidence of bradyarrhythmias (Siha et al 2012), the platelet function sub-study (Storey et al 2010), bleeding complications (Becker et al 2011), cystatin C as a biomarker (Akerblom et al 2012a, Akerblom et al 2012b, Akerblom et al 2013, Akerblom et al 2014), factors contributing to the lower mortality with ticagrelor compared with clopidogrel in patients undergoing coronary artery bypass surgery (Varenhorst et al 2012), angiographic outcomes (Kunadian et al 2013), outcomes of patients with prior coronary artery bypass graft surgery (Brilakis et al 2013), biomarkers in relation to the effects of ticagrelor (Wallentin et al 2014), extent of coronary artery disease and outcomes (Kotsia et al 2014), major bleeding and its assosciation to spontaneous procedure-related bleeding (Ducrocq et al 2014), and CV events in ACS patients with peripheral artery disease (Patel et al 2014).

– **AstraZeneca comment**: The PLATO trial has generated more than 40 manuscripts published in peer-reviewed journals. The results of subanalyses are consistent with the main study results and benefits in terms of mortality, MI, and net clinical benefit of ticagrelor compared with clopidogrel have been consistently reported.

9.3 Additional publications of interest

- Ticagrelor in clopidogrel-resistant patients undergoing maintenance haemodialysis subjects (Alexopoulos et al 2012).

This letter-to-the-editor states that patients with chronic kidney disease, particularly those receiving haemodialysis, frequently are poor responders to clopidogrel (ie, have high on-treatment platelet reactivity). A prospective 2-centre study is described in which consecutive patients receiving regular maintenance (>6 months) haemodialysis and ongoing (≥2 months) treatment with clopidogrel 75 mg daily were approached for platelet reactivity assessment. Patients with high on-treatment platelet reactivity were prescribed ticagrelor 90 mg BID for 15 days, when platelet reactivity was assessed. Baseline platelet reactivity in the analysed patients was 310.4±52.9 platelet reactivity units, and decreased to 137.7±77.9 platelet reactivity units after ticagrelor treatment ($p < 0.001$). Ticagrelor effectively reduced platelet reactivity to a level that (in studies of patients after PCI) has been shown to be associated with fewer ischaemic events. Drug tolerability was good, with few AEs reported. The authors concluded that the ticagrelor maintenance dose effectively

reduces platelet reactivity in haemodialysis patients who are clopidogrel poor responders. Whether this finding translates into clinical benefit needs further study.

- **AstraZeneca comment**: No dose adjustment is currently recommended for patients with renal impairment; however, no information was previously available on the treatment of patients on renal dialysis. This small study in haemodialysis patients who were clopidogrel poor responders demonstrates that ticagrelor effectively reduced platelet activity, with few AEs, suggesting a potential clinical benefit in this population. However, further investigation is required.

- Potential role of endogenous adenosine in ticagrelor-induced dyspnea (Belchikov et al 2013).

Ticagrelor, a platelet antagonist indicated for the reduction of thrombotic CV events in patients with ACS, has been reported to cause dyspnoea in more than 13% of patients. Dyspnoea is not a clinically relevant AE with other medications indicated for ACS. One suggested mechanism of ticagrelor-induced dyspnoea involves an increase in systemic adenosine concentrations through adenosine deaminase inhibition. Dyspnoea, a subjective finding resulting from physiologic and sensory mechanisms, may be a consequence of increased systemic adenosine concentrations, leading to amplified and prolonged receptor activity. Current literature suggests, however, that pulmonary status is not compromised, with no reduction of efficacy seen in patients with ticagrelor-induced dyspnoea, thus allowing clinicians to continue therapy without reservation. However, patients with a history of asthma or COPD may be more susceptible to ticagrelor-induced dyspnoea, potentially leading to nonadherence and exacerbations of morbidity.

- **AstraZeneca comment**: Ticagrelor-induced dyspnoea may predispose patients to unwanted AEs and deleterious atherothrombotic consequences. Therefore, it is paramount that health care providers continually monitor these patients with the aims of maintaining medication therapy adherence and providing relevant options if dyspnoea becomes intolerable.

- A case of pulmonary hemorrhage due to drug-induced pneumonitis secondary to ticagrelor therapy (Whitmore et al 2014).

A [redacted] man was admitted following his second presentation with 100 to 200 mL of haemoptysis over a 48-hour period. Ticagrelor 90 mg BID and aspirin 100 mg daily had been commenced 10 days previously following stenting of his proximal segment of the dominant left circumflex coronary artery. The patient had no shortness of breath, chest pain, fever, or infection symptoms. He had no other bleeding history. His other medications were diltiazem, rosuvastatin, fluticasone, and salmeterol inhaler. He was an ex-smoker but had no other significant exposure

history. On examination, the patient was afebrile and resting comfortably. His pulse rate was 80 beats/min; blood pressure, 132/91 mm Hg; respiratory rate, 24 breaths/min; and oxygen saturation level, 90% on room air. He had coarse crackles bilaterally throughout his lower lung fields. He had no mucosal ulceration, conjunctival pallor, or melena on rectal examination. The following laboratory findings were all normal: haemoglobin level, 137 g/L; white blood cell count, 9.07 x 10^9/L; platelet count, 392 x 10^9/L; C-reactive protein level, 1.0 mg/L; coagulation indicators (international normalized ratio, 1.1; activated partial thromboplastin time, 27.8 s; fibrinogen level, 4.3 g/L); and indicators of renal and hepatic function. Urinalysis showed no blood or protein, and vasculitis screen results (levels of antineutrophil cytoplasmic antibody, antinuclear antibody, antiglomerular basement membrane antibodies, and complement) were normal. Computed tomography imaging of the chest demonstrated bilateral ground-glass opacities consistent with peribronchovascular pulmonary haemorrhages. Diffusing capacity was elevated, consistent with fresh haemorrhage. Ticagrelor therapy was temporarily stopped, and the patient proceeded to bronchoscopy 1 day after admission, which demonstrated oedematous airways and frank blood within both lower lobes. Transbronchial biopsy was not undertaken secondary to ongoing bleeding. Bronchoalveolar lavage demonstrated frank blood with no pathogens identified. Haemoptysis recurred with recommencement of ticagrelor. The patient's treatment was changed to clopidogrel given the high risk of in-stent thrombosis, but he had ongoing haemoptysis. Twenty-five days after initially starting ticagrelor, he proceeded to undergo open lung biopsy and elective coronary artery bypass grafting (saphenous vein to obtuse marginal artery) to allow safe cessation of clopidogrel. A typical histologic section, with wedge-shaped lesions in the lung tissue with intervening areas of preserved architecture. Within the areas of lung injury, the alveolar septal walls show variable fibrous thickening and contain a very mild, chronic inflammatory-cell infiltrate. There was no tissue eosinophilia, and dense collections of intra-alveolar macrophages were not seen. There was both early and established fibrosis, as well as patchy bronchiolisation of the airways. While there was some congestion of the vasculature, no intra-alveolar haemorrhage was seen, and there was no evidence of vasculitis. Although nonspecific, in the clinical context, the pathology was most in keeping with drug-induced lung injury. Following this, the patient's haemoptysis ceased, and he was discharged on aspirin monotherapy. Six weeks postoperatively, he had experienced no further haemoptysis, and imaging of his chest was repeated and showed marked improvement.
The author states that the mechanism by which ticagrelor induced lung injury in this patient is unclear and that it has been hypothesized that the reversible nature of platelet inhibition with ticagrelor could lead to sequestration of overloaded, exhausted platelets in the pulmonary circulation, with subsequent disruption of endothelial function. However, this hypothesis remains unproven.

– **AstraZeneca comment:** This case is registered in the AstraZeneca global safety database (case ID 2013SE14448). Drug-induced pulmonary

pneumonitis is a very rare medical condition and there is no identified correlation between pulmonary pneumonitis and pulmonary haemorrhage which makes it difficult to assess the causality in this case report. A review of reports on pneumonitis including alveolits and interstitial pneumonitis in the AstraZeneca safety database could not identify a correlation between the reported event and ticagrelor. The cases are either confounded by concurrent disease, concomitant medication, or contain too limited information for a proper assessment. The topic will be surveilled during routine safety pharmacovigilance.

- Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance (Cattaneo et al 2014).

This review describes the evidence for the adenosine-mediated effects of ticagrelor and their potential clinical relevance. Data show that ticagrelor increases the half-life and plasma concentration of adenosine, thereby enhancing its physiological effects. Several studies provide evidence that ticagrelor inhibits cellular uptake of adenosine. Ticagrelor inhibited adenosine uptake by washed human erythrocytes under sodium-free conditions and using cell-lines that express ENT-1 but not ENT-2. Thus, it is assumed that ticagrelor inhibits sodium-independent ENT-1. Importantly, it has been demonstrated that ticagrelor does not display relevant direct activity on adenosine receptors nor is it metabolised to adenosine. Adenosine is formed locally at sites of hypoxia and tissue damage and is rapidly internalised by cells through ENT-1. As adenosine degradation is mostly restricted to the intercellular space, inhibition of cellular uptake of adenosine via ENT-1 effectively prolongs the half-life of adenosine, thereby increasing its extracellular concentration. As a consequence, inhibition by ticagrelor results in enhanced response to adenosine, mediated by interaction with adenosine receptors.

  - **AstraZeneca comment:** Several studies have consistently shown that ticagrelor inhibits the cellular uptake of adenosine, in addition to antagonizing the $P2Y_{12}$ ADP receptor. This effect of ticagrelor is sufficient to increase the circulating levels of adenosine in patients. The reduction of irreversible myocardial injury following ischaemia/reperfusion in animals, the reduction in total mortality in ACS patients and adverse effects like dyspnoea are all compatible with an adenosine-mediated effect of ticagrelor.

- Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome (Bonello et al 2014).

Sixty ACS patients were prospectively randomised to ticagrelor or clopidogrel. To assess the mechanism of adenosine plasma concentration variation, the following were measured: adenosine deaminase concentration, adenosine uptake by red-blood cells and cAMP production by cells over expressing adenosine receptors. $P2Y_{12}$

ADP receptor blockade was assessed by the vasodilator-stimulated phosphoprotein (VASP) index. The results showed that patients receiving ticagrelor had significantly higher adenosine plasma concentrations than those on clopidogrel. Adenosine plasma concentration was not correlated with VASP. Serum containing ticagrelor inhibited adenosine uptake by red blood cells compared with clopidogrel or controls. Adenosine deaminase activity was similar in serum of patients receiving clopidogrel or ticagrelor. Ticagrelor and clopidogrel had no impact on adenosine receptors.

– **AstraZeneca comment:** Ticagrelor increases adenosine plasma concentrations in ACS patients compared with clopidogrel, supporting the notion that ticagrelor has a dual mode of action that includes increasing extracelluar adenosine levels in patients.

- Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: The rapid activity of platelet inhibitor drugs (RAPID) primary PCI 2 study (Parodi et al 2014).

This study was conducted to evaluate whether an increased ticagrelor LD results in faster and more effective platelet inhibition compared with the standard prasugrel LD. Fifty patients with STEMI, pre-treated with IV aspirin, undergoing primary PCI were randomised to receive prasugrel 60 mg LD or ticagrelor 360 mg LD. Residual platelet activity was assessed by VerifyNow at baseline and 1, 2, 4, and 12 hours after the LD. An increased oral ticagrelor LD failed to achieve a faster and more intense platelet inhibition 1 hour after administration compared with the standard prasugrel LD. In patients with STEMI undergoing primary PCI, double (360 mg) ticagrelor LD did not result in significant adverse effects.

– **AstraZeneca comment:** A double dose of ticagrelor did not show faster or more intense platelet inhibition than the prasugrel recommended LD, nor did it result in a significant increase in AEs. The recommended ticagrelor LD for ACS patients is 180 mg, and these data do not suggest any value with a higher LD.

- Effects of ex vivo platelet supplementation on platelet aggregability in blood samples from patients (Hansson et al 2014a).

Platelet transfusion may be used to reduce bleeding in patients on dual antiplatelet therapy (DAPT), but little is known about its value with different antiplatelet agents. The effects of ex vivo platelet supplementation on platelet aggregation were monitored in CAD patients taking platelet inhibitors. Platelet supplementation improved platelet aggregability independent of antiplatelet therapy. Arachidonic acid induced aggregation, which is used to monitor antiplatelet effects of ASA, was completely restored, while recovery of ADP-dependent aggregation, used to monitor the antiplatelet effects of the $P2Y_{12}$ ADP antagonists, was limited ex vivo.

Arachidonic acid and ADP-dependent recovery was reduced in ticagrelor-treated patients 2 hours after last drug intake compared with clopidogrel-treated patients.

- Reversal strategy in antagonizing the $P2Y_{12}$-inhibitor ticagrelor (Hobl et al 2013).

  Reversal of antiplatelet drug effects is an important issue in trauma and emergency departments. In this study, an ex vivo model to reverse the effects of the novel and highly effective $P2Y_{12}$-inhibitor ticagrelor was tested in 20 healthy volunteers. To normalize platelet reactivity, increasing amounts of autologous platelet-rich plasma was added to whole blood, which was obtained 3 hours after the intake of 180 mg of ticagrelor. Platelet aggregation was assessed by whole blood multiple electrode aggregometry, which is based on impedance aggregometry. The basal ADP-induced platelet aggregation averaged 71±16 U (Units). Ticagrelor decreased ADP-induced platelet aggregation to 16±8 U. A clear dose-response was obtained after spiking whole blood with increasing amounts of platelet-rich plasma. It is estimated that ≥2 units of apheresis platelet concentrates will be necessary to completely restore baseline platelet aggregation in the majority of patients after ticagrelor.

  - **AstraZeneca comment:** The current ticagrelor SmPC states that there are no data regarding a haemostatic benefit of platelet transfusions, although these results indicate that platelet transfusion may improve platelet function in patients treated with ticagrelor.

- High rates of prasugrel and ticagrelor non-responders in patients treated with therapeutic hypothermia after cardiac arrest (Ibrahim et al 2014).

  After cardiac arrest due to ACS, therapeutic hypothermia is the standard care to reduce neurological damage. A total of 164 patients with ACS were prospectively enrolled in this study. Of these patients, 84 were treated with hypothermia and 80 were under normothermia. All patients were on DAPT. Patients treated with therapeutic hypothermia after cardiac arrest show deteriorated response to $P2Y_{12}$ receptor inhibitors as determined by PRI/VASP-index 24 hours after administration of the loading dose of clopidogrel, prasugrel or ticagrelor. This effect was most marked with the use of clopidogrel. Prasugrel and ticagrelor improved platelet inhibition in hypothermia, but did not completely prevent no-responsiveness.

  - **AstraZeneca comment:** These are limited data primarily looking at inhibition of platelet function, and it is difficult to draw firm conclusions on the clinical impact. However, the data suggests that ticagrelor may be a better alternative to clopidogrel also in patients treated with therapeutic hypothermia after cardiac arrest.

- Coronary artery bypass grafting-related bleeding complications in real-life acute coronary syndrome patients treated with clopidogrel or ticagrelor (Hansson et al

2014b).

The objective of this prospective, observational study was to determine the prevalence of major CABG-related bleeding complications in patients with ACS treated with ticagrelor or clopidogrel in a real-life setting. A total of 405 consecutive CABG patients with ACS were treated with aspirin and ticagrelor (n=173) or aspirin and clopidogrel (n=232). Ticagrelor/clopidogrel was discontinued 5 days before surgery whenever deemed possible. There was no difference in major bleeding complications overall or when ticagrelor or clopidogrel was used in accordance with guidelines. In patients on DAPT up to 1 day before surgery, there tended to be more bleeding complications in ticagrelor-treated patients.

- **AstraZeneca comment:** The present data suggest that ticagrelor and clopidogrel have similar CABG bleeding patterns when discontinued at least 1 day before surgery. Ticagrelor may have a faster offset than clopidogrel and mean IPA for ticagrelor at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The SmPC states that ticagrelor should be discontinued 7 days prior to surgery if an antiplatelet effect is not desired.

- First Report of hypersensitivity to ticagrelor (Quinn and Connelly 2014).

A previously healthy [redacted] gentleman with no known allergies developed a diffuse generalised pruritic, exanthematous rash over 24 hours. Five days before, he had suffered a NSTEMI. His treatment included primary PCI with drug-eluting stents and he was started on ticagrelor, aspirin, simvastatin, bisoprolol, and ramipril. The temporal relationship, along with a skin biopsy, which revealed perivascular dermatitis with a lymphocytic infiltrate, was consistent with a delayed (type IV) hypersensitivity reaction to a similar $P2Y_{12}$ inhibitor, clopidogrel. He was treated with a 3-week, tapering dose of 30 mg prednisone. Ticagrelor was immediately switched to clopidogrel for ongoing antiplatelet therapy to prevent stent thrombosis, and his other cardiac medications were reinstituted 3 days after admission to the hospital. He has had no recurrence of his symptoms despite completion of his prednisone taper. Drug-related rash is reported for nearly all prescription medications, with an estimated incidence of 10 cases per 1000 new users. The clinical spectrum ranges from simple drug reactions consisting primarily of cutaneous hypersensitivity, to complex drug reactions, including Steven-Johnson syndrome, drug reaction with systemic symptoms, toxic epidural necrolysis, and acute generalized exanthematous pustulosis. This report describes what is believed to be the first reported case of ticagrelor hypersensitivity manifesting as a simple drug reaction. The putative mechanism for drug reactions involves haptens, composed of the drug or its metabolites, which are presented by antigen-presenting cells to naive T cells.

- **AstraZeneca comment**: Hypersensitivity and rash are listed adverse drug reactions (ADRs) for ticagrelor and reviewed during routine pharmacovigilance. Several drugs, including ASA, were started simultaneously and there is no information on ticagrelor rechallenge available, which precludes causality assessment.

- A randomised trial of the pharmacodynamic and pharmacokinetic effects of ticagrelor compared with clopidogrel in Hispanic patients with stable coronary artery disease (Price et al 2014).

  The objective of this study was to compare the PD and PK effects of ticagrelor with clopidogrel among subjects of Hispanic ethnicity, as the PD and PK effects of antiplatelet agents among Hispanics are not specifically known. This was a randomised, open-label, crossover PD/PK study in 40 Hispanic subjects with stable CAD. Subjects were allocated to either ticagrelor 180 mg LD/90 mg BID MD followed by clopidogrel 600 mg LD/75 mg OD MD with an intervening washout period, or vice versa. The primary endpoint was on-treatment reactivity at 2 hours post-LD according to the VerifyNow $P2Y_{12}$ test. On-treatment reactivity was significantly lower at 2 hours post-LD with ticagrelor compared with clopidogrel ($p<0.001$). On-treatment reactivity was also lower with ticagrelor at 30 minutes and 8 hours post-LD ($p<0.001$). The greater magnitude of antiplatelet effect with ticagrelor persisted after 7 days of MD ($p<0.001$). Mean plasma concentration of ticagrelor and its active metabolite were greatest at 2 hours post-LD, with similar levels at 2 hours post-MD after 7 days of MD. Among Hispanic subjects with stable CAD, ticagrelor provided a more rapid onset of platelet inhibition and a significantly greater antiplatelet effect compared with clopidogrel during both the loading and maintenance phases of treatment.

  - **AstraZeneca comment:** The study referred to in the publication is the AstraZeneca-sponsored study D5130L00012. Racial and ethnic disparities in CV care are important public health care issues in the US. This study shows consistent PD effects with previous studies. Ticagrelor was generally well tolerated.

- Real world experience with ticagrelor in central Canada (Dehghani et al 2014).

  The Saskatchewan Registry is a prospective, observational, multicentre cohort study that identifies consecutive patients started on ticagrelor within the Regina Qu'Appelle Health Region (1 PCI and 9 non-PCI facilities). The aim was to evaluate both on- and off-label use, identify characteristics of patients who prematurely stop ticagrelor, and describe patient/physician behaviour contributing to inappropriate stoppage of this medication. From April 2012 to September 2013, 227 patients were initiated on ticagrelor, with a mean age of 62.2±12.1 years. The participants were 66% men and had a mean follow-up of 157.4±111.7 days. Seventy-four patients (32.4%) had off-label indications. Forty-seven patients

(20.7%) prematurely stopped ticagrelor and were likely to be older, women, non-white, present with shock, and complain of dyspnoea. Twenty-six of the 47 patients stopped ticagrelor inappropriately because of patient non-adherence (18 patients) and physician advice (8 patients). A composite outcome event of death from vascular causes, MI, or stroke occurred in 8.8% of the entire cohort and was more likely to occur in patients older than 65 years, those presenting with cardiogenic shock, and those who prematurely stopped ticagrelor. In conclusion, in this real–world registry of patients started on ticagrelor, a third have off-label indications and a fifth prematurely stop the medication. Premature discontinuation was an independent predictor of major life-threatening bleeding and increased composite event rate of death from vascular causes, MI, or stroke.

- **AstraZeneca comment:** The numbers of patients are few and the duration of the study is relatively short and there is no comparative group. These are limitations, which makes it difficult to assess the results. PLATO inclusion and exclusion criteria were used to assess the appropriate use of ticagrelor. The publication contains no information regarding what off-label use was not defined by the approved label. There is no information on which PLATO inclusion/exclusion criteria the patients did not meet.

- Prehospital ticagrelor in ST-segment elevation myocardial infarction (Montalescot et al 2014).

This was an international, multicentre, randomised, double-blind study involving 1862 patients with ongoing STEMI of less than 6 hours' duration, comparing pre-hospital (in the ambulance) versus in-hospital (in the catheterisation laboratory) treatment with ticagrelor. The co-primary end points were the proportion of patients who did not have a 70% or greater resolution of ST-segment elevation before PCI and the proportion of patients who did not have TIMI flow grade 3 in the infarct-related artery at initial angiography. Secondary endpoints included the rates of major adverse CV events and definite stent thrombosis at 30 days. The median time from randomisation to angiography was 48 minutes, and the median time difference between the 2 treatment strategies was 31 minutes. The 2 co-primary endpoints did not differ significantly between the pre-hospital and in-hospital groups. The absence of ST-segment elevation resolution of 70% or greater after PCI (as a secondary endpoint) was reported for 42.5% and 47.5% of patients, respectively. The rates of major adverse CV did not differ significantly between the 2 study groups. The rates of definite stent thrombosis were lower in the pre-hospital group than in the in-hospital group (0% vs. 0.8% in the first 24 hours; 0.2 % vs 1.2% at 30 days). Rates of major bleeding events were low and virtually identical in the two groups, regardless of the bleeding definition used. Thus, pre-hospital administration of ticagrelor in patients with acute STEMI appeared to be safe but did not improve pre-PCI coronary reperfusion.

- **AstraZeneca comment:** This is the publication of the recently completed study D5130L00006 (ATLANTIC). The study was not powered to look at outcomes, but there was no difference with regard to the pre-specified composite of death, MI, stroke, urgent revascularisation or definite acute stent thrombosis at 30 days. The result of the ATLANTIC study has not changed the benefit-risk balance for ticagrelor treatment in patients with ACS.

- Potential additive effects of ticagrelor, ivabradine, and carvedilol on sinus node (Di Serafino et al 2014).

A [redacted] male patient presented to the emergency room with an anterior STEMI. After a LD of both ticagrelor and aspirin, the patient underwent primary PCI. After successful revascularisation, medical therapy included beta-blockers, statins, and angiotensin II receptor antagonists. Two days later, ivabradine was also administered in order to reduce heart rate to target, but the patient developed a severe symptomatic bradycardia and sinus arrest, requiring administration of both atropine and adrenaline. Ivabradine and ticagrelor were suspended and ticagrelor was changed to prasugrel. No other similar event was reported during the following days.

- **AstraZeneca comment:** Bradyarrhythmia is kept under close surveillance. In the SmPC, caution is advised for patients at risk for bradyarrhythmia including those with sick sinus syndrome. In this case, the concomitant bradygenic medications, carvedilol and ivabradine, increased the risk for bradycardia thus, precluding a causality assessment.

- Perioperative outcomes of cardiac surgery patients with ongoing ticagrelor therapy: boon and bane of a new drug (Schotola et al 2014).

Ticagrelor and clopidogrel are used in patients with ACS and patients undergoing PCI. Ticagrelor has a quicker offset of action, and therefore, it seems that platelet function recovers faster on discontinuation of therapy. Antiplatelet drugs sometimes cannot be stopped before CABG because of the risk of stent thrombosis or in case of emergency operations. Therefore, the authors investigated how the continued preoperative use of ticagrelor influences the perioperative course of cardiac surgical patients. In total, 235 CABG patients were treated with DAPT (ASA and ticagrelor or ASA and clopidogrel) before cardiac surgery. A total of 81 patients, were included in the study who received either ticagrelor or clopidogrel with ASA, and for whom DAPT could not be discontinued before surgery due to clearly increased risk of stent thrombosis and deadly reinfarction. Preoperative data and intraoperative characteristics were similar among the groups. In the first 24 hours, the median blood loss was 850 (range 780 to 1600) mL in the ticagrelor group and 680 (400 to 860) mL in the clopidogrel group. Furthermore, the median red blood cell transfusion, the median pooled platelet transfusion, the median

prothrombin complex concentrate use and the median fibrinogen use were significantly higher in the ticagrelor group compared with the clopidogrel group. However, there was no statistical significance between the 2 groups regarding intensive care unit and hospital stay, mechanical ventilation time, incidence of acute kidney injury and mortality. Hence, a tendency towards more rethoracotomies due to bleeding in the ticagrelor group was observed.

– **AstraZeneca comment:** In this retrospective, observational analysis with a small sample size, cardiac surgery patients who were treated with ticagrelor until surgery had a higher blood loss, higher requirement of blood products and coagulation factors, and higher incidence of rethoracotomies. In the PLATO trial, ticagrelor treatment was recommended to be withheld for 1 to 3 days before CABG, in contrast to clopidogrel, which was recommended to be withheld for 5 days in advance. The SmPC states that ticagrelor should be discontinued 7 days prior to surgery if an antiplatelet effect is not desired.

10. LATE-BREAKING INFORMATION

Following the data lock for this Addendum, the PEGASUS (D5132C00001, see Section 8.2.1 for further details) study results read out in January 2015. The results of the PEGASUS study are still under evaluation, but AstraZeneca concludes that the benefit-risk balance associated with ticagrelor treatment in patients with ACS has not changed. The final study report is expected by the first quarter of 2015, and it will be included in a subsequent regulatory submission.

11. RISK EVALUATION

11.1 Summary of safety concerns

At the beginning of the reporting period, the ticagrelor safety specification (presented in the EU Risk Management Plan [RMP] version 4, dated 22 September 2010) included the following important identified and important potential risks, and missing information:

Important identified risks

- Increased risk of bleeding
- Dyspnoea
- Bradyarrhythmias (including Holter-detected ventricular pauses)
- Serum creatinine increases (Renal impairment)
- Hyperuricaemia

- Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin.

Important potential risks

- Drug induced liver injury (DILI)
- Gout/gouty arthritis and urate nephropathy
- Uterine malignancy

Removed during the reporting period

'Uterine malignancy' was removed as an 'important potential risk'. Following a review of the results of animal studies, it was concluded that the effects seen in animals were not relevant to humans (see Section 11.2.2.3 for details).

Missing information

- Interaction with P-gp-inhibitors
- Interactions with CYP2D6 substrates
- Use in patients with moderate to severe liver disease
- Patients at potentially increased risk of bleeding: Patients with active bleeding, past history of intracranial haemorrhage (ICH), gastrointestinal (GI) bleed within 6 months, major surgery within 30 days and clinically relevant thrombocytopaenia or anaemia. Oral anticoagulants and/or fibrinolytics within 24 hours of ticagrelor dosing. Non-steroidal anti-inflammatory drugs (NSAIDs) interaction
- Use in patients beyond the recommended 1-year treatment duration (off-label use)
- Use in children
- Use in pregnant and lactating women

Removed during the reporting period

'Interaction with P-gp-inhibitors' was removed as 'missing information' (see Section 11.2.3.1 for details).

'Interactions with CYP2D6 substrates' was removed as 'missing information' since study D5130C00073 indicated that ticagrelor has no effect on the CYP2D6-mediated metabolism (see Section 11.2.3.2 for details).

Added during the reporting period

'PEGASUS: patients ≥12 months distant from their MI who have a history of ischaemic stroke or other features associated with an increased risk of ICH' was added as 'missing information' (see Section 11.2.3.8 for details).

Amended wording during the reporting period

The wording for 'Patients at potentially increased risk of bleeding' was changed to:

'Use in patients with increased risk of bleeding: Patients with active bleeding, past history of ICH, GI bleed within 6 months, major surgery within 30 days and clinically relevant thrombocytopaenia or anaemia. Concomitant use of oral anticoagulants and/or fibrinolytics within 24 hours of ticagrelor dosing. Concomitant use of NSAIDs.'

11.2 Evaluation of risks and new information

11.2.1 New information on important identified risks

11.2.1.1 Increased risk of bleeding

There is a risk of bleeding across all degrees of severity from minimal nuisance bleeding to life-threatening and fatal bleeding that may occur related to cardiac and other surgical procedures as well as during long-term out-of-hospital use. No subgroup was identified as being at increased risk of bleeding during treatment with ticagrelor.

Bleedings, including ICH, are considered listed ADRs in Section 4.8 in the ticagrelor SmPC. This section has, during the period, been updated with a clarification that ICH may include fatal cases. Sections 4.4 and 4.5 in the SmPC contain information regarding concomitant use and interactions with medicinal products that may increase the risk of bleeding. Ticagrelor is contraindicated in patients with a history of ICH and active pathological bleeding (see Section 4.3 in the SmPC). Although bleedings are considered listed ADRs, all reports indicative of ICH are kept under close surveillance.

As part of the approval of the ticagrelor New Drug Application, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) (approved 20 July 2011) the purpose of which was to inform healthcare professionals and patients about the risk of bleeding associated with the use of ticagrelor, and about the proper dosing of concomitant aspirin. Ticagrelor was released from the requirement of the REMS on 30 October 2013.

Targeted questionnaires are distributed for spontaneous reports of ICH. Additional pharmacovigilance measures to assess all bleedings, including ICH, include 2 ongoing clinical studies:

- PEGASUS (D5132C00001): safety data with longer exposure and follow-up; detailed bleeding assessments using TIMI and PLATO scoring system and using Modified Rankin Score for all cases of ICH; and Data Monitoring Committee review, and safety data from longer exposure and follow-up.

- DUS (D5130N00010) will provide 'real life' data regarding hospitalisations for bleeding events of GI bleeding, ICH, and other bleeding events. For these patients, associated concomitant medication and relevant past medical history will be available and the study will also provide crude incidence rates of hospital admissions for these events.

During the reporting period, case reports of bleedings, including ICH, have been reviewed and presented in the PSURs/PBRERs. Based upon these reviews and taking into account the cumulative experience, no new significant safety information regarding ticagrelor and bleedings has been identified. Bleedings will be monitored as part of AstraZeneca's routine pharmacovigilance activities; however, ICH will continue to be kept under close surveillance. During the review period, no changes to the SmPC regarding the risk of bleeding have been considered warranted other than a clarification in Section 4.8 that ICH may include fatal cases.

11.2.1.2 Dyspnoea

In the PLATO study, dyspnoea was reported more frequently during treatment with ticagrelor. Dyspnoea is a listed ADR and in the current version of the SmPC, safety information regarding dyspnoea is included in Sections 4.4, 4.8, and 4.9. Dyspnoea is kept under close surveillance.

D5130C00067 study results indicate that ticagrelor increased the adenosine-induced coronary blood flow velocity response confirming an adenosine-mediated mechanism. In parallel, dyspnoea occurrence and severity were augmented by ticagrelor and reversed by theophylline, providing further support that adenosine may contribute to the dyspnoea reported by some patients taking ticagrelor. In patients who underwent pulmonary function testing in the clinical programme, there was no indication of an adverse effect of ticagrelor on pulmonary function.

Additional pharmacovigilance measures to assess dyspnoea, during ticagrelor treatment include 2 ongoing clinical studies:

- PEGASUS (D5132C00001) will provide safety data in patients with longer exposure and follow-up. Detailed baseline data will be collected regarding the severity of any baseline asthma or COPD.

- DUS (D5130N00010) will provide crude incidence rates of events being considered relevant to understand the possible clinical impact of dyspnoea in the ACS population: hospitalisation for congestive heart failure and outpatient events of dyspnoea. The prevalence of COPD, and CV disease at baseline in new users of ticagrelor, clopidogrel, and prasugrel will be described.

Based upon a review of reports of dyspnoea and reports of respiratory failure received during the reporting period, and taking into account the cumulative experience, no new significant safety information regarding ticagrelor and dyspnoea has been identified. Information

received is consistent with the known characterisation of dyspnoea. In particular, no safety signals with regard to change in characteristics such as worsened outcomes and change in severity have been identified. No change to the ticagrelor SmPC regarding dyspnoea is warranted at this time. Dyspnoea and respiratory failure will continue to be kept under close surveillance.

11.2.1.3 Bradyarrhythmias (including Holter-detected ventricular pauses)

At the beginning of the reporting period, the ticagrelor safety specification (presented in the EU RMP edition 4, dated 22 September 2010) included bradyarrhythmias as an important identified risk. This topic was included as an important identified risk on request from the European Medicines Agency (EMA). Bradyarrhythmia is considered an important potential risk in the Core RMP.

In a subset of PLATO patients who had Holter monitoring (3-lead digital continuous ECG) performed, an increased incidence of asymptomatic Holter-detected ventricular pauses was observed in patients receiving ticagrelor during the acute phase of their ACS. Overall, the occurrence of clinically important events in patients with ventricular pauses was generally similar with ticagrelor compared with clopidogrel and did not correlate with the occurrence of ventricular pauses.

Bradyarrhythmia is considered an unlisted event and it is not included in Section 4.8 in the SmPC. However, it is kept under close surveillance and information is included in Sections 4.4, 4.5, and 5.1 in the SmPC.

Bradyarrhythmias are followed in the routine pharmacovigilance and are kept under close surveillance. Targeted questionnaires are distributed for spontaneous reports of bradyarrhythmia.

Additional pharmacovigilance measures to assess this topic include 2 ongoing clinical studies:

- PEGASUS (D5132C00001) will allow for further assessment of clinically relevant bradyarrhythmias. The PEGASUS Data and Safety Monitoring Board has scheduled reviews of AEs of interest, including bradyarrhythmias, and has recommended that the study continues. The completion of PEGASUS is anticipated to provide further information regarding ticagrelor and bradyarrhythmias.

- Drug utilisation study (D5130N00010) will estimate the crude incidence rate of events being considered relevant to understand the possible clinical impact of bradycardia in the ACS population using a health care database: hospitalisation for pacemaker insertion, bradyarrhythmia, and cardiac arrest (CHD deaths occurring outside the hospital and death with a recording of cardiac arrest) and outpatient events of syncope.

During the reporting period, case reports on bradyarrhythmias have been monitored continually and presented in the PSURs/PBRERs. In response to a request from a regulatory

authority, a cumulative review through 29 February 2012 was performed and presented in the PSUR dated 15 August 2012. Further, AstraZeneca performed a formal, cumulative safety evaluation through 31 December 2012 presented in the PBRER dated 09 August 2013. These comprehensive evaluations of bradyarrhythmia and ticagrelor have included a review of available safety information, including data from the medical/scientific literature, short- and long-term clinical trials, and spontaneous reports. According to the reviews, no new safety signals were identified. Regarding the case reports received during the reporting period, some presented alternate explanations for the bradyarrhythmia event, such as use of a beta-blocker, medical history, and/or underlying disease. Some reports did not include sufficient information to assess causality, whereas a causal relationship between the event and ticagrelor could not be ruled out for other reports.

The outcomes of routine and additional pharmacovigilance will be reported via the PBRER. This safety topic will continue to be kept under close surveillance. No change to the ticagrelor SmPC regarding bradyarrhythmia is warranted at this time.

11.2.1.4 Serum creatinine increases (renal impairment)

'Serum creatinine increases (Renal impairment)' is included in the EU RMP as an important identified risk based on a request from the EMA. Renal impairment is considered an important potential risk in the Core RMP.

'Blood creatinine increased' is a listed ADR included in Section 4.8 of the SmPC as Rare (≥1/10000 to <1/1000) based on laboratory observations in the PLATO study. However, renal impairment, including renal failure, has not been causally associated with ticagrelor and these events are thus considered unlisted events (not included in Section 4.8). Further information on treatment in patients with renal impairment and creatinine elevations is included in Sections 4.2, 4.4, and 5.2 of the SmPC.

Renal impairment is kept under close surveillance and followed in the routine pharmacovigilance. Targeted questionnaires are distributed for spontaneous reports of renal impairment (including creatinine increased and renal failure).

Additional pharmacovigilance measures to assess this topic include 2 ongoing clinical studies:

- PEGASUS (D5132C00001) will capture additional information from reported AEs relating to renal function from targeted case report forms. Further, renal data, including urine data, will be collected in a population with a longer exposure and follow-up.

- DUS (D5130N00010) will capture hospitalised cases of acute renal failure and provide crude incidence rates in first-time users of ticagrelor, clopidogrel, and prasugrel.

In assessment reports received during the reporting period, AstraZeneca has been requested to present cumulative reviews of renal impairment cases with positive and negative dechallenge,

and rechallenge. These reviews did not demonstrate reasonable evidence of a possible causal relationship between acute renal failure or renal impairment and ticagrelor. No change to the ticagrelor safety specification was warranted regarding renal impairment and the safety topic was continued to be kept under close surveillance. These conclusions and actions were approved by the authorities.

AstraZeneca has also been requested to critically examine whether new information has suggested a clinically significant difference in the severity or frequency of the risks, whether such risks are newly found in an indicated subpopulation, and whether the new information warrants changes to the product information or other risk minimisation activities. AstraZeneca was also expected to provide numbers and severity of cases/events (interval and cumulative).

AstraZeneca concluded that an overall summary of renal impairment events did not identify any specific pattern of age, gender, time to onset in relation to ticagrelor, or other factors that may have played a role in the development of renal impairment. Taking into account the cumulative experience, no new significant safety issues regarding ticagrelor and renal impairment were identified. No change to the ticagrelor SmPC was warranted and it was again decided that renal impairment will continue to be kept under close surveillance. These conclusions and actions were also approved by the authorities.

11.2.1.5 Hyperuricaemia

The ticagrelor safety specification valid at the beginning of the reporting period (EU RMP version 4, dated 22 September 2010) includes 'Hyperuricaemia' as an important identified risk based on a request from regulatory authorities.

Hyperuricaemia is a listed ADR included in the SmPC (Section 4.8) as Rare (≥1/10000 to <1/1000). Section 4.4 of the SmPC includes information that caution should be exercised when administering ticagrelor to patients with a history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acid nephropathy is discouraged.

This topic is followed in the routine pharmacovigilance. Additional pharmacovigilance measures to assess 'Hyperuricaemia' include 2 ongoing clinical studies:

- PEGASUS (D5132C00001): AE and laboratory data from longer exposure and follow-up will be used to evaluate the potential for ticagrelor to cause increased reporting of gout/gouty arthritis.
- DUS (D5130N00010) will capture records of gout in patient registries and will provide crude incidence rates of gout.

The clinical conditions related to 'Hyperuricaemia' - gout, gouty arthritis, and urate nephropathy - are included in the EU RMP as important potential risk. For further information, see Section 11.2.2.2.

No new safety issues regarding 'Hyperuricaemia' were identified during the period.

11.2.1.6 Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin

There is a risk of increased ticagrelor levels in patients receiving CYP3A4 inhibitors, a risk of reduced ticagrelor levels with concomitant use of strong CYP3A4 inducers, and with concomitant use of ticagrelor there will be potentially higher levels of statins (eg, simvastatin and lovastatin), as well as potentially increased digoxin levels. Appropriate wording is included in the SmPC in Sections 4.3, 4.4, and 4.5.

During the reporting period, the SmPC (Section 4.5) was updated to include information on the co-administration of cyclosporine, a P-glycoprotein and CYP3A4 inhibitor (see Section 11.2.3.1 for further details).

Reviews of reports from AstraZeneca's global safety database regarding suspected drug-drug interactions have been performed continuously and addressed in 6-month reports. Taking into account the cumulative experience on this topic, the data did not demonstrate any new safety issues regarding interactions or on the clinical manifestations of known/listed interactions between ticagrelor and other substances as described in the heading of this section or between ticagrelor and grapefruit, a known CYP3A4 inhibitor.

No change to the SmPC regarding drug-drug interactions is considered warranted. Drug-drug interactions and interactions with grapefruit will continue to be kept under close surveillance.

11.2.2 New information on important potential risks

11.2.2.1 Drug-induced liver injury

No evidence of drug-induced liver injury was found with ticagrelor in the PLATO study. However, drug-induced liver injury is included as an important potential risk in the EU RMP and is currently kept under close surveillance.

The SmPC (Sections 4.2, 4.3, and 4.4) includes information on patients with hepatic impairment. Ticagrelor has not been studied in patients with moderate or severe hepatic impairment. Its use in patients with moderate to severe hepatic impairment is therefore contraindicated.

Targeted questionnaires are distributed for spontaneous reports of hepatic-related events. Pharmacovigilance actions will be continued on an ongoing basis.

Additional pharmacovigilance measures to assess this topic include 2 ongoing clinical studies:

- PEGASUS (D5132C00001): Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin) will be measured at enrolment and at end of treatment. Hepatic related AEs will be evaluated.

- DUS (D5130N00010) will identify cases (should they occur) of acute liver injury and estimate crude incidence rate.

A review of the AE reports received during the reporting period did not identify any specific pattern of age, gender, time to onset in relation to ticagrelor, or other factors that may have played a role in the development of liver injury. The reports contained alternative aetiologies to the events such as alcohol abuse, concurrent pancreatic cancer, and concomitant use of simvastatin, atorvastatin, furosemide, and amoxicillin/clavulanic acid. In addition, reports also contained insufficient information, including lack of medical history, concomitant medications, and therapy dates. No new safety issues regarding drug-induced liver injury were identified.

The outcomes of routine and additional pharmacovigilance will be reported via the PBRER. This safety topic will continue to be kept under close surveillance.

11.2.2.2 Gout/gouty arthritis and urate nephropathy

'Gout/gouty arthritis and urate nephropathy' is included as an important potential risk due to their possible relation to 'Hyperuricaemia', an important identified risk in the EU RMP, see Section 11.2.1.5. Hyperuricaemia is a listed ADR (frequency 'Rare' (≥1/10000 to <1/1000)) in the ticagrelor SmPC. Gout/gouty arthritis and urate nephropathy are not listed in the SmPC). Further information is included in Section 4.4 in the SmPC, which includes information stating that caution should be exercised when administering ticagrelor to patients with a history of hyperuricaemia or gouty arthritis.

Gout/gouty arthritis and urate nephropathy are currently kept under close surveillance within routine pharmacovigilance. Additional pharmacovigilance measures to assess this topic include 2 ongoing clinical studies with the objective to increase the understanding of this potential risk; ie, does the hyperuricaemia lead to an increased incidence of gout or urate nephropathy in the real world and during longer term prescription:

- PEGASUS (D5132C00001): AE and laboratory data from longer exposure and follow-up will be used to evaluate the potential for ticagrelor to cause increased frequency of reported gout/gouty arthritis.
- DUS (D5130N00010) will capture records of gout in patient registries and will provide crude incidence rates of gout.

These studies were started during the reporting period and are currently ongoing.

During the reporting period, gout/gouty arthritis and urate nephropathy have been monitored and analysed in the PSURs/PBRERs. Taking into account the number of reports, seriousness of the events, and increased risk of gout in the CAD population, the cumulative review of reports for gout received during this period did not indicate a causal association between gout/gouty arthritis, urate nephropathy, and ticagrelor. No new safety issues regarding these topics were identified. No change to the ticagrelor SmPC regarding gout, gouty arthritis, and

urate nephropathy was warranted during this period. This safety topic will continue to be kept under close surveillance.

11.2.2.3 Uterine malignancy

'Uterine malignancy' has been removed as an 'important potential risk' following review of the results of an AstraZeneca animal study.

At the beginning of the reporting period, the ticagrelor safety specification (EU RMP version 4, dated 22 September 2010) included 'Uterine malignancy' as an important potential risk. This risk was initially included due to findings of increased uterine adenocarcinomas in a rat carcinogenicity study.

AstraZeneca made a commitment to CHMP/EMA to conduct a non-clinical study on prolactin secretion (FUM003, Letter of Undertaking dated 24 September 2010). The study showed that that the same high oral dose of ticagrelor that caused uterine tumors in rats almost completely inhibited prolactin release in female rats. The final CHMP Assessment Report for FUM003 (Final AR PAC FUM003, dated 21 December 2011) concluded that the nonclinical study has sufficiently shown that suppression of prolactin in female rats is an acceptable mechanism of uterine tumours in rats. In addition, CHMP concludes that this mechanism is irrelevant for humans and is not expected to have clinical consequences. Based on these results, the CHMP requested AstraZeneca to update the EU RMP with these findings.

The results from the study were presented in the EU RMP version 6, dated 15 February 2012. 'Uterine malignancy' was no longer regarded as a potential human risk and was accordingly removed from the EU RMP. The topic is monitored as part of AstraZeneca's routine safety surveillance activities.

11.2.3 Update on missing information

11.2.3.1 Interaction with P-gp-inhibitors

Based on the results from study D5130C00074, the effect of cyclosporine, as a P-gp and CYP3A4 inhibitor, on ticagrelor AUC and C_{max} as well as information that ticagrelor had no effect on the exposure of cyclosporine was added to the SmPC. Consequently, the topic 'Interactions with P-gp inhibitors' was removed from missing information.

Study D5130C00074 was a Phase 1 clinical pharmacology study in healthy volunteers that investigated the potential PK interaction of cyclosporine and ticagrelor. The study results concluded that co-administration of cyclosporine (600 mg) increased ticagrelor C_{max} and AUC by 2.3-fold and 2.8-fold, respectively. The AUC of AR-C124910XX (active metabolite) was increased by 32% and C_{max} was decreased by 15% in the presence of cyclosporine. There was no effect of ticagrelor on cyclosporine blood levels.

11.2.3.2 Interactions with CYP2D6 substrates

Results from study D5130C00073 indicated that ticagrelor has no effect on the CYP2D6-mediated metabolism. Consequently, the topic 'Interactions with CYP2D6 substrates' was removed from missing information.

Study D5130C00073 was a Phase I PK study in healthy volunteers that evaluated the effect of ticagrelor on venlafaxine, a CYP2D6 substrate. The results showed that venlafaxine had no effect on the exposure (AUC and C_{max}) of ticagrelor or its metabolite AR-C124910XX. Ticagrelor had no effect on the overall exposure (AUC_{τ}) of venlafaxine; however, the associated C_{max} was increased by 22%.

11.2.3.3 Use in patients with moderate to severe liver disease

Ticagrelor use in patients with moderate to severe hepatic impairment is contraindicated as stated in the SmPC (Section 4.3). Further information regarding patients with moderate or severe liver disease is included in the SmPC (Sections 4.2, 4.4, and 5.2).

This topic is followed in the routine pharmacovigilance. Additional pharmacovigilance measures to assess this topic include 2 ongoing clinical studies:

- PEGASUS (D5132C00001), which will capture baseline liver function, AST, ALT, ALP, and total bilirubin. An exclusion criterion is known severe liver disease (eg, ascites or signs of coagulopathy). Patients with moderate liver disease are not excluded.

- DUS (D5130N00010) will assess the prevalence of baseline hepatic disease (liver cirrhosis and chronic hepatitis) in first-time users of ticagrelor, clopidogrel and prasugrel but severity will not be captured due to database limitations.

During the reporting period, AstraZeneca monitored case reports of AEs in patients reporting a history of hepatic impairment and these analyses were included in the PSURs/PBRERs. Reports received during the period included a broad spectrum of SOCs with multiple PTs. In most cases the hepatic impairment was unlikely to have contributed to the events reported. No new significant safety issues were identified regarding patients with a history of hepatic impairment.

As liver disease patients are inherently at higher bleeding risk due to the risk of hepatic coagulopathy, and there may also be higher ticagrelor plasma concentrations due to reduced hepatic metabolism, reports of bleeding were also reviewed to identify any patients with liver disease. Of the reports of bleeding received, only approximately 1% to 3% had a history of hepatic impairment (PBRER dated 09 August 2013 and PBRER dated 11 February 2013).

No new significant safety issues were identified regarding patients with a reported history of hepatic impairment and no changes to the ticagrelor SmPC regarding hepatic impairment are warranted at this time.

11.2.3.4 Use in patients with increased risk of bleeding: patients with active bleeding, past history of ICH, GI bleed within 6 months, major surgery within 30 days and clinically relevant thrombocytopaenia or anaemia, concomitant use of oral anticoagulants and/or fibrinolytics within 24 hours of ticagrelor dosing, concomitant use of NSAIDs

Ticagrelor should be used with caution in patients at known increased risk for bleeding. This safety information is included in Section 4.4 of the current SmPC. Information on this topic is also included in Sections 4.3 and 4.5 of the SmPC.

Additional pharmacovigilance measures to assess this topic include 2 ongoing clinical studies:

- PEGASUS (D5132C00001): see Section 11.2.1.1 (Increased risk of bleeding).
- DUS (D5130N00010) will assess the prevalence of ICH, GI bleed within 6 months, and concomitant dispensions of oral anticoagulants and NSAIDs.

Following the review of the PSUR dated 09 August 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) requested the MAH to revisit the current wording in the SmPC (Sections 4.4 and 4.5) regarding concomitant use and interactions with ASA, enoxaparin, and heparin. Based on the data presented, the MAH believed that the current wording regarding concomitant use and interaction with heparin, enoxaparin, and ASA provided sufficient information and the PRAC came to the same conclusion.

During the reporting period, continuous reviews of bleedings associated with ticagrelor use in patients with an increased risk have been conducted and presented in the PSURs/PBRERs. Risk factors studied were concomitant medications that may influence bleeding risk, such as NSAIDs and other antithrombotic agents (eg, heparin, enoxaparin, etc), as well as a medical history of bleeding, thrombocytopaenia, or anaemia.

No new significant safety information was identified and no change to the ticagrelor SmPC regarding use in patients at increased risk of bleeding is warranted. This topic will continue to be kept under close surveillance.

11.2.3.5 Use in patients beyond the recommended 1-year treatment duration (off-label use)

For use beyond the recommended 1-year treatment duration, the ongoing PEGASUS study (D5132C00001) will provide further data on longer-term exposure since patients will be treated for up to 3 years, although in a slightly different population than the current approved indication for ticagrelor.

Reports describing use of ticagrelor that are not in accordance with the local label are considered off-label use. A review of off-label use (all reasons) was presented in a separate section in the PSURs/PBRERs. Use beyond 1-year treatment duration comprises only a minor fraction of the case reports reported on off-label use. A review of reports identified as off-

label use did not reveal any new safety issues. No change to the ticagrelor SmPC is warranted at this time regarding off-label use.

Off-label use is monitored as part of AstraZeneca's routine safety surveillance activities and kept under close surveillance.

11.2.3.6 Use in children

Children below the age of 18 years have not been included in clinical studies. The SmPC (Section 4.2) states that safety and efficacy of ticagrelor in children below the age of 18 years in the approved adult indication has not been established, since data are not available.

ACS and other manifestations of atherosclerotic vascular disease are not prevalent before the age of 30 years. Therefore, paediatric studies with ticagrelor are not possible for the ACS indication.

The previously approved EU Paediatric Investigation Plan (PIP) was for the indication of prevention of thrombotic and thromboembolic events in paediatric patients with a central venous catheter.

AstraZeneca submitted applications for Clinical Trial Authorisations (CTAs) in 6 markets for Study D5136C00001 (A multi-centre, double-blind, placebo-controlled, PK, PD, safety, and tolerability study in patients aged 12 to <18 years with a central venous catheter to support prediction of the age-appropriate dose of ticagrelor with similar levels of inhibition of platelet aggregation [IPA] to 90 mg bid in adults) and this was the first study planned with ticagrelor in paediatric patients. On 02 August 2012, the US FDA placed the IND for this study (IND 112,336), on full clinical hold, citing the following: "It is not acceptable to conduct research in children that involves greater than minimal risk without potential for direct benefit. The proposed study does not appear to meet this standard. Treatment with ticagrelor places subjects at more than minimal risk. There does not appear to be potential of a direct clinical benefit." AstraZeneca received similar concerns from other authorities (eg, Germany) while the CTA was approved by others (eg, Hungary and France).

The currently approved EU PIP (P/0295/2014 dated 30 October 2014) is for the indication of prevention of vaso-occlusive crises in paediatric patients with sickle cell disease (SCD). Three paediatric studies are intended to provide important clinical information for the appropriate use of ticagrelor and evaluate its potential therapeutic benefits in children with SCD. A PK and PD dose-ranging Phase 2 study of ticagrelor followed by a 4-week extension phase in paediatric patients aged ≥2 years to <18 years with SCD has started enrolling patients. A Phase 3 study to determine the efficacy and safety of ticagrelor in paediatric patients aged ≥2 years to <18 years with SCD is planned. A PK study of ticagrelor in children aged 0 to 24 months will also be performed. Furthermore, a study to assess the relative bioavailability of ticagrelor granules for oral suspension and the mini ticagrelor tablet to the commercial ticagrelor tablet in healthy adult subjects will be included in the programme. A Phase 2b study in young adults (aged 18 to 30 years) with SCD is also planned.

There are no common childhood diseases that are treated with antiplatelet agents. Accordingly, no significant amount of off-label paediatric use is anticipated and only a few reports have been received during the update period. A review of reports identified as potential use in paediatric patients (off-label) did not reveal any new safety issues.

Ticagrelor is not considered to be at unusual risk of misuse in children. Four reports of accidental exposure in children (all asymptomatic) have been received. A review of all reports involving children was presented in consecutive PSURs/PBRERs and has not identified any safety trends or issues.

11.2.3.7 Use in pregnant or lactating women

No clinical studies have been conducted in pregnant women. As stated in the SmPC, ticagrelor is not recommended during pregnancy and women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during ticagrelor therapy.

During the reporting period, 2 spontaneous reports of ticagrelor exposure in pregnant women have been received. No AEs were reported and the outcome of these pregnancies was unknown/not reported.

Routine pharmacovigilance has not identified any safety issues regarding pregnancy. The SmPC has not been updated during the period with respect to pregnancy.

11.2.3.8 PEGASUS: patients ≥ 12 months distant from their MI who have a history of ischaemic stroke or other features associated with an increased risk of ICH

During the reporting period, this topic was added as missing information to the ticagrelor safety specification (presented in the EU RMP version 5, dated 23 March 2011) since this population was excluded from the PEGASUS trial. The reason for this exclusion criterion in the PEGASUS study is because accumulating data across a number of studies using a variety of antiplatelet drugs (not including ticagrelor) suggests that more intensive antiplatelet therapy may pose a particularly high risk of ICH in patients with a history of ischaemic stroke. This exclusion criterion in the PEGASUS study will limit information about the use of ticagrelor in patients ≥12 months distant from MI with a history of ischaemic stroke or other features associated with an increased risk of ICH.

This topic is followed in the routine pharmacovigilance and ICH is kept under close surveillance. Targeted questionnaires are distributed for spontaneous reports of ICH.

11.3 Characterisation of risks

In the following tables and text, detailed information is given on the important identified and important potential risks, and missing information.

The tables presented in this section are based on the characterisation presented in relevant tables in the EU RMP version 8, dated 09 August 2013. The clinical information for ticagrelor presented in these tables is mostly derived from the PLATO study.

Cumulative information from the global safety database on number of received AEs presented by seriousness and outcome have been added to Table 5, Table 7, Table 8, Table 9, Table 10, Table 12, and Table 13 below. Searches have been made in the AstraZeneca global safety database for AEs and SAEs received on the different items up to 08 November 2014 using MedDRA version 17.1. In these tables AEs from marketed use also include AEs from non-interventional sources, post-marketing studies, and other non-AstraZeneca studies. The term 'AE' refers to both non-serious and serious AEs when not stated otherwise.

11.3.1 Important identified risks

The following 6 safety concerns are important identified risks:

- Increased risk of bleeding (Table 5 and Table 6)
- Dyspnoea (Table 7)
- Bradyarrhythmias (including Holter-detected ventricular pauses) (Table 8)
- Serum creatinine increases (renal impairment) (Table 9)
- Hyperuricaemia (Table 10)
- Drug-drug interactions: strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin (Table 11)

11.3.1.1 Increased risk of bleeding

Table 5 Important identified risks – Increased risk of bleeding

Identified Risk	Increased risk of bleeding
Frequency with 95% CI	Rates of bleeding events using the PLATO-defined and TIMI-defined (Wiviott et al 2006) severity categories and clinical contexts are summarised below. 'Total Major' bleeding In PLATO, there was no significant difference in 'Total Major' bleeding (the study's primary safety endpoint) for ticagrelor (11.6% per year) compared to clopidogrel (11.2% per year; HR 1.04 [95% CI 0.95, 1.13]; p=0.4336). The rates of PLATO-defined 'Major Fatal/Life-threatening' bleeding, TIMI-defined 'Major' bleeding, and TIMI-defined 'Major + Minor' bleeding also did not differ significantly between treatments. Intracranial haemorrhage In PLATO, there were numerically more non-procedural ICHs in the ticagrelor treatment group (26 patients [0.3%]) compared to the clopidogrel treatment group (14 patients [0.2%]). The percentage of intracranial bleeding, however, was low in both treatment groups given the significant comorbidity and cardiovascular risk factors of the population under study, and the incidence in the PLATO ticagrelor group was similar to that which was seen for clopidogrel-treated patients in the TRITON TIMI-38 study, 0.3% (Wiviott et al 2007). There were more non-procedural Fatal intracranial bleeding events in the ticagrelor group compared to clopidogrel (11 versus 1, respectively). In the PLATO study, other non-procedural Fatal bleeding events, such as GI bleeding, were numerically lower with ticagrelor compared to clopidogrel. Given the similar overall non-procedural fatality incidence for both treatment groups in PLATO and the lack of consistent pattern for individual events between ticagrelor and clopidogrel, the clinical significance of these findings is not known. 'Combined Major + Minor' bleeding In PLATO, 'Combined Major + Minor' bleeding (using PLATO definitions) occurred more with ticagrelor (16.1% per year) than with clopidogrel (14.6% per year). This difference arose from more 'Minor' bleeding with ticagrelor, and included events such as epistaxis, subcutaneous, GI and urinary tract-related bleeding, and bleeding accompanying procedures. Minimal bleeding In the PLATO study, there was more PLATO-defined 'Minimal' bleeding (that not needing medical attention, eg, epistaxis, contusion, haematoma) in the ticagrelor group compared to clopidogrel (17.2% vs 10.6%). CABG bleeding In PLATO, CABG-related bleeding did not differ between treatment groups by PLATO or TIMI definition. Non-procedural bleeding In the PLATO study, comparatively more non-procedural bleeding was reported in the ticagrelor treatment group across the less severe bleeding categories, with little difference between treatment groups for the potentially more serious non-procedural bleeding events: PLATO-defined non-procedural Major: 235 (KM%=3.1%) vs 180 (KM%=2.3%) HR 1.31 (1.08, 1.60; p=0.0058) PLATO-defined non-procedural Major + Minor: 457 (KM%=5.9%) vs 332 (KM%=4.3%) HR 1.39 (1.21, 1.60; p<0.0001)

Table 5 Important identified risks – Increased risk of bleeding

Identified Risk	Increased risk of bleeding
Seriousness/outcomes	Despite greater inhibition of platelet aggregation with ticagrelor, PLATO 'Major' bleeding with ticagrelor did not differ from that with clopidogrel. Whether evaluated overall, or restricted to CABG-related bleeds, or restricted to non-procedural bleeds, ticagrelor and clopidogrel did not differ in fatal bleeding, or fatal/life-threatening bleeding in the PLATO study. However, ICH and non-procedural major bleeding were seen more commonly on ticagrelor than clopidogrel. Additional information is contained in Table II-34 in the EU RMP dated 9 August 2013. Cumulative data from the global safety database: In total 4131 AEs of Bleeding events had been received up to 8 November 2014. Of these, 2432 were serious and 1699 were non-serious and 592 were SAEs from AstraZeneca clinical studies. Reported outcome for the 4131 AEs: Died: 280 (6.8%) Not recovered: 451 (10.9%) Recovering: 275 (6.7%) Recovered with sequelae: 45 (1.1%) Recovered: 1422 (34.4%) Unknown: 1658 (40.1%)
Severity and nature of risk	Bleeding constitutes the most important safety issue for all antiplatelet medications. Inherent to their PD effects, antiplatelet agents increase the risk of bleeding. There is a risk of bleeding across all degrees of severity from minimal nuisance bleeding to life-threatening and fatal bleeding that may occur related to cardiac and other surgical procedures as well as during long-term out-of-hospital use. In the PLATO study, slightly more patients on ticagrelor (1339 [14.5%]) than on clopidogrel (1215 [13.2%]) experienced at least 1 major or minor bleed. The numbers of patients experiencing ≥1 major fatal/life-threatening bleed were similar (ticagrelor 491 [5.3%] vs clopidogrel 480 [5.2%]) as was the number of patients experiencing ≥1 major bleed (ticagrelor 494 (5.3%) vs clopidogrel 474 [5.2%]). Additional information is contained in Table II-35 in the EU RMP dated 09 August 2013.
Background incidence/prevalence	Comparative analysis of bleeding events between ticagrelor and clopidogrel treatment groups in the PLATO study using a number of pre-defined bleeding categories represents a more meaningful analysis than comparison with background incidence/prevalence because reported bleeding rates are highly dependent on definitions and exact patient group.
Risk groups or risk factors	In PLATO, no subgroup was identified as being at an increased risk of bleeding during treatment with ticagrelor. A small number of patients in PLATO were identified with a past medical history of ICH despite the protocol exclusion criteria. In this group, there was an increased risk of ICH with either ticagrelor or clopidogrel.
Potential mechanisms	Expected pharmacological effect of an effective antiplatelet agent.
Preventability	Careful wording in the SmPC including a contraindication for patients with a history of ICH and appropriate warnings and precautions for use. Similar appropriate content in patient information.

Table 5 Important identified risks – Increased risk of bleeding

Identified Risk	Increased risk of bleeding
Potential public health impact of safety concern/Impact on individual patient	Risk of increased bleeding during chronic use should be considered separately from risks at time of surgical procedures. Thrombotic events might be precipitated if antiplatelet therapy is unnecessarily discontinued by the patient. Patients may regard 'Minimal' bleeding events as an inconvenience at best or perhaps alarming at worst. Thus, 'Minimal' bleeding may have the potential to interfere with treatment compliance. With proper patient information emphasising the benefits of continuous antiplatelet therapy and appropriate supportive care for such 'Minimal' bleeding events, ticagrelor therapy can be maintained. Major and minor bleeding are the most important risks. Proper patient and prescriber information is required to provide adequate support and decision making regarding risks and benefits of antiplatelet therapy for the individual patient.
Evidence source	AstraZeneca clinical studies, literature and reports from marketed use
MedDRA terms	Table 6 presents a list of MedDRA PTs related to the PLATO study. Cumulative data in the global safety database: SMQ Haemorrhages (narrow).

CABG Coronary artery bypass graft; CI Confidence interval; EU European Union; GI Gastrointestinal; HR Hazard ratio; ICH Intracranial haemorrhage, KM Kaplan-Meier; MedDRA Medical Dictionary for Regulatory Activities; PD Pharmacodynamic; PLATO PLATelet inhibition and Patient Outcomes; PT Preferred Term; RMP Risk Management Plan; SmPC Summary of Product Characteristics; TIMI Thrombolysis in Myocardial Infarction – a cardiology clinical trials study group; TRITON TIMI-38 Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction.

Table 6 MedDRA Preferred Term – Increased risk of bleeding

Grouping	MedDRA PTs
Intracranial bleeding (which may be fatal or life-threatening)	Basal ganglia haemorrhage, Brainstem haemorrhage, Cerebellar haematoma, Cerebellar haemorrhage, Cerebral haematoma, Cerebral haemorrhage, Cerebral microhaemorrhage, Haemorrhage intracranial, Haemorrhagic cerebral infarction, Haemorrhagic stroke, Haemorrhagic transformation stroke, Intracranial haematoma, Intraventricular haemorrhage, Meningorrhagia, Subarachnoid haemorrhage, Subdural haemorrhage, Thalamus haemorrhage, Traumatic intracranial haemorrhage
Gastrointestinal haemorrhage	Diarrhoea haemorrhagic, Gastritis haemorrhagic, Gastric haemorrhage, Gastroduodenal haemorrhage, Gastrointestinal haemorrhage, Haemorrhagic erosive gastritis, Haematochezia, Intestinal haemorrhage, Large intestinal haemorrhage, Lower gastrointestinal haemorrhage, Melaena, Occult blood positive, Oesophageal haemorrhage, Oesophagitis haemorrhagic, Proctitis haemorrhagic, Small intestinal haemorrhage, Upper gastrointestinal haemorrhage, Rectal haemorrhage, Anal haemorrhage, Occult blood, Chronic gastrointestinal bleeding, Gastric occult blood positive, Gastroduodenitis haemorrhagic
Gastrointestinal ulcer haemorrhage	Duodenal ulcer haemorrhage, Gastric ulcer haemorrhage, Gastrointestinal ulcer haemorrhage, Large intestinal ulcer haemorrhage, Oesophageal ulcer haemorrhage, Peptic ulcer haemorrhage, Small intestinal ulcer haemorrhage, Rectal ulcer haemorrhage, Ulcer haemorrhage

Table 6 MedDRA Preferred Term – Increased risk of bleeding

Grouping	MedDRA PTs
Oral haemorrhage (including gingival bleeding)	Gingival bleeding, Lip haematoma, Lip haemorrhage, Mouth haemorrhage
Eye haemorrhage (Intraocular, conjunctival, and retinal)	Ciliary body haemorrhage, Conjunctival haemorrhage, Eye haemorrhage, Periorbital haematoma, Corneal bleeding, Scleral haemorrhage, Hyphaema, Iris haemorrhage, Lacrimal haemorrhage, Ocular retrobulbar haemorrhage, Optic disc haemorrhage
Subcutaneous or dermal bleeding	Haemorrhage subcutaneous, Haemorrhage subepidermal, Petechiae, Purpura, Skin haemorrhage, Subcutaneous haematoma
Procedural site haemorrhage	Vessel puncture site haematoma, Vessel puncture site haemorrhage, Injection site haematoma, Injection site haemorrhage, Puncture site haemorrhage, Catheter site haemorrhage, Infusion site haemorrhage, Catheter site haematoma, Implant site haematoma, Implant site haemorrhage, Incision site haematoma, Incision site haemorrhage, Infusion site haematoma
Bruising	Abdominal wall haematoma, Auricular haematoma, Breast haematoma, Contusion, Ecchymosis, Extravasation blood, Haematoma, Increased tendency to bruise, Spontaneous haematoma, Subcutaneous haematoma, Traumatic haematoma
Haemorrhage urinary tract	Blood urine, Blood urine present, Haematuria, Haematuria traumatic, Haemorrhage urinary tract, Renal haemorrhage, Urinary bladder haemorrhage, Ureteric haemorrhage
Other	Epistaxis, Haemoptysis, Haemorrhage, Haemorrhoidal haemorrhage, Operative haemorrhage, Post procedural haematoma, Post procedural haematuria, Post procedural haemorrhage, Haematemesis, Haemarthrosis, Retroperitoneal haematoma, Retroperitoneal haemorrhage, Ear haemorrhage, Vaginal Haemorrhage, Metrorrhagia, Traumatic haemorrhage, Wound haemorrhage

11.3.1.2 Dyspnoea

Table 7 Important identified risks - Dyspnoea

Identified Risk	Dyspnoea
Frequency with 95% CI	In PLATO, which included many patients with CHF, COPD, and asthma, dyspnoea AEs were reported more frequently during treatment with ticagrelor (13.8%) than with clopidogrel (7.8%). Most patients had only 1 episode of dyspnoea regardless of treatment group.

Table 7 Important identified risks - Dyspnoea

Identified Risk	Dyspnoea
Seriousness/outcomes	In PLATO, which included many patients with CHF, COPD, and asthma, dyspnoea events (% of AEs, % of SAEs) were reported more frequently during treatment with ticagrelor (13.8%, 0.7%) than with clopidogrel (7.8%, 0.4%) when combining counts of the 5 MedDRA PTs related to dyspnoea (for additional data see Table II-38 in the EU RMP dated 09 August 2013). More patients taking ticagrelor (0.9%) discontinued study drug due to dyspnoea than did patients taking clopidogrel (0.1%). Cumulative data from the global safety database: In total 3397 AEs of Dyspnoea had been received up to 08 November 2014. Of these, 712 were serious and 2685 were non-serious and 105 were SAEs from AstraZeneca clinical studies. Reported outcome for the 3397 AEs: Died: 15 (0.4%) Not recovered: 389 (11.5%) Recovering: 191 (5.6%) Recovered with sequelae: 10 (0.3%) Recovered: 1183 (34.8%) Unknown: 1609 (47.4%)
Severity and nature of risk	In the PLATO study, there was a 6% absolute excess risk of dyspnoea related to ticagrelor treatment and most reports of dyspnoea were mild to moderate in severity (see Table II-38 in the EU RMP dated 09 August 2013). Most dyspnoea AEs occurred soon after treatment initiation, and occurred earlier with ticagrelor (median 20 days) than clopidogrel (median 33 days). The duration of dyspnoea AEs was similar between treatment groups; approximately 30% resolved within 1 week (see Figure II-1 in the EU RMP dated 09 August 2013). In the overall population, the median durations of resolved events were similar among the ticagrelor and clopidogrel groups (9 days in both treatment groups) and approximately two-thirds of all dyspnoea events resolved. The excess dyspnoea with ticagrelor does not represent heart failure or lung disease, and ticagrelor treatment usually does not need to be stopped. Cardiopulmonary assessments in the Phase 2 study OFFSET showed no effect of ticagrelor compared to clopidogrel on pulmonary function. In Phase 1 studies that examined pulmonary function in healthy elderly volunteers and in patients with COPD or asthma, there was no effect of ticagrelor compared to placebo on pulmonary function. In PLATO, there was no adverse effect observed on pulmonary function with ticagrelor compared to clopidogrel in patients who participated in the pulmonary function substudy. When the primary efficacy endpoint in PLATO (CV death, MI, and stroke) was examined in patients experiencing dyspnoea on treatment, the benefit of ticagrelor was maintained in patients with a dyspnoea AE, as the relative risk of a cardiovascular event in these patients was 0.77.

Table 7 Important identified risks - Dyspnoea

Identified Risk	Dyspnoea
Background incidence/prevalence	Dyspnoea is a subjective term and as such is poorly collected in databases. The comparative analysis of dyspnoea between ticagrelor and clopidogrel treatment groups in the PLATO study represents the most meaningful analysis given that data on background incidence/prevalence are sparse and will be highly dependent on the collection tool and patient group.
Risk groups or risk factors	As would be expected, patients with baseline risk factors were more likely to report dyspnoea than the population as a whole, according to the data from PLATO. However, all subgroups evaluated show a similar risk increase (estimated HR 1.43 to 2.24). The subgroup with asthma patients showed the highest estimated HR; however, this is also the smallest subgroup evaluated and the confidence interval is wide (Table II-39 in the EU RMP dated 09 August 2013). There is some evidence of exposure relationship.
Potential mechanisms	Possible mechanisms include carotid chemoreceptor stimulation and pulmonary C fibre activation via adenosine receptors. Ticagrelor inhibits adenosine uptake into red blood cells in vitro, and thus could increase adenosine levels in the lung tissue, leading to dyspnoea.
Preventability	Careful wording in the SmPC and patient information to remind that concurrent conditions causing dyspnoea need to be identified and treated appropriately.
Potential public health impact of safety concern/Impact on individual patient	Patients with cardiac disease are at risk of developing dyspnoea related to causes other than ticagrelor (eg, heart failure, COPD), and it is important that such concurrent conditions are identified and treated appropriately. There is a risk that thrombotic events might be precipitated if antiplatelet therapy is unnecessarily discontinued by patients following dyspnoea events. Careful wording in the SmPC and patient information can be used to address this risk.
Evidence source	AstraZeneca clinical studies, literature and reports from marketed use
MedDRA terms	PTs: Dyspnoea, Dyspnoea at rest, Dyspnoea exertional, Dyspnoea paroxysmal nocturnal, and Nocturnal dyspnoea

AE Adverse event; CHF Congestive heart failure; CI Confidence intervals; COPD Chronic obstructive pulmonary disorder; CV Cardiovascular; EU European Union; HR Hazard ratio; MedDRA Medical Dictionary for Regulatory Activities; MI Myocardial infarction; PLATO PLATelet inhibition and Patient Outcomes; PT Preferred Term; RMP Risk Management Plan; SAE Serious adverse event; SmPC Summary of Product Characteristics.

11.3.1.3 Bradyarrhythmias

Table 8 Important identified risks - Bradyarrhythmias (including Holter-detected ventricular pauses)

Identified Risk	Bradyarrhythmias (including Holter-detected ventricular pauses)
Frequency with 95% CI	**Phase 3** Holter monitoring data from a subset of PLATO patients showed an increased incidence of asymptomatic Holter-detected ventricular pauses in patients receiving ticagrelor during the acute phase of their ACS (ventricular pauses ≥3 seconds [58 (6.0%)]; ventricular pauses ≥5 seconds [20 (2.1%)].
Seriousness/outcomes	A subset of patients within PLATO had Holter monitoring for up to 7 days at Visit 1 (immediately after randomisation) and again at Visit 2 (30 days after randomisation) to assess the occurrence of arrhythmias and, of these, 2908 patients were included in the Holter analysis set. The PLATO protocol specified the collection of paired readings (Holter recordings collected at Visit 1 and again at Visit 2 in the same patient) because studying patients with paired readings enables the examination of ventricular pauses in the same patient population at 2 points in time. Of the 2908 patients included in the Holter analysis set, 1949 had paired readings at Visit 1 and Visit 2 for up to 7 days at each occasion. In a subset of PLATO patients who had Holter monitoring (3-lead digital cECG recording) performed, an increased incidence of asymptomatic Holter-detected ventricular pauses was observed in patients receiving ticagrelor during the acute phase of their ACS (ventricular pauses ≥3 seconds ticagrelor 58 [6.0%] vs clopidogrel 34 [3.5%]; ventricular pauses ≥5 seconds ticagrelor 20 [2.1%] vs clopidogrel 10 [1.0%]). This increased incidence in asymptomatic Holter-detected ventricular pauses was less evident at 1 month (ventricular pauses ≥3 seconds ticagrelor 21 [2.2%] vs clopidogrel 16 [1.6%]; ventricular pauses ≥5 seconds ticagrelor 8 [0.8%] vs clopidogrel 5 [0.5%]). There were no adverse clinical consequences associated with this imbalance (including syncope or pacemaker insertions) in this population of patients (Table II-42 in the EU RMP dated 09 August 2013). In the PLATO safety analysis set, the number of patients with AEs in the cardiac arrhythmias HLGT was generally similar between treatment groups (14.2% with ticagrelor vs 14.6% with clopidogrel). SAEs and DAEs in the cardiac arrhythmias HLGT were also generally similar between treatment groups (SAEs ticagrelor [2.6%] clopidogrel [2.9%]; DAEs ticagrelor [0.6%] clopidogrel [0.7%]). In PLATO, the number of patients with investigator-reported bradycardic events that were severe or reported as SAEs was similar between treatment groups. Overall, 53 (0.6%) patients in the ticagrelor group and 57 (0.6%) in the clopidogrel group experienced bradycardic events that were considered severe and 75 (0.8%) patients in the ticagrelor group and 86 (0.9%) in the clopidogrel group reported bradycardic events that were SAEs (Table II-41 in the EU RMP dated 09 August 2013). Procedures of pacemaker placement in patients with ventricular pauses ≥5 seconds were infrequent during the entire PLATO study with 2 patients with pauses ≥5 seconds in the ticagrelor group and 0 (zero) in the clopidogrel group having permanent pacemakers implanted. Overall, the occurrence of clinically important events (eg, syncope, heart block, cardiac arrest and pacemaker insertion) in patients with ventricular pauses was generally similar with ticagrelor compared to clopidogrel and did not correlate well with the occurrence of ventricular pauses.

Table 8 Important identified risks - Bradyarrhythmias (including Holter-detected ventricular pauses)

Identified Risk	Bradyarrhythmias (including Holter-detected ventricular pauses)
	Cumulative data from the global safety database: In total 581 AEs of Bradyarrhythmias had been received up to 08 November 2014. Of these, 474 AEs were serious and 107 were non-serious and 189 were SAEs from AstraZeneca clinical studies.. Reported outcome for the 581 AEs: Died: 33 (5.7%) Not recovered: 35 (6.0%) Recovering: 20 (3.4%) Recovered with sequelae: 9 (1.5%) Recovered: 331 (57.0%) Unknown: 153 (26.4%)
Severity and nature of risk	Holter monitoring data from a subset of PLATO patients showed that the risk for having a ventricular pause ≥3 seconds was statistically greater with ticagrelor than clopidogrel during Visit 1 and this risk was numerically greater (but not statistically significant) during Visit 2. These patterns were apparent regardless of whether the analysis included all patients in the Holter analysis set or only patients with paired readings. Ventricular pauses detected by Holter monitoring were predominantly asymptomatic and infrequently coincided with clinically important events such as syncope, heart block, cardiac arrest or pacemaker insertion, regardless of treatment group. More patients had ventricular pauses with ticagrelor than with clopidogrel; however, there were no adverse clinical consequences associated with this imbalance in this study population at therapeutic doses. **Phase 1** Prolonged ventricular pauses were observed with ticagrelor in 2 isolated individual healthy volunteers during the Phase 1 single ascending dose and thorough QT studies. Both cases were at doses of 900 mg or higher. One healthy volunteer in the thorough QT study (Study D5130C00037) experienced episodes of AV block during telemetry. These occurred 1 to 1.5 hours after the 900 mg ticagrelor dose, and again approximately 70 hours post-dose. The volunteer was asymptomatic during these episodes. With the second observed event occurring at a low plasma concentration of ticagrelor, these observations could well be a normal physiologic variant and not a drug-related event. No pauses, notable bradycardia, or AV block was noted in any other volunteer in this study. In a single ascending dose study (Study D5130C00049), 1 healthy volunteer, a [redacted] male, experienced sinus arrest with a high grade AV block and ventricular escape and syncope within 30 minutes to 1 hour after a ticagrelor dose of 1260 mg, 14 times the 90 mg maintenance dose. Two prolonged ventricular pauses were observed, the longer of which lasted for 11.34 seconds. Prior to the pauses, the volunteer experienced dizziness, diaphoresis, and emesis. The second pause was associated with syncope, and the patient underwent approximately 5 to 6 compressions of the chest wall. The volunteer recovered without sequelae within 1 minute and resumed normal sinus rhythm without evidence of conduction

Table 8 Important identified risks - Bradyarrhythmias (including Holter-detected ventricular pauses)

Identified Risk	Bradyarrhythmias (including Holter-detected ventricular pauses)
	delay or block.
Background incidence/prevalence	There are several common patterns of bradycardic events, ie, bradyarrhythmias and conduction disturbances, following acute MI and they vary in aetiology, prognosis, and management, according to the site and nature of the infarction (Ryan et al 1996). Sinus bradycardia is seen in up to one-third of patients with acute MI. Patients with STEMI involving the right coronary artery often experience bradycardic events, especially after reperfusion, which is considered to be due to increased vagal tone (Bezold-Jarisch reflex), in addition to ongoing ischaemia or necrosis of the nodal and conduction tissue. Both sinus and atrioventricular node dysfunction are observed following ACS. In general, bradycardic events in patients with non-anterior wall MIs are transient and resolve within the first several days without requiring permanent pacemaker placement, whereas bradycardic events associated with anterior wall MIs indicate more extensive conduction system damage and often require a permanent pacemaker. In this context, prolonged ventricular pauses observed on ECG, with or without associated symptoms, will receive particular attention, regardless of their underlying cause.
Risk groups or risk factors	In patients with ACS, many factors predispose patients to arrhythmias, most notably ongoing ischaemia, which impairs normal myocardial depolarisation or repolarisation or suppresses the activity of the conduction tissues. In addition, necrosis of myocardial tissue leads to free radical production, acidosis, and derangement of ionic homeostasis, all of which promote electrophysiological instability (Higham et al 1993). Patients with an increased risk of bradycardic events (eg, known sick sinus syndrome, second or third degree AV block, or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker) have not been studied. It is clinically anticipated that these patients would be at increased risk for bradyarrhythmia-related AEs including ventricular pauses. Although mostly asymptomatic, prolonged ventricular pauses are more likely to be associated with symptoms such as dizziness, presyncope, or syncope. If these episodes were to occur with either increased frequency or increased severity on ticagrelor in the ACS population, it would be expected that they would occur within the first few days at a time when patients are already in the hospital and being monitored. After the first few days, these events become less frequent and more similar between ticagrelor and clopidogrel.
Potential mechanisms	The pathophysiological mechanism for the increase in ventricular pauses with ticagrelor is not known, but the prevailing hypothesis is that ticagrelor-induced adenosine reuptake inhibition may be important, especially in the setting of ACS, where there may be increased release of adenosine due to ischaemia. Adenosine depresses sinoatrial node activity, AV nodal conduction, and ventricular automaticity, and attenuates cardiac stimulatory action of catecholamines and the release of norepinephrine from nerve terminals (Belardinelli and Lerman 1991). However, other mechanisms may be involved in addition to an adenosine-mediated effect, eg, increased vagal tone.
Preventability	Not known.

Table 8 Important identified risks - Bradyarrhythmias (including Holter-detected ventricular pauses)

Identified Risk	Bradyarrhythmias (including Holter-detected ventricular pauses)
Potential public health impact of safety concern/Impact on individual patient	It is important to note that the management of sick sinus syndrome (often in patients with concurrent ischaemic heart disease) includes the use of medications such as beta-blockers and non-dihydropyridine calcium channel blockers in order to control the tachyarrhythmia component of sick sinus syndrome despite the risk of exacerbating the bradyarrhythmia component. So, in such patients, alternative therapies can be considered on an individual patient basis by the practitioner weighing the benefits and risks and in some cases a pacemaker is implanted so that the patient can continue to receive the benefit of otherwise effective medical therapy. This is a similar situation as the case of ticagrelor versus clopidogrel. If an individual patient has a bradyarrhythmia on ticagrelor, it is most likely to occur in the hospital in the first few days after the ACS event. A marked bradycardic event may lead to discontinuing ticagrelor and if warranted, placement of a pacemaker. However, after these first few days, such events should be rare even in high-risk patients. Nonetheless, if patients with a history of sick sinus syndrome or 2nd or 3rd degree AV block develop symptoms suggesting a bradycardic event, clinicians should be aware that ticagrelor may increase the risk of bradyarrhythmias in susceptible patients and, on an individual basis, determine whether treatment with ticagrelor should be modified based on an evaluation of the patient. Although Phase 1 and 2 observations suggested a possible safety concern with respect to bradyarrhythmias, the totality of clinical data, including evaluation of bradyarrhythmia-related AEs, SAEs, and DAEs, and the results of the extensive Holter monitoring assessment, confirms that there are no clinically important safety concerns related to bradyarrhythmias with ticagrelor in an extensive study population at therapeutic doses.
Evidence source	AstraZeneca clinical studies, literature and reports from marketed use
MedDRA terms	Clinical data: All terms refer to the cECG findings detected by Holter monitoring (which included bradycardia, ventricular pauses, and dropped beats). Cumulative data in the global safety database: SMQ Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (narrow) + additional PTs: Bradycardia, Syncope, Presyncope, Sudden cardiac death, Electrocardiogram abnormal, Maximum heart rate decreased, Heart rate decreased

ACS Acute coronary syndromes; AE Adverse event; AV Atrioventricular; cECG Continuous electrocardiogram; CI Confidence interval; DAE Discontinuation of study drug due to adverse event; ECG Electrocardiogram; EU European Union; HLGT High level group term; MedDRA Medical Dictionary for Regulatory Activities; MI Myocardial infarction; PLATO PLATelet inhibition and Patient Outcomes; PT Preferred Term; RMP Risk Management Plan; SAE Serious adverse event; STEMI ST segment elevation myocardial infarction.

11.3.1.4 Serum creatinine increases (renal impairment)

Table 9 Important identified risks - Serum creatinine increases (renal impairment)

Identified Risk	Serum creatinine increases (renal impairment)
Frequency with 95% CI	In PLATO, serum creatinine concentration increased by >30% in 25.5% of patients receiving ticagrelor compared to 21.3% of patients receiving clopidogrel and by >50% in 8.3% of patients receiving ticagrelor compared with 6.7% of patients receiving clopidogrel. On-treatment AE reports of increased blood creatinine were received in 49 (0.5%) and 26 (0.3%) subjects on ticagrelor and clopidogrel, respectively. Renal-related AEs were reported more frequently in subjects with greater degrees of baseline renal impairment. This was seen in both treatment arms (mild impairment: ticagrelor 4.0% vs clopidogrel 3.1%; moderate: 12.5% vs 8.6%; severe: 21.6% vs 24.7%, respectively (see Table II-46 in the EU RMP dated 09 August 2013). Renal-related AEs and SAEs were reported more frequently with increasing age in both treatment groups (Table II-47 and Table II-48 in the EU RMP dated 09 August 2013, respectively).
Seriousness/outcomes	During the course of the PLATO study, increases in mean serum creatinine values of approximately 10% relative to baseline were observed in both treatment groups. However, a 1.5% to 2% greater increase from baseline was observed in those patients receiving ticagrelor compared with those on clopidogrel. Although more subjects on ticagrelor showed maximal increases from baseline of >30% (25.5% of ticagrelor subjects vs 21.3% of clopidogrel subjects), there was not an associated increase in risk of primary endpoint in these subjects. In PLATO, the numbers of renal-related SAEs, deaths, and permanent discontinuations were similar in each treatment group, though the overall number of renal-related AEs was greater for ticagrelor (4.9% vs 3.8%). This is due to a difference only in non-serious renal-related AEs, which reflect creatinine elevation (see Table II-44 in the EU RMP dated 09 August 2013). Similar trends in non-serious AEs were observed in Phase 2 studies. For those patients in PLATO receiving laboratory monitoring, there was no difference in overall duration of study therapy between treatment arms. Cumulative data from the global safety database: In total 266 AEs of Renal impairment including serum creatinine increases had been received up to 08 November 2014. Of these, 222 were serious and 44 were non-serious and 96 were SAEs from AstraZeneca clinical studies. Reported outcome for the 266 AEs: Died: 18 (6.8%) Not recovered: 56 (21.0%) Recovering: 21 (7.9%) Recovered with sequelae: 3 (1.1%) Recovered: 93 (35.0%) Unknown: 75 (28.2%)

Table 9 Important identified risks - Serum creatinine increases (renal impairment)

Identified Risk	Serum creatinine increases (renal impairment)
Severity and nature of risk	In PLATO, the majority of patients in both treatment groups had baseline renal function measurements of at least 'mild renal impairment' (<90 mL/min). The 1.5% to 2% greater increase from baseline observed in those patients receiving ticagrelor compared with those on clopidogrel was not driven by differences in individual outliers. In both treatment arms, the increase in creatinine was noted to be non-progressive and the small treatment effect diminished on discontinuation of ticagrelor. No decrease in creatinine was noted on discontinuation from the clopidogrel arm (see Table II-45 in the EU RMP dated 09 August 2013).
Background incidence/prevalence	Renal impairment is observed frequently in patients with ACS. When measured in terms of GFR, ACS patients lose up to 5-6 mL/min, with the majority of that loss (2-3 mL/min of GFR), occurring during the first 3-10 days (Hillege et al 2003). A US study of 147007 elderly Medicare patients admitted with acute MI found that 19.4% of the patients had acute renal injury (defined as an increase in serum creatinine of ≥0.3 mg/dL over baseline) during their acute hospital admission, and that 5.2% had severe acute renal injury (increase in serum creatinine of >1.0 mg/dL) (Parikh et al 2008). A second US study of 483 patients admitted to a single centre with acute MI found that 22% had elevated serum creatinine levels (>1.5 mg/dL) (Walsh et al 2002). The widely varying estimates of prevalence are indicative of the lack of consensus on the definition of renal failure/injury. The paper by the ADQI group (Bellomo et al 2004) makes this point specifically with respect to the diagnosis of acute renal failure.
Risk groups or risk factors	Risk factors for serum creatinine elevations (eg, older age, concurrent conditions such as diabetes, hypertension, ischaemic heart disease, and atherosclerosis at other sites) are common in the target population. In PLATO, the majority of patients in both treatment groups were classified as having at least mild renal impairment at baseline; this was representative of the target population as many patients with ACS have a degree of renal impairment or increased creatinine. In PLATO, the results across subgroups stratified by baseline renal function were consistent with the overall PLATO results, in which ticagrelor-treated patients in each subgroup showed a higher frequency of renal-related AEs (except severe baseline renal impairment where reporting rates were higher on clopidogrel), but this did not translate to an imbalance in SAE reporting (Table II-46 in the EU RMP dated 09 August 2013). Renal-related AEs were reported more frequently with increasing age in both treatment groups (Table II-47 in the EU RMP dated 09 August 2013). Ticagrelor-treated patients experienced more renal-related AEs compared to clopidogrel-treated patients in the categories ≥65 to <75 years and ≥75 years. This pattern was also apparent for renal-related SAEs (Table II-48 in the EU RMP dated 09 August 2013). This did not result in an increased overall likelihood of death or permanent discontinuation of treatment. As would be expected, haemodynamic instability, intravenous contrast agents, and various concomitant medications known to affect the GFR (eg, ACE inhibitors, ARBs) can all contribute to renal impairment during both the index event and subsequent clinical course in ACS patients. AstraZeneca evaluated the effect of concomitant medications known to affect GFR, including ACE inhibitors and ARBs on creatinine increases and risk of renal AEs in PLATO. The analyses demonstrate that the treatment effect of ticagrelor compared to clopidogrel in patients receiving concomitant ACE inhibitor or ARB is consistent with the overall observed renal effects in the PLATO study population.

Table 9 Important identified risks - Serum creatinine increases (renal impairment)

Identified Risk	Serum creatinine increases (renal impairment)
	Patients with moderate or severe renal impairment at baseline were more likely to experience a renal-related AE than those with mild or no impairment, and this was similar between treatment arms.
Potential mechanisms	Observations of cystatin C and serum creatinine suggest an effect on GFR (possibly adenosine-mediated changes of the arteriolar tone/vasoactivity) rather than post-glomerular tubular handling of creatinine. The nature of the creatinine elevations and their impact as detailed above combined with urinalysis data from Phase 1 and 2 studies did not provide any evidence for drug-induced kidney injury. Urinalysis data were not collected during the PLATO study.
Preventability	Not known
Potential public health impact of safety concern/Impact on individual patient	Mild, non-progressive increases in serum creatinine that were slightly greater than those observed with clopidogrel have been associated with use of ticagrelor. In PLATO, this observation was neither translated into an imbalance of renal-related SAE nor associated with clinically meaningful outcomes, including death, dialysis, renal transplantation and permanent discontinuation of treatment. Therefore, the public health impact is considered to be minimal.
Evidence source	AstraZeneca clinical studies, literature, and reports from marketed use
MedDRA terms	Clinical data: PTs: Blood creatinine increased, Renal impairment Cumulative data in the global safety database: SMQ Acute Renal Failure

PLATO: A Randomised, Double-blind, Parallel Group, Phase 3, Efficacy and Safety Study of Ticagrelor Compared With Clopidogrel for Prevention of Vascular Events in Patients With Non-ST or ST Elevation Acute Coronary Syndromes
ACE Angiotensin converting enzyme; ACS Acute coronary syndromes; ADQI Acute Dialysis Quality Initiative; AE Adverse event; ARB Angiotensin receptor blocker; CI Confidence interval; EU European Union; GFR Glomerular filtration rate; MedDRA Medical Dictionary for Regulatory Activities; MI Myocardial infarction; PT Preferred Term; RMP Risk Management Plan; SAE Serious adverse event; US United States.

11.3.1.5 Hyperuricaemia

Table 10 Important identified risks - Hyperuricaemia

Identified Risk	Hyperuricaemia
Frequency with 95% CI	In PLATO, uric acid concentration crossed the threshold (ULN 7 mg/dL in men and 6 mg/dL in women) at 1 or more follow-up visits in approximately 20% patients receiving ticagrelor and 13% receiving clopidogrel. Relatively few patients 60 (0.6%) on ticagrelor reported AEs of elevation in uric acid vs 42 (0.5%) on clopidogrel.
Seriousness/outcomes	In the PLATO safety analysis set, the number of patients with potentially uric acid-related AEs on treatment was, though numerically higher for ticagrelor, generally similar between treatment groups (195 [2.1%] for ticagrelor vs 164 [1.8%] for clopidogrel). Overall, potential uric acid-related SAEs and DAEs in the treatment arms were similar in seriousness and outcome. In the ticagrelor arm, there were 2 DAEs, reported as non-serious, and there were no potential uric acid-related SAEs leading

Table 10 Important identified risks - Hyperuricaemia

Identified Risk	Hyperuricaemia
	to study discontinuation. There were no related deaths in the treatment arms (Table II-54 Gout in the EU RMP dated 09 August 2013). Data therefore demonstrate that the clinical consequences of the observed effect on uric acid levels are manifested only as an increase in reporting rates of laboratory events. Cumulative data from the global safety database. In total 21 AEs of Hyperuricaemia had been received up to 08 November 2014. Of these, 4 were serious and 17 were non-serious. There were no SAEs from AstraZeneca clinical studies. Reported outcome for the 21 AEs: Died: 0 (0.0%) Not recovered: 5 (23.8%) Recovering: 1 (4.7%) Recovered with sequelae: 0 (0.0%) Recovered: 6 (28.6%) Unknown: 9 (42.9%)
Severity and nature of risk	In a healthy volunteer clinical pharmacology study (D5130C00050), mean elevations of uric acid of less than 10% in ticagrelor-treated subjects fully resolved within 60 hours of the last dose. In the PLATO safety laboratory analysis set, the mean increase of serum uric acid from baseline for ticagrelor and clopidogrel treatment groups was 15% and 7.5%, respectively. In both treatment groups, these increases were not progressive and remained steady over time during treatment. Mean serum uric acid levels decreased after discontinuation of ticagrelor treatment but not after discontinuation of clopidogrel treatment. In PLATO, there were numerically more patients who crossed the ULN (7 mg/dL in men and 6 mg/dL in women) and also developed potential uric acid-related AEs for ticagrelor (33/1296 [2.5%]) than for clopidogrel (19/852 [2.2%]) (Table II-54 Gout in the EU RMP dated 09 August 2013).
Background incidence/prevalence	Hyperuricaemia, usually defined as an SU level >7 mg/dL, may be present in up to 18% of some populations (Luk and Simkin 2005).
Risk groups or risk factors	Diuretics use ≥50% of the time during the study treatment period in PLATO increased the frequency of uric acid-related AEs in both the ticagrelor and clopidogrel group (2.5% vs 2.2%) compared with no diuretic use (1.8% vs 1.6%, respectively) (see Table II-54 Gout in the EU RMP dated 09 August 2013) .
Potential mechanisms	There are 3 possible contributory mechanisms by which ticagrelor leads to increased serum uric acid levels: Inhibition of OAT1 and OAT3, potentially affecting trans-tubular transport of uric acid, therefore increasing serum uric acid levels. Inhibition of the adenosine transporter on RBCs. This blocks the uptake of adenosine into the RBCs, resulting in increased circulating adenosine, which then gets broken down, resulting in increased production of uric acid. Decreased renal excretion

Table 10 Important identified risks - Hyperuricaemia

Identified Risk	Hyperuricaemia
Preventability	Not known
Potential public health impact of safety concern/Impact on individual patient	Neither the data from the PLATO safety analysis set nor the scientific literature suggests that transient increases in serum uric acid levels predispose patients to gout and/or urate nephropathy in the future. Elevated uric acid has been recognised as an unreliable surrogate marker or predictor for the clinical diagnosis of gout. Overall, therefore, the potential public health impact is considered low.
Evidence source	AstraZeneca clinical studies, literature, and reports from marketed use
MedDRA terms	PTs: Hyperuricaemia, Blood uric acid increased, Blood uric acid abnormal

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AE Adverse event; CI Confidence interval; DAE Discontinuation of study drug due to an adverse event; EU European Union; MedDRA Medical Dictionary for Regulatory Activities; OAT1 Organic anion transporter 1; OAT3 Organic anion transporter 3; PT Preferred Term; RBC red blood cells; RMP Risk Management Plan; SAE serious adverse event; SU serum urate; ULN Upper limit of normal.

11.3.1.6 Drug-drug interactions: strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin

Table 11 Important identified risks - Drug-drug interactions: strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin

Identified Risk	Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin
Frequency with 95% CI	Not applicable
Seriousness/outcomes	There is a risk of increased ticagrelor levels in patients receiving CYP3A4 inhibitors, a risk of reduced ticagrelor levels with concomitant use of strong CYP3A4 inducers, and with concomitant use of ticagrelor, there will be potentially higher levels of simvastatin and lovastatin as well as potentially increased digoxin levels.

Table 11 Important identified risks - Drug-drug interactions: strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin

Identified Risk	Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin
Severity and nature of risk	Co-administration of ketoconazole (strong CYP3A4 inhibitor) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56%, respectively (Table II-59 in the EU RMP dated 09 August 2013). Co-administration of ticagrelor and diltiazem (moderate CYP3A4 inhibitor) increased the ticagrelor C_{max} by 69% and AUC by 174% and decreased the active metabolite C_{max} by 38% while AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels (Table II-60 in the EU RMP dated 09 August 2013). Co-administration of rifampicin (strong CYP3A4 inducer) with ticagrelor decreased ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46% (Table II-61 in the EU RMP dated 09 August 2013). Co-administration of ticagrelor (180 mg BID for 7 days) with simvastatin (single 80 mg dose on day 5) increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2- to 3-fold (Table II-62 in the EU RMP dated 09 August 2013). Concomitant administration of ticagrelor increased the digoxin C_{max} by 75%, C_{min} by 30%, and AUC by 28% (Table II-64 in the EU RMP dated 09 August 2013).
Background incidence/prevalence	In PLATO, prior to the index event, 36% of patients received lipid-lowering therapy. During randomised treatment, the majority (93%) of patients received lipid-lowering therapy. At some time between randomisation and last dose, 11% of patients in both treatment arms received a moderate CYP3A4 inhibitor (Table II-2 in the EU RMP dated 09 August 2013).
Risk groups or risk factors	Those receiving these drugs as concomitant therapy.
Potential mechanisms	Ticagrelor is metabolised via CYP3A4 and is also an inhibitor of CYP3A4. Inhibition of P-gp transporter by ticagrelor.
Preventability	Appropriate wording in the SmPC.
Potential public health impact of safety concern/ Impact on individual patient	Increased ticagrelor levels may increase the risk of bleeding and other adverse effects. However, in PLATO, in the exposure-response models developed for the safety endpoints in bleeding, dyspnoea, and ventricular pauses, it was consistently observed that the exposure-response relationships identified for these endpoints were relatively flat. Reduced levels of ticagrelor may reduce efficacy. High plasma concentrations of simvastatin and lovastatin are known to increase the risk of myopathy and rhabdomyolysis. Digoxin is a narrow therapeutic index drug and small changes in digoxin levels may be clinically significant. The most common clinical features of digoxin toxicity are anorexia, nausea, vomiting, and cardiac arrhythmias (eg, ventricular ectopics, AV block).

Table 11 Important identified risks - Drug-drug interactions: strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin

Identified Risk	Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin
Evidence source	AstraZeneca clinical studies
MedDRA terms	Not applicable

PLATO: A Randomised, Double-blind, Parallel Group, Phase 3, Efficacy and Safety Study of Ticagrelor Compared With Clopidogrel for Prevention of Vascular Events in Patients With Non-ST or ST Elevation Acute Coronary Syndromes
AUC Area under the plasma concentration-time curve; AV Atrioventricular; CI Confidence interval; C_{max} Maximum plasma concentration; C_{min} Minimum plasma concentration; CYP Cytochrome P450; EU European Union; MedDRA Medical Dictionary for Regulatory Activities; P-gp P-glycoprotein; RMP Risk Management Plan; SmPC Summary of Product Characteristics.

11.3.2 Important potential risks

The following 2 safety concerns are important potential risks:

- Drug-induced liver injury (Table 12)
- Gout/gouty arthritis and urate nephropathy (Table 13)

11.3.2.1 Drug-induced liver injury

Table 12 Important potential risks - Drug-induced liver injury

Potential Risk	Drug-induced liver injury
Frequency with 95 % CI	In the PLATO safety analysis set, the number of patients with hepatic-related AEs on treatment was similar between treatment groups (156 [1.7%] for ticagrelor vs 157 [1.7%] for clopidogrel). There were 219 (3.9%) and 210 (3.8%) patients in the ticagrelor and clopidogrel treatment groups, respectively, in the PLATO safety laboratory analysis set who had at least 1 LFT abnormality. The numbers of patients experiencing ALT or AST elevations during the treatment period at each of the following thresholds were balanced between ticagrelor and clopidogrel treatment groups: ≥3xULN, ≥5xULN, ≥10xULN, ≥20xULN. In PLATO, there were 16 ticagrelor patients and 9 clopidogrel patients whose bilirubin elevation of ≥2xULN was considered to be at least possibly related to study drug; 10/16 ticagrelor and 6/9 clopidogrel were homozygous Gilbert's Syndrome and 1 ticagrelor patient (1/16) was heterozygous Gilbert's syndrome. The remaining cases were not genotyped as no DNA samples were available for those patients. These data suggest that Gilbert's syndrome is a major factor explaining the bilirubin increases seen.
Seriousness/outcomes	In the PLATO analysis set, the number of patients with hepatic-related AEs on treatment was similar between treatment groups (156 [1.7%] for ticagrelor vs 157 [1.7%] for clopidogrel), 13 (0.1%) and 16 (0.1%) patients in the respective groups

Table 12 Important potential risks - Drug-induced liver injury

Potential Risk	Drug-induced liver injury
	who had hepatic-related SAEs, whereas 7 (0.1%) patients and 4 (0.1%) patients in these groups had AEs leading to discontinuation of study treatment, including 4 (0.0%) patients in the ticagrelor and 2 (0.0%) in the clopidogrel treatment group who had hepatic-related SAEs that led to discontinuation of study treatment. Cumulative data from the global safety database. In total 54 AEs of Drug-induced liver injury had been received up to 08 November 2014. Of these, 47 were serious and 7 were non-serious; 16 were SAEs from AstraZeneca clinical studies.. Reported outcome for the 54 AEs: Died: 6 (11.1%) Not recovered: 11 (20.4%) Recovering: 3 (5.6%) Recovered with sequelae: 2 (3.7%) Recovered: 16 (29.6%) Unknown: 16 (29.6%)

Table 12 Important potential risks - Drug-induced liver injury

Potential Risk	Drug-induced liver injury
Severity and nature of risk	In PLATO, absolute values of ALT, AST, ALP, and total bilirubin were generally similar over time and there was a similar frequency of abnormalities between treatment groups. However, there were more cases of elevated bilirubin (not associated with increases in transaminases) on ticagrelor than on clopidogrel. A total of 110 patients (62 in the ticagrelor group and 48 in the clopidogrel group) who experienced a hepatic-related SAE, ALT ≥8xULN, total bilirubin ≥2xULN, or direct bilirubin ≥1.5xULN were reviewed by an external blinded hepatologist. This review concluded that no patients in either treatment group were assessed as "definite" or "highly likely" causality. Most patients in both treatment groups were categorised as "probable" (ticagrelor 18 vs clopidogrel 10) and "possible" (ticagrelor 17 vs clopidogrel 8). The probable cases were mainly bilirubin elevations. The PLATO patients identified to have either an ALT ≥8xULN or evidence of hepatocellular toxicity at least 'possibly' related to study drug as evaluated by the external expert were individually reviewed (6 patients on ticagrelor vs 1 patient on clopidogrel). As would be expected in the ACS study population, ascription/exclusion of drug causality is difficult. The events in these 7 patients were most likely attributable to other causes or were heavily confounded; however, in 1 ticagrelor patient, there was a plausible association with study drug. Both cases of concurrent elevations of ALT ≥3xULN and total bilirubin ≥2xULN on ticagrelor had alternative explanations where elevated liver enzymes were observed minutes after ticagrelor ingestion and subsequently normalised throughout the remainder of the study. A single patient in the clopidogrel treatment group met enzymatic laboratory criteria but also had an alternative explanation for the laboratory abnormalities. A third patient with concurrent elevation of ALT ≥3xULN and total bilirubin ≥2xULN, on ticagrelor, was identified on the basis of unvalidated local laboratory values in an SAE narrative report with an alternative probable explanation to ticagrelor for the enzyme abnormalities. The Phase 1 data included a case of significantly elevated transaminases. Subject SC-532-5239/E0001139 had elevated ALT 266 IU/L and AST 141 IU/L after a ticagrelor dose escalation to 300 mg OD following 5 days of dosing at 200 mg OD. After discontinuation, the transaminase elevations resolved. A thorough investigation failed to identify an alternative cause and therefore AstraZeneca considers that there is a reasonable possibility of a causal association with ticagrelor to the biochemical changes seen. The Phase 2 data did not reveal any difference between ticagrelor and clopidogrel when assessing both laboratory values and adverse effects.
Background incidence/prevalence	The ACS population has many risk factors for hepatic injury; these patients are heavily comedicated. In PLATO, 90% of patients received concurrent statins. Statin use is associated with hepatic injury in 1% to 2% of patients. Non-alcoholic fatty liver disease is common in this patient population, which includes a high percentage of diabetic patients. Right heart failure and hypotension can lead to ischaemic hepatitis.
Risk groups or risk factors	No risk groups or risk factors have been identified for subjects with transaminase elevations. The patients with sporadic hyperbilirubinaemia and available DNA were mostly Gilbert's syndrome.
Potential mechanisms	Not known

Table 12 Important potential risks - Drug-induced liver injury

Potential Risk	Drug-induced liver injury
Preventability	Not known
Potential public health impact of safety concern/ Impact on individual patient	In PLATO, the majority of AEs were asymptomatic liver enzyme and bilirubin elevations. There were no cases of Hy's Law. There are 2 cases identified as plausibly ticagrelor related, both of these cases were isolated increases in transaminases without increased bilirubin. This has to be considered in the context of a large development programme of at least 10000 patients exposed to ticagrelor. The potential public health impact is likely to be low.
Evidence source	AstraZeneca clinical studies, literature, and reports from marketed use
MedDRA terms	MedDRA SMQs: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow); Hepatitis, non-infectious (narrow)

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ACS Acute coronary syndromes; AE Adverse event; ALP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; DNA Deoxyribonucleic acid; LFT Liver function test; MedDRA Medical Dictionary for Regulatory Activities; OD Once daily; PT Preferred term; SAE Serious adverse event; SMQ Standardized MedDRA Query; ULN Upper limit of normal.

11.3.2.2 Gout/gouty arthritis and urate nephropathy

Table 13 Important potential risks - Gout/gouty arthritis and urate nephropathy

Potential Risk	Gout/gouty arthritis and urate nephropathy
Frequency with 95 % CI	In PLATO, the number of patients with uric acid-related AEs by SOC and HLGT and AEs by PT was similarly infrequent in both treatments but was numerically greater for patients in the ticagrelor group compared with the clopidogrel group (overall 195 [2.1%] and 164 [1.8%] respectively). Taken together, AEs of gout, gouty arthritis, and podgra were similar between treatment groups. Overall, the imbalance in potential uric acid-related AEs was driven mainly by the PTs of hyperuricaemia and blood uric acid increased laboratory findings rather than clinical AEs. Data therefore demonstrate that the clinical consequences of the observed effect on uric acid levels are manifested only as an increase in reporting rates of laboratory events and not as an increase in clinical events of gout.
Seriousness/outcomes	In the PLATO safety analysis set, the number of patients with uric acid-related AEs on treatment was, though numerically higher for ticagrelor, generally similar between treatment groups (195 [2.1%] for ticagrelor vs 164 [1.8%] for clopidogrel) (Table II-50 in the EU RMP dated 09 August 2013). Of the 9 patients in the ticagrelor group who had SAEs potentially related to elevations of uric acid during treatment (vs 11 in the clopidogrel group), 5 of these were non-specific, including SAEs of calculus ureteric (2 patients), nephrolithiasis (2 patients), and monoarthritis (1 patient). Two patients had SAEs related to gout ('gout attack' and 'worsening of gout'), both of which resolved. Gouty arthritis was reported in 2 patients. Overall, uric acid-related SAEs and DAEs in the treatment arms were similar in

Table 13 Important potential risks - Gout/gouty arthritis and urate nephropathy

Potential Risk	Gout/gouty arthritis and urate nephropathy
	seriousness and outcome. In the ticagrelor arm, there were 2 DAEs, reported as non-serious, and there were no potential uric acid-related SAEs leading to study discontinuation. There were no related deaths in the treatment arms (Table II-50 in the EU RMP dated 09 August 2013). Cumulative data from the global safety database. In total 52 AEs of Gout/gouty arthritis **and 1 AE of Urate nephropathy** had been received up to 08 November 2014. Of these, 16 were serious and 37 were non-serious, and 6 were SAEs from AstraZeneca clinical studies.. Reported outcome for the 53 AEs: Died: 0 (0.0%) Not recovered: 9 (17.0%) Recovering: 5 (9.4%) Recovered with sequelae: 0 (0.0%) Recovered: 20 (37.7%) Unknown: 19 (35.9%)
Severity and nature of risk	In PLATO, there was no evidence suggesting that the elevated uric acid levels seen were associated with an increased risk of gout or related AEs.
Background incidence/prevalence	While it is acknowledged that some individuals with hyperuricaemia have been found to have a greater risk of developing episodes of gout than those with normal uric acid levels, tolerance for elevations of serum uric acid varies, and not all individuals with hyperuricaemia will experience episodes of gout (Halpern et al 2009, Lin et al 2000). Paradoxically, patients who experience an episode of gout often have normal levels of serum uric acid during the event (Logan et al 1997, Schlesinger et al 2009). The prevalence of gout is much higher in men than in women and rises with age; it affects 1% to 2% of adults in developed countries, where it is the most common inflammatory arthritis (Richette and Bardin 2010). Results from PLATO do not support a causal association between raised uric acid levels and increased risk of gout or uric acid nephropathy.

Table 13 Important potential risks - Gout/gouty arthritis and urate nephropathy

Potential Risk	Gout/gouty arthritis and urate nephropathy
Risk groups or risk factors	In PLATO, diuretic use ≥50% of the time during the study treatment period increased the frequency of uric acid-related AEs in both the ticagrelor and clopidogrel group (2.5% vs 2.2%) compared with no diuretic use (1.8% vs 1.6%, respectively). However, diuretic use ≥50% of the time did not appear to increase the likelihood of having an episode of gout in both treatment groups; the frequency of gout was similar in each treatment group with diuretic use (0.7%) and with no diuretic use (0.6%). This, therefore, suggests that the long-term impact on gout may be influenced by concomitant use of diuretics, regardless of whether patients receive ticagrelor or clopidogrel. Patients with a history of gout and uric acid nephropathy, as well as renal impairment and other risk factors for these conditions were not excluded from the PLATO study. In spite of this, uric acid-related AEs were infrequent in number, and similar in the ticagrelor and clopidogrel arms. There have been no AE reports of urate nephropathy from clinical study subjects receiving ticagrelor. The frequency of gout and gouty arthritis events in those subjects with and without a past history of gout by treatment in the PLATO study are shown in Table II-58 in the EU RMP dated 09 August 2013. Both arms show that those subjects with a past history of gout are observed to report further gout AEs with greater frequency (approximately 0.5% of subjects with no prior history of gout report a subsequent on-treatment event of gout or gouty arthritis compared with approximately 10% of those with a past history). This observation suggests that the frequency of reporting gout or gouty arthritis is independent of uric acid levels given the fact that ticagrelor is associated with a greater mean increase in uric acid level and more subjects crossing the ULN.
Potential mechanisms	It is possible that an increased serum uric acid level potentiates the risk of an individual experiencing gout or gouty arthritis although elevated uric acid has been recognised as an unreliable surrogate marker or predictor for the clinical diagnosis of gout.
Preventability	Not known
Potential public health impact of safety concern/ Impact on individual patient	An individual's risk of developing gout and urate nephropathy is complex and may be influenced by multiple factors, which may include obesity, alcohol consumption, diuretic use, and addition to uric acid levels. Neither the data from the PLATO safety analysis set nor the scientific literature suggests that transient increases in serum uric acid levels predispose patients to gout and / or urate nephropathy in the future. Elevated uric acid has been recognised as an unreliable surrogate marker or predictor for the clinical diagnosis of gout. Overall, therefore, the potential public health impact is considered low.
Evidence source	AstraZeneca clinical studies, literature, and reports from marketed use
MedDRA terms	PTs: Gout, Gouty arthritis, Urate nephropathy.

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AE Adverse event; CI Confidence interval; DAE Discontinuation of study drug due to an adverse event; EU European Union; HLGT Higher level group term; MedDRA Medical Dictionary of Regulatory activities; PT Preferred Term; RMP Risk Management Plan; SAE serious adverse event; SOC System Organ Class; ULN Upper limit of normal.

11.3.3 Important missing information

11.3.3.1 Use in patients with moderate to severe liver disease

Patients with moderate or severe liver disease have not been studied with regard to ticagrelor. This subgroup of patients was excluded from the PLATO study because the comparator, clopidogrel, is contraindicated in severe liver disease and must be used with caution in moderate hepatic disease. Ticagrelor use in patients with moderate to severe hepatic impairment is contraindicated, as stated in the SmPC (Section 4.3). Further information regarding patients with moderate or severe liver disease is included in the SmPC (Sections 4.2, 4.4, and 5.2).

In the EU RMP, it is stated that potentially, liver disease patients are inherently at higher bleeding risk due to the risk of hepatic coagulopathy, and there may also be higher ticagrelor plasma concentrations due to reduced hepatic metabolism.

11.3.3.2 Use in patients with increased risk of bleeding: patients with active bleeding, past history of ICH, GI bleed within 6 months, major surgery within 30 days and clinically relevant thrombocytopaenia or anaemia, concomitant use of oral anticoagulants and/or fibrinolytics within 24 hours of ticagrelor dosing, concomitant use of NSAIDs

The EU SmPC (Section 4.4) states that ticagrelor should be used with caution in patients at known increased risk for bleeding.

The following patients have an increased potential to bleed that may be exacerbated by the addition of ticagrelor: patients with active bleeding, past history of ICH, GI bleed within 6 months, major surgery within 30 days and clinically relevant thrombocytopaenia or anaemia; concomitant use of oral anticoagulants and/or fibrinolytics within 24 hours of ticagrelor dosing; concomitant use of NSAIDs. With the exception of concomitant use of NSAIDs, these patients were excluded from PLATO. NSAIDs were not excluded from PLATO and no specific studies have been conducted to assess possible PD interactions; ie, bleeding risk.

11.3.3.3 Use in patients beyond the recommended 1-year treatment duration (off-label use)

For use beyond the recommended 1-year treatment duration, the ongoing PEGASUS study (D5132C00001) will provide further data on longer-term exposure since patients will be treated for up to 3 years.

11.3.3.4 Use in children

ACS and other manifestations of atherosclerotic vascular disease are not prevalent before middle age. Patients aged <18 years have been excluded from the clinical studies. The SmPC (Section 4.2) states that the safety and efficacy of ticagrelor in children below the age of 18 years in the approved adult indication have not been established, since data are not available.

There are no common childhood diseases that are treated with antiplatelet agents. Accordingly, no significant amount of off-label paediatric use is anticipated. Ticagrelor is not considered to be at unusual risk of misuse by children. In most countries, it is available in standard clear polyvinyl chloride/aluminium blisters.

The approved EU Paediatric Investigation Plan (PIP) (P/0295/2014 dated 30 October 2014) is for the indication of Prevention of vaso-occlusive crises in paediatric patients with SCD (see Section 11.2.3.6 for further details).

11.3.3.5 Use in pregnant or lactating women

No clinical studies have been conducted in pregnant women. Ticagrelor treatment is not recommended during pregnancy. Routine pharmacovigilance has not identified any safety issues.

11.3.3.6 PEGASUS study: patients ≥12 months distant from their MI who have a history of ischaemic stroke or other features associated with an increased risk of ICH

Patients ≥12 months distant from their MI with a history of ischaemic stroke or other features associated with an increased risk of ICH are excluded from the PEGASUS study.

There are no data indicating that ticagrelor predisposes patients with prior ischaemic stroke to ICH. Based on data from PLATO, patients with a prior history of ischaemic stroke and recent ACS treated with ticagrelor plus aspirin did not experience more ICH than those treated with clopidogrel plus aspirin. However, the reason for including this exclusion criterion in PEGASUS is because accumulating data across a number of studies using a variety of antiplatelet drugs (not including ticagrelor) suggests that more intensive antiplatelet therapy may pose a particularly high risk of ICH in patients with a history of ischaemic stroke.

The EU SmPC (Sections 4.3 and 4.4) includes information stating that ticagrelor is contraindicated in patients with a known history of ICH.

11.4 Effectiveness of risk minimisation

Routine risk minimisation (including, for example, product labelling) is considered appropriate for ticagrelor.

The following initiatives to measure the effectiveness of risk minimisation have been in place during the reporting period.

As part of the approval of the New Drug Application, the FDA approved a REMS focusing on the potential risks of increased bleeding and decreased efficacy with higher aspirin doses (above 100 mg). The REMS was approved on 20 July 2011 with a timetable for submission of assessments at 18 months, 3 years, and 7 years from the date of the approval of the REMS. The FDA determined that the 18 months assessment demonstrated that the communication plan had been completed and had met its goals. Thus, ticagrelor was released from the requirement of the REMS on 30 October 2013.

In response to a request by the Canadian health authority, the prescriber Knowledge and Understanding (KAU) survey has been used as a tool to assess the efficacy of the risk minimisation measures outlined in the Canadian RMP. This survey is designed to be conducted in 3 waves, with approximately 9-month intervals between the waves. The first wave results were submitted to Health Canada in March 2013 and are discussed in detail in Section 16.5 of the ticagrelor PBRER covering the interval 01 January to 30 June 2013. During this reporting period (03 December 2010 to 08 November 2014), the results of the KAU Survey Wave 2 were submitted to Health Canada on 30 April 2014.

In the first wave, the KAU pertaining to the risk of bleeding did not meet the pre-determined criteria for adequacy; the results of Wave 2 were similar for the risk of bleeding while also demonstrating lower KAU pertaining to ASA dosing in combination with ticagrelor despite certain educational commitments implemented by AstraZeneca.

AstraZeneca has considered it necessary to conduct a root cause analysis in order to identify the factors associated with inadequate responses to survey questions related to bleeding and ASA safety messages. A brief summary of this project was submitted to Health Canada in June 2014, while the development of further measures addressing the knowledge gaps based on newly available information is ongoing. AstraZeneca also proposed delaying the third wave of the KAU survey until these additional recent responses are analysed and corresponding measures to address the knowledge gaps are implemented.

During the reporting period, the ticagrelorRMP has been updated from version 4.0, dated 22 September 2010, to the current version 8.0, dated 09 August 2013. In the absence of any data justifying further updates, AstraZeneca considers the current version 8.0 of the RMP to be up-to-date at the end of the reporting period. Therefore, no updated version of the RMP is included with the renewal application.

12. BENEFIT EVALUATION

12.1 Newly identified information on efficacy/effectiveness

No additional information on efficacy/effectiveness in the approved indication(s) became available during the reporting period.

12.2 Characterisation of benefits

The clinical evidence for the efficacy of ticagrelor is derived from PLATO (D5130C05262), a comparison of ticagrelor and clopidogrel, both given in combination with ASA and other standard therapy (Wallentin et al 2009).

The pivotal PLATO study was a randomised, double-blind, parallel-group, Phase 3 efficacy and safety study of ticagrelor compared with clopidogrel for prevention of vascular events in 18624 patients with ACS (UA, NSTEMI, or STEMI). The study enrolled patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. Patients were randomised to receive clopidogrel or ticagrelor. Clopidogrel was administered

as an initial LD of 300 mg if previous thienopyridine therapy had not been given followed by a MD of 75 mg OD. An additional LD of 300 mg was allowed at the investigator's discretion. Ticagrelor was administered as a LD of 180 mg followed by a MD of 90 mg BID. Patients could have been medically managed, treated with PCI or CABG.

In the PLATO study (N=18624), a highly significant relative risk reduction (RRR) of 16% was documented for the composite endpoint of CV death, MI, and stroke over 12 months. Thus, ticagrelor is superior to clopidogrel, which was the previous standard of care for preventing thrombotic events in patients with ACS (Wallentin et al 2009). The difference in treatment effect was apparent within the first 30 days of therapy and persisted throughout the 12-month study period. The benefits over clopidogrel were documented in a representative broad range of patients with ACS, including patients with UA, NSTEMI, and STEMI, also including patients who were managed medically, and those who were managed with PCI or CABG. In PLATO, the hierarchical testing of secondary endpoints showed significant reductions of the same magnitude as for the primary endpoint in the ticagrelor group compared with the clopidogrel group, with respect to the rates of the composite endpoint of all-cause death, MI, and stroke; the composite endpoint of CV death, MI, stroke, severe recurrent ischaemia, recurrent ischaemia, transient ischaemic attack, and other arterial thrombotic events; MI alone; and CV death. The rate of stroke alone did not differ significantly between the 2 treatment groups, but the benefit pattern was reflected in a reduction in the rate of all-cause death.

The consistency of findings and robustness of the results regarding the primary endpoint is also illustrated by the homogeneity of the pre-specified subgroups; there was no significant heterogeneity in analyses of 33 subgroups, with 3 exceptions: patients weighing less than the median weight for their sex, those not taking lipid-lowering drugs at randomisation, and those enrolled in North America.

The clinical relevance of the effect size documented in PLATO is also illustrated by the inclusion of ticagrelor in several international guidelines (Amsterdam et al 2014, Hamm et al 2011, Jneid et al 2012, Kolh et al 2014, Steg et al 2012). The recommendation is applicable to a broad range of NSTEMI, ACS, and STEMI patients, without restrictions related to age, body weight, or preloading with clopidogrel. Treatment with ticagrelor is recommended irrespective of planned invasive or non-invasive strategy, and even if the coronary anatomy has not been established.

The efficacy findings from PLATO are generalisable to patient populations treated in medical practice. In general, the PLATO patients represented a typical ACS population, as demonstrated by large-scale registry data from European and American practices. The Swedish ACS Registry (RIKS-HIA) includes data from all patients admitted to Swedish coronary care units. In RIKS-HIA, 64% of patients from 1998–2005 (n=205269) and 79% of patients from 2007 (n=24695) met PLATO inclusion criteria (Stenestrand et al 2010).

13. BENEFIT-RISK BALANCE

The updated discussion of the benefit-risk balance incorporates an evaluation of the safety and efficacy/effectiveness information that became available during the reporting period, in the context of what was known previously. This evaluation involves the following:

- Critically examining information that has emerged during the reporting period to determine whether it led to the identification of new potential or identified risks, or contributed to knowledge of previously identified risks.
- Critically summarising relevant new safety and efficacy/effectiveness information that could have an impact on the benefit-risk balance.
- Conducting an integrated benefit-risk analysis for all approved indication(s) based on the cumulative information available since the DIBD.
- Summarising any risk minimisation actions that may have been taken or implemented during the reporting period, as well as risk minimisation actions that are planned to be implemented.
- Outlining plans for risk evaluations, including timelines and/or proposals for additional pharmacovigilance activities.

13.1 Benefit-risk context - medical need and important alternatives

Ischaemic heart disease is the leading cause of death worldwide (Mackey and Mensah 2004). As the acute presentation of ischaemic heart disease, ACS accounts for the vast majority of CAD deaths and non-fatal CAD-related disability. For all types of ACS, early, effective antiplatelet therapy reduces subsequent atherothrombotic events.

Professional society guidelines recommend DAPT (ie, ASA in combination with ticagrelor, clopidogrel or prasugrel) to reduce subsequent CV events after ACS. Approved treatment indications vary by geographic location, and there may be variations in the label text for a given indication. The following examples of approved indications are from the EMA SmPCs:

- **Ticagrelor**
  Ticagrelor, co-administered with ASA, is indicated for the prevention of atherothrombotic events in adult patients with ACS (UA, NSTEMI, or STEMI), including patients managed medically, and those who are managed with PCI or CABG.
- **Clopidogrel**
  Clopidogrel is indicated in adult patients suffering from ACS:
  - Non-ST segment elevation ACS (UA or NSTEMI), including patients undergoing a stent placement following PCI, in combination with ASA.

- STEMI, in combination with ASA, in medically treated patients eligible for thrombolytic therapy.

- **Prasugrel**
  Prasugrel, co-administered with ASA, is indicated for the prevention of atherothrombotic events in patients with ACS (UA, NSTEMI, or STEMI) undergoing primary or delayed PCI.

13.2 Benefit-risk analysis evaluation

13.2.1 Context of use of the medicinal product

Ticagrelor, as part of DAPT, is an approved therapeutic option for the prevention of atherothrombotic events in a broad spectrum of adult patients with ACS, irrespective of whether the treatment approach is non-invasive medical management or invasive with PCI or CABG (Hamm et al 2011, Kolh et al 2014, Steg et al 2012). In addition, recent guidelines from the American Heart Association/American College of Cardiology Foundation recommend ticagrelor or clopidogrel, with ASA, administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with either an early invasive strategy or medical management (Amsterdam et al 2014).

13.2.2 Considerations relating to key benefit(s)

The ticagrelor clinical development programme for the approved ACS indication included a substantial clinical pharmacology programme of 41 studies in approximately 1000 subjects, 4 Phase 2 studies in more than 1400 patients with CAD (Cannon et al 2007, Gurbel et al 2009, Gurbel et al 2010, Husted et al 2006), and the pivotal PLATO study in 18624 patients (Wallentin et al 2009). The PLATO study included a broad range of ACS patients, including those with UA, NSTEMI and STEMI, and NSTE-ACS intended for either invasive or non-invasive management (Wallentin et al 2009). Over 12 months of treatment, ticagrelor, compared with clopidogrel, decreased the rate of major clinically important thrombotic events after ACS (RRR=16%; ARR=1.9%), regardless of the type of ACS and of the intended treatment path. The efficacy of ticagrelor is robust to multiple sensitivity analyses and consistent across ACS subtypes and patient subgroups, although a possible efficacy interaction with higher doses of ASA has led to the recommendation that patients taking ticagrelor should take 75 mg to 150 mg ASA OD on a chronic basis, unless specifically contraindicated. The key benefits of ticagrelor are presented in the SmPC.

13.2.3 Considerations relating to key risk(s)

On the basis of data from the ticagrelor clinical trial programme and post-marketing experience, the important identified risks related to ticagrelor (EU RMP version 8, dated 09 August 2013) are Increased risk of bleeding, Dyspnoea, Bradyarrhythmias (including Holter-detected ventricular pauses), Serum creatinine increases (renal impairment), Hyperuricaemia, and Drug-drug interactions: strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (ie, simvastatin and lovastatin) and digoxin.

The assessment of clinical safety for ticagrelor relies to a great extent on the previous large pool of clinical safety data from the PLATO study, which is supported by post-marketing clinical experience. The known or identified risks of ticagrelor are presented in the SmPC. The important identified risks are discussed in Section 11.

Routine risk minimisation is considered appropriate for ticagrelor. For detailed information on routine and additional pharmacovigilance activities for each important safety concern, see Section 11.

13.2.4 Strengths, weaknesses, and uncertainties of the evidence

The benefit risk profile of ticagrelor for the ACS indication has been established through the clinical development programme, which included more than 20000 adult patients with CAD. Ticagrelor has been evaluated in patients with significant disease burden, interventions, and concomitant medications. The pivotal PLATO study in 18624 patients provides the main evidence in support of efficacy and safety. The strength of the PLATO study resides in its design, conduct, and homogeneous results within a large number of pre-defined subgroups. The study was performed in a large, representative patient population, and it met high quality standards. The study was randomised, double-blind, and used an effective comparator treatment for control. The safety profile of ticagrelor in ACS is further supported by post-marketing data. In addition, ticagrelor, as part of DAPT, is acknowledged by international guidelines as an important treatment option for ACS, irrespective of ACS subtype or intended treatment strategy.

However, and as reflected in the SmPC, the clinical development programme excluded certain patients, namely those with a propensity to bleed due to recent trauma, recent surgery, active or recent GI or intracranial bleeding, and/or those with moderate or severe hepatic impairment. These exclusions generally apply to antiplatelet agents as a class. Hence, in PLATO, patients receiving concomitant medicinal products that may increase the risk of bleeding, such as fibrinolytics or oral anticoagulants, within 24 hours of ticagrelor dosing were excluded. This exclusion applies to potent antiplatelet agents as a class. Patients with an increased risk of bradycardic events, such as those without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope were also excluded. This exclusion arose from a safety signal of ventricular pauses detected in DISPERSE2 (a dose confirmation study assessing the anti-platelet effects of ticagrelor vs. clopidogrel in NSTEMI) during Phase 2 of the ticagrelor development programme (Cannon et al 2007). Limited clinical experience suggests that caution be advised when considering therapy with ticagrelor for patients with these conditions who are at risk of bradycardia, and have no implanted pacemaker. PLATO enrolled a predominantly Caucasian (91.1%) population, with 5.8% Asians, 1.2% Blacks, and 1.4% other. These racial demographics resemble those of other worldwide ACS trials (Yusuf et al 2001). The efficacy and safety of ticagrelor were consistent irrespective of ethnicity. Pregnant or lactating women were excluded from PLATO, as is generally the case in large clinical studies, and no clinical study has been conducted in the paediatric population to date because ACS very rarely occurs in children.

There are no uncertainties of the evidence in the patient population studied, and it is not expected that the relative efficacy of ticagrelor would be different in the subgroups of patients who have not been studied.

13.2.5 Methodology and reasoning used to develop the benefit-risk evaluation

A qualitative assessment of ticagrelor benefits and risks has been performed. This assessment was based upon data from clinical studies, published literature, and the safety database. The evaluation of benefits and risks considered all available information from all sources.

All safety information collected on ticagrelor during the reporting period has been reviewed and evaluated by AstraZeneca, irrespective of the reporting source, or the seriousness, or causality of events. This includes an analysis of studies and safety topics reported in the literature that are kept under close surveillance, as well as an assessment of any new safety issues.

The significance of the data collected during the reporting period, and from the perspective of the cumulative experience, has been evaluated.

The benefit of treatment with ticagrelor in the approved indication has been weighed against safety experience in the clinical programme as well as post-marketing experience. The clinical benefit demonstrated in clinical studies, combined with the overall safety profile of ticagrelor establishes the positive benefit-risk profile for the approved indication in ACS. The safety data received during the reporting period do not indicate a change in this positive benefit-risk profile.

14. CONCLUSIONS AND EXPERT STATEMENT

ACS is a serious, life-threatening medical condition that contributes substantially to morbidity and mortality worldwide. Compared with clopidogrel, ticagrelor prevents more major adverse cardiac events after ACS, most notably reducing CV mortality, without adding any clinically important safety concerns. A comprehensive review of clinical studies and post-marketing experience reveals that no new information that alters the overall positive benefit-risk profile for ticagrelor has become available during the reporting period. It is the opinion of AstraZeneca that the efficacy and safety information in the proposed ticagrelor SmPC accurately reflects the known benefit-risk profile for ticagrelor.

Based upon the absence of any data justifying further updates to the ticagrelor RMP, AstraZeneca considers the current version of the RMP (version 8.0, dated 09 August 2013) as being up-to-date at the end of the reporting period. Therefore, no updated RMP is included with the renewal application.

The updated benefit-risk evaluation has been addressed adequately (taking account of the consolidated version of the file and all relevant new information).

Furthermore, regulatory authorities have been kept informed of any additional data considered significant to the assessment of the benefit-risk balance of ticagrelor.

The ticagrelor product information is up-to-date with current scientific knowledge (including the conclusions of assessments and recommendations made publicly available by regulatory authorities).

The product can be safely renewed for an unlimited period.

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Addendum to the Clinical Overview Appendix 1

Medicinal Product(s)	Ticagrelor
Period covered	3 December 2010 to 8 November 2014
Date	16 January 2015

Appendix 1

Worldwide Marketing Authorisation Status

WORLDWIDE MARKETING STATUS

Brilique
Brilinta
Product (invented) name: Possia
Product Number (EMEA): EMEA/H/C/001241
Product Number (EU): EU/1/10/655

Version Number: 1
Version Updated: 2014-12-01

Additional information: Marketed Y/N based upon sales data Nov 2014

Country	Presentation(s)			Authorisation date	[redacted]
	strength	pharmaceutical form	Trade name		
Algeria	90 mg	Film-coated tablet	Brilinta	15-09-2013	
Argentina	90 mg	Film-coated tablet	Brilinta	27-12-2011	
Aruba	90 mg	Film-coated tablet	Brilinta	19-01-2012	
Australia	90 mg	Film-coated tablet	Brilinta	09-06-2011	
Austria	90 mg	Film-coated tablet	Brilique	03-12-2010	
Bahrain	90 mg	Film-coated tablet	Brilinta	17-10-2011	
Belgium	90 mg	Film-coated tablet	Brilique	03-12-2010	
Bosnia and Herzegovina	90 mg	Film-coated tablet	Brilique	28-11-2011	
Brazil	90 mg	Film-coated tablet	Brilinta	27-12-2010	
Brunei Darussalam	90 mg	Film-coated tablet	Brilinta	17-04-2012	
Bulgaria	90 mg	Film-coated tablet	Brilique	03-12-2010	
Canada	90 mg	Film-coated tablet	Brilinta	30-05-2011	
Chile	90 mg	Film-coated tablet	Brilinta	29-09-2011	
China	90 mg	Film-coated tablet	Brilinta	22-11-2012	
Colombia	90 mg	Film-coated tablet	Brilinta	15-02-2012	
Costa Rica	90 mg	Film-coated tablet	Brilinta	03-09-2012	
Croatia	90 mg	Film-coated tablet	Brilique	22-09-2011	
Cuba	90 mg	Film-coated tablet	Brilinta	23-03-2012	
Curaçao	90 mg	Film-coated tablet	Brilinta	13-09-2011	
Cyprus	90 mg	Film-coated tablet	Brilique	03-12-2010	
Czech Republic	90 mg	Film-coated tablet	Brilique	03-12-2010	

Country	Presentation(s)			Authorisation date	[redacted]
	strength	pharmaceutical form	Trade name		
Denmark	90 mg	Film-coated tablet	Brilique	03-12-2010	
Dominican Republic	90 mg	Film-coated tablet	Brilinta	05-06-2013	
Ecuador	90 mg	Film-coated tablet	Brilinta	13-11-2012	
El Salvador	90 mg	Film-coated tablet	Brilinta	08-02-2012	
Estonia	90 mg	Film-coated tablet	Brilique	03-12-2010	
Finland	90 mg	Film-coated tablet	Brilique	03-12-2010	
France	90 mg	Film-coated tablet	Brilique	03-12-2010	
Georgia	90 mg	Film-coated tablet	Brilinta	29-11-2012	
Germany	90 mg	Film-coated tablet	Brilique	03-12-2010	
Ghana	90 mg	Film-coated tablet	Brilinta	27-04-2012	
Greece	90 mg	Film-coated tablet	Brilique	03-12-2010	
Guatemala	90 mg	Film-coated tablet	Brilinta	27-12-2011	
Honduras	90 mg	Film-coated tablet	Brilinta	12-01-2012	
Hong Kong	90 mg	Film-coated tablet	Brilinta	23-03-2012	
Hungary	90 mg	Film-coated tablet	Brilique	03-12-2010	
Iceland	90 mg	Film-coated tablet	Brilique	13-12-2010	
India	90 mg	Film-coated tablet	Brilinta	03-05-2012	
Indonesia	90 mg	Film-coated tablet	Brilinta	16-04-2012	
Iraq	90 mg	Film-coated tablet	Brilinta	17-06-2012	
Ireland	90 mg	Film-coated tablet	Brilique	03-12-2010	
Israel	90 mg	Film-coated tablet	Brilinta	02-10-2011	
Italy	90 mg	Film-coated tablet	Brilique	03-12-2010	
Jamaica	90 mg	Film-coated tablet	Brilinta	19-03-2012	
Jordan	90 mg	Film-coated tablet	Brilinta	11-07-2012	
Kazakhstan	90 mg	Film-coated tablet	Brilinta	12-12-2011	
Kenya	90 mg	Film-coated tablet	Brilinta	01-08-2013	
Korea, Republic of	90 mg	Film-coated tablet	Brilinta	22-07-2011	
Kuwait	90 mg	Film-coated tablet	Brilinta	28-12-2011	
Latvia	90 mg	Film-coated tablet	Brilique	03-12-2010	
Lebanon	90 mg	Film-coated tablet	Brilinta	27-12-2011	
Libya	90 mg	Film-coated tablet	Brilinta	29-05-2013	

Country	Presentation(s)			Authorisation date	[redacted]
	strength	pharmaceutical form	Trade name		
Liechtenstein	90 mg	Film-coated tablet	Brilique	13-07-2011	
Lithuania	90 mg	Film-coated tablet	Brilique	03-12-2010	
Luxembourg	90 mg	Film-coated tablet	Brilique	03-12-2010	
Macao	90 mg	Film-coated tablet	Brilinta	27-04-2011	
Malaysia	90 mg	Film-coated tablet	Brilinta	17-03-2011	
Malta	90 mg	Film-coated tablet	Brilique	03-12-2010	
Mauritius	90 mg	Film-coated tablet	Brilinta	19-07-2011	
Mexico	90 mg	Film-coated tablet	Brilinta	08-09-2011	
Namibia	90 mg	Film-coated tablet	Brilinta	04-09-2014	
Montenegro	90 mg	Film-coated tablet	Brilique	12-04-2013	
Netherlands	90 mg	Film-coated tablet	Brilique	03-12-2010	
New Zealand	90 mg	Film-coated tablet	Brilinta	18-08-2011	
Nicaragua	90 mg	Film-coated tablet	Brilinta	01-02-2012	
Nigeria	90 mg	Film-coated tablet	Brilinta	-	
Norway	90 mg	Film-coated tablet	Brilique	17-12-2010	
Oman	90 mg	Film-coated tablet	Brilinta	19-08-2014	
Pallestines	90 mg	Film-coated tablet	Brilinta	25-03-2014	
Panama	90 mg	Film-coated tablet	Brilinta	30-10-2012	
Peru	90 mg	Film-coated tablet	Brilinta	15-11-2011	
Philippines	90 mg	Film-coated tablet	Brilinta	21-03-2012	
Poland	90 mg	Film-coated tablet	Brilique	03-12-2010	
Portugal	90 mg	Film-coated tablet	Brilique	03-12-2010	
Qatar	90 mg	Film-coated tablet	Brilinta	04-01-2012	
Romania	90 mg	Film-coated tablet	Brilique	03-12-2010	
Russian Federation	90 mg	Film-coated tablet	Brilinta	27-10-2011	
Saudi Arabia	90 mg	Film-coated tablet	Brilinta	14-07-2013	
Serbia	90 mg	Film-coated tablet	Brilique	08-05-2012	
Singapore	90 mg	Film-coated tablet	Brilinta	13-03-2012	
Slovakia	90 mg	Film-coated tablet	Brilique	03-12-2010	
Slovenia	90 mg	Film-coated tablet	Brilique	03-12-2010	
South Africa	90 mg	Film-coated tablet	Brilinta	10-04-2014	

Country	Presentation(s)			Authorisation date	[redacted]
	strength	pharmaceutical form	Trade name		
Spain	90 mg	Film-coated tablet	Brilique	03-12-2010	[redacted]
Sri Lanka	90 mg	Film-coated tablet	Brilinta	24-04-2013	[redacted]
Sudan	90 mg	Film-coated tablet	Brilinta	16-12-2013	[redacted]
Sweden	90 mg	Film-coated tablet	Brilique	03-12-2010	[redacted]
Switzerland	90 mg	Film-coated tablet	Brilinta	30-06-2011	[redacted]
Syrian Arab Republic	90 mg	Film-coated tablet	Brilinta	14-07-2011	[redacted]
Taiwan, Province of China	90 mg	Film-coated tablet	Brilinta	11-05-2012	[redacted]
Tanzania, United Republic of	90 mg	Film-coated tablet	Brilinta	06-06-2013	[redacted]
Thailand	90 mg	Film-coated tablet	Brilinta	30-11-2011	[redacted]
Trinidad and Tobago	90 mg	Film-coated tablet	Brilinta	15-10-2012	[redacted]
Turkey	90 mg	Film-coated tablet	Brilinta	1-11-2011	[redacted]
Uganda	90 mg	Film-coated tablet	Brilinta	05-01-2012	[redacted]
Ukraine	90 mg	Film-coated tablet	Brilinta	20-04-2012	[redacted]
United Arab Emirates	90 mg	Film-coated tablet	Brilinta	30-10-2011	[redacted]
United Kingdom	90 mg	Film-coated tablet	Brilique	03-12-2010	[redacted]
United States	90 mg	Film-coated tablet	Brilinta	20-07-2011	[redacted]
Uruguay	90 mg	Film-coated tablet	Brilinta	04-07-2011	[redacted]
Venezuela, Bolivarian Republic of	90 mg	Film-coated tablet	Brilinta	10-12-2012	[redacted]
Vietnam	90 mg	Film-coated tablet	Brilinta	05-07-2013	[redacted]
Yemen	90 mg	Film-coated tablet	Brilinta	30-04-2012	[redacted]

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Addendum to the Clinical Overview Appendix 2	
Medicinal Product(s)	Ticagrelor
Period covered	3 December 2010 to 8 November 2014
Date	16 January 2015

Appendix 2

Reference Information (AstraZeneca Core Data Sheet)

Core Data Sheet in effect at the end of the reporting period:

Core Data Sheet Dated 03 March 2014 – clean version

Core Data Sheet Dated 03 March 2014 – annotated version showing changes compared with the CDS in effect at the beginning of the reporting period

The ticagrelor Core Data Sheet presented below is dated 3 March 2014 and it is the edition that was in effect at the end of the reporting period (8 November 2014).

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CDS	
Drug Substance	BRILINTA™ (ticagrelor)
Date	3 March 2014
Supersedes	March 26, 2013

Core Data Sheet
BRILINTA™ (ticagrelor) 90 mg Tablets

Use of this data sheet must conform to the current AstraZeneca IP for "Management of Core Product Information and Market Product Information"

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

1. NAME OF MEDICINAL PRODUCT

Name of the medicinal product

BRILINTA™ (ticagrelor), 90 mg, film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 90 mg of ticagrelor

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

90 mg - Round, biconvex, yellow, film-coated tablets. The tablets are marked with "90" above "T" on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRILINTA is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes ([ACS] unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

4.2 Posology and method of administration

BRILINTA treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily.

For oral use. BRILINTA can be taken with or without food. For patients who are unable to swallow the tablet(s) whole, Brilinta tablets (90 mg and 2x90 mg) can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

Patients taking BRILINTA should also take ASA daily unless specifically contraindicated. Following an initial dose of ASA, BRILINTA should be used with a maintenance dose of ASA of 75-150 mg (see section 5.1).

Lapses in therapy should be avoided. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

Physicians who desire to switch patients from clopidogrel to BRILINTA should administer the first 90 mg dose of BRILINTA 24 hours following the last dose of clopidogrel (see section 5.1).

Treatment is recommended for at least 12 months unless discontinuation of BRILINTA is clinically indicated (see section 5.1). In patients with Acute Coronary Syndromes (ACS), premature discontinuation with any antiplatelet therapy, including BRILINTA, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease (see section 4.4).

Special Populations
Paediatric patients:

Safety and efficacy in children below the age of 18 have not been established.

Elderly patients:

No dose adjustment is required.

Patients with renal impairment:

No dose adjustment is necessary for patients with renal impairment (see section 5.2). No information is available concerning treatment of patients on renal dialysis.

Patients with hepatic impairment:

No dose adjustment is necessary for patients with mild hepatic impairment. BRILINTA has not been studied in patients with moderate or severe hepatic impairment. (see section 5.2)

4.3 Contraindications

Hypersensitivity to ticagrelor or any of the excipients (see section 4.8).
Active pathological bleeding
History of intracranial haemorrhage
Severe hepatic impairment

4.4 Special warnings and special precautions for use

Bleeding risk
As with other antiplatelet agents, the use of BRILINTA in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events. If clinically indicated, BRILINTA should be used with caution in the following patient groups:

Consideration should be given to the following:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, active or recent gastrointestinal bleeding or moderate hepatic impairment). The use of BRILINTA is contraindicated in patients with active pathological bleeding and in those with history of intracranial haemorrhage, and severe hepatic impairment (see section 4.3).
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDS), oral anticoagulants and/or fibrinolytics within 24 hours of BRILINTA dosing).

No data exist with BRILINTA regarding a haemostatic benefit of platelet transfusions; circulating BRILINTA may inhibit transfused platelets. Since co administration of BRILINTA with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may augment haemostasis. BRILINTA may be resumed after the cause of bleeding has been identified and controlled.

Surgery

- If a patient requires surgery, physicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.
- Because of the reversible binding of BRILINTA, restoration of platelet aggregation occurs faster with BRILINTA compared to clopidogrel. In the OFFSET study, mean Inhibition of Platelet Aggregation (IPA) for BRILINTA at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, eg, in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.
- In PLATO patients under going CABG, BRILINTA had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where BRILINTA had a higher rate of major bleeding.
- If a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery. (see section 5.1).

Patients with moderate hepatic impairment

Caution is advised in patients with moderate hepatic impairment because BRILINTA has not been studied in these patients. Use of BRILINTA is contraindicated in patients with severe hepatic impairment (see section 4.3).

Patients at risk for bradycardic events

Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) were excluded from the main study evaluating the safety and efficacy of BRILINTA. Therefore, due to the limited clinical experience in these patients, caution is advised (see section 5.1).

Dyspnoea

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported in patients treated with BRILINTA (approximately 13.8%) (see section 4.8). The mechanism has not yet been elucidated. If a patient reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with BRILINTA should be stopped.

Other

Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high maintenance dose ASA (>300 mg) is not recommended (see section 5.1).

Co-administration of BRILINTA with strong CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, nefazadone, ritonavir, and atazanavir) should be avoided as co-administration may lead to a substantial increase in exposure to BRILINTA (see section 4.5).

Discontinuations

Patients who require discontinuation of BRILINTA are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event(s), it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Drug-Drug Interactions

Effects of Other Drugs on BRILINTA

Medicinal Products metabolised by CYP3A4

Ketoconazole (Strong CYP3A4 Inhibitors) Co-administration of ketoconazole with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56% respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir, and atazanavir) would be

expected to have similar effects and should not be given concomitantly with BRILINTA (see section 4.4).

Diltiazem (Moderate CYP3A4 inhibitors)
Co-administration of ticagrelor and diltiazem increased the C_{max} of ticagrelor by 69% and AUC by 174% and decreased the active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin, fluconazole, and verapamil) can as well be co-administered with BRILINTA.

Rifampin and Other CYP3A Inducers
Co-administration of rifampin with ticagrelor decreased ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46% respectively. Other CYP3A4 inducers (e.g. phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of BRILINTA.

Cyclosporine (PgP and CYP3A inhibitor)[1]
Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and C_{max} was decreased by 15% in the presence of cyclosporine. There was no effect of ticagrelor on cyclosporine blood levels.

Others
Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and aspirin did not have any effect on ticagrelor or the active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co-administration of ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay.

Effects of BRILINTA on Other Drugs

Medicinal Products metabolised by CYP3A4
Simvastatin
Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3 fold. Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin. There was no effect of simvastatin on ticagrelor plasma levels. BRILINTA may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.

Atorvastatin
Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Medicinal Products metabolised by CYP2C9 - Tolbutamide
Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which suggest that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of drugs like warfarin and tolbutamide.

Oral Contraceptives
Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure approximately 20% but did not alter the PK of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with BRILINTA.

Digoxin (PgP substrate)
Concomitant administration of ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin concomitantly with BRILINTA.

Other Concomitant Therapy
In clinical studies, BRILINTA was commonly administered with acetylsalicylic acid, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

No clinical study has been conducted in pregnant or lactating women.

Limited clinical data on exposure to BRILINTA during pregnancy are available.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Ticagrelor had no effect on male or female fertility (see section 5.3).

Because animal reproduction studies are not always predictive of a human response, ticagrelor should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the foetus.

Lactation

It is not known whether this medicinal product is excreted in human milk. Studies in rats have shown that ticagrelor and active metabolites are excreted in the milk. The use of BRILINTA during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. BRILINTA has no or negligible influence on the ability to drive and use machines. During treatment for Acute Coronary Syndromes, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

4.8 Undesirable effects

The safety of BRILINTA in patients with acute coronary syndromes (UA, NSTEMI and STEMI) was evaluated in a single large phase 3 study (PLATO [PLATelet Inhibition and Patient Outcomes] study), which compared patients treated with BRILINTA (loading dose of 180 mg of BRILINTA and a maintenance dose of 90 mg bd) to patients treated with clopidogrel (300-600 mg loading dose followed by 75 mg od maintenance dose) both given in combination with acetylsalicylic acid (ASA) and other standard therapies.

Median treatment duration for BRILINTA was 277 days (6762 patients were treated for greater than 6 months and 3138 were treated for greater than 12 months).

The most commonly reported adverse events in patients treated with ticagrelor were dyspnoea, headache, and epistaxis and these events occurred at higher rates than in the clopidogrel treatment group. During the treatment period, the BRILINTA group had a higher incidence of discontinuation due to adverse events than clopidogrel (7.4% vs. 5.4%).

Bleeding

The following bleeding definitions were used in the PLATO study:

'Major Fatal/Life-threatening': fatal, or intracranial, or intrapericardial bleed with cardiac tamponade, or hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, or clinically overt or apparent bleeding associated with a decrease in haemoglobin of more than 50 g/L, or transfusion of 4 or more units (whole blood or PRBCs) for bleeding.

'Major Other': Significantly disabling (e.g., intraocular with permanent vision loss), or clinically overt or apparent bleeding associated with a decrease in haemoglobin of 30 to 50 g/L, or transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

'Minor': Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).

Minimal bleeds included all other bleeds; these were collected but not adjudicated.

Bleeding events reported in PLATO were also mapped to the TIMI (Thrombolysis in Myocardial Infarction) scale, to facilitate comparison with other similar studies. **TIMI Major** is defined as clinically overt bleeding associated with a fall in hemoglobin > 5 g/dL, or intracranial hemorrhage, and **TIMI Minor** is defined as overt bleeding associated with a fall in hemoglobin of 3 g/dL but ≤ 5 g/dL.

Overall outcome of bleeding events in the PLATO study are shown in Figure 1 and Table 1.

Figure 1 – Kaplan Meier estimate of time to first PLATO-defined 'Total Major' bleeding event

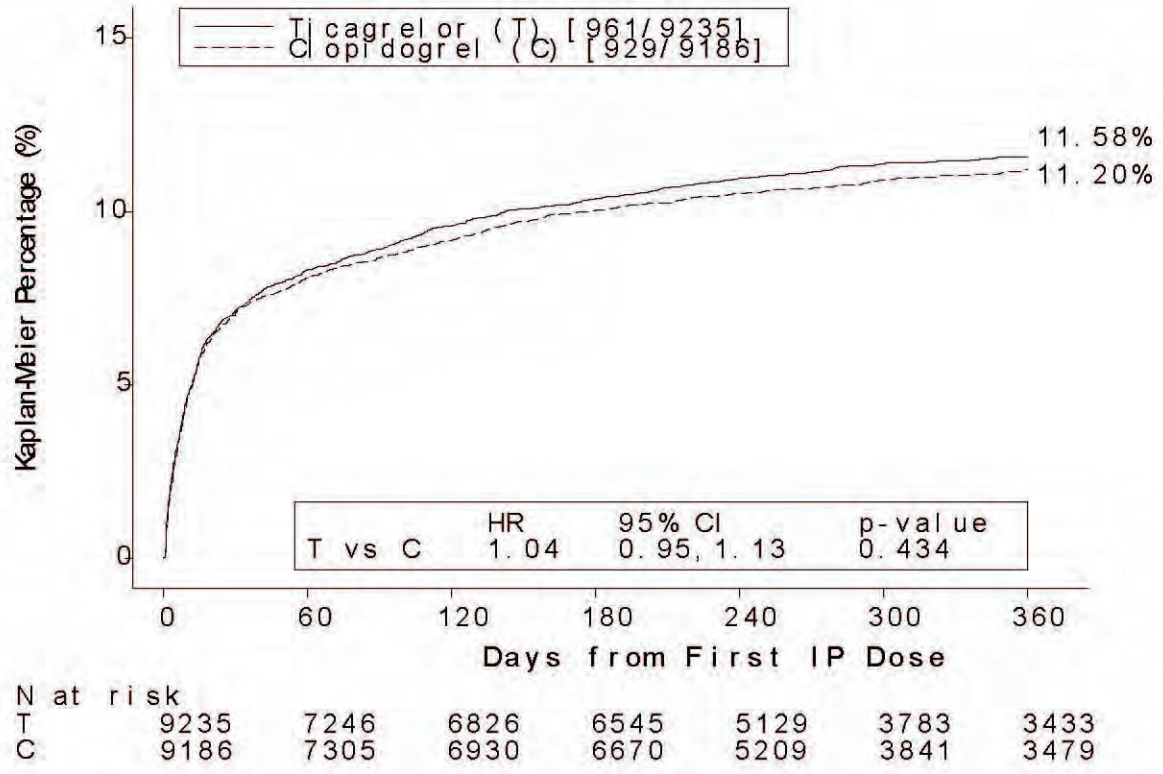


Table 1 – Analysis of Overall Bleeding Events

	BRILINTA (%)	Clopidogrel (%)	

	N=9235	N=9186	p-value
Primary Safety Endpoint Total Major	11.6	11.2	0.4336
Secondary Endpoints Fatal/Life-Threatening	5.8	5.8	0.6988
Combined Total Major + Minor bleeding	16.1	14.6	0.0084
Non-CABG Major	4.5	3.8	0.0264
Non-Procedural Major	3.1	2.3	0.0058
Non-Procedural Major + Minor	5.9	4.3	<0.0001
TIMI-defined bleeding category TIMI-defined Major	7.9	7.7	0.5669
TIMI-defined Major + Minor	11.4	10.9	0.3272

In PLATO, time to first PLATO-defined 'Total Major' bleeding for BRILINTA did not differ significantly from that of clopidogrel. There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA and 23 (0.3%) for clopidogrel. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on BRILINTA than on clopidogrel. Overall rates of TIMI-defined bleeding events did not differ significantly between BRILINTA and clopidogrel.

CABG-related bleeding: In PLATO, 1584 patients (12%) underwent coronary artery bypass graft (CABG) surgery. 'Major Fatal/Life-threatening' bleeding was approximately 42% in both treatment groups. There was no difference between the treatment groups with respect to risk of 'Major Fatal/Life-threatening' CABG bleeding relative to time of last dose before the procedure. Fatal CABG bleeding occurred uncommonly, 6 patients in each treatment group (0.8% and 0.7% of CABG patients on BRILINTA and clopidogrel, respectively).

Non-CABG related bleeding: When CABG bleeding is removed from the analysis (see Table 2), the absolute bleeding rates for all categories are lower. The groups did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening bleeding, but PLATO-defined 'Total Major', TIMI Major, and TIMI Major + Minor bleeding was more common with BRILINTA.

Table 2 - Non-CABG Related PLATO-defined Major Bleeding Events and TIMI-defined Bleeding Events

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	p-value
PLATO-defined			

bleeding category Total Major Bleeding	4.5	3.8	0.0264
Major Fatal/Life-Threatening	2.1	1.9	0.2516
TIMI-defined bleeding category TIMI-defined Major	2.8	2.2	0.0246
TIMI-defined Major + Minor	4.5	3.6	0.0093

Bleeding unrelated to any procedure: As shown in Table 1 PLATO-defined 'Major' and 'Major + Minor' non-procedural bleeding was more frequent with BRILINTA. Discontinuation of treatment due to non-procedural bleeding was more common for BRILINTA (2.9%) than for clopidogrel (1.2%; $p<0.001$). Clinically important locations for 'Major + Minor' bleeding in rank order by frequency were (BRILINTA vs clopidogrel): intracranial (27 vs 14 events), pericardial (11 vs 11), retroperitoneal (3 vs 3), intraocular (2 vs 4) and intra-articular (2 vs 1). Other common locations were in rank order of frequency: gastrointestinal (170 vs 135 events), epistaxis (116 vs 61), urinary (45 vs 37), subcutaneous/dermal (43 vs 38) and haemoptysis (13 vs 7).

There was no difference with BRILINTA compared to clopidogrel for fatal non-procedural bleeding. 'Major Fatal/Life-threatening' gastrointestinal bleeding was the same with BRILINTA and clopidogrel, with numerically more fatal events for clopidogrel (5) than for BRILINTA (none). There were numerically more 'Major Fatal/Life-threatening' intracranial non-procedural bleeding events with BRILINTA (n=27 events in 26 patients, 0.3%) than with clopidogrel (n=14 events, 0.2%), of which 11 bleeding events with BRILINTA and 1 with clopidogrel were fatal.

Baseline characteristics including age, gender, weight, race, geographic region, medical history, concurrent conditions and concomitant therapy were assessed to explore any increase in risk of bleeding with BRILINTA. No particular risk group was identified for any subset of bleeding.

Dyspnoea:
Dyspnoea occurs during treatment with ticagrelor. Dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, and nocturnal dyspnoea), when combined, were reported in 13.8% of patients taking ticagrelor and in 7.8% taking clopidogrel in the PLATO study. The study did not exclude patients with underlying congestive heart failure (CHF), chronic obstructive pulmonary disorder (COPD), or asthma. Most of the dyspnoea AEs were mild to moderate in intensity. Dyspnoea Serious Adverse Events were reported in 0.7% taking BRILINTA and 0.4% taking clopidogrel. More patients taking BRILINTA 0.9% discontinued study drug than did patients taking clopidogrel 0.1% due to dyspnoea. Dyspnoea was usually reported in the initial phase of treatment. Eighty-seven percent of patients taking BRILINTA that reported dyspnoea experienced a single episode. Approximately 30% of all dyspnoea resolved within 7 days. Patients who reported

dyspnoea tended to be older and more frequently had dyspnoea, CHF, COPD, or asthma at baseline. PLATO data do not suggest that the higher frequency of dyspnoea with BRILINTA is due to new or worsening heart or lung disease (see section 4.4).

In patients who underwent pulmonary function testing in the clinical program, there was no indication of an adverse effect of BRILINTA on pulmonary function.

Lab Abnormalities
In PLATO, serum uric acid concentration increased to more than upper limit of normal in 22% of patients receiving BRILINTA compared to 13% of patients receiving clopidogrel. Mean serum uric acid concentration increased approximately 15% with BRILINTA compared to approximately 7% with clopidogrel and reduced after treatment was stopped. There was no difference in the frequency of clinical adverse events.

In PLATO, serum creatinine concentration increased by >50% in 8% of patients receiving BRILINTA compared to 7% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Signs of reversibility on discontinuation were observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for related serious adverse events.

Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following conventions: Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000)

The following adverse reactions have been identified following studies with BRILINTA.

Table 3 - Adverse Drug Reactions by System Organ Class (SOC) and by Adverse Event Frequency

System Organ Classification	Very Common	Common	Uncommon	Rare
Metabolism and nutrition disorders	Hyperuricaemia[a]			
Psychiatric disorders			Confusion	
Nervous system disorders		Headache, Dizziness	Intracranial haemorrhage[b], Paraesthesia	
Eye disorders			Eye haemorrhage (intraocular, conjunctival,	

System Organ Classification	Very Common	Common	Uncommon	Rare
			retinal)	
Ear and labyrinth disorders		Vertigo		
Respiratory, thoracic and mediastinal disorders	Dyspnoea [b]	Epistaxis	Haemoptysis	
Gastrointestinal Disorders		Abdominal pain, Constipation, Diarrhoea, Dyspepsia, Gastrointestinal haemorrhage [b], Nausea, Vomiting	Gastritis, Retroperitoneal haemorrhage [b]	
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding [b], Rash, Pruritus		
Musculoskeletal connective tissue and bone				Haemarthrosis
Renal and urinary disorders		Urinary tract bleeding [b]		
Investigations		Blood creatinine increased [a]		
Injury, poisoning and procedural complications		Post procedural haemorrhage		

[a] Frequencies derived from lab observations (uric acid to >ULN of 7and 6.5 mg/dl for males and females respectively and creatinine increases of >50% from baseline) and not crude adverse event report frequency- see lab section
[b] Represents multiple related adverse events terms

Postmarketing Experience[i]
The following adverse reactions have been identified during post-approval use of BRILINTA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.

Immune system disorders - Hypersensitivity reactions including angioedema (see section 4.3).

4.9 Overdose

There is currently no known antidote to reverse the effects of BRILINTA, and BRILINTA is not expected to be dialysable (see section 4.4). Treatment of overdose should follow local standard medical practice. The expected effect of excessive BRILINTA dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs appropriate supportive measures should be taken.

Ticagrelor is well tolerated in single doses up to 900 mg. GI toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse effects which may occur with overdose include dyspnoea and ventricular pauses.

In the event of overdose, observe for these potential adverse effects and consider ECG monitoring.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group (ATC code): B01AC24
Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin

5.1 Pharmacodynamic properties

Mechanism of action:

BRILINTA contains ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as death, myocardial infarction or stroke.

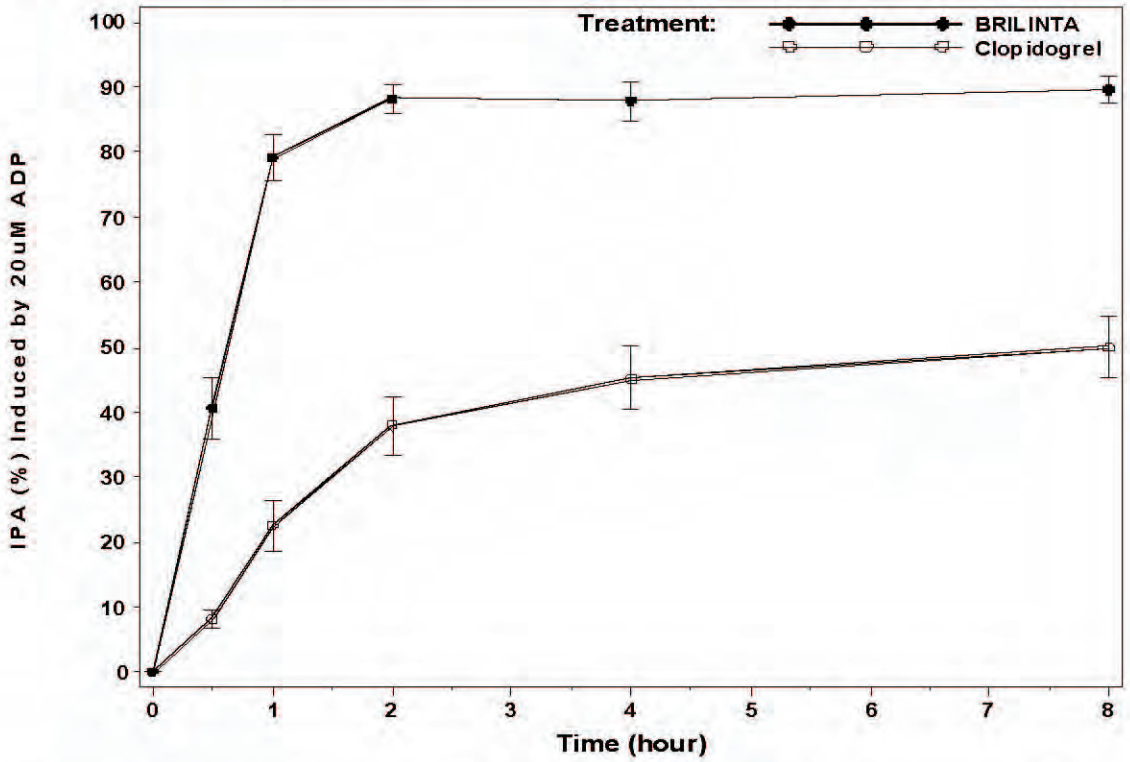
Ticagrelor has an additional mechanism of action, increasing local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1). Adenosine is formed locally at sites of hypoxia and tissue damage through degradation of released adenosine tri- and di-phosphate (ATP and ADP). As adenosine degradation is essentially restricted to the

intracellular space, inhibition of ENT-1 by ticagrelor prolongs the half-life of adenosine and thereby increases its local extracellular concentration providing enhanced local adenosine responses. Ticagrelor has no clinically significant direct effect on adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and is not metabolised to adenosine. Adenosine has been documented to have a number of effects that include: vasodilation, cardioprotection, platelet inhibition, modulation of inflammation and induction of dyspnoea, which may contribute to the clinical profile of ticagrelor.

Pharmacodynamic effects:

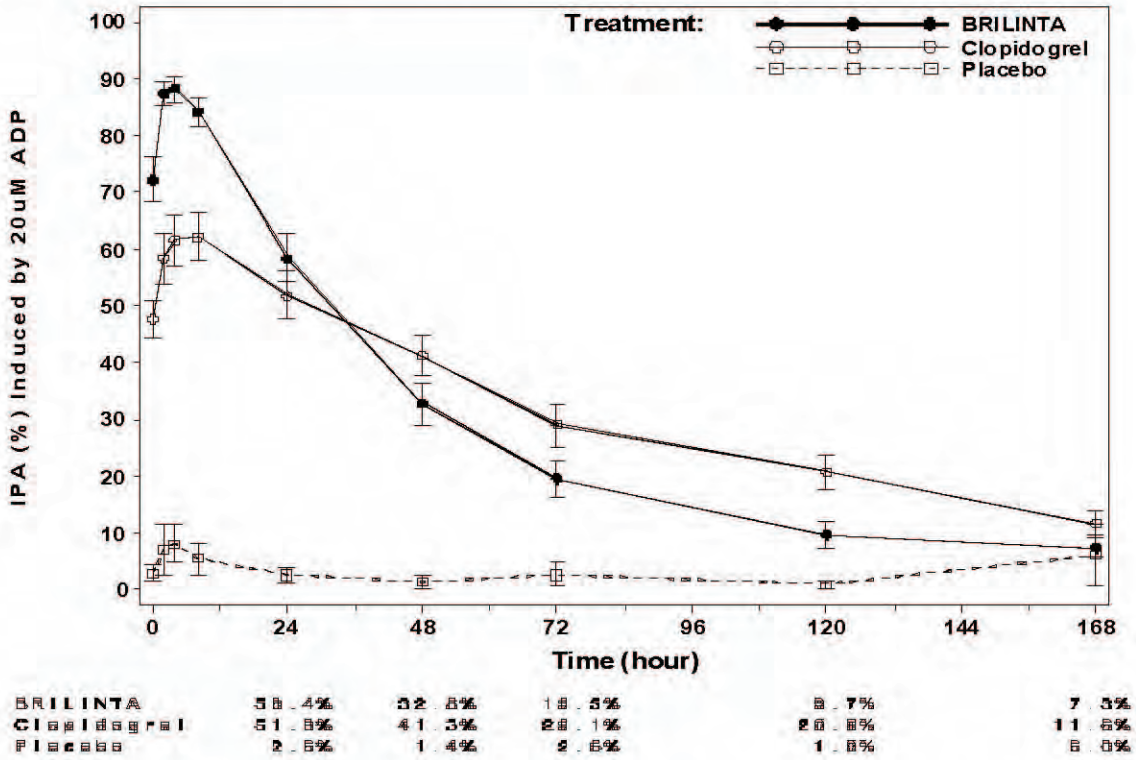
Onset of Action

Mean final extent Inhibition (±SE) of Platelet Aggregation (IPA) following single oral doses of 180 mg BRILINTA or 600 mg clopidogrel in patients with stable CAD



In patients with stable coronary artery disease on ASA, BRILINTA demonstrates a rapid onset of pharmacological effect as demonstrated by a mean Inhibition of Platelet Aggregation (IPA) for BRILINTA at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA effect of 87.9% to 89.6% by 2-4 hours post dose. 90% of patients had final extent IPA >70% by 2 hours post dose. The high IPA effect of BRILINTA between 87%-89% was maintained between 2-8 hours.

Mean final extent Inhibition (±SE) of Platelet Aggregation (IPA) following the last maintenance dose of 90 mg bid BRILINTA or 75 mg clopidogrel qd or placebo



Offset of Effect

After the BRILINTA and the active metabolite concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since BRILINTA bind reversibly, the recovery of platelet function does not depend on replacement of platelets. BRILINTA has a faster rate of offset of IPA as compared to clopidogrel as determined by the slope of offset from 4-72 hours after last dose (see section 4.4).

Median final extent IPA measured after the last dose of BRILINTA is approximately 20-30% higher for BRILINTA compared to clopidogrel. However, by 24 hours post-dose, %IPA is similar between BRILINTA and clopidogrel, and is lower for BRILINTA from 72 hours through 7 days compared with the clopidogrel. Mean %IPA for BRILINTA at 72 hours (Day 3) post last dose was comparable to clopidogrel at Day 5, and %IPA for BRILINTA at Day 5 was similar to clopidogrel at Day 7, which is not statistically different from placebo.

Responders to BRILINTA

IPA induced by BRILINTA has less variability at peak plasma concentrations of BRILINTA and the active metabolite observed with the 90 mg bd dose compared to clopidogrel. Patients with stable coronary artery disease predetermined to have low IPA response to clopidogrel (non-responders), and given a concomitant dose of ASA, exhibited higher mean IPA response after administration of BRILINTA as compared to clopidogrel. In Non-responders to

clopidogrel, the IPA response to BRILINTA was observed to be higher and more consistent. BRILINTA treatment resulted in consistently higher IPA compared with clopidogrel, and this was apparent post dose for both responders and non-responders.

Switching Data
Switching from clopidogrel to BRILINTA results in an absolute IPA increase of 26.4% and switching from BRILINTA to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to BRILINTA without interruption of anti-platelet effect.

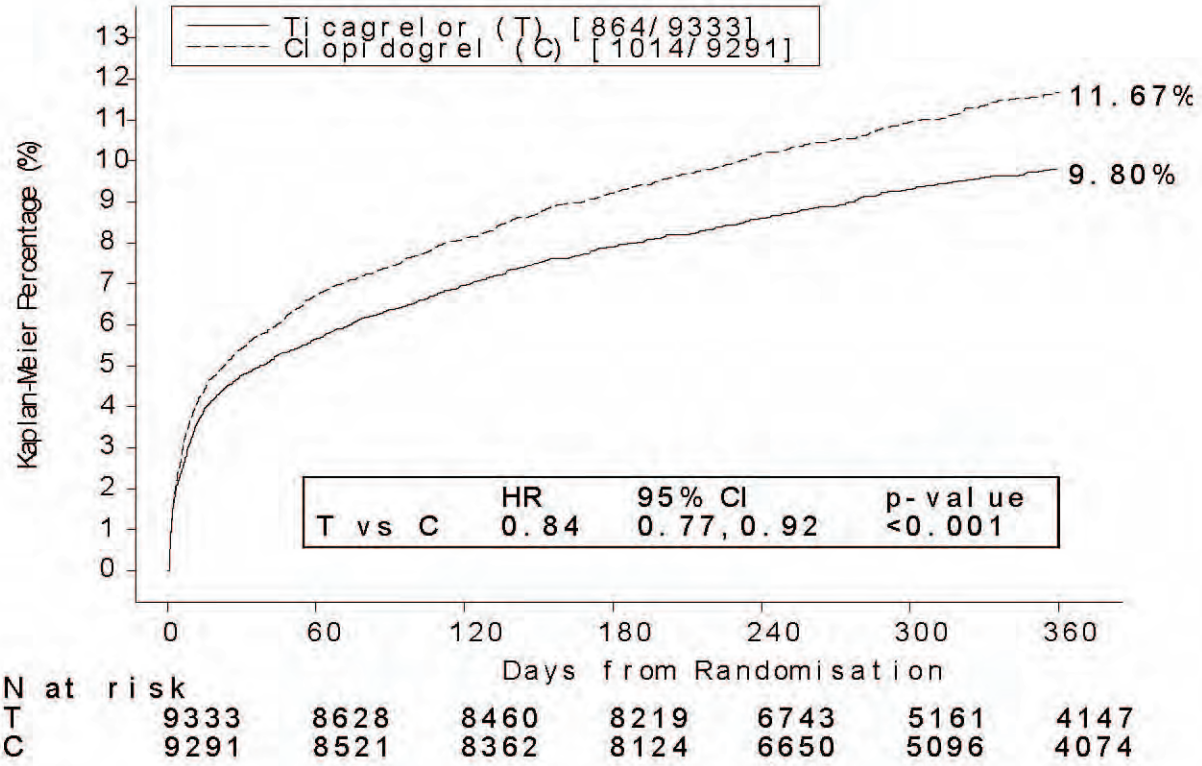
Adenosine mechanism (ENT-1)
Ticagrelor increased plasma adenosine concentrations in ACS patients and has been shown to augment several physiological responses to adenosine. Adenosine is a vasodilator; ticagrelor has been shown to augment adenosine-induced coronary blood flow increases in healthy volunteers and ACS patients. Adenosine is an endogenous platelet inhibitor; ticagrelor has been shown to augment adenosine-mediated inhibition of platelet aggregation in addition to platelet inhibition due to its $P2Y_{12}$ antagonism. Adenosine has been linked to the cardio-protective effect of preconditioning; ticagrelor has been shown to reduce infarct size via an adenosine-mediated mechanism in a rat model of reperfusion injury. Adenosine also induces dyspnoea; ticagrelor has been shown to augment adenosine-induced dyspnoea in healthy volunteers. Thus, the dyspnoea observed in some patients taking ticagrelor (see section 4.8) may partly or completely be mediated by adenosine.

Clinical efficacy:

The clinical evidence for the efficacy of BRILINTA is derived from the PLATO [PLATelet Inhibition and Patient Outcomes] study, a comparison of BRILINTA to clopidogrel, both given in combination with acetylsalicylic acid (ASA) and other standard therapy.

The PLATO study was an 18,624 patient randomized, double-blind, parallel group, phase III, efficacy and safety study of BRILINTA compared with clopidogrel for prevention of vascular events in patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI].
The study was comprised of patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. Patients were randomized to receive clopidogrel (75 mg once daily, with an initial loading dose of 300 mg if previous thienopyridine therapy had not been given. An additional loading dose of 300 mg was allowed at investigator discretion), or a loading dose of 180 mg of BRILINTA followed by a maintenance dose of 90 mg of BRILINTA twice daily. Patients could have been medically managed, treated with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).

Figure 2 shows the estimate of the risk to the first occurrence of any event in the composite efficacy endpoint



BRILINTA reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population.[4]

Table 4 – Outcome Events in PLATO

	Patients with Events				
Primary Endpoint	**BRILINTA (%) N=9333**	**Clopidogrel (%) N=9291**	**Relative Risk Reduction[a] (%)**	**Hazard Ratio (95% CI)**	**p-value**
Composite of CV Death/MI (excl. silent					

MI)/Stroke	9.3	10.9	16	0.84(0.77,0.92)	p=0.0003
CV death	3.8	4.8	21	0.79(0.69,0.91)	p=0.0013
MI (excl. silent MI)[a]	5.4	6.4	16	0.84(0.75,0.95)	p=0.0045
Stroke	1.3	1.1	-17	1.17(0.91,1.52)	p=0.2249
Secondary Endpoints					
Composite of CV Death/MI (excl. silent MI)/Stroke – intent to invasively manage[a]	8.5	10.0	16	0.84(0.75,0.94)	p=0.0025
Composite of all-cause mortality/MI (excl. silent MI)/Stroke	9.7	11.5	16	0.84(0.77,0.92)	p=0.0001
Composite of CV Death/Total MI/Stroke/SRI/RI/TIA /Other ATE	13.8	15.7	12	0.88(0.81,0.95)	p=0.0006
All-cause mortality	4.3	5.4	22	0.78(0.69,0.89)	p=0.0003**

[a]RRR= (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase
**nominal p-value

BRILINTA is superior to clopidogrel in the prevention of thrombotic events (RRR 16%, ARR 1.9%, NNT =54) of the composite efficacy endpoint (cardiovascular (CV) death, myocardial infarction (MI) and stroke) over 12 months. The difference in treatments was driven by cardiovascular death and myocardial infarction with no difference on strokes. BRILINTA demonstrated a statistically significant relative risk reduction of 16% (ARR 1.1%) for MI and a 21% relative risk reduction (ARR 1.1%) for CV death. Treating 91 patients with BRILINTA instead of clopidogrel will prevent 1 CV death.

BRILINTA showed superiority to clopidogrel in preventing the composite endpoint (cardiovascular [CV] death, myocardial infarction [MI], or stroke). This result appeared early (absolute risk reduction [ARR] 0.6% and Relative Risk Reduction [RRR] of 12% at 30 days), with a constant treatment effect over the entire 12 month period, yielding ARR 1.9% per year with RRR of 16%. This suggests it is appropriate to treat for at least 12 months (see section 4.2).

In PLATO a large number of subgroup comparisons were conducted for the primary efficacy endpoint to assess the robustness and consistency of the overall benefit. The treatment effect of BRILINTA over clopidogrel appears consistent across multiple patient subgroups by demographic characteristics including weight, gender, medical history, concomitant therapy, and by final index event diagnosis (STEMI, NSTEMI, and UA).

A weakly significant treatment interaction was observed with region whereby the HR for the primary endpoint favours BRILINTA in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045).

This apparent treatment-by-region interaction observed in PLATO could plausibly be attributed to chance, at least in part. Additional analyses suggest that the efficacy of BRILINTA relative to clopidogrel is associated with ASA dose during maintenance therapy. The data show greater efficacy of ticagrelor compared to clopidogrel when used in conjunction with low maintenance dose ASA (75-150 mg). The relative efficacy of ticagrelor versus clopidogrel when used with high doses of ASA (>300 mg) is less certain. Based on this observed relationship between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, it is recommended that BRILINTA is used with a low maintenance dose of ASA 75-150 mg (see sections 4.2 and 4.4).

The benefits associated with BRILINTA were also independent of the use of other acute and long-term cardiovascular therapies, including heparin, low molecular weight heparin (LMWH), intravenous GpIIb/IIIa inhibitors, lipid-lowering drugs, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and proton pump inhibitors (see section 4.5).

BRILINTA demonstrated a statistically significant relative risk reduction (RRR) in the composite endpoint cardiovascular (CV) death, myocardial infarction (MI) and stroke in ACS patients planned for invasive management (RRR 16%, ARR 1.7%, p=0.0025). In an exploratory analysis, BRILINTA demonstrated a relative risk reduction of the primary composite endpoint in ACS patients intended for medical management (RRR 15%, ARR 2.3%, nominal p=0.0444). Consistent with the primary endpoint of the study, the effect in these two groups was driven by CV death and MI with no effect on stroke. In patients receiving stents there were numerically fewer definite stent thromboses among patients treated with ticagrelor compared to clopidogrel (73 vs. 107, RRR 32%, ARR 0.6%, nominal p=0.0123).

BRILINTA demonstrated a statistically significant RRR of 16% (ARR 2.1%) for the composite of all-cause mortality, MI and stroke compared to clopidogrel.

The final secondary endpoint (all-cause mortality) was evaluated. BRILINTA demonstrated a RRR of 22% for all-cause mortality compared to clopidogrel at a nominal significance level of p=0.0003 and an ARR of 1.4%.

Holter Substudy
To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3000 patients, of whom approximately 2000 had recordings both in the acute phase of their ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. More patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; and 2.2% and 1.6% respectively after 1 month. More patients had ventricular pauses with BRILINTA than with clopidogrel, however, there were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

Ticagrelor is orally active. Unlike clopidogrel, it does not require CYP450 enzyme activity to inhibit platelet aggregation. Polymorphisms in the gene coding for CYP450 enzyme 2C19 may impact clopidogrel efficacy. Polymorphism in the gene coding for P-glycoprotein transport (ABCB1) may impact efficacy of both clopidogrel and ticagrelor.
In PLATO, 10,285 patients provided genetic samples for genotype determination of CPY2C19 and ABCB1 loci. An analysis provided these associations of genotype groupings on efficacy and safety outcomes in PLATO.

- The superiority of BRILINTA over clopidogrel is not significantly affected by patient CYP2C19 genotype
- BRILINTA reduced major CV events compared to clopidogrel independently of CYP2C19 genotype.
- Event rates for BRILINTA did not vary with CYP2C19 genotype.
- In clopidogrel treated group, CYP2C19 Loss of Function (LOF) allele carriers had increased primary endpoint event rates compared with non-carriers.
- Similar to the overall PLATO study, Total Major Bleeding did not differ between BRILINTA and clopidogrel regardless of CYP2C19 genotype, although patients with one or more Gain of Function(GOF) alleles on clopidogrel had the highest rate of major bleeding.
- Similar to the overall PLATO study, Non-CABG bleeding was increased with BRILINTA compared clopidogrel in patients with a CYP2C19 LOF allele.
- Non-CABG bleeding was similar with BRILINTA and clopidogrel in patients with no CYP2C19 LOF allele.

Combined Efficacy and Safety Composite
A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined 'Total Major' bleeding) supports the clinical benefit of ticagrelor compared to clopidogrel (RRR 8%, ARR 1.4%, HR 0.92; p=0.0257) over 12 months after ACS events.

5.2 Pharmacokinetic properties

General:

Ticagrelor demonstrates linear pharmacokinetics and exposure to BRILINTA and the active metabolite (AR-C124910XX) are approximately dose proportional.

Absorption:

Absorption of BRILINTA is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from BRILINTA is rapid with a median t_{max} of approximately 2.5 hours. The C_{max} and AUC of BRILINTA and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1260 mg).

The mean absolute bioavailability of BRILINTA was estimated to be 36%, (range 25.4% to 64.0%). Ingestion of a high-fat meal had no effect on BRILINTA C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in BRILINTA AUC and 22% decrease in the active metabolite C_{max}. These small changes are considered of minimal clinical significance; therefore, BRILINTA can be given with or without food.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and C_{max} within 80-125% for ticagrelor and the active metabolite). Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

Distribution:

The steady state volume of distribution of BRILINTA is 87.5 L. BRILINTA and the active metabolite is extensively bound to human plasma protein (>99.0%).

Metabolism:

CYP3A is the major enzyme responsible for BRILINTA metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition. BRILINTA and the active metabolite are weak P-glycoprotein inhibitors.

The major metabolite of BRILINTA is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet $P2Y_{12}$ ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for BRILINTA.

Excretion:

The primary route of BRILINTA elimination is via hepatic metabolism. When radiolabeled BRILINTA is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of BRILINTA and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is mostly via biliary secretion. The mean $t_{1/2}$ was approximately 6.9 hours (range 4.5-12.8 hours) for BRILINTA and 8.6 hours (range 6.5-12.8 hours) for the active metabolite.

Special populations:

Elderly:

Higher exposures to BRILINTA (approximately 60% for both C_{max} and AUC) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in elderly (≥65 years) subjects compared to younger subjects. These differences are not considered clinically significant. (see section 4.2).

Paediatric:
BRILINTA has not been evaluated in a pediatric population. (see section 4.2).

Sex:
Higher exposures to BRILINTA (approximately 52% and 37% for C_{max} and AUC, respectively) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in women compared to men. These differences are not considered clinically significant.

Renal impairment:
Exposure to BRILINTA was approximately 20% lower and exposure to the active metabolite was approximately 17% higher in patients with severe renal impairment compared to subjects with normal renal function.[2] The IPA effect of BRILINTA was similar between the two groups, however there was more variability observed in individual response in patients with severe renal impairment. No dosing adjustment is needed in patients with renal impairment. No information is available concerning treatment of patients on renal dialysis. (see section 4.2).

Hepatic impairment:
C_{max} and AUC for BRILINTA were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however the IPA effect of BRILINTA was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. BRILINTA has not been studied in patients with moderate or severe hepatic impairment. (see section 4.2).

Race
Patients of Asian descent have a 39% higher mean bioavailability compared to Caucasian patients. Patients self-identified as Black had an 18% lower bioavailability of BRILINTA compared to Caucasian patients. In clinical pharmacology studies, the exposure (C_{max} and AUC) to BRILINTA in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians.

5.3 Preclinical safety data

Preclinical data for ticagrelor and major metabolite have not demonstrated unacceptable risk for adverse effects for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxic potential.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar or above to clinical exposure levels and with possible relevance to clinical use were as follows: GI and gastrointestinal irritation.

No compound-related tumours were observed in a 2-year mouse study at oral doses up to 250 mg/kg/day (>18-fold the human therapeutic exposure). There was no increase in tumours in male rats oral doses up to 120 mg/kg/day (>15-fold the human therapeutic exposure). There

was an increase in uterine adenocarcinomas and hepatocellular adenomas plus adenocarcinomas and a decrease in pituitary adenomas and mammary fibroadenomas in female rats only exposed to high doses (>25-fold the human therapeutic exposures). No change in tumour incidence was observed at 60 mg/kg/day (>8-fold difference to the human therapeutic dose.) The uterine tumours seen only in rats were found to be the result of a non-genotoxic endocrine effect of hormonal imbalance present in rats given high doses of ticagrelor. The benign liver tumours are considered secondary to the response by the liver to the metabolic load placed on the liver from the high doses of ticagrelor.

Ticagrelor has been tested in a range of *in vitro* and *in vivo* tests, and was not shown to be genotoxic.

Ticagrelor was found to have no effect on fertility of female rats at oral doses up to 200 mg/kg per day (approximately 20 times the human therapeutic exposure) and had no effect on fertility of male rats at doses up to 180 mg/kg/day (15.7 times the human therapeutic exposure).

Ticagrelor had no effect on foetal development at oral doses up to 100 mg/kg per day in rats (5.1 times the human therapeutic exposure) and up to 42 mg/kg per day in rabbits (equivalent to the human therapeutic exposure). Ticagrelor had no effects on parturition or postnatal development in rats at doses up to 60 mg/kg/day (4.6 times the human therapeutic exposure).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Mannitol (E421)
Dibasic calcium phosphate
Magnesium stearate
Sodium starch glycolate
Hydroxypropyl cellulose

Coating
Talc
Titanium dioxide (E171)
Ferric oxide yellow
Polyethylene glycol 400
Hypromellose

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

Standard foil blister packs in cartons of 60 and 180 tablets
Calendar foil blister packs in cartons of 14, 56, and 168 tablets
Perforated foil blister pack of 100x1 tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

No special requirements.

APPENDIX

This section includes language that should be used if your Health Authority requires adverse reactions by ADR frequency. Replace the text in the CDS with the corresponding text listed below in the appropriate section. All other text in theses sections remains the same.

Section 4.4 Special warnings and special precautions for use

Dyspnoea

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation occurs at approximately 2.2% in patients treated with BRILINTA (see section 4.8).

Section 4.8 Undesirable effects

The most commonly reported adverse reactions in patients treated with ticagrelor were dyspnoea, contusion and epistaxis, and these events occurred at higher rates than in the clopidogrel treatment group.

Dyspnoea:

Dyspnoea occurs during treatment with ticagrelor. Dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, and nocturnal dyspnoea), when combined, occurred at approximately 2.2% in patients taking ticagrelor and in 0.6% taking clopidogrel in the PLATO study.

ADR Table by System Organ Class (SOC) with ADR Frequency

The following table provides ADRs based on ADR frequency. If this is the manner that your Health Authority presents adverse reactions (by ADR frequency), please replace the table in section 4.8 with this table.

Table 1 - Adverse drug reactions by frequency and System Organ Class (SOC)

System organ classification	Common	Uncommon	Rare
Metabolism and nutrition disorders			Hyperuricaemia[a]
Psychiatric disorders			Confusion
Nervous system disorders		Intracranial haemorrhage[b], Dizziness, Headache	Paraesthesia
Eye disorders		Eye haemorrhage (intraocular, conjunctival, retinal)	
Ear and labyrinth disorders			Ear haemorrhage, Vertigo
Respiratory, thoracic and mediastinal disorders	Dyspnoea[c], Epistaxis	Haemoptysis	

Table 1 - Adverse drug reactions by frequency and System Organ Class (SOC)			
System organ classification	**Common**	**Uncommon**	**Rare**
Gastrointestinal disorders	Gastrointestinal haemorrhage[d]	Haematemesis, Gastroinstestinal ulcer haemorrhage[e], Haemorrhoidal haemorrhage, Gastritis, Oral haemorrhage (including gingival bleeding), Vomiting, Diarrhoea, Abdominal pain, Nausea, Dyspepsia	Retroperitoneal haemorrhage, Constipation
Skin and subcutaneous tissue disorders	Subcutaneous or dermal bleeding[f], Bruising[g]	Rash, Pruritus	
Musculoskeletal and connective tissue disorders			Haemarthrosis[#]
Renal and urinary disorders		Haemorrhage urinary tract[h]	
Reproductive system and breast disorders		Vaginal bleeding (including metrorrhagia)	
Investigations			Blood creatinine increased
Injury, poisoning and procedural complications	Procedural site haemorrhage[i]	Post procedural haemorrhage, Haemorrhage	Wound haemorrhage, Traumatic haemorrhage

Multiple related adverse reaction terms have been grouped together in the table and include medical terms as described below:[3]

[a] Hyperuricaemia, Blood uric acid increased

[b] Cerebral haemorrhage, Haemorrhage intracranial, Haemorrhagic stroke,

[c] Dyspnoea, Dyspnoea exertional, Dyspnoea at rest, Nocturnal dyspnoea

[d] Gastrointestinal haemorrhage, Rectal haemorrhage, Intestinal haemorrhage, Melaena, Occult blood

[e] Gastrointestinal ulcer haemorrhage, Gastric ulcer haemorrhage, Duodenal ulcer haemorrhage, Peptic ulcer haemorrhage

[f] Subcutaneous haematoma, Skin haemorrhage, Haemorrhage subcutaneous, Petechiae

[g] Contusion, Haematoma, Ecchymosis, Increased tendency to bruise, Traumatic haematoma

[h] Haematuria, Blood urine present, Haemorrhage urinary tract

[i] Vessel puncture site haemorrhage, Vessel puncture site haematoma, Injection site haemorrhage, Puncture site haemorrhage, Catheter site haemorrhage

[#] There were no reported ADRs of haemarthrosis reported in the ticagrelor arm (n=9235) of the PLATO study, the frequency has been calculated using the upper limit of the 95% confidence interval for the point

estimate (based on 3/X, where X represents the total sample size e.g. 9235). This is calculated as 3/9235 which equates to a frequency category of 'rare'

CDS	
Drug Substance	BRILINTA™ (ticagrelor)
Date	~~August 25, 2010~~ 3 March 2014
Supersedes	~~May 18, 2010~~ March 26, 2013

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Core Data Sheet
BRILINTA™ (ticagrelor) 90 mg Tablets

Use of this data sheet must conform to the current AstraZeneca ~~SOP~~IP for "~~Development, Approval and Maintenance~~Management of Core Product Information and Market Product Information"

1. NAME OF MEDICINAL PRODUCT

Name of the medicinal product

BRILINTA™ (ticagrelor), 90 mg, film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 90 mg of ticagrelor

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

90 mg - Round, biconvex, yellow, film-coated tablets. The tablets are marked with "90" above "T" on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRILINTA is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes ([ACS] unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

4.2 Posology and method of administration

BRILINTA treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily.

For oral use. BRILINTA can be taken with or without food. For patients who are unable to swallow the tablet(s) whole, Brilinta tablets (90 mg and 2x90 mg) can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

Patients taking BRILINTA should also take ASA daily unless specifically contraindicated. Following an initial dose of ASA, BRILINTA should be used with a maintenance dose of ASA of 75-150 mg (see section 5.1).

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Lapses in therapy should be avoided. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

Physicians who desire to switch patients from clopidogrel to BRILINTA should administer the first 90 mg dose of BRILINTA 24 hours following the last dose of clopidogrel (see section 5.1).

Treatment is recommended for at least 12 months unless discontinuation of BRILINTA is clinically indicated (see section 5.1). In patients with Acute Coronary Syndromes (ACS), premature discontinuation with any antiplatelet therapy, including BRILINTA, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease (see section 4.4).

Special Populations
Paediatric patients:

Safety and efficacy in children below the age of 18 have not been established.

Elderly patients:

No dose adjustment is required.

Patients with renal impairment:

No dose adjustment is necessary for patients with renal impairment (see section 5.2). No information is available concerning treatment of patients on renal dialysis.

Patients with hepatic impairment:

No dose adjustment is necessary for patients with mild hepatic impairment. BRILINTA has not been studied in patients with moderate or severe hepatic impairment. (see section 5.2)

4.3 Contraindications

Hypersensitivity to ticagrelor or any of the excipients~~.~~ (see section 4.8).
Active pathological bleeding
History of intracranial haemorrhage
Severe hepatic impairment

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4.4 Special warnings and special precautions for use

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Bleeding risk
As with other antiplatelet agents, the use of BRILINTA in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events. If clinically indicated, BRILINTA should be used with caution in the following patient groups:

Consideration should be given to the following:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, active or recent gastrointestinal bleeding or moderate hepatic impairment). The use of BRILINTA is contraindicated in patients with active pathological bleeding and in those with history of intracranial haemorrhage, and severe hepatic impairment (see section 4.3).
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDS), oral anticoagulants and/or fibrinolytics within 24 hours of BRILINTA dosing).

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No data exist with BRILINTA regarding a haemostatic benefit of platelet transfusions; circulating BRILINTA may inhibit transfused platelets. Since co administration of BRILINTA with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may augment haemostasis. BRILINTA may be resumed after the cause of bleeding has been identified and controlled.

Surgery

- If a patient requires surgery, physicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.
- Because of the reversible binding of BRILINTA, restoration of platelet aggregation occurs faster with BRILINTA compared to clopidogrel. In the OFFSET study, mean Inhibition of Platelet Aggregation (IPA) for BRILINTA at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, eg, in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.
- In PLATO patients under going CABG, BRILINTA had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where BRILINTA had a higher rate of major bleeding.
- If a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery. (see section 5.1).

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Patients with moderate hepatic impairment

Caution is advised in patients with moderate hepatic impairment because BRILINTA has not been studied in these patients. Use of BRILINTA is contraindicated in patients with severe hepatic impairment (see section 4.3).

Patients at risk for bradycardic events

Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) were excluded from the main study evaluating the safety and efficacy of BRILINTA. Therefore, due to the limited clinical experience in these patients, caution is advised (see section 5.1).

Dyspnoea

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported in patients treated with BRILINTA (approximately 13.8%) (see section 4.8). The mechanism has not yet been elucidated. If a patient reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with BRILINTA should be stopped.

Other

Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high maintenance dose ASA (>300 mg) is not recommended (see section 5.1).

Co-administration of BRILINTA with strong CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, nefazadone, ritonavir, and ~~atanazavir~~atazanavir) should be avoided as co-administration may lead to a substantial increase in exposure to BRILINTA (see section 4.5).

Discontinuations

Patients who require discontinuation of BRILINTA are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event(s), it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

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Drug-Drug Interactions

Effects of Other Drugs on BRILINTA

Medicinal Products metabolised by CYP3A4

Ketoconazole (Strong CYP3A4 Inhibitors) Co-administration of ketoconazole with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56% respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir, and ~~atanazavir~~atazanavir) would

be expected to have similar effects and should not be given concomitantly with BRILINTA (see section 4.4).

Diltiazem (Moderate CYP3A4 inhibitors)
Co-administration of ticagrelor and diltiazem increased the C_{max} of ticagrelor by 69% and AUC by 174% and decreased the active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin, fluconazole, and verapamil) can as well be co-administered with BRILINTA.

Rifampin and Other CYP3A Inducers
Co-administration of rifampin with ticagrelor decreased ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46% respectively. Other CYP3A4 inducers (e.g. ~~dexamethasone,~~ phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of BRILINTA.

Cyclosporine (PgP and CYP3A inhibitor)[1]
Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and C_{max} was decreased by 15% in the presence of cyclosporine. There was no effect of ticagrelor on cyclosporine blood levels.

Others
Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and aspirin did not have any effect on ticagrelor or the active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co-administration of ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay.

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Effects of BRILINTA on Other Drugs

Medicinal Products metabolised by CYP3A4
Simvastatin
Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3 fold. Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin. There was no effect of simvastatin on ticagrelor plasma levels. BRILINTA may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.

Atorvastatin
Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Medicinal Products metabolised by CYP2C9 - Tolbutamide
Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which suggest that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of drugs like warfarin and tolbutamide.

Oral Contraceptives
Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure approximately 20% but did not alter the PK of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with BRILINTA.

Digoxin (PgP substrate)
Concomitant administration of ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin concomitantly with BRILINTA.

Other Concomitant Therapy
In clinical studies, BRILINTA was commonly administered with acetylsalicylic acid, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

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No clinical study has been conducted in pregnant or lactating women.

Limited clinical data on exposure to BRILINTA during pregnancy are available.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Ticagrelor had no effect on male or female fertility (see section 5.3).

Because animal reproduction studies are not always predictive of a human response, ticagrelor should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the foetus.

Lactation

It is not known whether this medicinal product is excreted in human milk. Studies in rats have shown that ticagrelor and active metabolites are excreted in the milk. The use of BRILINTA during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines

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No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. BRILINTA has no or negligible influence on the ability to drive and use machines. During treatment for Acute Coronary Syndromes, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

4.8 Undesirable effects

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The safety of BRILINTA in patients with acute coronary syndromes (UA, NSTEMI and STEMI) was evaluated in a single large phase 3 study (PLATO [PLATelet Inhibition and Patient Outcomes] study), which compared patients treated with BRILINTA (loading dose of 180 mg of BRILINTA and a maintenance dose of 90 mg bd) to patients treated with clopidogrel (300-600 mg loading dose followed by 75 mg od maintenance dose) both given in combination with acetylsalicylic acid (ASA) and other standard therapies.

Median treatment duration for BRILINTA was 277 days (6762 patients were treated for greater than 6 months and 3138 were treated for greater than 12 months).

The most commonly reported adverse events in patients treated with ticagrelor were dyspnoea, headache, and epistaxis and these events occurred at higher rates than in the clopidogrel treatment group. During the treatment period, the BRILINTA group had a higher incidence of discontinuation due to adverse events than clopidogrel (7.4% vs. 5.4%).

Bleeding

The following bleeding definitions were used in the PLATO study:

'Major Fatal/Life-threatening': fatal, or intracranial, or intrapericardial bleed with cardiac tamponade, or hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, or clinically overt or apparent bleeding associated with a decrease in haemoglobin of more than 50 g/L, or transfusion of 4 or more units (whole blood or PRBCs) for bleeding.

'Major Other': Significantly disabling (e.g., intraocular with permanent vision loss), or clinically overt or apparent bleeding associated with a decrease in haemoglobin of 30 to 50 g/L, or transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

'Minor': Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).

Minimal bleeds included all other bleeds; these were collected but not adjudicated.

Bleeding events reported in PLATO were also mapped to the TIMI (Thrombolysis in Myocardial Infarction) scale, to facilitate comparison with other similar studies. **TIMI Major** is defined as clinically overt bleeding associated with a fall in hemoglobin > 5 g/dL, or intracranial hemorrhage, and **TIMI Minor** is defined as overt bleeding associated with a fall in hemoglobin of 3 g/dL but ≤ 5 g/dL.

Overall outcome of bleeding events in the PLATO study are shown in Figure 1 and Table 1.

Figure 1 – Kaplan Meier estimate of time to first PLATO-defined 'Total Major' bleeding event

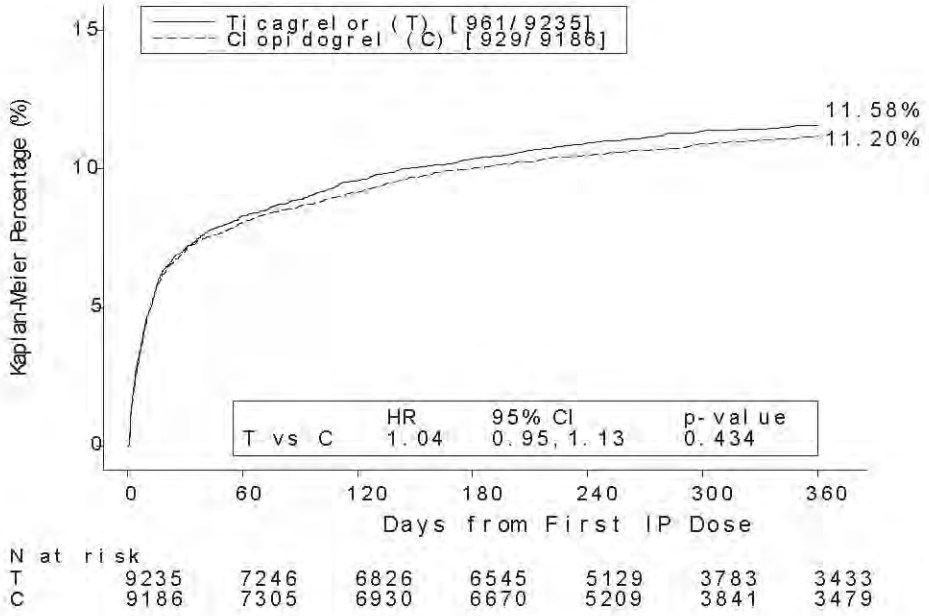

Table 1 – Analysis of Overall Bleeding Events

	BRILINTA (%)	Clopidogrel (%)	

	N=9235	N=9186	p-value
Primary Safety Endpoint Total Major	11.6	11.2	0.4336
Secondary Endpoints Fatal/Life-Threatening	5.8	5.8	0.6988
Combined Total Major + Minor bleeding	16.1	14.6	0.0084
Non-CABG Major	4.5	3.8	0.0264
Non-Procedural Major	3.1	2.3	0.0058
Non-Procedural Major + Minor	5.9	4.3	<0.0001
TIMI-defined bleeding category TIMI-defined Major	7.9	7.7	0.5669
TIMI-defined Major + Minor	11.4	10.9	0.3272

In PLATO, time to first PLATO-defined 'Total Major' bleeding for BRILINTA did not differ significantly from that of clopidogrel. There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA and 23 (0.3%) for clopidogrel. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on BRILINTA than on clopidogrel. Overall rates of TIMI-defined bleeding events did not differ significantly between BRILINTA and clopidogrel.

CABG-related bleeding: In PLATO, 1584 patients (12%) underwent coronary artery bypass graft (CABG) surgery. 'Major Fatal/Life-threatening' bleeding was approximately 42% in both treatment groups. There was no difference between the treatment groups with respect to risk of 'Major Fatal/Life-threatening' CABG bleeding relative to time of last dose before the procedure. Fatal CABG bleeding occurred uncommonly, 6 patients in each treatment group (0.8% and 0.7% of CABG patients on BRILINTA and clopidogrel, respectively).

Non-CABG related bleeding: When CABG bleeding is removed from the analysis (see Table 2), the absolute bleeding rates for all categories are lower. The groups did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening bleeding, but PLATO-defined 'Total Major', TIMI Major, and TIMI Major + Minor bleeding was more common with BRILINTA.

Table 2 - Non-CABG Related PLATO-defined Major Bleeding Events and TIMI-defined Bleeding Events

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	p-value
PLATO-defined			

bleeding category Total Major Bleeding	4.5	3.8	0.0264
Major Fatal/Life-Threatening	2.1	1.9	0.2516
TIMI-defined bleeding category TIMI-defined Major	2.8	2.2	0.0246
TIMI-defined Major + Minor	4.5	3.6	0.0093

Bleeding unrelated to any procedure: As shown in Table 1 PLATO-defined 'Major' and 'Major + Minor' non-procedural bleeding was more frequent with BRILINTA. Discontinuation of treatment due to non-procedural bleeding was more common for BRILINTA (2.9%) than for clopidogrel (1.2%; p<0.001). Clinically important locations for 'Major + Minor' bleeding in rank order by frequency were (BRILINTA vs clopidogrel): intracranial (27 vs 14 events), pericardial (11 vs 11), retroperitoneal (3 vs 3), intraocular (2 vs 4) and intra-articular (2 vs 1). Other common locations were in rank order of frequency: gastrointestinal (170 vs 135 events), epistaxis (116 vs 61), urinary (45 vs 37), subcutaneous/dermal (43 vs 38) and haemoptysis (13 vs 7).

There was no difference with BRILINTA compared to clopidogrel for fatal non-procedural bleeding. 'Major Fatal/Life-threatening' gastrointestinal bleeding was the same with BRILINTA and clopidogrel, with numerically more fatal events for clopidogrel (5) than for BRILINTA (none). There were numerically more 'Major Fatal/Life-threatening' intracranial non-procedural bleeding events with BRILINTA (n=27 events in 26 patients, 0.3%) than with clopidogrel (n=14 events, 0.2%), of which 11 bleeding events with BRILINTA and 1 with clopidogrel were fatal.

Baseline characteristics including age, gender, weight, race, geographic region, medical history, concurrent conditions and concomitant therapy were assessed to explore any increase in risk of bleeding with BRILINTA. No particular risk group was identified for any subset of bleeding.

Dyspnoea:
Dyspnoea occurs during treatment with ticagrelor. Dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, and nocturnal dyspnoea), when combined, were reported in 13.8% of patients taking ticagrelor and in 7.8% taking clopidogrel in the PLATO study. The study did not exclude patients with underlying congestive heart failure (CHF), chronic obstructive pulmonary disorder (COPD), or asthma. Most of the dyspnoea AEs were mild to moderate in intensity. Dyspnoea Serious Adverse Events were reported in 0.7% taking BRILINTA and 0.4% taking clopidogrel. More patients taking BRILINTA 0.89% discontinued study drug than did patients taking clopidogrel 0.1% due to dyspnoea. Dyspnoea was usually reported in the initial phase of treatment. Eighty-seven percent of patients taking BRILINTA that reported dyspnoea experienced a single episode. Approximately 30% of all dyspnoea resolved within 7 days. Patients who reported

dyspnoea tended to be older and more frequently had dyspnoea, CHF, COPD, or asthma at baseline. PLATO data do not suggest that the higher frequency of dyspnoea with BRILINTA is due to new or worsening heart or lung disease (see section 4.4).

In patients who underwent pulmonary function testing in the clinical program, there was no indication of an adverse effect of BRILINTA on pulmonary function.

Lab Abnormalities
In PLATO, serum uric acid concentration increased to more than upper limit of normal in 22% of patients receiving BRILINTA compared to 13% of patients receiving clopidogrel. Mean serum uric acid concentration increased approximately 15% with BRILINTA compared to approximately 7% with clopidogrel and reduced after treatment was stopped. There was no difference in the frequency of clinical adverse events.

In PLATO, serum creatinine concentration increased by >50% in 8% of patients receiving BRILINTA compared to 7% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Signs of reversibility on discontinuation were observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for related serious adverse events.

Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following conventions: Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000)

The following adverse reactions have been identified following studies with BRILINTA.

Table 3 - Adverse Drug Reactions by System Organ Class (SOC) and by Adverse Event Frequency

System Organ Classification	Very Common	Common	Uncommon	Rare
Metabolism and nutrition disorders	Hyperuricaemia[a]			
Psychiatric disorders			Confusion	
Nervous system disorders		Headache, Dizziness	Intracranial haemorrhage[b], Paraesthesia	
Eye disorders			Eye haemorrhage (intraocular, conjunctival,	

System Organ Classification	Very Common	Common	Uncommon	Rare
			retinal)	
Ear and labyrinth disorders		Vertigo		
Respiratory, thoracic and mediastinal disorders	Dyspnoea [b]	Epistaxis	Haemoptysis	
Gastrointestinal Disorders		Abdominal pain, Constipation, Diarrhoea, Dyspepsia, Gastrointestinal haemorrhage [b], Nausea, Vomiting	Gastritis, Retroperitoneal haemorrhage [b]	
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding [b], Rash, Pruritus		
Musculoskeletal connective tissue and bone				Haemarthrosis
Renal and urinary disorders		Urinary tract bleeding [b]		
Investigations		Blood creatinine increased [a]		
Injury, poisoning and procedural complications		Post procedural haemorrhage		

[a] Frequencies derived from lab observations (uric acid to >ULN of 7and 6 5 mg/dl for males and females respectively and creatinine increases of >50% from baseline) and not crude adverse event report frequency- see lab section
[b] Represents multiple related adverse events terms

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Postmarketing Experience[i]
The following adverse reactions have been identified during post-approval use of BRILINTA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.

Immune system disorders - Hypersensitivity reactions including angioedema (see section 4.3).

4.9 Overdose

There is currently no known antidote to reverse the effects of BRILINTA, and BRILINTA is not expected to be dialysable (see section 4.4). Treatment of overdose should follow local standard medical practice. The expected effect of excessive BRILINTA dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs appropriate supportive measures should be taken.

Ticagrelor is well tolerated in single doses up to 900 mg. GI toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse effects which may occur with overdose include dyspnoea and ventricular pauses.

In the event of overdose, observe for these potential adverse effects and consider ECG monitoring.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group (ATC code): B01AC24
Pharmacotherapeutic group: ~~Not yet assigned.~~ Platelet aggregation inhibitors excluding heparin

~~ATC code: Not yet assigned.~~

5.1 Pharmacodynamic properties

Mechanism of action:

BRILINTA contains ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is ~~a~~an oral, direct acting, selective and ~~reversible~~ reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP~~) receptor antagonist acting on the $P2Y_{12}$ ADP receptor that can prevent ADP~~)-mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor ~~is orally active, and reversibly interacts with~~does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet ~~$P2Y_{12}$ ADP receptor.~~ function has been shown to reduce the risk of cardiovascular events such as death, myocardial infarction or stroke.

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Ticagrelor ~~does not interact with the ADP binding site itself, but~~ has an additional mechanism of action, increasing local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1). Adenosine is formed locally at sites of hypoxia and tissue damage through degradation of released adenosine tri- and di-phosphate (ATP and ADP). As adenosine degradation is essentially restricted to the intracellular space, inhibition of ENT-1 by ticagrelor prolongs the half-life of adenosine and thereby increases its ~~interaction with~~local extracellular concentration providing enhanced local adenosine responses. Ticagrelor has no clinically significant direct effect on adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and is not metabolised to adenosine. Adenosine has been documented to have a number of effects that include: vasodilation, cardioprotection, platelet ~~$P2Y_{12}$ ADP receptor prevents signal transduction~~inhibition, modulation of inflammation and induction of dyspnoea, which may contribute to the clinical profile of ticagrelor.

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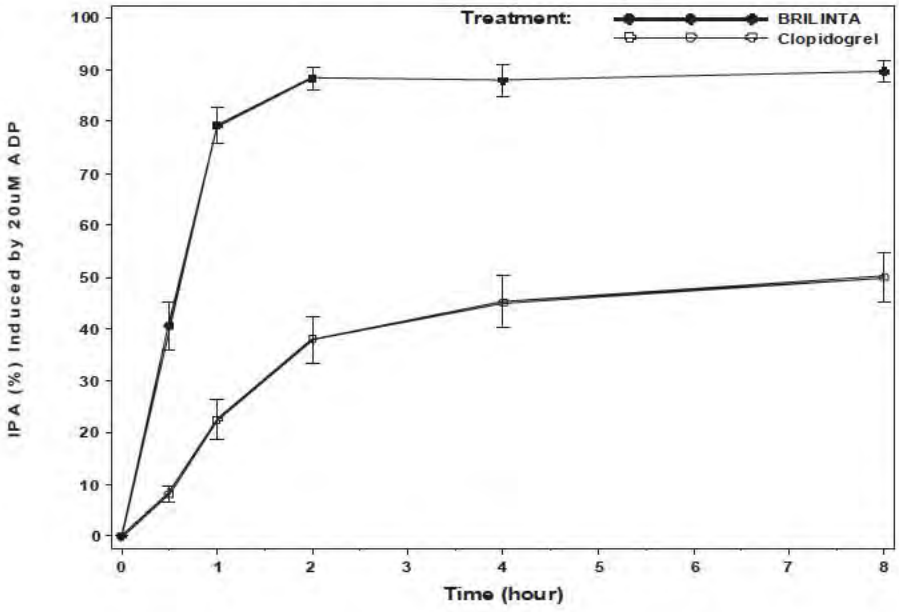
Pharmacodynamic effects:

Onset of Action

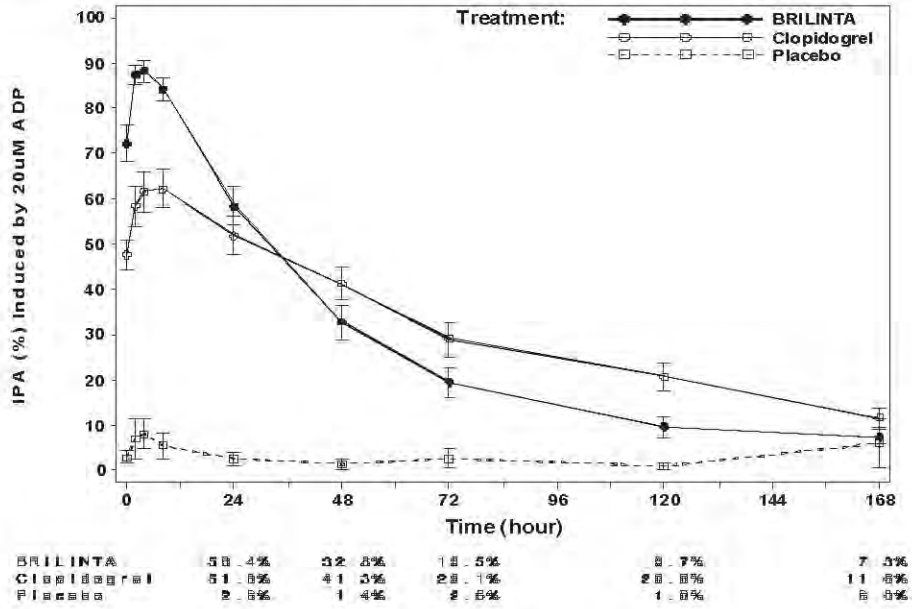
Mean final extent Inhibition (±SE) of Platelet Aggregation (IPA) following single oral doses of 180 mg BRILINTA or 600 mg clopidogrel in patients with stable CAD



In patients with stable coronary artery disease on ASA, BRILINTA demonstrates a rapid onset of pharmacological effect as demonstrated by a mean Inhibition of Platelet Aggregation (IPA) for BRILINTA at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA

effect of 87.9% to 89.6% by 2-4 hours post dose. 90% of patients had final extent IPA >70% by 2 hours post dose. The high IPA effect of BRILINTA between 87%-89% was maintained between 2-8 hours.

Mean final extent Inhibition (±SE) of Platelet Aggregation (IPA) following the last maintenance dose of 90 mg bid BRILINTA or 75 mg clopidogrel qd or placebo



Offset of Effect

After the BRILINTA and the active metabolite concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since BRILINTA bind reversibly, the recovery of platelet function does not depend on replacement of platelets. BRILINTA has a faster rate of offset of IPA as compared to clopidogrel as determined by the slope of offset from 4-72 hours after last dose (see section 4.4).

Median final extent IPA measured after the last dose of BRILINTA is approximately 20-30% higher for BRILINTA compared to clopidogrel. However, by 24 hours post-dose, %IPA is similar between BRILINTA and clopidogrel, and is lower for BRILINTA from 72 hours through 7 days compared with the clopidogrel. Mean %IPA for BRILINTA at 72 hours (Day 3) post last dose was comparable to clopidogrel at Day 5, and %IPA for BRILINTA at Day 5 was similar to clopidogrel at Day 7, which is not statistically different from placebo.

Responders to BRILINTA
IPA induced by BRILINTA has less variability at peak plasma concentrations of BRILINTA and the active metabolite observed with the 90 mg bd dose compared to clopidogrel. Patients with stable coronary artery disease predetermined to have low IPA response to clopidogrel (non-responders), and given a concomitant dose of ASA, exhibited higher mean IPA response after administration of BRILINTA as compared to clopidogrel. In Non-responders to clopidogrel, the IPA response to BRILINTA was observed to be higher and more consistent. BRILINTA treatment resulted in consistently higher IPA compared with clopidogrel, and this was apparent post dose for both responders and non-responders.

Switching Data
Switching from clopidogrel to BRILINTA results in an absolute IPA increase of 26.4% and switching from BRILINTA to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to BRILINTA without interruption of anti-platelet effect.

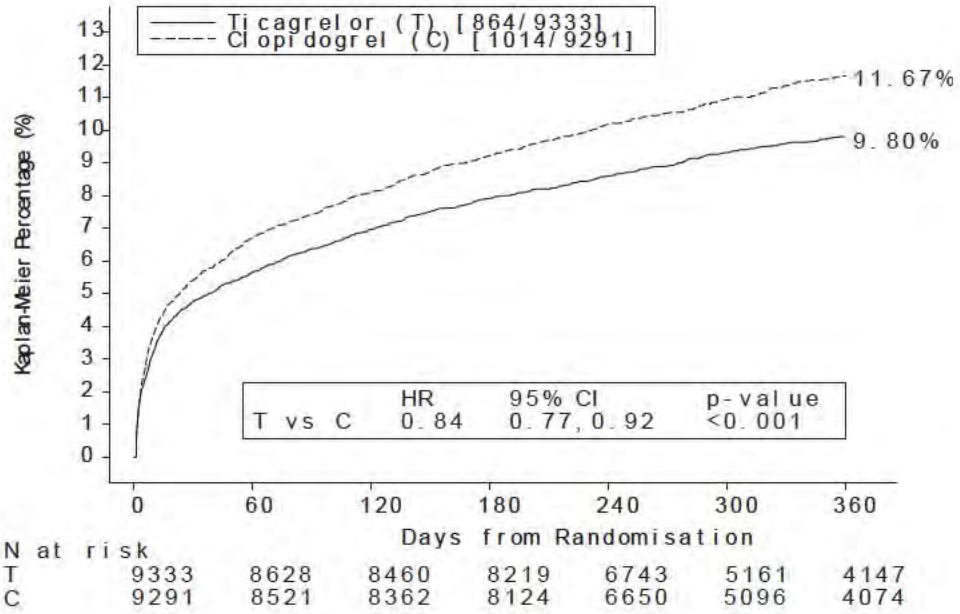
Adenosine mechanism (ENT-1)
Ticagrelor increased plasma adenosine concentrations in ACS patients and has been shown to augment several physiological responses to adenosine. Adenosine is a vasodilator; ticagrelor has been shown to augment adenosine-induced coronary blood flow increases in healthy volunteers and ACS patients. Adenosine is an endogenous platelet inhibitor; ticagrelor has been shown to augment adenosine-mediated inhibition of platelet aggregation in addition to platelet inhibition due to its $P2Y_{12}$ antagonism. Adenosine has been linked to the cardio-protective effect of preconditioning; ticagrelor has been shown to reduce infarct size via an adenosine-mediated mechanism in a rat model of reperfusion injury. Adenosine also induces dyspnoea; ticagrelor has been shown to augment adenosine-induced dyspnoea in healthy volunteers. Thus, the dyspnoea observed in some patients taking ticagrelor (see section 4.8) may partly or completely be mediated by adenosine.

Clinical efficacy:

The clinical evidence for the efficacy of BRILINTA is derived from the PLATO [PLATelet Inhibition and Patient Outcomes] study, a comparison of BRILINTA to clopidogrel, both given in combination with acetylsalicylic acid (ASA) and other standard therapy.

The PLATO study was an 18,624 patient randomized, double-blind, parallel group, phase III, efficacy and safety study of BRILINTA compared with clopidogrel for prevention of vascular events in patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI].
The study was comprised of patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. Patients were randomized to receive clopidogrel (75 mg once daily, with an initial loading dose of 300 mg if previous thienopyridine therapy had not been given. An additional loading dose of 300 mg was allowed at investigator discretion), or a loading dose of 180 mg of BRILINTA followed by a maintenance dose of 90 mg of BRILINTA twice daily. Patients could have been medically managed, treated with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).

Figure 2 shows the estimate of the risk to the first occurrence of any event in the composite efficacy endpoint



BRILINTA reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/~~STEMI and~~ NSTEMI and STEMI population~~s~~.[4]

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Table 4 – Outcome Events in PLATO

	Patients with Events			

Primary Endpoint	BRILINTA (%) N=9333	Clopidogrel (%) N=9291	Relative Risk Reduction[a] (%)	Hazard Ratio (95% CI)	p-value
Composite of CV Death/MI (excl. silent MI)/Stroke	9.3	10.9	16	0.84(0.77,0.92)	p=0.0003
CV death	3.8	4.8	21	0.79(0.69,0.91)	p=0.0013
MI (excl. silent MI)[a]	5.4	6.4	16	0.84(0.75,0.95)	p=0.0045
Stroke	1.3	1 1	-17	1.17(0.91,1.52)	p=0.2249
Secondary Endpoints					
Composite of CV Death/MI (excl. silent MI)/Stroke – intent to invasively manage[a]	8.5	10.0	16	0.84(0.75,0.94)	p=0.0025
Composite of all-cause mortality/MI (excl. silent MI)/Stroke	9.7	11.5	16	0.84(0.77,0.92)	p=0.0001
Composite of CV Death/Total MI/Stroke/SRI/RI/TIA /Other ATE	13.8	15.7	12	0.88(0.81,0.95)	p=0.0006
All-cause mortality	4.3	5.4	22	0.78(0.69,0.89)	p=0.0003**

[a]RRR= (1-Hazard Ratio) x 100% Values with a negative relative risk reduction indicate a relative risk increase
**nominal p-value

BRILINTA is superior to clopidogrel in the prevention of thrombotic events (RRR 16%, ARR 1.9%, NNT =54) of the composite efficacy endpoint (cardiovascular (CV) death, myocardial infarction (MI) and stroke) over 12 months. The difference in treatments was driven by cardiovascular death and myocardial infarction with no difference on strokes. BRILINTA demonstrated a statistically significant relative risk reduction of 16% (ARR 1.1%) for MI and a 21% relative risk reduction (ARR 1.1%) for CV death. Treating 91 patients with BRILINTA instead of clopidogrel will prevent 1 CV death.

BRILINTA showed superiority to clopidogrel in preventing the composite ~~endpint~~endpoint (cardiovascular [CV] death, myocardial infarction [MI], or stroke). This result appeared early (absolute risk reduction [ARR] ~~1.~~0.6% and Relative Risk Reduction [RRR] of 12% at 30 days), with a constant treatment effect over the entire 12 month period, yielding ARR 1.9% per year with RRR of 16%. This suggests it is appropriate to treat for at least 12 months (see section 4.2).

In PLATO a large number of subgroup comparisons were conducted for the primary efficacy endpoint to assess the robustness and consistency of the overall benefit. The treatment effect of BRILINTA over clopidogrel appears consistent across multiple patient subgroups by

demographic characteristics including weight, gender, medical history, concomitant therapy, and by final index event diagnosis (STEMI, NSTEMI, and UA).

A weakly significant treatment interaction was observed with region whereby the HR for the primary endpoint favours BRILINTA in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045).

This apparent treatment-by-region interaction observed in PLATO could plausibly be attributed to chance, at least in part. Additional analyses suggest that the efficacy of BRILINTA relative to clopidogrel is associated with ASA dose during maintenance therapy. The data show greater efficacy of ticagrelor compared to clopidogrel when used in conjunction with low maintenance dose ASA (75-150 mg). The relative efficacy of ticagrelor versus clopidogrel when used with high doses of ASA (>300 mg) is less certain. Based on this observed relationship between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, it is recommended that BRILINTA is used with a low maintenance dose of ASA 75-150 mg (see sections 4.2 and 4.4).

The benefits associated with BRILINTA were also independent of the use of other acute and long-term cardiovascular therapies, including heparin, low molecular weight heparin (LMWH), intravenous GpIIb/IIIa inhibitors, lipid-lowering drugs, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and proton pump inhibitors (see section 4.5).

BRILINTA demonstrated a statistically significant relative risk reduction (RRR) in the composite endpoint cardiovascular (CV) death, myocardial infarction (MI) and stroke in ACS patients planned for invasive management (RRR 16%, ARR 1.7%, p=0.0025). In an exploratory analysis, BRILINTA demonstrated a relative risk reduction of the primary composite endpoint in ACS patients intended for medical management (RRR 15%, ARR 2.3%, nominal p=0.0444). Consistent with the primary endpoint of the study, the effect in these two groups was driven by CV death and MI with no effect on stroke. In patients receiving stents there were numerically fewer definite stent thromboses among patients treated with ticagrelor compared to clopidogrel (73 vs. 107, RRR 32%, ARR 0.6%, nominal p=0.0123).

BRILINTA demonstrated a statistically significant RRR of 16% (ARR 2.1%) for the composite of all-cause mortality, MI and stroke compared to clopidogrel.

The final secondary endpoint (all-cause mortality) was evaluated. BRILINTA demonstrated a RRR of 22% for all-cause mortality compared to clopidogrel at a nominal significance level of p=0.0003 and an ARR of 1.4%.

Holter Substudy
To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3000 patients, of whom

approximately 2000 had recordings both in the acute phase of their ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. More patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; and 2.2% and 1.6% respectively after 1 month. More patients had ventricular pauses with BRILINTA than with clopidogrel, however, there were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

Ticagrelor is orally active. Unlike clopidogrel, it does not require CYP450 enzyme activity to inhibit platelet aggregation. Polymorphisms in the gene coding for CYP450 enzyme 2C19 may impact clopidogrel efficacy. Polymorphism in the gene coding for P-glycoprotein transport (ABCB1) may impact efficacy of both clopidogrel and ticagrelor.
In PLATO, 10,285 patients provided genetic samples for genotype determination of CPY2C19 and ABCB1 loci. An analysis provided these associations of genotype groupings on efficacy and safety outcomes in PLATO.

- The superiority of BRILINTA over clopidogrel is not significantly affected by patient CYP2C19 genotype
- BRILINTA reduced major CV events compared to clopidogrel independently of CYP2C19 genotype.
- Event rates for BRILINTA did not vary with CYP2C19 genotype.
- In clopidogrel treated group, CYP2C19 Loss of Function (LOF) allele carriers had increased primary endpoint event rates compared with non-carriers.
- Similar to the overall PLATO study, Total Major Bleeding did not differ between BRILINTA and clopidogrel regardless of CYP2C19 genotype, although patients with one or more Gain of Function(GOF) alleles on clopidogrel had the highest rate of major bleeding.
- Similar to the overall PLATO study, Non-CABG bleeding was increased with BRILINTA compared clopidogrel in patients with a CYP2C19 LOF allele.
- Non-CABG bleeding was similar with BRILINTA and clopidogrel in patients with no CYP2C19 LOF allele.

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Combined Efficacy and Safety Composite
A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined 'Total Major' bleeding) supports the clinical benefit of ticagrelor compared to clopidogrel (RRR 8%, ARR 1.4%, HR 0.92; p=0.0257) over 12 months after ACS events.

5.2 Pharmacokinetic properties

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General:

Ticagrelor demonstrates linear pharmacokinetics and exposure to BRILINTA and the active metabolite (AR-C124910XX) are approximately dose proportional.

Absorption:

Absorption of BRILINTA is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from BRILINTA is rapid with a median t_{max} of approximately 2.5 hours. The C_{max} and AUC of BRILINTA and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1260 mg).

The mean absolute bioavailability of BRILINTA was estimated to be 36%, (range 25.4% to 64.0%). Ingestion of a high-fat meal had no effect on BRILINTA C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in BRILINTA AUC and 22% decrease in the active metabolite C_{max}. These small changes are considered of minimal clinical significance; therefore, BRILINTA can be given with or without food.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and C_{max} within 80-125% for ticagrelor and the active metabolite). Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

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Distribution:

The steady state volume of distribution of BRILINTA is 87.5 L. BRILINTA and the active metabolite is extensively bound to human plasma protein (>99.~~7~~0%).

Metabolism:

CYP3A is the major enzyme responsible for BRILINTA metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition. BRILINTA and the active metabolite are weak P-glycoprotein inhibitors.

The major metabolite of BRILINTA is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet $P2Y_{12}$ ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for BRILINTA.

Excretion:

The primary route of BRILINTA elimination is via hepatic metabolism. When radiolabeled BRILINTA is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of BRILINTA and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is mostly via biliary secretion. The mean $t_{1/2}$ was approximately 6.9 hours (range 4.5-12.8 hours) for BRILINTA and 8.6 hours (range 6.5-12.8 hours) for the active metabolite.

Special populations:

Elderly:

Higher exposures to BRILINTA (approximately 60% for both C_{max} and AUC) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in elderly (≥65 years) subjects compared to younger subjects. These differences are not considered clinically significant. (see section 4.2).

Paediatric:
BRILINTA has not been evaluated in a pediatric population. (see section 4.2).

Sex:
Higher exposures to BRILINTA (approximately 52% and 37% for C_{max} and AUC, respectively) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in women compared to men. These differences are not considered clinically significant.

Renal impairment:
Exposure to BRILINTA was approximately 20% lower and exposure to the active metabolite ~~were~~was approximately ~~20% lower~~17% higher in patients with severe renal impairment compared to subjects with normal renal function~~.~~. The IPA effect of BRILINTA was similar between the two groups, however there was more variability observed in individual response in patients with severe renal impairment. No dosing adjustment is needed in patients with renal impairment. No information is available concerning treatment of patients on renal dialysis. (see section 4.2).

Hepatic impairment:
C_{max} and AUC for BRILINTA were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however the IPA effect of BRILINTA was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. BRILINTA has not been studied in patients with moderate or severe hepatic impairment. (see section 4.2).

Race
Patients of Asian descent have a 39% higher mean bioavailability compared to Caucasian patients. Patients self-identified as Black had an 18% lower bioavailability of BRILINTA compared to Caucasian patients. In clinical pharmacology studies, the exposure (C_{max} and AUC) to BRILINTA in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians.

5.3 Preclinical safety data

Preclinical data for ticagrelor and major metabolite have not demonstrated unacceptable risk for adverse effects for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxic potential.

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Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar or above to clinical exposure levels and with possible relevance to clinical use were as follows: GI and gastrointestinal irritation.

No compound-related tumours were observed in a 2-year mouse study at oral doses up to 250 mg/kg/day (>18-fold the human therapeutic exposure). There was no increase in tumours in male rats oral doses up to 120 mg/kg/day (>15-fold the human therapeutic exposure). There was an increase in uterine adenocarcinomas and hepatocellular adenomas plus adenocarcinomas and a decrease in pituitary adenomas and mammary fibroadenomas in female rats only exposed to high doses (>25-fold the human therapeutic exposures). No change in tumour incidence was observed at 60 mg/kg/day (>8-fold difference to the human therapeutic dose.) The uterine tumours seen only in rats were found to be the result of a non-genotoxic endocrine effect of hormonal imbalance present in rats given high doses of ticagrelor. The benign liver tumours are considered secondary to the response by the liver to the metabolic load placed on the liver from the high doses of ticagrelor.

Ticagrelor has been tested in a range of *in vitro* and *in vivo* tests, and was not shown to be genotoxic.

Ticagrelor was found to have no effect on fertility of female rats at oral doses up to 200 mg/kg per day (approximately 20 times the human therapeutic exposure) and had no effect on fertility of male rats at doses up to 180 mg/kg/day (15.7 times the human therapeutic exposure).

Ticagrelor had no effect on foetal development at oral doses up to 100 mg/kg per day in rats (5.1 times the human therapeutic exposure) and up to 42 mg/kg per day in rabbits (equivalent to the human therapeutic exposure). Ticagrelor had no effects on parturition or postnatal development in rats at doses up to 60 mg/kg/day (4.6 times the human therapeutic exposure).

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Mannitol (E421)
Dibasic calcium phosphate
Magnesium stearate
Sodium starch glycolate
Hydroxypropyl cellulose

Coating
Talc
Titanium dioxide (E171)
Ferric oxide yellow

Polyethylene glycol 400
Hypromellose

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

~~2~~3 years

6.4 Special precautions for storage

~~This medicinal product does not require any special storage conditions.~~
Do not store above 30°C

6.5 Nature and contents of container

Standard foil blister packs in cartons of 60 and 180 tablets
Calendar foil blister packs in cartons of 14, 56, and 168 tablets
Perforated foil blister pack of 100x1 tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

No special requirements.

APPENDIX

This section includes language that should be used if your Health Authority requires adverse reactions by ADR frequency. Replace the text in the CDS with the corresponding text listed below in the appropriate section. All other text in theses sections remains the same.

Section 4.4 Special warnings and special precautions for use

Dyspnoea

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation occurs at approximately 2.2% in patients treated with BRILINTA (see section 4.8).

Section 4.8 Undesirable effects

The most commonly reported adverse reactions in patients treated with ticagrelor were dyspnoea, contusion and epistaxis, and these events occurred at higher rates than in the clopidogrel treatment group.

Dyspnoea:

Dyspnoea occurs during treatment with ticagrelor. Dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, and nocturnal dyspnoea), when combined, occurred at approximately 2.2% in patients taking ticagrelor and in 0.6% taking clopidogrel in the PLATO study.

ADR Table by System Organ Class (SOC) with ADR Frequency

The following table provides ADRs based on ADR frequency. If this is the manner that your Health Authority presents adverse reactions (by ADR frequency), please replace the table in section 4.8 with this table.

Table 1- Adverse drug reactions by frequency and System Organ Class (SOC)

System organ classification	Common	Uncommon	Rare
Metabolism and nutrition disorders			Hyperuricaemia[a]
Psychiatric disorders			Confusion
Nervous system disorders		Intracranial haemorrhage[b], Dizziness, Headache	Paraesthesia
Eye disorders		Eye haemorrhage (intraocular, conjunctival, retinal)	
Ear and labyrinth disorders			Ear haemorrhage, Vertigo
Respiratory, thoracic and mediastinal disorders	Dyspnoea[c], Epistaxis	Haemoptysis	

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Table 1 - Adverse drug reactions by frequency and System Organ Class (SOC)

System organ classification	Common	Uncommon	Rare
Gastrointestinal disorders	Gastrointestinal haemorrhage[d]	Haematemesis, Gastroinstestinal ulcer haemorrhage[e], Haemorrhoidal haemorrhage, Gastritis, Oral haemorrhage (including gingival bleeding), Vomiting, Diarrhoea, Abdominal pain, Nausea, Dyspepsia	Retroperitoneal haemorrhage, Constipation
Skin and subcutaneous tissue disorders	Subcutaneous or dermal bleeding[f], Bruising[g]	Rash, Pruritus	
Musculoskeletal and connective tissue disorders			Haemarthrosis[#]
Renal and urinary disorders		Haemorrhage urinary tract[h]	
Reproductive system and breast disorders		Vaginal bleeding (including metrorrhagia)	
Investigations			Blood creatinine increased
Injury, poisoning and procedural complications	Procedural site haemorrhage[i]	Post procedural haemorrhage, Haemorrhage	Wound haemorrhage, Traumatic haemorrhage

Multiple related adverse reaction terms have been grouped together in the table and include medical terms as described below:[3]

[a] Hyperuricaemia, Blood uric acid increased

[b] Cerebral haemorrhage, Haemorrhage intracranial, Haemorrhagic stroke,

[c] Dyspnoea, Dyspnoea exertional, Dyspnoea at rest, Nocturnal dyspnoea

[d] Gastrointestinal haemorrhage, Rectal haemorrhage, Intestinal haemorrhage, Melaena, Occult blood

[e] Gastrointestinal ulcer haemorrhage, Gastric ulcer haemorrhage, Duodenal ulcer haemorrhage, Peptic ulcer haemorrhage

[f] Subcutaneous haematoma, Skin haemorrhage, Haemorrhage subcutaneous, Petechiae

[g] Contusion, Haematoma, Ecchymosis, Increased tendency to bruise, Traumatic haematoma

[h] Haematuria, Blood urine present, Haemorrhage urinary tract

[i] Vessel puncture site haemorrhage, Vessel puncture site haematoma, Injection site haemorrhage, Puncture site haemorrhage, Catheter site haemorrhage

[#] There were no reported ADRs of haemarthrosis reported in the ticagrelor arm (n=9235) of the PLATO study, the frequency has been calculated using the upper limit of the 95% confidence interval for the point

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estimate (based on 3/X, where X represents the total sample size e.g. 9235). This is calculated as 3/9235 which equates to a frequency category of 'rare'

AstraZeneca

Addendum to the Clinical Overview Appendix 3	
Medicinal Product(s)	Ticagrelor
Period covered	3 December 2010 to 8 November 2014
Date	16 January 2015

Appendix 3

Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials

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Interval/Cumulative Summary Tabulations of Serious and Non-Serious Adverse Reactions from Marketed Experience

1. GENERAL CONSIDERATIONS

The summary tabulations presented here contain the case reports that were received and evaluated by AstraZeneca and entered into the AstraZeneca Patient Safety database before the end of the Addendum to the Clinical Overview reporting period. The interval counts presented in Table 2 represent new case reports or previously reported case reports with significant new or changed information that were received and processed during the Addendum to the Clinical Overview reporting period.

The numbers of events are presented at the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) and System Organ Class (SOC) level.

Within a given case report, where 2 events code to the same MedDRA PT, they have been counted as 1 event at the PT level in the tabulations (except in Table 2 if seriousness differs for each event).

2. TABLE 1 - CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE EVENTS FROM CLINICAL TRIALS

Table 1 includes case reports containing Serious Adverse Events (SAEs) from AstraZeneca-sponsored interventional clinical trials from the Development International Birth Date (DIBD) to the data lock point. Cumulative counts of SAEs are presented under the following treatment column headings: Investigational product (ticagrlelor), Blinded, Study procedure, Active comparator, and Placebo / No study product.

Each case report included in the tabulation is assigned to one of the treatment columns, based on the primary study treatment for the case as judged by AstraZeneca. The Active comparator column includes SAEs associated with study treatment(s) not otherwise categorised in the tabulation.

Case reports containing a Suspected Unexpected Serious Adverse Reaction (SUSAR) are unblinded by AstraZeneca, and the event counts are presented in the table under the appropriate unblinded column heading.

Case reports containing only expected Suspected Serious Adverse Reactions (SSARs) remain blinded, and the event counts are presented under the Blinded column heading.

3. TABLE 2 - NUMBERS OF ADVERSE DRUG REACTIONS BY TERM FROM POST-MARKETING SOURCES

Table 2 presents numbers of adverse reactions from spontaneous notifications and from non-interventional post-marketing studies for ticagrelor from the International Birth Date (IBD) to the data lock point. This includes cases reported on AstraZeneca brand(s) and case

reports on the non-proprietary name of the product (including reports on brands maintained by any licence partners, if applicable).

Spontaneous data include case reports from healthcare professionals, consumers, scientific literature, and worldwide regulatory authorities, irrespective of the causality assessment made by the reporter. Interval and cumulative adverse reaction counts are presented for serious and non-serious reactions.

The data presented for non-interventional post-marketing studies also include reports from other non-interventional solicited sources. Case reports are included where either the reporter or AstraZeneca has considered there was a reasonable possibility of a causal relationship with the medicinal product, or a causality assessment is unavailable from both the reporter and AstraZeneca. Interval and cumulative counts are presented for serious adverse reactions.

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Infections and infestations	**417**	**1615**	**5**	**344**	**61**
Abdominal abscess	1	6	0	1	0
Abdominal sepsis	0	2	0	0	0
Abdominal wall abscess	0	1	0	0	0
Abdominal wall infection	0	2	0	1	0
Abscess	0	2	0	0	0
Abscess jaw	0	1	0	0	0
Abscess limb	4	5	0	0	0
Abscess neck	0	2	0	0	0
Acquired immunodeficiency syndrome	1	1	0	0	0
Acute hepatitis B	0	1	0	0	0
Acute sinusitis	1	2	0	0	0
Acute tonsillitis	2	0	0	0	0
Amoebiasis	0	1	0	0	0
Anal abscess	2	6	0	4	0
Appendiceal abscess	0	1	0	0	1
Appendicitis	6	31	0	2	1
Appendicitis perforated	1	5	0	0	0
Arthritis bacterial	1	2	0	1	0
Arthritis infective	1	4	0	0	0
Atypical pneumonia	0	2	0	0	0
Avian influenza	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Bacteraemia	3	3	0	1	0
Bacterial infection	1	3	0	1	0
Bacterial prostatitis	0	2	0	0	0
Bacterial pyelonephritis	0	1	0	0	0
Bartholin's abscess	0	1	0	0	0
Biliary sepsis	1	1	0	0	0
Bone abscess	0	2	0	0	0
Brain empyema	0	1	0	0	0
Breast abscess	0	2	0	1	0
Bronchitis	16	77	1	15	1
Bronchitis bacterial	0	3	0	0	0
Bronchitis viral	0	0	0	1	0
Bronchopneumonia	12	34	0	5	1
Bronchopulmonary aspergillosis	0	1	0	0	0
Bursitis infective	0	1	0	0	0
Campylobacter gastroenteritis	0	2	0	0	0
Candida infection	0	0	0	1	0
Carbuncle	0	2	0	0	0
Catheter site infection	0	1	0	1	0
Cellulitis	13	72	0	12	3
Cellulitis laryngeal	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Cellulitis of male external genital organ	0	1	0	0	0
Cellulitis orbital	1	0	0	0	0
Cerebral toxoplasmosis	0	1	0	0	0
Chest wall abscess	0	1	0	0	0
Cholangitis infective	0	1	0	0	0
Cholecystitis infective	0	3	0	1	0
Chorioretinitis	0	0	0	1	0
Chronic hepatitis C	0	1	0	0	0
Chronic sinusitis	1	0	0	0	0
Clostridium colitis	0	1	0	0	0
Clostridium difficile colitis	1	10	0	1	1
Clostridium difficile infection	0	7	0	0	0
Clostridium difficile sepsis	0	1	0	0	0
Colonic abscess	0	1	0	0	0
Congo-Crimean haemorrhagic fever	0	1	0	0	0
Cystitis	3	7	0	2	0
Dengue fever	0	2	0	1	0
Device related infection	2	14	0	0	0
Device related sepsis	0	2	0	0	0
Diabetic foot infection	0	6	0	0	2
Diabetic gangrene	0	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Diarrhoea infectious	1	1	0	0	0
Diverticulitis	8	39	0	8	2
Ear infection	0	1	0	0	0
Echinococciasis	0	1	0	0	0
Emphysematous cholecystitis	0	1	0	0	0
Empyema	0	0	0	0	2
Encephalitis	0	0	0	1	0
Encephalitis brain stem	0	1	0	0	0
Endocarditis	3	4	0	2	0
Endocarditis bacterial	0	2	0	0	0
Endometritis	1	0	0	0	0
Endophthalmitis	0	1	0	0	0
Enteritis infectious	0	1	0	0	0
Enterococcal infection	0	0	0	1	0
Enterococcal sepsis	0	0	0	0	1
Enterocolitis infectious	0	1	0	0	0
Epididymitis	4	7	0	1	0
Epiglottitis	0	2	0	0	0
Erysipelas	4	22	0	4	1
Escherichia bacteraemia	0	3	0	0	0
Escherichia pyelonephritis	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Escherichia sepsis	0	1	0	0	0
Escherichia urinary tract infection	0	1	0	0	0
Extradural abscess	0	1	0	0	0
Eye infection	0	1	0	0	0
Febrile infection	1	0	0	0	0
Furuncle	0	2	0	0	0
Gallbladder empyema	0	1	0	0	0
Gangrene	2	19	0	3	1
Gastric infection	1	0	0	0	0
Gastritis viral	0	1	0	0	0
Gastroenteritis	23	61	0	11	2
Gastroenteritis bacterial	2	0	0	0	0
Gastroenteritis norovirus	1	3	0	0	0
Gastroenteritis rotavirus	0	1	0	1	0
Gastroenteritis salmonella	1	2	0	0	0
Gastroenteritis viral	3	8	0	0	0
Gastrointestinal infection	3	2	0	1	0
Gingivitis	0	2	0	0	0
Graft infection	0	5	0	0	1
Groin abscess	1	2	0	1	0
Groin infection	1	4	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
H1N1 influenza	0	2	0	0	1
Haematoma infection	3	1	0	0	0
Helicobacter gastritis	1	1	0	1	0
Helicobacter infection	0	0	0	1	0
Hepatitis A	0	1	0	0	0
Hepatitis C	0	0	0	0	1
Hepatitis viral	1	1	0	0	0
Herpes simplex meningoencephalitis	0	1	0	0	0
Herpes zoster	2	10	0	1	2
Histoplasmosis	1	0	0	0	0
Impetigo	0	0	0	1	0
Incision site abscess	1	0	0	0	0
Incision site infection	0	2	0	1	0
Infected dermal cyst	0	2	0	0	0
Infected skin ulcer	1	4	0	0	0
Infection	4	5	0	7	1
Infectious colitis	1	2	0	0	0
Infectious pleural effusion	1	3	0	0	1
Infective exacerbation of chronic obstructive airways disease	4	11	0	0	0
Infective tenosynovitis	0	0	0	1	0
Influenza	0	9	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Injection site abscess	1	0	0	0	0
Injection site cellulitis	0	0	0	1	0
Intervertebral discitis	0	3	0	1	0
Joint abscess	1	0	0	0	0
Kidney infection	0	1	0	0	0
Klebsiella sepsis	0	2	0	0	1
Labyrinthitis	0	1	0	0	0
Laryngitis	1	2	0	0	0
Leishmaniasis	0	1	0	0	0
Listeria sepsis	0	1	0	0	0
Liver abscess	1	4	0	0	0
Lobar pneumonia	0	11	0	2	0
Localised infection	0	6	0	2	2
Lower respiratory tract infection	6	16	0	3	0
Lower respiratory tract infection bacterial	0	2	0	0	0
Lung abscess	0	2	0	0	0
Lung infection	6	4	0	2	1
Lyme disease	0	2	0	1	0
Lymphangitis	0	1	0	0	0
Malaria	0	1	0	0	0
Mediastinitis	11	0	0	6	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Meningitis	0	1	0	1	0
Meningitis bacterial	0	1	0	0	0
Muscle abscess	0	1	0	0	0
Myringitis	0	2	0	0	0
Nasal abscess	0	1	0	0	0
Nasopharyngitis	0	4	0	0	0
Necrotising fasciitis	1	2	0	0	0
Neutropenic sepsis	0	1	0	0	0
Ophthalmic herpes zoster	0	3	0	0	0
Orchitis	0	3	0	1	0
Osteomyelitis	4	24	0	3	1
Osteomyelitis chronic	0	1	0	0	0
Otitis externa	0	1	0	0	0
Otitis media acute	1	1	0	0	1
Otitis media chronic	0	2	0	0	0
Pancreatic abscess	1	2	0	0	0
Paraspinal abscess	0	1	0	0	0
Parotitis	0	3	0	0	0
Pelvic abscess	0	1	0	0	0
Perichondritis	0	2	0	0	0
Perineal abscess	1	0	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Periodontitis	3	2	0	0	0
Perirectal abscess	0	1	0	0	0
Peritonitis	3	13	1	3	0
Peritonsillar abscess	0	1	0	0	0
Pharyngeal abscess	0	1	0	0	0
Pharyngitis	0	0	0	1	0
Pilonidal cyst	0	1	0	0	0
Pleural infection bacterial	1	0	0	0	0
Pneumococcal sepsis	1	0	0	1	0
Pneumocystis jirovecii pneumonia	0	2	0	0	0
Pneumonia	91	357	0	107	12
Pneumonia bacterial	0	34	0	0	0
Pneumonia cryptococcal	1	0	0	0	0
Pneumonia cytomegaloviral	0	1	0	0	0
Pneumonia haemophilus	0	1	0	0	0
Pneumonia influenzal	0	2	0	0	0
Pneumonia klebsiella	0	1	0	0	0
Pneumonia legionella	0	1	0	0	0
Pneumonia necrotising	0	1	0	0	0
Pneumonia pneumococcal	1	0	0	0	0
Pneumonia pseudomonal	0	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Pneumonia staphylococcal	0	0	0	1	0
Pneumonia streptococcal	0	2	0	0	0
Pneumonia viral	0	1	0	0	0
Post procedural cellulitis	0	1	0	1	0
Post procedural infection	0	9	0	2	0
Post procedural pneumonia	0	2	0	0	0
Post procedural sepsis	0	0	0	1	0
Postoperative wound infection	9	22	0	7	2
Pseudomembranous colitis	0	2	0	0	0
Pseudomonal sepsis	0	1	0	0	0
Pseudomonas infection	0	3	0	0	0
Pulmonary sepsis	1	4	0	0	0
Pulmonary tuberculosis	1	6	0	0	0
Pyelonephritis	4	19	0	2	1
Pyelonephritis acute	1	12	0	1	0
Pyelonephritis chronic	0	1	0	0	0
Pyopneumothorax	0	1	0	0	0
Rectal abscess	0	4	0	1	0
Relapsing fever	1	0	0	0	0
Renal abscess	1	0	0	1	0
Respiratory tract infection	11	15	1	9	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Respiratory tract infection viral	0	1	1	0	0
Retroperitoneal abscess	0	1	0	1	0
Rhinitis	0	1	0	0	0
Salmonellosis	0	1	0	0	0
Scrotal abscess	0	4	0	0	0
Sepsis	22	77	0	28	0
Septic necrosis	0	1	0	0	0
Septic shock	6	33	1	11	1
Sialoadenitis	0	2	0	0	0
Sinusitis	2	9	0	0	0
Skin infection	2	2	0	1	0
Soft tissue infection	0	3	0	0	0
Splenic abscess	0	1	0	0	0
Staphylococcal bacteraemia	0	1	0	0	0
Staphylococcal infection	2	2	0	0	1
Staphylococcal sepsis	3	4	0	1	0
Sternitis	1	0	0	0	0
Streptococcal abscess	0	1	0	0	0
Streptococcal bacteraemia	0	1	0	0	0
Streptococcal infection	0	2	0	0	0
Subacute endocarditis	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Subcutaneous abscess	0	5	0	1	0
Superinfection	1	0	0	0	0
Syphilis	1	0	0	0	0
Tonsillitis	0	1	0	0	0
Tooth abscess	0	0	0	1	0
Tooth infection	0	0	0	2	0
Toxoplasmosis	0	1	0	0	0
Tracheitis	1	1	0	0	0
Tracheobronchitis	1	2	0	1	0
Tuberculosis	1	5	0	1	1
Upper respiratory tract infection	4	13	0	3	4
Urethritis	0	1	0	0	0
Urinary bladder abscess	0	2	0	0	0
Urinary tract infection	32	108	0	19	3
Urinary tract infection bacterial	0	1	0	0	0
Urinary tract infection fungal	0	1	0	0	0
Urinary tract infection pseudomonal	0	1	0	0	0
Urosepsis	6	36	0	2	1
Vestibular neuronitis	0	5	0	3	0
Viral diarrhoea	0	2	0	0	0
Viral infection	1	6	0	0	1

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Viral myocarditis	2	0	0	1	0
Viral pericarditis	0	0	0	1	0
Wound infection	10	18	0	6	2
Wound infection bacterial	0	1	0	0	0
Wound infection pseudomonas	0	1	0	0	0
Wound infection staphylococcal	0	2	0	0	0
Yersinia infection	0	1	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**169**	**1183**	**4**	**135**	**30**
Abdominal neoplasm	1	0	0	0	0
Acinic cell carcinoma of salivary gland	0	1	0	0	0
Acute myeloid leukaemia	1	7	0	0	0
Adenocarcinoma	1	1	0	0	0
Adenocarcinoma gastric	0	15	0	4	0
Adenocarcinoma of colon	4	31	0	1	0
Adenocarcinoma pancreas	0	2	0	1	0
Adenolymphoma	0	1	0	0	0
Adenoma benign	1	0	0	0	0
Adrenal adenoma	0	2	0	0	0
Adrenal neoplasm	0	1	0	0	0
Ameloblastoma	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Anal cancer	0	1	0	0	0
Anal cancer metastatic	0	1	0	0	0
Anaplastic large cell lymphoma T- and null-cell types	0	1	0	0	0
Anogenital warts	0	2	0	0	0
Astrocytoma malignant	0	1	0	0	0
Atypical fibroxanthoma	0	1	0	0	0
B-cell lymphoma	0	5	0	1	0
Basal cell carcinoma	1	22	0	0	0
Benign cardiac neoplasm	1	0	0	0	0
Benign duodenal neoplasm	1	0	0	0	0
Benign laryngeal neoplasm	0	1	0	0	0
Benign neoplasm of bladder	1	3	0	0	0
Benign neoplasm of seminal vesicle	0	1	0	0	0
Benign neoplasm of skin	0	0	0	1	0
Benign neoplasm of thyroid gland	0	4	0	0	0
Benign neoplasm of ureter	0	2	0	0	0
Benign ovarian tumour	0	2	0	1	0
Benign renal neoplasm	0	1	0	0	0
Benign salivary gland neoplasm	0	2	0	0	1
Benign soft tissue neoplasm	0	1	0	0	0
Benign uterine neoplasm	0	0	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Bile duct adenocarcinoma	0	1	0	0	0
Bile duct cancer	0	1	0	0	0
Biliary neoplasm	0	1	0	0	0
Bladder cancer	5	41	0	10	1
Bladder cancer recurrent	0	8	0	1	0
Bladder neoplasm	3	15	0	2	0
Bladder papilloma	0	2	0	0	0
Bladder transitional cell carcinoma	2	14	0	1	1
Bladder transitional cell carcinoma metastatic	0	1	0	0	0
Bladder transitional cell carcinoma recurrent	0	3	0	0	0
Bone cancer	0	3	0	1	0
Bone cancer metastatic	0	3	0	0	0
Bone sarcoma	0	1	0	0	0
Bowen's disease	1	2	0	0	0
Brain cancer metastatic	0	3	0	0	0
Brain neoplasm	1	8	0	3	0
Brain neoplasm benign	0	1	0	0	0
Brain neoplasm malignant	0	1	0	0	0
Breast cancer	2	3	0	7	0
Breast cancer female	1	19	0	1	1
Breast cancer male	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Breast cancer metastatic	4	8	0	0	0
Breast cancer recurrent	0	1	0	0	0
Brenner tumour	0	1	0	0	0
Bronchial carcinoma	2	4	0	3	1
Burkitt's lymphoma	0	1	0	0	0
Carcinoid tumour of the caecum	1	0	0	1	0
Carcinoid tumour of the duodenum	0	0	0	1	0
Carcinoid tumour pulmonary	2	0	0	0	0
Cardiac myxoma	1	0	0	0	0
Cerebral haemangioma	0	1	0	0	0
Cervix cancer metastatic	0	1	0	0	0
Cervix carcinoma	0	1	0	0	0
Cervix carcinoma stage 0	0	1	0	0	0
Cholangiocarcinoma	0	3	0	0	0
Cholesteatoma	0	1	0	0	0
Choroid melanoma	0	1	0	0	0
Chronic leukaemia	1	0	0	2	0
Chronic lymphocytic leukaemia	3	5	0	1	0
Chronic myeloid leukaemia	0	2	0	0	0
Clear cell renal cell carcinoma	0	2	0	0	0
Colon adenoma	1	15	0	1	2

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Colon cancer	9	38	0	5	2
Colon cancer metastatic	1	21	0	0	1
Colon neoplasm	1	3	0	3	0
Colorectal adenocarcinoma	0	1	0	0	0
Colorectal cancer	2	3	0	1	0
Colorectal cancer metastatic	0	1	0	0	0
Diffuse large B-cell lymphoma	0	5	0	0	0
Endometrial adenocarcinoma	1	1	0	0	0
Endometrial cancer	0	5	0	0	1
Endometrial cancer stage I	0	1	0	0	0
Epithelioid mesothelioma	0	0	0	0	2
Essential thrombocythaemia	0	2	0	0	0
Extradural neoplasm	0	1	0	0	0
Extranodal marginal zone B-cell lymphoma (MALT type)	1	1	0	0	0
Extraskeletal myxoid chondrosarcoma	0	1	0	0	0
Fallopian tube cancer	0	1	0	0	0
Fibroma	1	0	0	0	0
Follicle centre lymphoma, follicular grade I, II, III	0	1	0	0	0
Follicle centre lymphoma, follicular grade I, II, III stage IV	0	1	0	0	0
Gallbladder adenocarcinoma	0	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Gallbladder cancer	0	5	0	0	0
Gallbladder cancer metastatic	0	2	0	0	0
Gastric adenoma	0	2	0	0	0
Gastric cancer	8	28	0	2	2
Gastric neoplasm	1	1	0	0	0
Gastrointestinal cancer metastatic	0	1	0	0	0
Gastrointestinal carcinoma	1	1	0	1	0
Gastrointestinal neoplasm	1	0	0	0	0
Gastrointestinal stromal cancer	0	1	0	0	0
Gastrointestinal stromal tumour	0	2	0	2	0
Gastrointestinal submucosal tumour	0	1	0	0	0
Gastrointestinal tract adenoma	0	4	0	0	0
Glioblastoma	1	4	0	0	0
Glioblastoma multiforme	1	3	0	0	0
Haemangioma	0	2	0	0	0
Haemangioma of liver	1	0	0	0	0
Hepatic cancer	1	4	0	0	0
Hepatic cancer metastatic	1	3	0	1	0
Hepatic neoplasm	0	5	0	1	0
Hepatobiliary cancer	0	0	0	0	1
Hepatocellular carcinoma	1	7	1	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Hodgkin's disease	0	4	0	0	0
Hypergammaglobulinaemia benign monoclonal	0	1	0	0	0
Inflammatory pseudotumour	0	1	0	0	0
Intestinal adenocarcinoma	0	3	0	1	0
Intraductal papillary mucinous neoplasm	0	1	0	0	0
Intraocular melanoma	0	1	0	0	0
Invasive ductal breast carcinoma	0	5	0	1	0
Large cell lung cancer	0	1	0	0	0
Large intestine benign neoplasm	0	3	0	0	0
Laryngeal cancer	0	8	0	2	0
Laryngeal neoplasm	0	2	0	0	0
Laryngeal squamous cell carcinoma	0	4	0	0	0
Leiomyoma	0	1	0	0	0
Leiomyosarcoma	0	1	0	0	0
Lentigo maligna	0	3	0	0	0
Leukaemia	0	0	0	0	1
Lip and/or oral cavity cancer	0	3	0	1	0
Lip neoplasm malignant stage unspecified	0	1	0	0	0
Lipoma	0	3	0	0	0
Lung adenocarcinoma	2	20	0	1	0
Lung adenocarcinoma metastatic	0	8	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Lung cancer metastatic	1	40	0	1	0
Lung carcinoma cell type unspecified recurrent	0	2	0	0	1
Lung carcinoma cell type unspecified stage I	0	1	0	0	0
Lung carcinoma cell type unspecified stage IV	0	3	0	0	0
Lung neoplasm	3	11	0	3	1
Lung neoplasm malignant	13	51	0	13	3
Lymphangiosis carcinomatosa	0	0	0	1	0
Lymphocytic lymphoma	1	0	0	0	0
Lymphoma	4	4	0	1	1
Lymphoma cutis	1	0	0	0	0
Lymphoplasmacytoid lymphoma/immunocytoma	0	1	0	0	0
Malignant anorectal neoplasm	1	0	0	0	0
Malignant ascites	1	0	0	0	0
Malignant fibrous histiocytoma	0	1	0	0	0
Malignant melanoma	0	22	0	2	0
Malignant neoplasm of ampulla of Vater	0	2	0	0	0
Malignant neoplasm of pleura	1	0	0	0	0
Malignant neoplasm of unknown primary site	0	5	0	0	0
Malignant neoplasm progression	0	1	0	0	0
Malignant peritoneal neoplasm	1	0	0	0	0
Malignant pleural effusion	1	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Malignant respiratory tract neoplasm	0	1	0	0	0
Mediastinum neoplasm	0	1	0	0	0
Melanocytic naevus	0	2	0	0	0
Melanoma recurrent	1	0	0	0	0
Meningioma	1	6	0	0	0
Meningioma benign	0	3	0	0	0
Mesothelioma	0	2	0	0	0
Metastases to bone	1	2	0	1	0
Metastases to central nervous system	0	1	0	2	0
Metastases to liver	0	2	0	3	0
Metastases to lung	1	3	0	2	0
Metastases to lymph nodes	2	1	0	0	1
Metastases to pancreas	0	2	0	0	0
Metastases to peritoneum	0	2	0	0	0
Metastasis	0	0	0	1	0
Metastatic bronchial carcinoma	0	6	0	0	0
Metastatic carcinoma of the bladder	0	2	0	0	0
Metastatic gastric cancer	0	10	0	0	0
Metastatic malignant melanoma	0	6	0	0	0
Metastatic neoplasm	2	5	1	0	0
Metastatic pain	0	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Metastatic salivary gland cancer	0	1	0	0	0
Metastatic squamous cell carcinoma	0	3	0	0	0
Monoclonal gammopathy	0	1	0	0	0
Myelodysplastic syndrome	1	2	0	0	0
Myelofibrosis	1	0	0	0	0
Myeloproliferative disorder	1	1	0	0	0
Nasal neoplasm benign	0	1	0	0	0
Nasal sinus cancer	0	1	0	0	0
Neoplasm	0	1	0	0	0
Neoplasm malignant	0	4	0	1	0
Neoplasm prostate	0	1	0	1	0
Neoplasm skin	0	2	0	0	0
Neuroendocrine carcinoma	0	2	0	0	0
Neuroendocrine carcinoma metastatic	0	3	0	0	0
Neuroendocrine tumour	0	1	0	0	0
Neuroma	1	0	0	0	0
Nipple neoplasm	0	0	0	1	0
Nodular melanoma	0	1	0	0	0
Non-Hodgkin's lymphoma	0	4	0	0	0
Non-Hodgkin's lymphoma recurrent	0	1	0	0	0
Non-Hodgkin's lymphoma stage I	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Non-Hodgkin's lymphoma stage II	0	1	0	0	0
Non-Hodgkin's lymphoma unspecified histology aggressive	0	1	0	0	0
Non-small cell lung cancer	0	5	0	0	0
Non-small cell lung cancer metastatic	0	1	0	0	0
Non-small cell lung cancer stage IV	0	1	0	0	0
Oesophageal adenocarcinoma	1	4	0	0	0
Oesophageal adenocarcinoma metastatic	0	1	0	0	0
Oesophageal cancer metastatic	1	1	0	0	2
Oesophageal carcinoma	1	16	0	2	0
Oesophageal squamous cell carcinoma	0	2	0	0	0
Oncocytoma	0	1	0	0	0
Oral cavity cancer metastatic	0	1	0	0	0
Oropharyngeal cancer recurrent	0	1	0	0	0
Ovarian cancer	2	1	0	1	0
Ovarian cancer metastatic	0	2	0	0	0
Ovarian cancer stage III	0	1	0	0	0
Ovarian germ cell teratoma benign	0	1	0	0	0
Pancoast's tumour	0	1	0	0	0
Pancreatic carcinoma	1	23	0	0	0
Pancreatic carcinoma metastatic	1	16	0	1	0
Pancreatic carcinoma recurrent	1	0	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Pancreatic neoplasm	0	5	0	0	0
Paranasal sinus neoplasm	0	1	0	0	0
Parathyroid tumour benign	0	3	0	0	0
Pelvic neoplasm	0	1	0	0	0
Penile squamous cell carcinoma	0	2	0	0	0
Penis carcinoma metastatic	0	3	0	0	0
Pericardial effusion malignant	0	0	0	1	0
Peritoneal neoplasm	0	1	0	0	0
Pharyngeal cancer	0	3	0	0	0
Pharyngeal cancer metastatic	1	0	0	0	0
Pituitary tumour benign	0	5	0	0	0
Plasma cell myeloma	0	4	0	0	0
Pleomorphic adenoma	0	1	0	0	0
Pleural mesothelioma	1	1	0	0	0
Pleural mesothelioma malignant	0	2	0	1	0
Polycythaemia vera	1	1	0	0	0
Prostate cancer	9	111	0	8	1
Prostate cancer metastatic	2	16	0	1	1
Prostate cancer recurrent	1	2	0	0	0
Prostate cancer stage II	0	1	0	0	0
Prostatic adenoma	1	6	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Rectal adenocarcinoma	1	6	0	2	0
Rectal adenoma	0	2	0	0	0
Rectal cancer	2	10	0	2	0
Rectal cancer metastatic	1	3	0	0	0
Rectal neoplasm	1	0	0	0	0
Rectosigmoid cancer	0	1	0	0	0
Rectosigmoid cancer metastatic	0	1	0	0	0
Renal cancer	3	8	0	2	1
Renal cancer metastatic	3	2	0	1	0
Renal cell carcinoma	1	10	0	0	1
Renal cell carcinoma recurrent	0	1	0	0	0
Renal neoplasm	3	6	0	2	0
Renal oncocytoma	0	1	0	0	0
Retroperitoneal neoplasm	0	0	0	1	0
Salivary gland adenoma	0	3	0	0	0
Salivary gland cancer	0	5	0	0	0
Salivary gland cancer recurrent	0	1	0	0	0
Salivary gland neoplasm	0	3	0	0	0
Sarcoma	0	1	0	0	0
Sarcomatoid mesothelioma	0	1	0	0	0
Skin cancer	0	6	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Small cell lung cancer	1	12	0	2	0
Small cell lung cancer metastatic	0	3	0	0	0
Small intestine adenocarcinoma	0	1	0	0	0
Small intestine carcinoma	0	2	0	0	0
Spinal cord neoplasm	0	0	0	1	0
Spindle cell sarcoma	0	1	0	0	0
Splenic marginal zone lymphoma	0	1	0	0	0
Squamous cell carcinoma	2	6	0	1	0
Squamous cell carcinoma of lung	1	15	0	0	0
Squamous cell carcinoma of pharynx	0	1	0	0	0
Squamous cell carcinoma of skin	0	4	0	0	0
Squamous cell carcinoma of the oral cavity	1	3	0	0	0
Squamous cell carcinoma of the tongue	0	2	0	0	0
T-cell lymphoma	0	1	0	0	0
Testis cancer	1	0	0	0	0
Throat cancer	0	1	0	0	0
Thyroid adenoma	1	3	0	0	0
Thyroid cancer	0	1	0	0	0
Thyroid cancer metastatic	1	1	0	0	0
Thyroid neoplasm	0	1	0	1	0
Tongue cancer metastatic	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Tongue neoplasm malignant stage unspecified	0	1	0	1	0
Tonsil cancer	0	1	0	0	0
Tonsillar neoplasm	0	1	0	0	0
Transitional cell carcinoma	3	16	2	1	0
Transitional cell carcinoma metastatic	0	2	0	0	0
Tumour associated fever	0	1	0	0	0
Tumour haemorrhage	0	4	0	2	0
Tumour pain	0	1	0	0	0
Undifferentiated nasopharyngeal carcinoma	0	1	0	0	0
Ureteric cancer	1	1	0	0	0
Urethral cancer	0	1	0	0	0
Urinary tract neoplasm	0	1	0	0	0
Uterine cancer	0	1	0	0	0
Uterine leiomyoma	1	2	0	0	0
Vulval cancer stage 0	0	1	0	0	0
Blood and lymphatic system disorders	**120**	**132**	**6**	**70**	**13**
Anaemia	53	40	0	35	5
Anaemia macrocytic	0	2	0	0	0
Anaemia megaloblastic	0	1	0	0	0
Anaemia of chronic disease	0	4	0	0	0
Anaemia of malignant disease	4	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Anaemia vitamin B12 deficiency	0	2	0	0	0
Aplastic anaemia	1	1	0	0	0
Autoimmune aplastic anaemia	1	0	0	0	0
Coagulation factor deficiency	0	1	0	0	0
Coagulopathy	2	1	0	1	1
Disseminated intravascular coagulation	0	0	0	2	1
Febrile neutropenia	0	2	0	0	0
Granulocytopenia	1	0	0	0	0
Haemolysis	0	1	0	0	0
Haemolytic anaemia	0	0	0	1	0
Haemorrhagic anaemia	4	8	0	0	0
Heparin-induced thrombocytopenia	0	1	0	0	0
Hypercoagulation	0	1	0	0	0
Hypochromic anaemia	1	2	0	0	0
Immune thrombocytopenic purpura	1	2	0	0	0
Increased tendency to bruise	1	3	1	0	0
Iron deficiency anaemia	19	18	3	8	2
Leukocytosis	1	3	0	1	0
Leukopenia	3	2	0	2	0
Lymphadenitis	2	0	0	0	0
Lymphadenopathy	0	1	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Lymphadenopathy mediastinal	0	0	0	0	1
Microcytic anaemia	3	9	1	3	0
Nephrogenic anaemia	2	3	0	0	0
Neutropenia	1	0	0	1	0
Normochromic normocytic anaemia	1	4	0	1	0
Pancytopenia	4	3	0	0	0
Pernicious anaemia	0	1	0	0	0
Polycythaemia	1	0	0	1	0
Splenic haemorrhage	0	1	0	0	0
Splenomegaly	1	0	0	0	0
Spontaneous haematoma	1	3	0	2	0
Spontaneous haemorrhage	1	0	0	0	0
Thrombocytopenia	11	10	1	10	3
Thrombocytosis	0	0	0	1	0
Immune system disorders	**7**	**23**	**0**	**13**	**1**
Allergy to arthropod sting	0	2	0	1	0
Allergy to chemicals	0	1	0	0	0
Anaphylactic reaction	0	3	0	3	0
Anaphylactic shock	3	3	0	2	0
Anti-neutrophil cytoplasmic antibody positive vasculitis	0	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Contrast media allergy	0	1	0	1	0
Drug hypersensitivity	2	5	0	2	0
Hypersensitivity	2	2	0	4	1
Immunodeficiency	0	1	0	0	0
Kidney transplant rejection	0	1	0	0	0
Reaction to food additive	0	1	0	0	0
Sarcoidosis	0	1	0	0	0
Endocrine disorders	**4**	**17**	**0**	**4**	**1**
Adrenal insufficiency	1	0	0	0	0
Autoimmune thyroiditis	0	1	0	0	0
Goitre	0	6	0	1	0
Hyperthyroidism	2	4	0	2	1
Hypothyroidism	0	3	0	0	0
Inappropriate antidiuretic hormone secretion	0	2	0	0	0
Pituitary-dependent Cushing's syndrome	1	0	0	0	0
Thyrotoxic crisis	0	0	0	1	0
Toxic nodular goitre	0	1	0	0	0
Metabolism and nutrition disorders	**72**	**309**	**3**	**65**	**13**
Abnormal loss of weight	0	1	0	0	0
Acidosis	1	0	0	0	0
Decreased appetite	4	2	0	0	1

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Dehydration	14	39	0	8	0
Diabetes mellitus	8	62	0	9	0
Diabetes mellitus inadequate control	7	43	0	9	1
Diabetic complication	0	1	0	0	0
Diabetic ketoacidosis	2	13	0	1	0
Electrolyte imbalance	1	4	0	1	0
Failure to thrive	1	1	0	1	0
Fluid overload	0	0	0	2	0
Fluid retention	0	0	0	0	1
Glucose tolerance impaired	0	1	0	0	0
Gout	2	8	1	2	2
Hypercalcaemia	0	4	0	0	0
Hyperglycaemia	7	25	0	6	2
Hyperglycaemic hyperosmolar nonketotic syndrome	0	1	0	0	0
Hyperkalaemia	2	14	1	5	1
Hyperosmolar state	0	0	0	1	0
Hypocalcaemia	0	1	0	0	0
Hypoglycaemia	11	36	0	10	2
Hypokalaemia	1	8	0	1	0
Hypomagnesaemia	0	0	0	0	1
Hyponatraemia	5	11	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Hypovolaemia	2	5	0	0	0
Ketoacidosis	1	0	0	0	0
Lactic acidosis	0	2	1	0	0
Lactose intolerance	0	1	0	0	0
Malnutrition	0	2	0	0	1
Metabolic acidosis	0	4	0	2	0
Metabolic disorder	0	0	0	3	0
Metabolic syndrome	0	1	0	1	0
Obesity	0	1	0	0	0
Shock hypoglycaemic	0	1	0	0	0
Type 1 diabetes mellitus	0	1	0	0	0
Type 2 diabetes mellitus	3	16	0	2	1
Psychiatric disorders	**48**	**112**	**0**	**31**	**5**
Acute psychosis	0	1	0	0	0
Acute stress disorder	0	0	0	1	0
Affective disorder	0	2	0	0	0
Aggression	0	1	0	0	0
Agitation	1	0	0	0	0
Alcohol abuse	1	4	0	0	0
Alcoholism	0	1	0	1	0
Anger	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Anxiety	13	13	0	7	1
Anxiety disorder	1	0	0	2	1
Bipolar I disorder	0	2	0	0	0
Completed suicide	2	5	0	1	0
Confusional state	7	3	0	2	0
Conversion disorder	0	1	0	0	0
Delirium	1	1	0	1	0
Depressed mood	0	1	0	0	0
Depression	10	36	0	7	2
Disorientation	0	1	0	0	0
Drug abuse	0	0	0	1	0
Drug dependence	0	1	0	0	0
Hallucination	0	0	0	1	0
Insomnia	1	2	0	0	0
Major depression	0	5	0	0	0
Mania	1	0	0	0	0
Mental disorder	0	0	0	1	0
Mental status changes	0	11	0	0	0
Nervousness	1	0	0	1	0
Neurosis	0	0	0	1	0
Panic attack	1	4	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Panic disorder	0	1	0	0	0
Post-traumatic amnestic disorder	1	0	0	0	0
Post-traumatic stress disorder	0	1	0	0	0
Psychiatric decompensation	0	1	0	0	0
Psychiatric symptom	0	1	0	0	0
Psychotic behaviour	0	1	0	0	0
Psychotic disorder	2	0	0	0	0
Schizophrenia, paranoid type	0	0	0	1	0
Sleep disorder	1	0	0	0	0
Somatoform disorder cardiovascular	0	2	0	0	0
Stress	1	0	0	0	1
Substance abuse	0	1	0	0	0
Suicidal ideation	1	4	0	1	0
Suicide attempt	2	4	0	2	0
Nervous system disorders	**365**	**621**	**8**	**263**	**48**
Altered state of consciousness	0	3	0	2	0
Amyotrophic lateral sclerosis	0	4	0	0	0
Aphasia	0	1	0	1	0
Balance disorder	1	0	0	0	0
Brain hypoxia	0	0	0	1	0
Brain injury	0	3	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Brain oedema	1	2	0	0	0
Brain stem infarction	0	1	0	1	0
Brain stem ischaemia	0	0	0	2	0
Brain stem stroke	0	0	0	0	1
Brain stem syndrome	0	1	0	0	0
Carotid arteriosclerosis	0	3	0	0	0
Carotid artery aneurysm	0	2	0	0	0
Carotid artery disease	0	2	0	1	0
Carotid artery dissection	1	0	0	0	0
Carotid artery occlusion	0	2	0	1	0
Carotid artery stenosis	4	56	0	3	3
Carotid artery thrombosis	0	0	0	1	0
Carotid sinus syndrome	1	1	0	0	0
Carpal tunnel syndrome	0	5	0	0	0
Cauda equina syndrome	0	3	0	0	0
Central nervous system lesion	0	1	0	0	0
Cerebellar ataxia	0	1	0	0	0
Cerebellar haemorrhage	0	1	0	0	0
Cerebellar infarction	1	0	0	0	0
Cerebral arteriosclerosis	0	5	0	0	0
Cerebral atrophy	0	1	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Cerebral cyst	0	1	0	0	0
Cerebral haemorrhage	21	11	0	6	1
Cerebral infarction	14	6	0	10	2
Cerebral ischaemia	3	3	0	1	0
Cerebral microangiopathy	0	1	0	0	0
Cerebral microhaemorrhage	0	1	0	0	0
Cerebral thrombosis	1	0	0	0	0
Cerebral vasoconstriction	0	1	0	0	0
Cerebral venous thrombosis	0	0	0	1	0
Cerebrovascular accident	73	5	2	51	7
Cerebrovascular disorder	0	2	0	2	0
Cerebrovascular insufficiency	1	1	0	0	0
Cervical cord compression	0	1	0	0	0
Cervical myelopathy	0	1	0	0	0
Cervical radiculopathy	0	1	0	0	0
Cervicobrachial syndrome	0	3	0	1	0
Cluster headache	1	1	0	0	0
Cognitive disorder	0	3	0	1	0
Coma	0	0	0	1	0
Complex partial seizures	0	0	0	1	0
Complex regional pain syndrome	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Convulsion	4	14	0	3	0
Convulsions local	1	0	0	0	0
Dementia	0	2	0	2	1
Dementia Alzheimer's type	0	4	0	0	0
Demyelinating polyneuropathy	0	1	0	0	0
Depressed level of consciousness	0	0	0	3	0
Diabetic coma	0	1	0	0	0
Diabetic hyperosmolar coma	1	0	0	0	0
Diabetic neuropathy	2	5	0	0	0
Dizziness	16	25	0	7	0
Dysaesthesia	1	1	0	0	0
Dysarthria	1	0	0	0	0
Embolic cerebral infarction	1	0	0	0	0
Embolic stroke	0	2	0	0	1
Encephalopathy	3	4	0	1	1
Epilepsy	2	13	0	1	0
Extrapyramidal disorder	0	1	0	1	0
Facial paresis	1	0	0	0	0
Generalised tonic-clonic seizure	1	1	1	0	0
Guillain-Barre syndrome	1	4	0	0	0
Haemorrhage intracranial	5	5	0	3	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Haemorrhagic cerebral infarction	0	1	0	0	0
Haemorrhagic stroke	11	21	1	10	4
Haemorrhagic transformation stroke	0	3	0	0	0
Headache	5	12	0	3	1
Hemianopia	0	1	0	0	0
Hemiparesis	5	5	0	2	0
Hepatic encephalopathy	0	0	0	1	0
Hippocampal sclerosis	0	1	0	0	0
Hyperaesthesia	0	1	0	0	0
Hypercapnic coma	0	1	0	0	0
Hypertensive encephalopathy	0	1	0	0	0
Hypoaesthesia	3	1	0	4	2
Hypoglycaemic coma	0	1	0	0	0
Hypotonia	3	0	0	0	0
Hypoxic-ischaemic encephalopathy	1	4	0	2	0
IIIrd nerve paresis	0	1	0	0	0
Intercostal neuralgia	2	0	0	0	0
Intracranial aneurysm	0	4	0	0	0
Intracranial haematoma	0	0	0	1	1
Intraventricular haemorrhage	0	0	0	1	0
Ischaemic cerebral infarction	1	2	0	1	1

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Ischaemic stroke	29	43	0	32	6
Lacunar infarction	3	1	0	0	2
Leukoencephalopathy	0	1	0	0	0
Loss of consciousness	7	3	0	3	0
Lumbar radiculopathy	1	4	0	0	0
Mental impairment	0	0	0	1	0
Metabolic encephalopathy	1	2	0	0	0
Migraine	3	4	0	1	0
Mononeuritis	0	1	0	0	0
Mononeuropathy	0	1	0	0	0
Monoparesis	0	1	0	0	0
Multiple sclerosis	0	1	0	0	0
Multiple sclerosis relapse	2	0	0	0	0
Muscle contractions involuntary	1	0	0	0	0
Myelitis transverse	0	0	0	2	0
Myelopathy	0	2	0	0	0
Myoclonus	0	2	0	0	0
Narcolepsy	0	0	0	1	0
Nerve root compression	0	1	0	0	0
Nervous system disorder	1	1	0	0	0
Neuralgia	2	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Neuritis	0	1	0	0	0
Neuritis cranial	0	1	0	0	0
Neurological decompensation	0	1	0	0	0
Neuropathy peripheral	0	4	0	0	0
Normal pressure hydrocephalus	0	2	0	0	0
Occipital neuralgia	0	1	0	0	0
Orthostatic intolerance	0	1	0	0	0
Paraesthesia	8	4	0	4	0
Paralysis	0	1	0	0	0
Paraparesis	0	1	0	0	0
Parkinson's disease	1	2	0	5	1
Parkinsonism	0	1	0	0	0
Partial seizures	3	0	0	0	0
Partial seizures with secondary generalisation	0	1	0	0	0
Peripheral nerve paresis	0	1	0	0	0
Phrenic nerve paralysis	1	0	0	0	0
Polyneuropathy	0	3	0	0	0
Post herpetic neuralgia	0	0	0	1	0
Presyncope	12	22	0	5	3
Progressive supranuclear palsy	0	0	0	1	0
Psychomotor hyperactivity	0	0	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Quadriparesis	0	1	0	0	0
Radicular pain	0	2	0	0	0
Radiculopathy	0	4	0	0	0
Ruptured cerebral aneurysm	0	1	0	1	0
Sciatica	0	12	0	2	0
Senile dementia	0	3	0	0	1
Sensory disturbance	0	1	0	0	0
Serotonin syndrome	0	1	0	0	0
Somnolence	0	1	0	0	0
Speech disorder	1	0	0	0	0
Spinal claudication	0	3	0	0	0
Spinal cord compression	0	5	0	1	1
Spinal cord disorder	0	1	0	0	0
Spondylitic myelopathy	1	0	0	0	0
Status epilepticus	0	1	0	0	0
Stroke in evolution	0	1	0	0	0
Subarachnoid haemorrhage	7	9	0	3	1
Syncope	51	113	3	35	3
Temporal lobe epilepsy	0	1	0	0	0
Tension headache	1	1	0	0	0
Thalamus haemorrhage	1	0	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Thrombotic stroke	1	0	0	0	1
Toxic encephalopathy	1	2	0	0	0
Transient global amnesia	0	5	0	0	0
Transient ischaemic attack	27	33	1	27	3
Trigeminal neuralgia	0	1	0	0	0
Uraemic encephalopathy	0	1	0	0	0
VIIth nerve paralysis	1	4	0	0	0
VIth nerve paralysis	0	0	0	1	0
VIth nerve paresis	0	2	0	0	0
Vagus nerve disorder	0	1	0	0	0
Vascular dementia	0	1	0	0	0
Vascular encephalopathy	2	4	0	0	0
Vascular parkinsonism	0	1	0	0	0
Vertebral artery stenosis	0	1	0	0	0
Vertebrobasilar insufficiency	1	3	0	1	0
Vocal cord paresis	1	0	0	0	0
Eye disorders	**24**	**118**	**1**	**17**	**5**
Age-related macular degeneration	1	1	0	0	0
Amaurosis	1	0	0	0	0
Amaurosis fugax	0	0	0	1	0
Angle closure glaucoma	0	3	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Blindness	1	1	0	0	0
Blindness transient	0	1	0	0	0
Blindness unilateral	2	1	0	0	0
Cataract	5	53	0	4	3
Cataract nuclear	1	1	0	0	0
Conjunctival haemorrhage	1	4	0	0	0
Diabetic retinopathy	2	3	0	0	1
Diplopia	2	2	0	1	0
Endocrine ophthalmopathy	0	1	0	0	0
Exfoliation glaucoma	1	0	0	0	0
Extraocular muscle paresis	0	1	0	0	0
Eye haemorrhage	2	5	0	3	0
Eyelid ptosis	0	1	0	0	0
Glaucoma	0	4	0	0	0
Macular degeneration	1	1	0	1	0
Macular fibrosis	0	3	0	0	0
Open angle glaucoma	0	2	0	0	0
Opsoclonus myoclonus	0	1	0	0	0
Optic ischaemic neuropathy	0	1	0	0	0
Posterior capsule rupture	0	1	0	0	0
Pterygium	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Retinal artery embolism	0	1	0	1	0
Retinal artery occlusion	0	1	0	0	0
Retinal degeneration	0	2	0	0	0
Retinal detachment	2	10	0	3	0
Retinal haemorrhage	0	5	0	0	0
Retinal vein occlusion	0	2	0	0	1
Strabismus	0	1	0	0	0
Tolosa-Hunt syndrome	0	1	0	0	0
Vision blurred	1	0	0	0	0
Visual acuity reduced	0	0	0	1	0
Vitreous detachment	1	0	0	0	0
Vitreous haemorrhage	0	3	1	2	0
Ear and labyrinth disorders	**20**	**58**	**0**	**7**	**1**
Acute vestibular syndrome	0	3	0	0	0
Deafness	1	1	0	0	0
Deafness unilateral	0	1	0	0	1
Hypoacusis	2	0	0	0	0
Inner ear disorder	0	1	0	0	0
Meniere's disease	0	2	0	0	0
Middle ear effusion	1	1	0	0	0
Presbyacusis	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Sudden hearing loss	2	3	0	1	0
Tinnitus	1	1	0	0	0
Tympanic membrane perforation	0	1	0	0	0
Vertigo	11	25	0	6	0
Vertigo labyrinthine	0	1	0	0	0
Vertigo positional	1	17	0	0	0
Vestibular disorder	1	0	0	0	0
Cardiac disorders	**1165**	**2573**	**21**	**888**	**139**
Acute coronary syndrome	2	21	0	1	1
Acute left ventricular failure	5	9	0	2	1
Acute myocardial infarction	18	79	1	4	7
Adams-Stokes syndrome	0	2	0	0	0
Angina pectoris	39	398	2	18	18
Angina unstable	26	378	1	9	13
Aortic valve disease	0	1	0	0	0
Aortic valve incompetence	1	0	0	0	0
Aortic valve stenosis	2	12	0	3	0
Arrhythmia	15	10	0	3	0
Arrhythmia supraventricular	1	2	0	2	0
Arteriosclerosis coronary artery	0	6	0	2	0
Arteriospasm coronary	3	0	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Atrial fibrillation	101	325	1	88	9
Atrial flutter	15	52	0	8	0
Atrial rupture	1	0	0	0	0
Atrial tachycardia	1	4	0	3	1
Atrial thrombosis	0	1	0	0	0
Atrioventricular block	4	10	1	5	0
Atrioventricular block complete	24	20	2	20	5
Atrioventricular block second degree	10	10	0	2	1
Bifascicular block	1	0	0	0	0
Bradyarrhythmia	3	7	0	4	1
Bradycardia	31	22	0	32	0
Bundle branch block	0	0	0	1	0
Bundle branch block left	0	3	0	1	1
Bundle branch block right	0	1	0	0	0
Cardiac aneurysm	1	0	0	4	0
Cardiac arrest	58	21	4	47	4
Cardiac asthma	3	1	0	6	1
Cardiac failure	169	253	1	159	7
Cardiac failure acute	27	27	0	23	1
Cardiac failure chronic	11	60	0	3	1
Cardiac failure congestive	74	310	0	76	7

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Cardiac fibrillation	1	0	0	0	0
Cardiac flutter	0	1	0	0	0
Cardiac perforation	0	1	0	0	1
Cardiac tamponade	14	1	0	21	0
Cardiac valve disease	1	2	0	0	0
Cardiac ventricular thrombosis	10	6	0	5	0
Cardio-respiratory arrest	9	20	1	11	1
Cardiogenic shock	99	23	2	71	4
Cardiomegaly	0	1	0	0	0
Cardiomyopathy	3	9	0	3	0
Cardiopulmonary failure	2	3	0	2	0
Cardiovascular disorder	0	0	0	2	1
Cardiovascular insufficiency	1	1	0	1	1
Chordae tendinae rupture	0	0	0	1	0
Conduction disorder	0	2	0	0	0
Congestive cardiomyopathy	1	1	0	0	0
Cor pulmonale chronic	0	1	0	0	0
Coronary artery disease	12	73	0	5	1
Coronary artery dissection	6	1	0	2	1
Coronary artery insufficiency	0	2	0	0	0
Coronary artery occlusion	0	3	1	2	2

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Coronary artery perforation	4	0	0	1	1
Coronary artery stenosis	16	28	0	1	15
Coronary artery thrombosis	3	3	0	4	0
Cyanosis	1	0	0	0	0
Dissecting coronary artery aneurysm	0	0	0	1	0
Dressler's syndrome	5	2	0	4	0
Extrasystoles	1	0	0	1	0
Gastrocardiac syndrome	0	1	0	0	0
Hypertensive heart disease	0	2	0	0	0
Interventricular septum rupture	2	0	0	0	0
Intracardiac thrombus	9	0	0	10	0
Ischaemic cardiomyopathy	2	16	0	0	0
Left ventricular dysfunction	3	6	0	3	0
Left ventricular failure	10	10	1	7	0
Long QT syndrome	0	0	0	1	0
Low cardiac output syndrome	2	0	0	2	1
Mitral valve calcification	0	1	0	0	0
Mitral valve disease	0	0	0	1	0
Mitral valve incompetence	4	9	0	5	1
Mitral valve prolapse	0	1	0	0	0
Mitral valve stenosis	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Myocardial fibrosis	0	3	0	0	0
Myocardial infarction	13	30	0	9	3
Myocardial ischaemia	12	38	0	4	5
Myocardial oedema	0	0	0	0	1
Myocardial rupture	6	1	0	3	2
Myocarditis	2	1	0	0	1
Nodal arrhythmia	0	4	0	0	0
Nodal rhythm	1	1	0	2	0
Palpitations	10	11	0	6	0
Papillary muscle disorder	0	0	0	1	0
Papillary muscle rupture	2	0	0	1	0
Pericardial effusion	17	6	0	10	0
Pericardial haemorrhage	3	1	0	3	0
Pericarditis	8	6	0	9	2
Postinfarction angina	1	0	0	0	0
Prinzmetal angina	1	3	0	1	1
Pulseless electrical activity	4	1	0	4	0
Rhythm idioventricular	1	0	0	0	0
Right ventricular failure	2	2	0	1	0
Sick sinus syndrome	12	21	0	2	1
Silent myocardial infarction	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Sinoatrial block	0	1	0	0	0
Sinus arrest	3	2	0	3	1
Sinus arrhythmia	0	2	0	0	0
Sinus bradycardia	7	21	0	4	0
Sinus tachycardia	0	7	0	0	0
Stress cardiomyopathy	1	0	0	1	1
Subendocardial ischaemia	0	1	0	0	0
Supraventricular extrasystoles	1	2	0	0	0
Supraventricular tachycardia	12	14	0	8	0
Systolic dysfunction	0	3	0	0	0
Tachyarrhythmia	2	1	0	1	0
Tachycardia	2	8	0	4	0
Tachycardia paroxysmal	0	2	0	0	0
Torsade de pointes	1	0	0	1	0
Ventricle rupture	4	0	0	4	1
Ventricular arrhythmia	2	8	0	5	0
Ventricular dysfunction	0	1	0	1	0
Ventricular extrasystoles	11	9	0	1	0
Ventricular fibrillation	107	29	2	67	5
Ventricular septal defect acquired	1	0	0	0	0
Ventricular tachyarrhythmia	0	0	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Ventricular tachycardia	49	56	1	38	6
Vascular disorders	**210**	**536**	**4**	**200**	**42**
Accelerated hypertension	2	2	1	5	0
Aneurysm	0	2	0	0	0
Aneurysm ruptured	1	0	1	0	0
Angiodysplasia	0	1	0	0	0
Aortic aneurysm	0	63	0	7	0
Aortic aneurysm rupture	2	5	0	1	0
Aortic dilatation	1	0	0	1	0
Aortic dissection	6	5	0	4	2
Aortic dissection rupture	0	0	0	1	0
Aortic rupture	2	0	0	0	0
Aortic stenosis	2	13	0	3	1
Aortic thrombosis	0	4	0	0	0
Aorto-duodenal fistula	1	0	0	0	0
Arterial disorder	1	0	0	0	0
Arterial occlusive disease	1	0	0	2	2
Arterial rupture	2	2	0	1	0
Arterial stenosis	1	0	0	0	0
Arterial thrombosis	0	1	0	5	0
Arteriosclerosis	3	6	0	3	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Arteriovenous fistula	3	2	0	1	0
Arteritis	0	0	0	1	0
Artery dissection	3	0	1	1	0
Circulatory collapse	9	3	0	2	0
Deep vein thrombosis	9	32	0	11	4
Diabetic vascular disorder	1	4	0	0	0
Embolism venous	1	0	0	0	0
Essential hypertension	0	1	0	0	0
Extremity necrosis	1	3	0	0	0
Femoral artery aneurysm	1	1	0	2	0
Femoral artery occlusion	3	1	0	1	1
Haematoma	6	8	0	9	0
Haemodynamic instability	2	0	0	0	0
Haemorrhage	4	6	0	6	1
Hot flush	0	1	0	0	0
Hypertension	22	63	0	28	4
Hypertensive crisis	10	43	1	12	1
Hypertensive emergency	5	5	0	3	1
Hypotension	24	34	0	23	2
Hypothenar hammer syndrome	0	1	0	0	0
Hypovolaemic shock	3	1	0	4	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Iliac artery occlusion	3	0	0	1	0
Intermittent claudication	6	14	0	6	0
Ischaemia	2	0	0	0	1
Ischaemic limb pain	1	0	0	1	0
Leriche syndrome	1	1	0	1	0
Lymphatic fistula	0	1	0	0	0
Lymphocele	0	2	0	0	0
Lymphoedema	0	2	0	0	0
Malignant hypertension	0	1	0	0	0
Necrosis ischaemic	0	0	0	1	0
Orthostatic hypotension	5	17	0	3	3
Penetrating atherosclerotic ulcer	0	1	0	0	0
Peripheral arterial occlusive disease	8	42	0	10	4
Peripheral artery aneurysm	3	6	0	1	1
Peripheral artery dissection	1	0	0	0	0
Peripheral artery stenosis	2	34	0	3	2
Peripheral artery thrombosis	3	14	0	4	1
Peripheral circulatory failure	0	1	0	0	0
Peripheral embolism	2	6	0	2	0
Peripheral ischaemia	15	22	0	7	6
Peripheral vascular disorder	2	14	0	3	1

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Peripheral venous disease	0	3	0	1	0
Phlebitis	1	2	0	1	0
Phlebitis superficial	0	1	0	0	0
Poor peripheral circulation	0	1	0	0	0
Reperfusion injury	0	0	0	1	0
Secondary hypertension	0	1	0	0	0
Shock	4	3	0	1	0
Shock haemorrhagic	3	0	0	0	2
Steal syndrome	0	1	0	0	0
Subclavian artery stenosis	1	2	0	2	0
Subclavian artery thrombosis	0	0	0	1	0
Subclavian vein thrombosis	1	1	0	0	0
Superior vena cava syndrome	0	1	0	0	0
Temporal arteritis	1	2	0	0	0
Thrombophlebitis	3	6	0	3	0
Thrombophlebitis superficial	2	2	0	1	0
Thrombosis	3	3	0	4	1
Varicose vein	0	9	0	0	0
Varicose vein ruptured	0	1	0	0	0
Vascular occlusion	1	0	0	0	0
Vasculitis	1	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Vena cava thrombosis	1	2	0	0	0
Venous thrombosis	2	1	0	2	1
Venous thrombosis limb	0	2	0	3	0
Respiratory, thoracic and mediastinal disorders	**415**	**782**	7	**353**	**39**
Acute pulmonary oedema	28	13	1	35	2
Acute respiratory distress syndrome	4	3	0	2	0
Acute respiratory failure	6	18	0	6	1
Adenoidal hypertrophy	1	0	0	0	0
Apnoea	0	0	0	1	0
Asphyxia	0	1	0	0	0
Aspiration	0	1	0	2	0
Asthma	5	32	0	3	1
Asthmatic crisis	1	0	0	0	0
Atelectasis	1	0	0	0	1
Bronchial haemorrhage	1	0	0	1	0
Bronchial hyperreactivity	0	2	0	0	0
Bronchial obstruction	1	1	0	0	0
Bronchiectasis	2	1	0	0	0
Bronchitis chronic	2	1	0	0	0
Bronchopneumopathy	0	1	0	0	0
Bronchospasm	2	2	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Choking	0	1	0	0	0
Chronic obstructive pulmonary disease	39	259	1	29	11
Chronic respiratory failure	1	3	0	0	0
Cough	3	3	0	0	0
Diaphragmatic paralysis	1	1	0	0	1
Diffuse panbronchiolitis	0	1	0	0	0
Dyspnoea	93	96	0	55	5
Dyspnoea at rest	0	0	0	1	0
Dyspnoea exertional	7	6	0	3	1
Dyspnoea paroxysmal nocturnal	0	0	0	1	0
Emphysema	2	2	0	0	0
Epiglottic cyst	0	2	0	0	0
Epiglottic oedema	0	1	0	0	0
Epistaxis	18	36	2	16	1
Haemoptysis	11	11	0	11	0
Haemothorax	2	0	1	2	1
Hiccups	0	0	0	1	0
Hydrothorax	2	1	0	5	0
Hyperventilation	3	0	0	1	0
Hypoxia	0	0	0	1	1
Idiopathic pulmonary fibrosis	0	2	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Interstitial lung disease	1	8	0	1	2
Laryngeal leukoplakia	1	0	0	0	0
Laryngeal oedema	1	3	0	1	0
Laryngeal stenosis	0	0	0	1	0
Laryngospasm	1	0	0	0	0
Lung consolidation	1	0	0	0	0
Lung cyst	0	1	0	0	0
Lung disorder	5	2	0	1	0
Mediastinal haematoma	0	0	0	1	0
Mediastinal haemorrhage	0	0	0	1	0
Nasal polyps	0	5	0	1	0
Nasal septum deviation	0	2	0	0	0
Nocturnal dyspnoea	1	1	0	0	0
Obstructive airways disorder	0	3	0	0	0
Organising pneumonia	0	1	0	0	0
Oropharyngeal spasm	0	1	0	0	0
Pharyngeal haemorrhage	0	2	0	0	0
Pharyngeal oedema	0	1	0	0	0
Pleural adhesion	0	1	0	0	0
Pleural disorder	0	0	0	1	0
Pleural effusion	28	34	0	24	2

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Pleurisy	2	8	0	4	0
Pleuritic pain	0	5	0	3	0
Pneumonia aspiration	3	15	0	7	2
Pneumonitis	3	0	0	0	0
Pneumothorax	2	26	0	10	0
Pneumothorax spontaneous	2	4	0	0	0
Pulmonary alveolar haemorrhage	1	0	0	1	0
Pulmonary arterial hypertension	0	0	0	0	1
Pulmonary congestion	5	1	0	2	0
Pulmonary embolism	39	73	1	24	1
Pulmonary fibrosis	2	6	0	1	0
Pulmonary granuloma	0	1	0	0	0
Pulmonary haematoma	0	0	0	1	0
Pulmonary haemorrhage	1	2	0	2	0
Pulmonary hilum mass	0	1	0	0	0
Pulmonary hypertension	1	3	0	0	0
Pulmonary mass	3	9	0	2	0
Pulmonary microemboli	1	0	0	0	0
Pulmonary oedema	45	17	0	61	0
Respiratory arrest	2	1	0	3	0
Respiratory distress	4	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Respiratory failure	19	25	1	17	1
Respiratory tract haemorrhage	1	1	0	1	0
Respiratory tract inflammation	0	1	0	0	0
Rhinorrhoea	1	0	0	0	0
Sleep apnoea syndrome	1	12	0	0	4
Systemic sclerosis pulmonary	0	0	0	1	0
Tachypnoea	1	0	0	0	0
Thoracic haemorrhage	0	1	0	0	0
Tonsillar hypertrophy	0	1	0	0	0
Tracheal stenosis	0	0	0	1	0
Vocal cord leukoplakia	0	1	0	0	0
Vocal cord polyp	1	0	0	1	0
Wheezing	0	0	0	1	0
Gastrointestinal disorders	**469**	**943**	**17**	**299**	**50**
Abdominal adhesions	1	2	0	0	0
Abdominal discomfort	1	4	0	1	0
Abdominal distension	0	0	0	1	0
Abdominal hernia	1	11	0	0	0
Abdominal hernia obstructive	0	2	0	0	0
Abdominal incarcerated hernia	1	1	0	0	0
Abdominal pain	22	35	1	11	1

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Abdominal pain lower	1	2	0	0	0
Abdominal pain upper	11	12	0	16	2
Abdominal wall haematoma	0	2	0	0	0
Acute abdomen	0	3	1	0	1
Alcoholic pancreatitis	0	1	0	0	0
Anal fissure	0	2	0	0	0
Anal fistula	0	8	0	1	0
Anal haemorrhage	0	1	0	3	0
Anal polyp	0	1	0	0	0
Anal stenosis	0	1	0	0	0
Appendiceal mucocoele	0	1	0	0	0
Ascites	0	2	0	0	0
Barrett's oesophagus	0	1	0	0	0
Chronic gastritis	1	7	0	1	0
Coeliac artery stenosis	0	1	0	0	0
Colitis	1	15	1	0	0
Colitis ischaemic	4	8	0	1	1
Colitis ulcerative	0	3	0	1	0
Constipation	1	15	0	2	0
Crohn's disease	0	3	0	0	0
Dental caries	0	1	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Diaphragmatic hernia	0	1	0	0	0
Diarrhoea	16	15	0	12	2
Diarrhoea haemorrhagic	1	0	0	0	0
Dieulafoy's vascular malformation	2	0	0	0	0
Diverticular perforation	0	3	0	1	0
Diverticulitis intestinal haemorrhagic	5	2	0	0	4
Diverticulum	11	7	0	0	1
Diverticulum intestinal	3	7	0	0	0
Diverticulum intestinal haemorrhagic	9	12	0	12	2
Duodenal stenosis	0	2	0	0	0
Duodenal ulcer	8	3	0	4	0
Duodenal ulcer haemorrhage	13	11	2	4	1
Duodenitis	1	1	1	2	0
Dyspepsia	5	12	0	8	0
Dysphagia	2	8	0	2	0
Enteritis	0	1	0	3	0
Enterocolitis	0	3	0	0	1
Enterocolitis haemorrhagic	3	3	0	0	0
Enterovesical fistula	0	1	0	0	0
Epigastric discomfort	1	1	0	0	0
Erosive duodenitis	2	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Erosive oesophagitis	2	1	0	0	0
Faecal incontinence	0	2	0	1	0
Faecalith	0	1	0	0	0
Faecaloma	0	1	0	0	0
Faeces discoloured	1	0	0	2	0
Femoral hernia	0	1	0	0	0
Femoral hernia, obstructive	0	1	0	0	0
Food poisoning	0	5	1	1	0
Gastric disorder	1	0	0	1	0
Gastric haemorrhage	3	11	0	8	0
Gastric perforation	0	1	0	0	0
Gastric polyps	0	2	0	0	0
Gastric ulcer	14	12	1	5	5
Gastric ulcer haemorrhage	27	30	1	9	3
Gastric ulcer perforation	1	0	0	1	0
Gastritis	9	41	1	11	1
Gastritis alcoholic	0	1	0	0	0
Gastritis erosive	8	7	0	2	0
Gastritis haemorrhagic	4	4	0	5	0
Gastritis hypertrophic	1	0	0	0	0
Gastroduodenal haemorrhage	3	0	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Gastroduodenitis	0	2	0	0	0
Gastroduodenitis haemorrhagic	1	0	0	0	0
Gastrointestinal angiodysplasia	0	2	0	0	1
Gastrointestinal angiodysplasia haemorrhagic	2	3	0	0	0
Gastrointestinal disorder	1	1	0	2	0
Gastrointestinal erosion	0	0	1	0	0
Gastrointestinal haemorrhage	73	76	2	51	6
Gastrointestinal inflammation	0	1	0	0	0
Gastrointestinal mucosal disorder	0	1	0	0	0
Gastrointestinal necrosis	3	3	0	1	0
Gastrointestinal pain	1	3	0	0	0
Gastrointestinal perforation	0	1	0	0	0
Gastrointestinal polyp haemorrhage	3	8	0	0	0
Gastrointestinal telangiectasia	1	0	0	0	0
Gastrointestinal ulcer haemorrhage	1	3	0	3	0
Gastrointestinal vascular malformation	2	2	0	0	0
Gastrooesophageal reflux disease	6	33	0	8	0
Gingival bleeding	2	2	0	0	0
Gingivitis ulcerative	0	0	0	1	0
Haematemesis	8	1	0	3	1
Haematochezia	4	4	0	4	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Haemorrhagic erosive gastritis	1	3	0	5	0
Haemorrhoidal haemorrhage	3	11	0	4	0
Haemorrhoids	4	9	0	1	0
Hiatus hernia	3	4	0	1	0
Ileus	4	18	0	1	0
Ileus paralytic	3	4	0	0	0
Impaired gastric emptying	0	15	0	0	0
Incarcerated inguinal hernia	0	5	0	0	0
Incarcerated umbilical hernia	0	3	0	0	0
Inguinal hernia	5	86	0	5	0
Inguinal hernia strangulated	0	3	0	1	2
Intestinal haemorrhage	1	6	0	1	0
Intestinal infarction	0	3	0	0	0
Intestinal ischaemia	2	8	0	3	0
Intestinal obstruction	1	13	1	0	0
Intestinal perforation	2	2	0	0	0
Intra-abdominal haemorrhage	1	0	0	1	0
Intussusception	0	1	0	0	0
Irritable bowel syndrome	1	0	0	0	0
Large intestinal ulcer haemorrhage	1	1	0	0	0
Large intestine perforation	3	4	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Large intestine polyp	6	33	0	3	1
Loose tooth	1	0	0	0	0
Lower gastrointestinal haemorrhage	3	8	0	4	1
Mallory-Weiss syndrome	4	3	0	1	0
Mechanical ileus	2	2	0	0	0
Melaena	16	5	1	6	2
Mesenteric arterial occlusion	0	1	0	0	0
Mesenteric vein thrombosis	0	1	0	0	0
Mouth haemorrhage	0	3	0	1	0
Nausea	3	2	0	4	0
Noninfective sialoadenitis	0	1	0	0	0
Oedematous pancreatitis	0	1	0	0	0
Oesophageal achalasia	0	3	0	0	0
Oesophageal food impaction	1	0	0	0	0
Oesophageal haemorrhage	0	1	0	1	0
Oesophageal obstruction	0	1	0	0	0
Oesophageal pain	1	1	0	0	0
Oesophageal rupture	1	0	0	0	0
Oesophageal spasm	0	1	0	0	0
Oesophageal stenosis	0	1	0	0	0
Oesophageal ulcer	0	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Oesophageal ulcer haemorrhage	1	1	1	0	0
Oesophageal varices haemorrhage	1	1	0	3	0
Oesophagitis	2	8	0	2	0
Oesophagitis haemorrhagic	2	1	0	0	1
Pancreatic duct obstruction	0	1	0	0	0
Pancreatic fistula	0	1	0	0	0
Pancreatic haemorrhage	0	0	0	1	0
Pancreatic mass	0	1	0	0	0
Pancreatic pseudocyst	0	1	0	0	0
Pancreatitis	6	27	0	5	2
Pancreatitis acute	6	29	0	1	1
Pancreatitis chronic	0	2	0	0	0
Pancreatitis haemorrhagic	0	0	0	0	1
Pancreatitis relapsing	0	2	0	0	0
Papilla of Vater stenosis	0	1	0	0	0
Peptic ulcer	0	0	0	1	0
Peptic ulcer haemorrhage	3	5	0	4	0
Peritoneal haemorrhage	0	2	0	0	0
Pneumoperitoneum	1	0	0	0	0
Proctitis	1	1	0	0	0
Proctitis haemorrhagic	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Radicular cyst	0	0	0	0	1
Rectal haemorrhage	11	12	0	6	0
Rectal polyp	2	2	0	0	0
Reflux gastritis	0	1	0	0	0
Retroperitoneal fibrosis	1	0	0	0	0
Retroperitoneal haematoma	6	1	0	3	0
Retroperitoneal haemorrhage	7	1	0	5	0
Small intestinal haemorrhage	3	2	0	0	0
Small intestinal obstruction	2	13	0	1	1
Small intestinal perforation	0	1	0	0	0
Small intestinal ulcer haemorrhage	1	0	0	0	0
Small intestine ulcer	1	0	0	0	0
Stomach mass	1	0	0	0	0
Subileus	1	3	0	0	0
Thrombosis mesenteric vessel	0	0	0	1	1
Tongue blistering	0	1	0	0	0
Tongue oedema	1	1	0	0	0
Tooth disorder	0	1	0	0	0
Toothache	1	1	0	0	0
Umbilical hernia	0	17	0	0	0
Umbilical hernia, obstructive	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Upper gastrointestinal haemorrhage	15	15	1	9	2
Volvulus	0	2	0	1	0
Volvulus of small bowel	0	1	0	0	0
Vomiting	11	7	0	6	1
Hepatobiliary disorders	**61**	**247**	**5**	**44**	**9**
Acute hepatic failure	0	1	0	0	0
Autoimmune hepatitis	0	1	0	0	0
Bile duct obstruction	1	0	0	0	0
Bile duct stenosis	0	5	0	0	0
Bile duct stone	4	22	0	3	2
Biliary colic	2	0	0	2	0
Biliary dyskinesia	0	1	0	0	0
Biliary fistula	0	1	0	0	0
Biloma	0	1	0	0	0
Cholangiolitis	0	1	0	0	0
Cholangitis	4	8	0	2	0
Cholangitis sclerosing	0	1	0	0	0
Cholecystitis	9	45	0	10	1
Cholecystitis acute	9	41	2	10	3
Cholecystitis chronic	2	7	0	0	0
Cholelithiasis	9	79	0	8	1

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Cholestasis	1	6	0	0	0
Chronic hepatitis	1	0	0	0	0
Cirrhosis alcoholic	0	2	0	0	0
Drug-induced liver injury	1	1	0	1	0
Gallbladder disorder	1	1	0	0	0
Gallbladder necrosis	1	0	0	0	0
Gallbladder perforation	0	1	0	0	0
Hepatic cirrhosis	3	3	0	2	2
Hepatic failure	2	4	1	4	0
Hepatic function abnormal	4	0	1	0	0
Hepatic vein thrombosis	0	1	0	0	0
Hepatitis acute	1	0	0	0	0
Hepatitis alcoholic	0	1	0	0	0
Hepatitis toxic	1	0	0	0	0
Hepatocellular injury	1	0	0	0	0
Hepatomegaly	0	1	0	0	0
Hepatorenal failure	0	1	0	0	0
Hydrocholecystis	0	1	0	0	0
Hyperplastic cholecystopathy	0	2	0	0	0
Ischaemic hepatitis	1	0	0	0	0
Jaundice	0	3	0	2	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Jaundice cholestatic	0	2	0	0	0
Liver disorder	2	1	1	0	0
Non-alcoholic steatohepatitis	1	1	0	0	0
Portal vein thrombosis	0	1	0	0	0
Skin and subcutaneous tissue disorders	**35**	**63**	**0**	**32**	**3**
Actinic keratosis	0	3	0	0	0
Alopecia	0	0	0	1	0
Angioedema	3	7	0	7	1
Blister	0	0	0	1	0
Cutaneous sarcoidosis	0	1	0	0	0
Decubitus ulcer	2	5	0	0	0
Dermal cyst	0	1	0	0	0
Dermatitis	2	0	0	0	0
Dermatitis allergic	2	2	0	4	0
Dermatomyositis	1	0	0	0	0
Diabetic foot	1	12	0	0	1
Drug eruption	0	2	0	0	0
Dry gangrene	1	2	0	0	1
Ecchymosis	1	1	0	1	0
Eczema	0	2	0	0	0
Eczema nummular	0	0	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Erythema	0	0	0	1	0
Hyperhidrosis	2	1	0	0	0
Hyperkeratosis	0	1	0	0	0
Hypersensitivity vasculitis	0	1	0	1	0
Panniculitis	0	1	0	0	0
Pruritus	2	1	0	3	0
Psoriasis	0	2	0	0	0
Pyoderma gangrenosum	0	2	0	0	0
Rash	3	1	0	4	0
Rash erythematous	1	0	0	0	0
Rash generalised	1	1	0	0	0
Rash pruritic	1	0	0	0	0
Seborrhoeic dermatitis	0	0	0	1	0
Skin haemorrhage	0	1	0	1	0
Skin mass	1	0	0	0	0
Skin necrosis	2	0	0	1	0
Skin ulcer	5	9	0	0	0
Stasis dermatitis	1	1	0	0	0
Stevens-Johnson syndrome	0	1	0	0	0
Toxic epidermal necrolysis	1	0	0	0	0
Urticaria	2	2	0	5	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Musculoskeletal and connective tissue disorders	**92**	**638**	**1**	**64**	**11**
Ankylosing spondylitis	0	1	0	0	0
Arthralgia	3	7	0	4	0
Arthritis	2	24	0	2	0
Arthropathy	0	2	0	0	0
Back pain	4	28	0	6	1
Bone pain	0	1	0	0	0
Bursitis	2	3	0	1	0
Cervical spinal stenosis	0	6	0	0	0
Chondritis	0	1	0	0	0
Chondrocalcinosis pyrophosphate	1	2	0	0	0
Chondropathy	0	1	0	1	0
Costochondritis	2	3	0	1	0
Dupuytren's contracture	0	4	0	0	0
Facet joint syndrome	0	2	0	0	0
Fibromyalgia	0	2	0	0	0
Finger deformity	0	1	0	0	0
Fistula	0	1	0	0	0
Foot deformity	0	3	0	0	0
Fracture malunion	0	1	0	0	0
Fracture nonunion	0	2	0	0	0
Gouty arthritis	3	3	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Groin pain	1	1	0	0	0
Haemarthrosis	1	0	0	0	0
Intervertebral disc compression	0	2	0	0	0
Intervertebral disc degeneration	0	9	0	1	0
Intervertebral disc disorder	0	5	0	1	0
Intervertebral disc protrusion	4	46	0	1	0
Jaw cyst	0	1	0	0	0
Jaw disorder	0	1	0	0	0
Joint ankylosis	0	1	0	0	0
Joint effusion	1	0	0	0	0
Joint swelling	1	0	0	0	0
Limb discomfort	1	0	0	0	0
Lumbar spinal stenosis	1	23	0	1	1
Meniscal degeneration	0	1	0	0	0
Mobility decreased	0	1	0	0	0
Monarthritis	1	1	0	0	0
Muscle haemorrhage	1	3	0	0	0
Muscle hypertrophy	0	1	0	0	0
Muscle spasms	0	5	0	0	0
Muscle tightness	1	0	0	0	0
Muscular weakness	2	2	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Musculoskeletal chest pain	17	63	1	14	1
Musculoskeletal pain	5	13	0	4	1
Myalgia	2	5	0	3	0
Myalgia intercostal	3	1	0	0	0
Myopathy	0	2	0	0	0
Myositis	0	0	0	1	0
Neck pain	1	2	0	2	1
Osteitis	0	0	0	1	1
Osteoarthritis	13	192	0	7	1
Osteochondrosis	1	0	0	0	0
Osteolysis	1	1	0	0	0
Osteonecrosis	0	4	0	0	0
Osteoporosis	0	2	0	1	1
Pain in extremity	5	7	0	2	0
Pain in jaw	2	1	0	0	0
Pathological fracture	1	1	0	0	0
Periarthritis	0	2	0	0	0
Polyarthritis	1	4	0	1	0
Polymyalgia rheumatica	2	2	0	0	0
Polymyositis	0	1	0	1	0
Pseudarthrosis	0	3	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Psoriatic arthropathy	0	1	0	0	0
Resorption bone increased	0	1	0	0	0
Rhabdomyolysis	2	5	0	1	1
Rheumatoid arthritis	1	10	0	0	0
Rotator cuff syndrome	0	25	0	1	0
Sacroiliitis	0	1	0	0	0
Scleroderma	0	1	0	0	0
Soft tissue necrosis	0	0	0	1	1
Spinal column stenosis	0	25	0	0	1
Spinal disorder	1	1	0	0	0
Spinal ligament ossification	0	1	0	0	0
Spinal osteoarthritis	1	21	0	1	0
Spinal pain	0	13	0	3	0
Spondylitis	0	1	0	0	0
Spondylolisthesis	0	7	0	0	0
Spondylolysis	0	1	0	0	0
Sympathetic posterior cervical syndrome	0	2	0	0	0
Synovial cyst	0	4	0	0	0
Synovial disorder	0	1	0	0	0
Synovitis	0	1	0	0	0
Systemic lupus erythematosus	0	2	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Systemic sclerosis	1	0	0	0	0
Tendon calcification	0	1	0	0	0
Tendon disorder	0	1	0	0	0
Tendonitis	0	2	0	0	0
Trigger finger	0	2	0	0	0
Vertebral foraminal stenosis	0	1	0	0	0
Renal and urinary disorders	**171**	**425**	**4**	**134**	**15**
Acute prerenal failure	0	4	0	1	0
Anuria	1	0	0	1	0
Azotaemia	2	0	0	1	0
Bladder diverticulum	0	2	0	0	0
Bladder neck sclerosis	0	1	0	0	0
Bladder prolapse	0	2	0	1	0
Bladder tamponade	0	1	0	3	0
Calculus bladder	0	8	0	1	0
Calculus ureteric	2	16	0	3	0
Calculus urethral	1	5	0	0	0
Calculus urinary	1	8	0	4	0
Cystitis haemorrhagic	0	1	0	2	0
Cystitis noninfective	0	1	0	1	0
Diabetic nephropathy	1	0	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Dysuria	1	0	0	0	0
Glomerulonephritis	1	0	0	0	0
Glomerulonephritis membranoproliferative	0	1	0	0	0
Glomerulonephritis membranous	0	1	0	1	0
Glomerulonephropathy	0	0	0	1	0
Haematuria	20	28	2	19	1
Haemorrhage urinary tract	7	1	0	2	0
Hydronephrosis	0	10	0	1	0
Hypertensive nephropathy	0	2	0	0	0
Nephritis	0	3	0	0	0
Nephritis autoimmune	1	0	0	0	0
Nephrolithiasis	6	47	0	4	1
Nephropathy	3	1	0	1	0
Nephropathy toxic	1	0	0	1	0
Nephrotic syndrome	0	3	0	1	0
Neurogenic bladder	0	1	0	0	0
Obstructive uropathy	0	1	0	1	0
Oliguria	1	0	0	0	0
Pelvi-ureteric obstruction	0	1	0	0	0
Proteinuria	0	1	0	0	0
Renal arteriosclerosis	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Renal artery stenosis	2	2	0	3	2
Renal artery thrombosis	1	0	0	0	0
Renal atrophy	0	1	0	0	0
Renal colic	5	11	0	2	0
Renal cyst	0	4	0	1	0
Renal cyst ruptured	0	1	0	0	0
Renal disorder	2	1	0	0	0
Renal failure	31	49	0	24	1
Renal failure acute	46	129	2	30	7
Renal failure chronic	14	33	0	7	3
Renal haemorrhage	1	1	0	0	0
Renal impairment	6	11	0	4	0
Renal injury	0	0	0	1	0
Renal mass	1	1	0	0	0
Renal tubular acidosis	0	1	0	0	0
Renal tubular necrosis	0	1	0	0	0
Stress urinary incontinence	0	1	0	0	0
Tubulointerstitial nephritis	0	1	0	0	0
Ureteric stenosis	1	1	0	0	0
Urethral haemorrhage	2	1	0	0	0
Urethral stenosis	1	4	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Urinary bladder haemorrhage	2	2	0	0	0
Urinary bladder polyp	0	6	0	2	0
Urinary bladder rupture	0	0	0	1	0
Urinary incontinence	1	1	0	1	0
Urinary retention	6	9	0	7	0
Urinary tract disorder	0	1	0	0	0
Urinary tract obstruction	0	0	0	1	0
Urinoma	0	1	0	0	0
Reproductive system and breast disorders	**21**	**139**	**1**	**14**	**2**
Acquired hydrocele	0	11	0	0	0
Acquired phimosis	0	4	0	0	0
Balanoposthitis	0	0	0	1	0
Benign prostatic hyperplasia	9	70	1	5	1
Breast fibrosis	0	1	0	0	0
Calculus prostatic	0	1	0	0	0
Cervical cyst	0	1	0	0	0
Cervical dysplasia	1	1	0	0	0
Cystocele	0	2	0	0	0
Endometrial hyperplasia	0	3	0	0	0
Gynaecomastia	1	0	0	0	0
Menometrorrhagia	0	0	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Menorrhagia	0	1	0	0	0
Metrorrhagia	0	2	0	1	0
Ovarian cyst	0	4	0	1	0
Ovarian necrosis	0	1	0	0	0
Postmenopausal haemorrhage	0	2	0	0	0
Prostatic haemorrhage	1	0	0	1	0
Prostatic mass	0	1	0	0	0
Prostatism	1	0	0	0	0
Prostatitis	6	16	0	2	0
Prostatomegaly	0	3	0	0	0
Scrotal cyst	0	1	0	0	0
Spermatocele	0	0	0	1	0
Testicular atrophy	0	1	0	0	0
Uterine cyst	0	1	0	0	0
Uterine haemorrhage	1	1	0	0	1
Uterine pain	0	1	0	0	0
Uterine polyp	0	2	0	0	0
Uterine prolapse	1	2	0	0	0
Uterovaginal prolapse	0	1	0	0	0
Vaginal haemorrhage	0	0	0	1	0
Vaginal prolapse	0	3	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Varicocele	0	1	0	0	0
Vulvovaginal pain	0	1	0	0	0
Congenital, familial and genetic disorders	**6**	**4**	**0**	**4**	**1**
Adenomatous polyposis coli	1	0	0	0	0
Anomalous arrangement of pancreaticobiliary duct	0	0	0	0	1
Arteriovenous malformation	1	0	0	0	0
Atrial septal defect	0	2	0	0	0
Carbohydrate metabolism disorder	0	0	0	2	0
Congenital cystic kidney disease	0	1	0	0	0
Diverticulitis Meckel's	1	0	0	0	0
Haemorrhagic arteriovenous malformation	1	0	0	0	0
Hypertrophic cardiomyopathy	1	0	0	1	0
Phimosis	0	1	0	0	0
Ventricular septal defect	1	0	0	1	0
General disorders and administration site conditions	**514**	**822**	**6**	**473**	**44**
Accidental death	1	0	0	1	0
Alcohol interaction	1	0	0	0	0
Application site inflammation	1	0	0	0	0
Arterial restenosis	10	4	0	7	0
Asthenia	7	16	0	5	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Cardiac death	3	4	0	3	0
Carotid artery restenosis	0	1	0	0	0
Catheter site haemorrhage	2	4	0	3	0
Chest discomfort	14	11	0	3	0
Chest pain	83	36	0	78	2
Complication of device insertion	1	0	0	1	0
Condition aggravated	0	1	0	0	0
Coronary artery restenosis	60	7	0	40	25
Death	25	107	0	32	1
Device battery issue	0	2	0	0	0
Device breakage	0	1	0	2	0
Device defective	0	1	0	0	0
Device dislocation	0	4	0	1	0
Device failure	0	1	0	0	0
Device lead damage	1	2	0	0	0
Device lead issue	0	1	0	0	0
Device malfunction	3	5	0	2	0
Device material issue	0	1	0	0	0
Device occlusion	2	3	0	2	1
Discomfort	1	1	0	0	0
Drowning	0	2	0	2	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Drug ineffective	1	0	0	0	0
Drug withdrawal syndrome	0	1	0	0	0
Dysplasia	0	1	0	0	0
Euthanasia	0	1	0	0	0
Fatigue	1	3	0	2	0
Foaming at mouth	1	0	0	0	0
Gait disturbance	0	3	0	1	0
General physical health deterioration	2	4	0	5	0
Generalised oedema	2	0	0	0	0
Hernia	1	1	0	0	0
Hyperthermia	0	1	0	0	0
Hypothermia	2	0	0	0	0
Impaired healing	3	7	0	4	1
Implant site haematoma	0	1	0	0	0
Implant site pain	0	1	0	0	0
Incarcerated hernia	0	1	0	0	0
Inflammation	0	0	0	1	0
Injection site bruising	0	1	0	0	0
Injection site haemorrhage	1	0	0	0	0
Malaise	6	5	0	3	0
Medical device complication	3	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Multi-organ failure	14	9	0	11	1
Non-cardiac chest pain	140	434	2	117	7
Oedema peripheral	3	3	0	1	0
Pain	1	2	0	1	1
Pelvic mass	0	0	0	1	0
Peripheral artery restenosis	0	1	0	0	0
Peripheral swelling	1	1	0	0	0
Puncture site haemorrhage	2	1	1	2	0
Pyrexia	10	14	0	7	0
Sense of oppression	0	0	0	1	0
Stent-graft endoleak	0	1	0	0	0
Sudden cardiac death	18	80	1	24	1
Sudden death	24	24	0	27	1
Systemic inflammatory response syndrome	1	2	0	2	0
Thrombosis in device	44	0	1	62	3
Vessel puncture site haematoma	7	2	0	11	0
Vessel puncture site haemorrhage	11	1	1	8	0
Investigations	**50**	**34**	**1**	**47**	**1**
Alanine aminotransferase increased	1	0	0	3	0
Angiogram	2	0	0	0	0
Antiphospholipid antibodies	0	0	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Aspartate aminotransferase	0	0	0	1	0
Aspartate aminotransferase increased	1	0	0	3	0
Aspiration bronchial	0	0	0	1	0
Blood creatine phosphokinase MB increased	0	0	0	1	0
Blood creatine phosphokinase increased	1	0	0	0	0
Blood creatinine increased	1	4	0	0	0
Blood electrolytes decreased	0	1	0	0	0
Blood glucose decreased	0	1	0	0	0
Blood glucose increased	3	0	0	1	0
Blood potassium decreased	1	0	0	0	0
Blood potassium increased	0	0	0	2	0
Blood pressure decreased	1	0	0	1	0
Blood pressure increased	3	1	0	4	0
Blood urine present	0	1	0	0	0
Body temperature increased	2	0	0	0	0
C-reactive protein increased	1	0	0	0	0
Cardiac stress test abnormal	0	3	0	0	0
Clostridium test positive	0	2	0	0	0
Computerised tomogram thorax abnormal	0	1	0	0	0
Cystoscopy abnormal	0	1	0	0	0
Ejection fraction decreased	0	4	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Electrocardiogram QT prolonged	1	0	0	1	0
Electrocardiogram ST segment depression	0	1	0	0	0
Electrocardiogram ST segment elevation	0	0	0	0	1
Electrocardiogram T wave inversion	1	0	0	0	0
Electrocardiogram abnormal	1	1	1	0	0
Exercise test abnormal	1	0	0	0	0
Fibrin D dimer increased	0	0	0	1	0
Glycosylated haemoglobin increased	0	1	0	0	0
Haematocrit decreased	1	0	0	0	0
Haemoglobin decreased	11	0	0	9	0
Hepatic enzyme abnormal	0	1	0	0	0
Hepatic enzyme increased	4	2	0	4	0
Influenza A virus test positive	0	1	0	0	0
International normalised ratio increased	1	0	0	2	0
Intraocular pressure increased	0	0	0	1	0
Liver function test abnormal	1	1	0	3	0
Lymph node palpable	0	1	0	0	0
Myocardial necrosis marker increased	1	0	0	0	0
Nutritional condition abnormal	1	0	0	0	0
Occult blood	1	0	0	0	0
Occult blood positive	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Pancreatic enzymes increased	0	0	0	1	0
Platelet count decreased	1	1	0	1	0
Prostatic specific antigen increased	2	0	0	0	0
Red blood cell sedimentation rate increased	1	0	0	0	0
Renal function test abnormal	0	0	0	1	0
Scan myocardial perfusion abnormal	0	1	0	0	0
Stool analysis abnormal	0	1	0	0	0
Transplant evaluation	0	1	0	0	0
Troponin I increased	1	0	0	0	0
Troponin increased	2	0	0	3	0
Weight decreased	1	0	0	1	0
Weight increased	0	1	0	0	0
Injury, poisoning and procedural complications	**226**	**795**	**7**	**188**	**28**
Abdominal wound dehiscence	0	1	0	0	0
Accidental overdose	0	3	0	0	0
Acetabulum fracture	0	1	0	0	0
Alcohol poisoning	2	6	0	1	0
Anaemia postoperative	0	6	0	1	0
Anastomotic complication	0	1	0	0	0
Anastomotic haemorrhage	0	1	0	0	0
Anastomotic stenosis	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Anastomotic ulcer haemorrhage	0	1	0	1	0
Ankle fracture	2	24	0	0	0
Arterial injury	0	1	0	0	0
Arthropod sting	0	2	0	0	0
Avulsion fracture	0	1	0	0	0
Back injury	0	1	0	0	0
Bone fissure	0	2	0	0	0
Brain contusion	2	5	0	0	0
Brain herniation	0	3	0	0	0
Burns second degree	0	2	0	0	0
Burns third degree	0	1	0	0	0
Carbon monoxide poisoning	0	1	0	0	0
Cardiac procedure complication	2	0	0	0	0
Cardiac valve replacement complication	0	1	0	0	0
Cervical vertebral fracture	0	5	0	0	0
Chemical peritonitis	0	1	0	0	0
Chest injury	1	1	0	0	0
Clavicle fracture	1	2	0	3	0
Comminuted fracture	0	1	0	0	0
Compression fracture	0	1	0	0	0
Concussion	4	5	0	2	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Contrast media reaction	0	0	0	1	0
Contusion	0	13	0	0	0
Coronary artery reocclusion	0	0	0	1	0
Cranial nerve injury	0	1	0	0	0
Craniocerebral injury	2	5	0	0	2
Cystitis radiation	1	2	0	0	0
Dislocation of sternum	0	0	0	1	1
Dumping syndrome	0	1	0	0	0
Extradural haematoma	0	0	0	1	0
Face injury	2	2	0	0	0
Facial bones fracture	2	3	0	1	0
Fall	2	21	0	6	0
Fat embolism	1	0	0	0	1
Femoral neck fracture	6	27	0	7	1
Femur fracture	3	47	0	7	0
Fibula fracture	0	3	0	0	1
Foot fracture	0	12	0	2	0
Forearm fracture	1	1	0	0	0
Foreign body	0	1	0	0	0
Fracture	1	0	0	1	0
Fractured ischium	0	0	0	0	1

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Gas poisoning	0	1	0	0	0
Gastrointestinal injury	0	1	0	0	0
Gastrointestinal stoma complication	0	1	0	0	0
Graft haemorrhage	1	0	0	0	0
Graft thrombosis	1	0	0	2	0
Gun shot wound	0	2	0	0	0
Haematuria traumatic	1	1	0	0	0
Haemodilution	0	1	0	0	0
Hand fracture	3	5	0	0	0
Head injury	1	12	0	2	0
Heat exhaustion	0	1	0	0	0
Heat illness	0	2	0	0	0
Heat stroke	0	1	0	0	0
Hip fracture	3	29	0	3	2
Humerus fracture	3	18	0	1	0
Incision site erythema	0	1	0	0	0
Incision site haemorrhage	1	0	0	0	0
Incisional hernia	0	9	0	1	1
Incisional hernia, obstructive	0	1	0	0	0
Inflammation of wound	1	1	0	0	0
Injury	1	2	0	3	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Intentional overdose	0	1	0	0	1
Intestinal anastomosis complication	1	0	0	0	0
Joint capsule rupture	0	1	0	0	0
Joint dislocation	2	15	0	2	0
Joint injury	1	6	0	1	0
Kidney contusion	1	0	0	1	0
Laceration	0	2	0	2	0
Ligament injury	1	1	0	0	0
Ligament rupture	0	3	0	0	1
Ligament sprain	0	5	0	1	0
Limb crushing injury	0	1	0	0	0
Limb injury	1	12	0	0	0
Limb traumatic amputation	1	3	0	0	0
Lip injury	0	1	0	0	0
Lower limb fracture	0	11	0	2	0
Lumbar vertebral fracture	0	6	0	0	1
Meniscus injury	1	15	0	0	1
Mountain sickness acute	0	1	0	0	0
Multiple fractures	1	5	0	0	0
Multiple injuries	0	1	0	0	0
Muscle injury	0	0	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Muscle rupture	0	3	0	0	0
Muscle strain	0	1	0	0	0
Neck injury	0	1	0	0	0
Open fracture	0	1	0	0	0
Osteoradionecrosis	0	1	0	0	0
Overdose	3	6	0	0	0
Pancreatic injury	0	0	0	0	1
Pancreatic leak	0	1	0	0	0
Patella fracture	1	2	0	0	0
Pelvic fracture	0	1	0	2	1
Peripheral arterial reocclusion	0	3	0	0	0
Periprosthetic fracture	0	2	0	0	0
Pneumothorax traumatic	2	3	1	0	0
Poisoning	0	1	0	0	0
Post concussion syndrome	0	1	0	0	0
Post procedural complication	6	3	0	4	0
Post procedural fistula	1	3	0	0	0
Post procedural haematoma	9	10	1	2	0
Post procedural haematuria	2	6	1	0	0
Post procedural haemorrhage	56	32	1	48	1
Post procedural myocardial infarction	1	0	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Post procedural persistent drain fluid	0	1	0	0	0
Post-traumatic pain	0	2	0	0	0
Postoperative ileus	0	5	0	0	0
Postoperative respiratory failure	0	2	0	0	1
Postoperative thoracic procedure complication	2	1	0	2	1
Postoperative wound complication	1	2	0	2	0
Postpericardiotomy syndrome	5	1	0	2	1
Procedural complication	0	1	0	2	0
Procedural dizziness	1	0	0	0	0
Procedural haemorrhage	6	18	1	7	0
Procedural hypotension	0	3	0	2	0
Procedural nausea	1	1	0	0	0
Procedural pain	2	4	0	0	0
Pubis fracture	1	5	0	0	1
Pulmonary contusion	0	1	0	0	0
Radial nerve injury	0	1	0	0	0
Radiation dysphagia	0	1	0	0	0
Radius fracture	2	12	0	1	1
Remnant gastritis	0	1	0	0	0
Renal haematoma	0	1	0	0	0
Rib fracture	0	27	0	1	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Road traffic accident	2	13	0	0	0
Scapula fracture	0	4	0	0	0
Scrotal haematoma	1	0	0	0	0
Seroma	0	3	0	0	0
Shunt stenosis	0	0	0	1	0
Skin wound	0	1	0	0	0
Skull fracture	0	1	0	0	0
Soft tissue injury	0	2	0	0	0
Spinal column injury	1	0	0	0	0
Spinal compression fracture	4	19	0	1	1
Spinal cord injury	1	0	0	0	0
Spinal cord injury cervical	0	1	0	0	0
Spinal fracture	0	10	0	2	0
Splenic injury	1	0	0	0	0
Splenic rupture	0	1	0	0	0
Sternal fracture	0	2	0	0	0
Sternal injury	0	1	0	0	0
Subcutaneous haematoma	3	1	0	0	0
Subdural haematoma	4	14	0	5	0
Subdural haemorrhage	0	3	0	0	0
Suture related complication	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Suture rupture	0	0	0	1	0
Tendon injury	1	3	0	0	0
Tendon rupture	2	11	0	2	0
Thermal burn	2	3	0	0	0
Thoracic vertebral fracture	0	5	0	0	0
Tibia fracture	2	12	0	1	0
Toxicity to various agents	0	3	0	0	0
Tracheal haemorrhage	0	0	0	1	0
Tracheal obstruction	0	0	0	1	0
Traumatic fracture	0	1	0	0	0
Traumatic haematoma	2	25	0	1	1
Traumatic haemorrhage	1	1	0	2	0
Traumatic haemothorax	0	3	0	1	0
Traumatic intracranial haemorrhage	2	40	1	2	0
Traumatic spinal cord compression	0	1	0	0	0
Ulna fracture	0	3	0	1	0
Upper limb fracture	2	11	0	2	0
Urinary retention postoperative	0	2	0	0	0
Urinary tract injury	1	1	0	0	0
VIIIth nerve injury	0	1	0	0	0
Vascular graft complication	0	1	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014 Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Vascular graft occlusion	2	1	0	0	2
Vascular graft thrombosis	0	1	0	0	0
Vascular injury	0	1	0	0	0
Vascular procedure complication	0	1	0	0	0
Vascular pseudoaneurysm	18	1	1	25	1
Vascular pseudoaneurysm ruptured	1	0	0	0	0
Venous injury	0	1	0	0	0
Weaning failure	1	0	0	0	0
Wound	1	2	0	1	0
Wound complication	1	0	0	0	1
Wound dehiscence	3	5	0	2	0
Wound haemorrhage	0	0	0	2	0
Wound secretion	0	0	0	1	0
Wrist fracture	4	8	0	0	0
Surgical and medical procedures	**5**	**3**	**0**	7	**0**
Cardiac pacemaker insertion	1	0	0	0	0
Carotid endarterectomy	0	1	0	0	0
Coronary artery bypass	1	0	0	3	0
Dupuytren's contracture operation	0	0	0	1	0
Enterostomy	0	1	0	0	0
Finger amputation	1	0	0	0	0

Table 1 - Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

System Organ Class Preferred Term	Total Up to 08-NOV-2014				
	Investigational Product	Blinded	Study Procedure	Active Comparator	Placebo / No Study Product
Implantable defibrillator insertion	0	0	0	1	0
Inguinal hernia repair	0	1	0	0	0
Leg amputation	1	0	0	0	0
Mechanical ventilation	1	0	0	0	0
Thoracic cavity drainage	0	0	0	1	0
Transurethral prostatectomy	0	0	0	1	0

Listing of MedDRA SOCs in the Internationally Agreed Order

MedDRA Version : 17.1

Infections and infestations
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Blood and lymphatic system disorders
Immune system disorders
Endocrine disorders
Metabolism and nutrition disorders
Psychiatric disorders
Nervous system disorders
Eye disorders
Ear and labyrinth disorders
Cardiac disorders
Vascular disorders
Respiratory, thoracic and mediastinal disorders
Gastrointestinal disorders
Hepatobiliary disorders
Skin and subcutaneous tissue disorders
Musculoskeletal and connective tissue disorders
Renal and urinary disorders
Pregnancy, puerperium and perinatal conditions
Reproductive system and breast disorders
Congenital, familial and genetic disorders
General disorders and administration site conditions
Investigations
Injury, poisoning and procedural complications
Surgical and medical procedures
Social circumstances

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Infections and infestations	**92**	**92**	**101**	**101**	**193**	**0**	**0**
Abdominal infection	0	0	1	1	1	0	0
Abscess limb	0	0	1	1	1	0	0
Amoebiasis	0	0	1	1	1	0	0
Appendicitis	1	1	0	0	1	0	0
Bacterial infection	1	1	0	0	1	0	0
Bronchiolitis	0	0	2	2	2	0	0
Bronchitis	0	0	5	5	5	0	0
Bronchopneumonia	4	4	0	0	4	0	0
CNS ventriculitis	1	1	0	0	1	0	0
Cellulitis	2	2	0	0	2	0	0
Cholecystitis infective	1	1	0	0	1	0	0
Conjunctivitis	0	0	1	1	1	0	0
Cystitis	0	0	1	1	1	0	0
Dengue fever	1	1	1	1	2	0	0
Device related infection	0	0	1	1	1	0	0
Diabetic foot infection	1	1	0	0	1	0	0
Diverticulitis	2	2	3	3	5	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Dysentery	0	0	1	1	1	0	0
Ear infection	0	0	1	1	1	0	0
Endocarditis	2	2	0	0	2	0	0
Escherichia urinary tract infection	0	0	1	1	1	0	0
Fungal infection	0	0	1	1	1	0	0
Gastritis bacterial	1	1	0	0	1	0	0
Gastrointestinal infection	2	2	3	3	5	0	0
Gingivitis	0	0	1	1	1	0	0
Helicobacter infection	0	0	1	1	1	0	0
Herpes virus infection	1	1	0	0	1	0	0
Herpes zoster	2	2	0	0	2	0	0
Hordeolum	0	0	1	1	1	0	0
Infection	3	3	3	3	6	0	0
Infective exacerbation of chronic obstructive airways disease	1	1	0	0	1	0	0
Influenza	0	0	20	20	20	0	0
Labyrinthitis	0	0	1	1	1	0	0
Laryngitis	0	0	1	1	1	0	0
Lobar pneumonia	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Localised infection	1	1	2	2	3	0	0
Lower respiratory tract infection	1	1	1	1	2	0	0
Lung infection	4	4	0	0	4	0	0
Meningitis pneumococcal	1	1	0	0	1	0	0
Nasopharyngitis	0	0	13	13	13	0	0
Necrotising fasciitis	1	1	0	0	1	0	0
Neurocysticercosis	1	1	0	0	1	0	0
Nosocomial infection	2	2	0	0	2	0	0
Pertussis	0	0	1	1	1	0	0
Pharyngitis streptococcal	0	0	1	1	1	0	0
Pneumonia	27	27	8	8	35	0	0
Pneumonia staphylococcal	1	1	0	0	1	0	0
Pseudomembranous colitis	1	1	0	0	1	0	0
Pulpitis dental	0	0	1	1	1	0	0
Rash pustular	0	0	1	1	1	0	0
Respiratory tract infection	0	0	2	2	2	0	0
Respiratory tract infection viral	0	0	1	1	1	0	0
Rhinitis	0	0	3	3	3	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Roseola	0	0	1	1	1	0	0
Sepsis	7	7	0	0	7	0	0
Septic embolus	1	1	0	0	1	0	0
Septic shock	4	4	0	0	4	0	0
Sinusitis	1	1	4	4	5	0	0
Staphylococcal infection	3	3	1	1	4	0	0
Staphylococcal sepsis	1	1	0	0	1	0	0
Syphilis	1	1	0	0	1	0	0
Thrombophlebitis septic	1	1	0	0	1	0	0
Tooth infection	0	0	4	4	4	0	0
Urinary tract infection	5	5	3	3	8	0	0
Urosepsis	1	1	0	0	1	0	0
Viral infection	0	0	2	2	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**51**	**51**	**4**	**4**	**55**	**1**	**1**
Adenocarcinoma of colon	1	1	0	0	1	0	0
Adenocarcinoma pancreas	1	1	0	0	1	0	0
Basal cell carcinoma	2	2	0	0	2	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Benign neoplasm of prostate	1	1	0	0	1	0	0
Bladder cancer	1	1	0	0	1	0	0
Brain neoplasm	1	1	0	0	1	0	0
Breast cancer	1	1	0	0	1	0	0
Breast cancer female	3	3	0	0	3	0	0
Breast cancer metastatic	1	1	0	0	1	0	0
Cholangiocarcinoma	1	1	0	0	1	0	0
Colon cancer	1	1	0	0	1	0	0
Gastric cancer	2	2	0	0	2	0	0
Gastric neoplasm	1	1	0	0	1	0	0
Gastrointestinal carcinoma	1	1	0	0	1	0	0
Haemangioma	2	2	1	1	3	0	0
Hepatic neoplasm	2	2	0	0	2	0	0
Lipoma	0	0	1	1	1	0	0
Lung adenocarcinoma	1	1	0	0	1	0	0
Lung neoplasm malignant	5	5	0	0	5	0	0
Lymphoma	2	2	0	0	2	0	0
Malignant neoplasm of unknown primary site	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Melanocytic naevus	1	1	1	1	2	0	0
Metastases to liver	1	1	0	0	1	0	0
Metastases to spine	1	1	0	0	1	0	0
Myelodysplastic syndrome	2	2	0	0	2	0	0
Neoplasm	1	1	0	0	1	0	0
Neoplasm malignant	3	3	0	0	3	0	0
Neoplasm prostate	1	1	0	0	1	0	0
Neoplasm skin	1	1	0	0	1	0	0
Oesophageal carcinoma	1	1	0	0	1	0	0
Plasma cell myeloma	0	0	0	0	0	1	1
Prostate cancer	1	1	0	0	1	0	0
Salivary gland neoplasm	1	1	0	0	1	0	0
Seborrhoeic keratosis	0	0	1	1	1	0	0
Soft tissue neoplasm	1	1	0	0	1	0	0
Squamous cell carcinoma	1	1	0	0	1	0	0
Thyroid neoplasm	1	1	0	0	1	0	0
Tumour haemorrhage	2	2	0	0	2	0	0
Uterine leiomyoma	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Blood and lymphatic system disorders	**179**	**179**	**107**	**107**	**286**	**4**	**4**
Agranulocytosis	2	2	0	0	2	0	0
Anaemia	68	68	24	24	92	1	1
Anaemia macrocytic	1	1	0	0	1	0	0
Aplastic anaemia	2	2	0	0	2	0	0
Bandaemia	0	0	1	1	1	0	0
Blood disorder	0	0	4	4	4	0	0
Bone marrow failure	1	1	0	0	1	0	0
Coagulopathy	3	3	5	5	8	0	0
Disseminated intravascular coagulation	4	4	0	0	4	0	0
Eosinophilia	1	1	2	2	3	0	0
Haemoconcentration	0	0	2	2	2	0	0
Haemolysis	0	0	1	1	1	0	0
Haemolytic anaemia	2	2	0	0	2	0	0
Haemorrhagic anaemia	8	8	0	0	8	1	1
Haemorrhagic diathesis	5	5	10	10	15	2	2
Haemorrhagic disorder	0	0	1	1	1	0	0
Heparin-induced thrombocytopenia	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Hypercoagulation	1	1	0	0	1	0	0
Hypocoagulable state	0	0	2	2	2	0	0
Immune thrombocytopenic purpura	1	1	0	0	1	0	0
Increased tendency to bruise	2	2	13	13	15	0	0
Iron deficiency anaemia	5	5	0	0	5	0	0
Leukopenia	4	4	1	1	5	0	0
Lymphadenopathy	0	0	2	2	2	0	0
Microangiopathic haemolytic anaemia	1	1	0	0	1	0	0
Microcytic anaemia	1	1	0	0	1	0	0
Monocytopenia	0	0	1	1	1	0	0
Neutropenia	4	4	6	6	10	0	0
Normochromic normocytic anaemia	1	1	0	0	1	0	0
Pancytopenia	2	2	2	2	4	0	0
Platelet aggregation inhibition	2	2	1	1	3	0	0
Platelet disorder	1	1	1	1	2	0	0
Polycythaemia	0	0	1	1	1	0	0
Red blood cell abnormality	1	1	0	0	1	0	0
Spontaneous haematoma	4	4	5	5	9	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Thrombocytopenia	42	42	20	20	62	0	0
Thrombocytopenic purpura	1	1	0	0	1	0	0
Thrombocytosis	0	0	1	1	1	0	0
Thrombotic thrombocytopenic purpura	6	6	0	0	6	0	0
White blood cell disorder	2	2	1	1	3	0	0
Immune system disorders	**24**	**24**	**74**	**74**	**98**	**5**	**5**
Allergy to chemicals	0	0	1	1	1	0	0
Anaphylactic reaction	2	2	0	0	2	0	0
Anaphylactic shock	6	6	0	0	6	0	0
Decreased immune responsiveness	0	0	1	1	1	0	0
Drug hypersensitivity	9	9	34	34	43	1	1
Food allergy	0	0	1	1	1	0	0
Hypersensitivity	6	6	30	30	36	4	4
Iodine allergy	0	0	1	1	1	0	0
Multiple allergies	0	0	4	4	4	0	0
Reaction to drug excipients	0	0	1	1	1	0	0
Seasonal allergy	0	0	1	1	1	0	0
Serum sickness							

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	1	1	0	0	1	0	0
Endocrine disorders	**1**	**1**	**10**	**10**	**11**	**0**	**0**
Diabetes insipidus	1	1	0	0	1	0	0
Hyperthyroidism	0	0	1	1	1	0	0
Hypothyroidism	0	0	3	3	3	0	0
Thyroid disorder	0	0	5	5	5	0	0
Thyroid pain	0	0	1	1	1	0	0
Metabolism and nutrition disorders	**61**	**61**	**166**	**166**	**227**	**0**	**0**
Abnormal loss of weight	1	1	0	0	1	0	0
Appetite disorder	1	1	1	1	2	0	0
Decreased appetite	7	7	33	33	40	0	0
Dehydration	9	9	2	2	11	0	0
Diabetes mellitus	10	10	23	23	33	0	0
Diabetes mellitus inadequate control	3	3	3	3	6	0	0
Diabetic complication	1	1	0	0	1	0	0
Dyslipidaemia	0	0	6	6	6	0	0
Electrolyte imbalance	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Enzyme abnormality	1	1	0	0	1	0	0
Failure to thrive	1	1	0	0	1	0	0
Fluid intake reduced	1	1	0	0	1	0	0
Fluid retention	0	0	2	2	2	0	0
Food intolerance	0	0	2	2	2	0	0
Glucose tolerance impaired	0	0	3	3	3	0	0
Gout	9	9	29	29	38	0	0
Hypercholesterolaemia	0	0	3	3	3	0	0
Hyperglycaemia	4	4	8	8	12	0	0
Hyperkalaemia	2	2	2	2	4	0	0
Hyperlipidaemia	0	0	11	11	11	0	0
Hyperuricaemia	2	2	4	4	6	0	0
Hypoglycaemia	2	2	3	3	5	0	0
Hypokalaemia	1	1	2	2	3	0	0
Hyponatraemia	0	0	3	3	3	0	0
Hypophagia	1	1	0	0	1	0	0
Impaired fasting glucose	0	0	1	1	1	0	0
Increased appetite	0	0	2	2	2	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Iron deficiency	0	0	1	1	1	0	0
Lactose intolerance	0	0	2	2	2	0	0
Metabolic acidosis	1	1	0	0	1	0	0
Metabolic syndrome	0	0	1	1	1	0	0
Obesity	1	1	2	2	3	0	0
Overweight	0	0	2	2	2	0	0
Type 1 diabetes mellitus	0	0	1	1	1	0	0
Type 2 diabetes mellitus	2	2	8	8	10	0	0
Underweight	0	0	1	1	1	0	0
Vitamin D deficiency	0	0	1	1	1	0	0
Weight fluctuation	0	0	1	1	1	0	0
Weight loss poor	0	0	3	3	3	0	0
Psychiatric disorders	**86**	**86**	**263**	**263**	**349**	**1**	**1**
Abnormal behaviour	2	2	2	2	4	0	0
Abnormal dreams	0	0	2	2	2	0	0
Abnormal sleep-related event	0	0	1	1	1	0	0
Affect lability	0	0	1	1	1	0	0
Aggression							

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	4	4	7	7	11	0	0
Agitation	7	7	7	7	14	0	0
Agoraphobia	0	0	1	1	1	0	0
Anger	1	1	3	3	4	0	0
Anxiety	11	11	42	42	53	1	1
Anxiety disorder	1	1	0	0	1	0	0
Anxiety disorder due to a general medical condition	0	0	1	1	1	0	0
Apathy	1	1	5	5	6	0	0
Attention deficit/hyperactivity disorder	0	0	1	1	1	0	0
Aversion	0	0	1	1	1	0	0
Bipolar disorder	1	1	0	0	1	0	0
Boredom	0	0	1	1	1	0	0
Breathing-related sleep disorder	0	0	2	2	2	0	0
Bruxism	0	0	1	1	1	0	0
Completed suicide	2	2	0	0	2	0	0
Confusional state	21	21	15	15	36	0	0
Conversion disorder	0	0	1	1	1	0	0
Daydreaming	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Delirium	3	3	2	2	5	0	0
Depressed mood	1	1	6	6	7	0	0
Depression	1	1	15	15	16	0	0
Disorientation	8	8	6	6	14	0	0
Dissociation	0	0	1	1	1	0	0
Drug abuse	0	0	1	1	1	0	0
Eating disorder	0	0	2	2	2	0	0
Emotional disorder	0	0	3	3	3	0	0
Fear	1	1	3	3	4	0	0
Fear of death	1	1	0	0	1	0	0
Fear of disease	1	1	0	0	1	0	0
Feeling of despair	0	0	1	1	1	0	0
Frustration	0	0	3	3	3	0	0
Hallucination	3	3	3	3	6	0	0
Hallucination, auditory	0	0	1	1	1	0	0
Hallucination, visual	0	0	1	1	1	0	0
Impatience	0	0	1	1	1	0	0
Insomnia	4	4	30	30	34	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Irritability	0	0	4	4	4	0	0
Libido decreased	0	0	1	1	1	0	0
Listless	0	0	4	4	4	0	0
Loss of libido	0	0	1	1	1	0	0
Mania	0	0	1	1	1	0	0
Mental disorder	0	0	2	2	2	0	0
Mental status changes	0	0	1	1	1	0	0
Middle insomnia	0	0	1	1	1	0	0
Mood altered	0	0	1	1	1	0	0
Mood swings	0	0	1	1	1	0	0
Nervousness	1	1	10	10	11	0	0
Nightmare	0	0	7	7	7	0	0
Panic attack	2	2	8	8	10	0	0
Panic disorder	0	0	2	2	2	0	0
Panic reaction	0	0	1	1	1	0	0
Personality change	0	0	1	1	1	0	0
Phobia	0	0	2	2	2	0	0
Post-traumatic stress disorder	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Psychotic disorder	2	2	0	0	2	0	0
Reactive psychosis	0	0	1	1	1	0	0
Restlessness	1	1	5	5	6	0	0
Schizophrenia	0	0	1	1	1	0	0
Screaming	1	1	0	0	1	0	0
Seasonal affective disorder	0	0	1	1	1	0	0
Sleep disorder	0	0	6	6	6	0	0
Sleep disorder due to a general medical condition	0	0	11	11	11	0	0
Sleep disorder due to general medical condition, insomnia type	2	2	4	4	6	0	0
Social avoidant behaviour	0	0	1	1	1	0	0
Stress	0	0	5	5	5	0	0
Suicidal ideation	2	2	0	0	2	0	0
Suicide attempt	1	1	0	0	1	0	0
Tachyphrenia	0	0	1	1	1	0	0
Tearfulness	0	0	1	1	1	0	0
Tension	0	0	1	1	1	0	0
Terminal insomnia	0	0	1	1	1	0	0
Thinking abnormal	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Nervous system disorders	**683**	**683**	**526**	**526**	**1209**	**26**	**26**
Ageusia	0	0	3	3	3	0	0
Allodynia	1	1	0	0	1	0	0
Altered state of consciousness	4	4	0	0	4	0	0
Amnesia	2	2	10	10	12	0	0
Aphasia	7	7	0	0	7	0	0
Aphonia	0	0	3	3	3	0	0
Areflexia	1	1	0	0	1	0	0
Ataxia	1	1	0	0	1	0	0
Balance disorder	3	3	9	9	12	0	0
Basal ganglia infarction	1	1	0	0	1	0	0
Brain hypoxia	1	1	0	0	1	0	0
Brain injury	3	3	0	0	3	0	0
Brain oedema	3	3	1	1	4	0	0
Brain stem haemorrhage	1	1	0	0	1	0	0
Brain stem stroke	1	1	0	0	1	0	0
Burning sensation	0	0	10	10	10	0	0
Carotid arteriosclerosis	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Carotid artery disease	0	0	1	1	1	0	0
Carotid artery occlusion	9	9	0	0	9	0	0
Carotid artery stenosis	3	3	0	0	3	0	0
Carotid artery thrombosis	1	1	0	0	1	0	0
Central nervous system lesion	1	1	0	0	1	0	0
Central nervous system necrosis	1	1	0	0	1	0	0
Cerebellar haemorrhage	7	7	0	0	7	0	0
Cerebellar infarction	2	2	0	0	2	0	0
Cerebral haematoma	10	10	0	0	10	0	0
Cerebral haemorrhage	109	109	0	0	109	0	0
Cerebral infarction	0	0	0	0	0	1	1
Cerebral ischaemia	4	4	0	0	4	0	0
Cerebral thrombosis	1	1	0	0	1	0	0
Cerebrovascular accident	61	61	0	0	61	1	1
Cerebrovascular disorder	1	1	0	0	1	0	0
Cognitive disorder	1	1	1	1	2	0	0
Coma	19	19	0	0	19	0	0
Convulsion	10	10	0	0	10	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Coordination abnormal	0	0	2	2	2	0	0
Decreased vibratory sense	1	1	0	0	1	0	0
Dementia	1	1	1	1	2	0	0
Dementia Alzheimer's type	1	1	1	1	2	0	0
Depressed level of consciousness	5	5	0	0	5	0	0
Diabetic neuropathy	1	1	0	0	1	0	0
Diplegia	1	1	0	0	1	0	0
Disturbance in attention	1	1	5	5	6	0	0
Dizziness	46	46	171	171	217	13	13
Dizziness postural	0	0	2	2	2	0	0
Dysaesthesia	0	0	2	2	2	0	0
Dysarthria	1	1	1	1	2	1	1
Dysgeusia	1	1	14	14	15	0	0
Dysstasia	1	1	2	2	3	0	0
Embolic stroke	1	1	0	0	1	0	0
Encephalopathy	1	1	0	0	1	0	0
Epilepsy	1	1	0	0	1	0	0
Facial paresis	2	2	0	0	2	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Haemorrhage intracranial	87	87	0	0	87	0	0
Haemorrhagic cerebral infarction	1	1	0	0	1	0	0
Haemorrhagic stroke	30	30	0	0	30	0	0
Haemorrhagic transformation stroke	2	2	0	0	2	0	0
Head discomfort	1	1	7	7	8	0	0
Headache	24	24	108	108	132	4	4
Hemiparesis	5	5	1	1	6	0	0
Hemiplegia	9	9	0	0	9	0	0
Hydrocephalus	2	2	0	0	2	0	0
Hypersomnia	0	0	1	1	1	0	0
Hypoaesthesia	6	6	20	20	26	1	1
Hypokinesia	0	0	2	2	2	0	0
IIIrd nerve paresis	1	1	0	0	1	0	0
Intracranial aneurysm	3	3	0	0	3	0	0
Intracranial haematoma	3	3	0	0	3	0	0
Intracranial pressure increased	3	3	0	0	3	0	0
Intraventricular haemorrhage	4	4	0	0	4	0	0
Ischaemic stroke	13	13	0	0	13	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Lethargy	2	2	11	11	13	0	0
Loss of consciousness	23	23	1	1	24	3	3
Memory impairment	2	2	28	28	30	0	0
Mental impairment	0	0	6	6	6	0	0
Migraine	1	1	6	6	7	0	0
Monoplegia	1	1	0	0	1	0	0
Motor neurone disease	1	1	0	0	1	0	0
Movement disorder	0	0	1	1	1	0	0
Multiple sclerosis	0	0	1	1	1	0	0
Muscle spasticity	1	1	0	0	1	0	0
Myasthenia gravis	0	0	1	1	1	0	0
Nervous system disorder	4	4	0	0	4	0	0
Neuralgia	0	0	4	4	4	0	0
Neurological symptom	2	2	0	0	2	0	0
Neuropathy peripheral	2	2	4	4	6	0	0
Paraesthesia	11	11	18	18	29	1	1
Paralysis flaccid	1	1	0	0	1	0	0
Paresis	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Parkinson's disease	1	1	1	1	2	0	0
Parosmia	0	0	2	2	2	0	0
Petit mal epilepsy	0	0	1	1	1	0	0
Polyneuropathy	2	2	0	0	2	0	0
Presyncope	7	7	2	2	9	0	0
Psychomotor hyperactivity	1	1	0	0	1	0	0
Quadriplegia	1	1	0	0	1	0	0
Restless legs syndrome	0	0	3	3	3	0	0
Sedation	1	1	1	1	2	0	0
Senile dementia	1	1	0	0	1	0	0
Sensory disturbance	1	1	0	0	1	0	0
Sensory loss	2	2	2	2	4	0	0
Somnolence	2	2	22	22	24	0	0
Speech disorder	1	1	7	7	8	0	0
Spinal cord haemorrhage	1	1	0	0	1	0	0
Spinal haematoma	2	2	0	0	2	0	0
Subarachnoid haemorrhage	13	13	0	0	13	0	0
Syncope	37	37	8	8	45	1	1

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Tension headache	0	0	1	1	1	0	0
Thalamus haemorrhage	1	1	0	0	1	0	0
Thrombotic cerebral infarction	1	1	0	0	1	0	0
Tongue biting	1	1	1	1	2	0	0
Transient ischaemic attack	13	13	0	0	13	0	0
Tremor	4	4	11	11	15	0	0
Trigeminal neuralgia	1	1	2	2	3	0	0
Unresponsive to stimuli	8	8	0	0	8	0	0
VIIth nerve paralysis	1	1	1	1	2	0	0
VIth nerve paralysis	1	1	0	0	1	0	0
Eye disorders	**71**	**71**	**63**	**63**	**134**	**5**	**5**
Blepharospasm	0	0	1	1	1	0	0
Blindness	4	4	0	0	4	0	0
Blindness unilateral	1	1	0	0	1	0	0
Cataract	9	9	0	0	9	0	0
Conjunctival haemorrhage	3	3	6	6	9	0	0
Corneal endothelial cell loss	1	1	0	0	1	0	0
Diabetic eye disease							

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	1	1	0	0	1	0	0
Episcleritis	0	0	1	1	1	0	0
Excessive eye blinking	0	0	1	1	1	0	0
Eye disorder	1	1	6	6	7	0	0
Eye haemorrhage	18	18	8	8	26	4	4
Eye inflammation	0	0	1	1	1	0	0
Eye pain	0	0	2	2	2	0	0
Eye swelling	1	1	1	1	2	0	0
Eyelid bleeding	0	0	1	1	1	0	0
Eyelid disorder	0	0	1	1	1	0	0
Lacrimation increased	0	0	2	2	2	0	0
Mydriasis	1	1	1	1	2	0	0
Ocular discomfort	0	0	2	2	2	0	0
Ocular hyperaemia	0	0	4	4	4	0	0
Ocular icterus	0	0	0	0	0	1	1
Ocular ischaemic syndrome	1	1	0	0	1	0	0
Photophobia	1	1	1	1	2	0	0
Photopsia	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Pupil fixed	1	1	0	0	1	0	0
Pupils unequal	1	1	0	0	1	0	0
Retinal detachment	2	2	0	0	2	0	0
Retinal disorder	1	1	0	0	1	0	0
Retinal haemorrhage	7	7	0	0	7	0	0
Retinopathy	1	1	0	0	1	0	0
Scleral disorder	0	0	1	1	1	0	0
Scleral haemorrhage	1	1	1	1	2	0	0
Vision blurred	2	2	4	4	6	0	0
Visual acuity reduced	2	2	5	5	7	0	0
Visual impairment	8	8	10	10	18	0	0
Vitreous floaters	0	0	1	1	1	0	0
Vitreous haemorrhage	3	3	1	1	4	0	0
Ear and labyrinth disorders	**16**	**16**	**41**	**41**	**57**	**0**	**0**
Deafness	3	3	0	0	3	0	0
Deafness unilateral	2	2	0	0	2	0	0
Ear discomfort	0	0	2	2	2	0	0
Ear haemorrhage							

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	5	5	5	5	10	0	0
Ear swelling	1	1	1	1	2	0	0
Hearing impaired	0	0	4	4	4	0	0
Hypoacusis	1	1	5	5	6	0	0
Otorrhoea	0	0	1	1	1	0	0
Tinnitus	0	0	7	7	7	0	0
Vertigo	4	4	16	16	20	0	0
Cardiac disorders	**1095**	**1095**	**209**	**209**	**1304**	**20**	**20**
Acute coronary syndrome	24	24	1	1	25	0	0
Acute left ventricular failure	2	2	0	0	2	0	0
Acute myocardial infarction	81	81	0	0	81	12	12
Adams-Stokes syndrome	1	1	0	0	1	0	0
Angina pectoris	32	32	19	19	51	0	0
Angina unstable	12	12	0	0	12	0	0
Aortic valve disease	1	1	0	0	1	0	0
Aortic valve incompetence	1	1	1	1	2	0	0
Aortic valve sclerosis	0	0	1	1	1	0	0
Arrhythmia							

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	15	15	7	7	22	0	0
Arrhythmia supraventricular	1	1	0	0	1	0	0
Arteriosclerosis coronary artery	3	3	2	2	5	0	0
Atrial fibrillation	27	27	11	11	38	0	0
Atrial flutter	2	2	0	0	2	0	0
Atrial hypertrophy	0	0	1	1	1	0	0
Atrioventricular block	16	16	4	4	20	0	0
Atrioventricular block complete	23	23	0	0	23	0	0
Atrioventricular block first degree	3	3	1	1	4	0	0
Atrioventricular block second degree	9	9	0	0	9	0	0
Atrioventricular dissociation	3	3	0	0	3	0	0
Bradyarrhythmia	2	2	3	3	5	0	0
Bradycardia	63	63	55	55	118	0	0
Bundle branch block	1	1	0	0	1	0	0
Bundle branch block right	2	2	1	1	3	0	0
Cardiac aneurysm	1	1	0	0	1	0	0
Cardiac arrest	48	48	0	0	48	2	2
Cardiac discomfort	2	2	1	1	3	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Cardiac disorder	23	23	23	23	46	0	0
Cardiac failure	26	26	0	0	26	2	2
Cardiac failure acute	2	2	0	0	2	0	0
Cardiac failure chronic	1	1	0	0	1	0	0
Cardiac failure congestive	11	11	1	1	12	0	0
Cardiac fibrillation	2	2	0	0	2	0	0
Cardiac tamponade	9	9	0	0	9	0	0
Cardiac valve disease	1	1	0	0	1	0	0
Cardiac ventricular disorder	1	1	0	0	1	0	0
Cardiac ventricular thrombosis	1	1	0	0	1	0	0
Cardio-respiratory arrest	12	12	0	0	12	1	1
Cardiogenic shock	17	17	0	0	17	0	0
Cardiomegaly	1	1	0	0	1	0	0
Cardiomyopathy	1	1	3	3	4	0	0
Cardiovascular disorder	3	3	0	0	3	0	0
Cardiovascular insufficiency	1	1	0	0	1	0	0
Conduction disorder	1	1	0	0	1	0	0
Coronary artery disease	15	15	5	5	20	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Coronary artery dissection	5	5	0	0	5	0	0
Coronary artery insufficiency	2	2	0	0	2	0	0
Coronary artery occlusion	145	145	2	2	147	2	2
Coronary artery stenosis	10	10	2	2	12	0	0
Coronary artery thrombosis	14	14	0	0	14	0	0
Cyanosis	0	0	1	1	1	0	0
Diastolic dysfunction	1	1	1	1	2	0	0
Dilatation ventricular	1	1	0	0	1	0	0
Dressler's syndrome	1	1	0	0	1	0	0
Extrasystoles	5	5	4	4	9	0	0
Heart valve calcification	0	0	1	1	1	0	0
Heart valve incompetence	0	0	1	1	1	0	0
Hyperdynamic left ventricle	0	0	1	1	1	0	0
Hypertensive cardiomyopathy	1	1	0	0	1	0	0
Hypertensive heart disease	1	1	0	0	1	0	0
Intracardiac mass	1	1	0	0	1	0	0
Intracardiac thrombus	5	5	0	0	5	0	0
Ischaemic cardiomyopathy	2	2	0	0	2	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Left ventricular dysfunction	1	1	0	0	1	0	0
Left ventricular hypertrophy	1	1	0	0	1	0	0
Mitral valve calcification	0	0	1	1	1	0	0
Mitral valve disease	1	1	0	0	1	0	0
Mitral valve incompetence	3	3	3	3	6	0	0
Myocardial infarction	267	267	0	0	267	1	1
Myocardial ischaemia	9	9	0	0	9	0	0
Myocardial rupture	5	5	0	0	5	0	0
Nodal rhythm	2	2	0	0	2	0	0
Palpitations	3	3	29	29	32	0	0
Pericardial effusion	14	14	0	0	14	0	0
Pericardial haemorrhage	12	12	0	0	12	0	0
Pericarditis	6	6	0	0	6	0	0
Pulseless electrical activity	1	1	0	0	1	0	0
Rhythm idioventricular	3	3	0	0	3	0	0
Sick sinus syndrome	0	0	1	1	1	0	0
Sinoatrial block	2	2	0	0	2	0	0
Sinus arrest	14	14	2	2	16	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Sinus arrhythmia	1	1	0	0	1	0	0
Sinus bradycardia	8	8	1	1	9	0	0
Supraventricular extrasystoles	0	0	1	1	1	0	0
Supraventricular tachycardia	0	0	1	1	1	0	0
Systolic dysfunction	0	0	1	1	1	0	0
Tachyarrhythmia	2	2	0	0	2	0	0
Tachycardia	8	8	13	13	21	0	0
Torsade de pointes	2	2	0	0	2	0	0
Tricuspid valve disease	1	1	0	0	1	0	0
Ventricle rupture	1	1	0	0	1	0	0
Ventricular arrhythmia	2	2	1	1	3	0	0
Ventricular asystole	2	2	0	0	2	0	0
Ventricular dyssynchrony	1	1	0	0	1	0	0
Ventricular extrasystoles	4	4	2	2	6	0	0
Ventricular fibrillation	12	12	0	0	12	0	0
Ventricular hypokinesia	2	2	0	0	2	0	0
Ventricular tachyarrhythmia	1	1	0	0	1	0	0
Ventricular tachycardia	7	7	0	0	7	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Vascular disorders	**518**	**518**	**423**	**423**	**941**	**52**	**52**
Aneurysm	1	1	0	0	1	0	0
Angiodysplasia	1	1	0	0	1	0	0
Angiopathy	3	3	1	1	4	2	2
Aortic aneurysm	5	5	0	0	5	0	0
Aortic aneurysm rupture	1	1	0	0	1	0	0
Aortic arteriosclerosis	1	1	0	0	1	0	0
Aortic disorder	1	1	0	0	1	0	0
Aortic dissection	4	4	0	0	4	0	0
Aortic occlusion	3	3	0	0	3	0	0
Aortic stenosis	1	1	0	0	1	1	1
Aortic thrombosis	2	2	0	0	2	0	0
Arterial disorder	0	0	2	2	2	0	0
Arterial haemorrhage	2	2	1	1	3	0	0
Arterial occlusive disease	37	37	0	0	37	0	0
Arterial stenosis	1	1	0	0	1	0	0
Arterial thrombosis	1	1	0	0	1	0	0
Arteriosclerosis	1	1	2	2	3	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Arteritis	0	0	1	1	1	0	0
Bleeding varicose vein	0	0	0	0	0	1	1
Blood pressure fluctuation	1	1	10	10	11	0	0
Blood pressure inadequately controlled	0	0	3	3	3	0	0
Bloody discharge	1	1	0	0	1	0	0
Capillary fragility	0	0	4	4	4	0	0
Circulatory collapse	6	6	0	0	6	0	0
Deep vein thrombosis	6	6	0	0	6	0	0
Embolism	3	3	0	0	3	0	0
Essential hypertension	2	2	2	2	4	0	0
Extravasation blood	0	0	2	2	2	0	0
Flushing	2	2	12	12	14	0	0
Haematoma	44	44	150	150	194	1	1
Haemodynamic instability	10	10	0	0	10	0	0
Haemorrhage	173	173	133	133	306	45	45
Hot flush	1	1	3	3	4	0	0
Hypertension	18	18	38	38	56	1	1
Hypertensive crisis	4	4	0	0	4	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Hypotension	25	25	31	31	56	0	0
Hypovolaemic shock	2	2	0	0	2	0	0
Iliac artery occlusion	1	1	0	0	1	0	0
Infarction	22	22	0	0	22	0	0
Intermittent claudication	1	1	0	0	1	0	0
Intra-abdominal haematoma	2	2	0	0	2	0	0
Ischaemia	4	4	1	1	5	0	0
Labile blood pressure	0	0	1	1	1	0	0
Lymphoedema	0	0	1	1	1	0	0
Malignant hypertension	1	1	0	0	1	0	0
Orthostatic hypotension	3	3	1	1	4	0	0
Pallor	1	1	3	3	4	0	0
Pelvic venous thrombosis	1	1	0	0	1	0	0
Peripheral arterial occlusive disease	2	2	1	1	3	0	0
Peripheral artery thrombosis	3	3	0	0	3	0	0
Peripheral coldness	1	1	4	4	5	1	1
Peripheral embolism	2	2	1	1	3	0	0
Peripheral ischaemia	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Peripheral vascular disorder	1	1	1	1	2	0	0
Peripheral venous disease	0	0	1	1	1	0	0
Poor peripheral circulation	1	1	1	1	2	0	0
Raynaud's phenomenon	1	1	1	1	2	0	0
Shock	8	8	0	0	8	0	0
Shock haemorrhagic	8	8	0	0	8	0	0
Temporal arteritis	0	0	1	1	1	0	0
Thrombophlebitis	0	0	1	1	1	0	0
Thrombosis	50	50	4	4	54	0	0
Varicose vein	0	0	2	2	2	0	0
Vascular compression	1	1	0	0	1	0	0
Vascular occlusion	4	4	1	1	5	0	0
Vascular pain	0	0	1	1	1	0	0
Vascular rupture	1	1	0	0	1	0	0
Vascular stenosis	2	2	0	0	2	0	0
Vasculitis	2	2	0	0	2	0	0
Vasospasm	1	1	0	0	1	0	0
Venous haemorrhage	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Venous occlusion	24	24	0	0	24	0	0
Venous stenosis	1	1	0	0	1	0	0
Venous thrombosis	3	3	0	0	3	0	0
Venous thrombosis limb	2	2	0	0	2	0	0
Respiratory, thoracic and mediastinal disorders	**792**	**792**	**2631**	**2631**	**3423**	**83**	**83**
Acute interstitial pneumonitis	1	1	0	0	1	0	0
Acute lung injury	2	2	0	0	2	0	0
Acute pulmonary oedema	6	6	1	1	7	0	0
Acute respiratory distress syndrome	6	6	0	0	6	0	0
Acute respiratory failure	1	1	0	0	1	0	0
Allergic sinusitis	0	0	1	1	1	0	0
Alveolitis allergic	1	1	0	0	1	0	0
Anoxia	1	1	0	0	1	0	0
Apnoea	2	2	0	0	2	0	0
Apnoeic attack	0	0	1	1	1	1	1
Asphyxia	1	1	0	0	1	0	0
Aspiration	2	2	0	0	2	0	0
Asthma							

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	1	1	12	12	13	0	0
Asthmatic crisis	2	2	0	0	2	0	0
Atelectasis	0	0	1	1	1	0	0
Bronchospasm	7	7	2	2	9	0	0
Cheyne-Stokes respiration	2	2	0	0	2	0	0
Choking	2	2	0	0	2	0	0
Choking sensation	3	3	1	1	4	0	0
Chronic obstructive pulmonary disease	3	3	9	9	12	0	0
Cough	10	10	101	101	111	0	0
Diffuse panbronchiolitis	0	0	1	1	1	0	0
Dry throat	0	0	1	1	1	0	0
Dysphonia	2	2	6	6	8	0	0
Dyspnoea	455	455	2032	2032	2487	62	62
Dyspnoea at rest	5	5	13	13	18	0	0
Dyspnoea exertional	15	15	27	27	42	1	1
Dyspnoea paroxysmal nocturnal	3	3	6	6	9	0	0
Emphysema	2	2	1	1	3	0	0
Epiglottic oedema	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Epistaxis	81	81	273	273	354	13	13
Haemoptysis	23	23	16	16	39	3	3
Haemothorax	2	2	0	0	2	0	0
Hiccups	0	0	2	2	2	0	0
Hydrothorax	1	1	0	0	1	0	0
Hyperventilation	2	2	2	2	4	0	0
Hypopnoea	0	0	2	2	2	0	0
Hypoxia	5	5	1	1	6	0	0
Interstitial lung disease	3	3	1	1	4	0	0
Laryngeal oedema	2	2	0	0	2	0	0
Laryngospasm	1	1	0	0	1	0	0
Lung disorder	2	2	7	7	9	0	0
Lung infiltration	1	1	0	0	1	0	0
Lupus pneumonitis	0	0	1	1	1	0	0
Nasal congestion	0	0	4	4	4	0	0
Nasal discomfort	0	0	2	2	2	0	0
Nasal dryness	0	0	1	1	1	0	0
Nasal mucosal disorder	0	0	1	1	1	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Nocturnal dyspnoea	4	4	12	12	16	0	0
Oropharyngeal blistering	0	0	1	1	1	0	0
Oropharyngeal pain	0	0	7	7	7	0	0
Orthopnoea	2	2	6	6	8	0	0
Paranasal sinus discomfort	0	0	2	2	2	0	0
Pharyngeal haemorrhage	1	1	0	0	1	0	0
Pharyngeal oedema	3	3	4	4	7	1	1
Pleural adhesion	1	1	0	0	1	0	0
Pleural effusion	4	4	2	2	6	0	0
Pneumonia aspiration	4	4	0	0	4	0	0
Pneumonitis	1	1	0	0	1	0	0
Pneumothorax	1	1	0	0	1	0	0
Productive cough	0	0	2	2	2	0	0
Pulmonary alveolar haemorrhage	6	6	0	0	6	0	0
Pulmonary congestion	1	1	1	1	2	0	0
Pulmonary embolism	15	15	0	0	15	0	0
Pulmonary fibrosis	1	1	1	1	2	0	0
Pulmonary haematoma	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Pulmonary haemorrhage	20	20	0	0	20	0	0
Pulmonary hilar enlargement	1	1	0	0	1	0	0
Pulmonary hypertension	3	3	1	1	4	0	0
Pulmonary mass	0	0	2	2	2	0	0
Pulmonary oedema	28	28	2	2	30	0	0
Rales	0	0	2	2	2	0	0
Respiration abnormal	1	1	0	0	1	0	0
Respiratory arrest	2	2	0	0	2	1	1
Respiratory depression	2	2	0	0	2	0	0
Respiratory disorder	2	2	7	7	9	0	0
Respiratory distress	2	2	1	1	3	0	0
Respiratory failure	9	9	0	0	9	0	0
Respiratory tract congestion	0	0	1	1	1	0	0
Respiratory tract haemorrhage	0	0	1	1	1	0	0
Rhinorrhoea	0	0	5	5	5	0	0
Sinus congestion	0	0	1	1	1	0	0
Sinus disorder	1	1	2	2	3	0	0
Sleep apnoea syndrome	2	2	7	7	9	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Sneezing	0	0	3	3	3	0	0
Snoring	0	0	2	2	2	0	0
Sputum increased	0	0	1	1	1	0	0
Stridor	1	1	0	0	1	0	0
Suffocation feeling	3	3	5	5	8	0	0
Tachypnoea	5	5	3	3	8	0	0
Thoracic haemorrhage	2	2	0	0	2	0	0
Throat irritation	1	1	7	7	8	0	0
Throat tightness	1	1	3	3	4	1	1
Wheezing	2	2	8	8	10	0	0
Gastrointestinal disorders	**749**	**749**	**925**	**925**	**1674**	**63**	**63**
Abdominal compartment syndrome	1	1	0	0	1	0	0
Abdominal discomfort	2	2	44	44	46	0	0
Abdominal distension	3	3	11	11	14	0	0
Abdominal hernia	0	0	1	1	1	0	0
Abdominal pain	11	11	30	30	41	4	4
Abdominal pain upper	9	9	53	53	62	2	2
Abdominal symptom							

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	0	0	2	2	2	0	0
Abdominal wall haematoma	2	2	0	0	2	0	0
Abdominal wall haemorrhage	1	1	0	0	1	0	0
Acute abdomen	1	1	0	0	1	0	0
Anal fissure	0	0	3	3	3	0	0
Anal fistula	0	0	1	1	1	0	0
Anal haemorrhage	2	2	3	3	5	0	0
Anal inflammation	0	0	1	1	1	0	0
Anorectal discomfort	1	1	1	1	2	0	0
Aphagia	0	0	4	4	4	0	0
Ascites	1	1	0	0	1	0	0
Barrett's oesophagus	1	1	1	1	2	0	0
Bowel movement irregularity	0	0	2	2	2	0	0
Chapped lips	0	0	1	1	1	0	0
Cheilitis	0	0	3	3	3	0	0
Chronic gastritis	0	0	1	1	1	1	1
Chronic gastrointestinal bleeding	1	1	0	0	1	0	0
Colitis	0	0	1	1	1	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Colitis ischaemic	2	2	0	0	2	0	0
Colitis ulcerative	0	0	1	1	1	0	0
Constipation	2	2	30	30	32	0	0
Diabetic gastroparesis	1	1	0	0	1	0	0
Diarrhoea	15	15	97	97	112	3	3
Diarrhoea haemorrhagic	6	6	0	0	6	2	2
Diverticulitis intestinal haemorrhagic	3	3	0	0	3	0	0
Diverticulum	0	0	1	1	1	0	0
Diverticulum intestinal	3	3	2	2	5	0	0
Diverticulum intestinal haemorrhagic	2	2	0	0	2	0	0
Dry mouth	0	0	16	16	16	0	0
Duodenal polyp	0	0	1	1	1	0	0
Duodenal ulcer	6	6	2	2	8	0	0
Duodenal ulcer haemorrhage	4	4	0	0	4	1	1
Duodenitis	2	2	1	1	3	0	0
Dyschezia	0	0	1	1	1	0	0
Dyspepsia	5	5	32	32	37	2	2
Dysphagia	8	8	33	33	41	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Epigastric discomfort	0	0	4	4	4	0	0
Erosive duodenitis	3	3	1	1	4	0	0
Erosive oesophagitis	1	1	0	0	1	0	0
Eructation	0	0	4	4	4	0	0
Faecal incontinence	1	1	1	1	2	0	0
Faeces discoloured	8	8	10	10	18	0	0
Faeces hard	0	0	1	1	1	0	0
Flatulence	0	0	12	12	12	0	0
Frequent bowel movements	0	0	4	4	4	0	0
Gastric dilatation	0	0	1	1	1	0	0
Gastric disorder	2	2	13	13	15	0	0
Gastric haemorrhage	40	40	8	8	48	3	3
Gastric polyps	0	0	1	1	1	0	0
Gastric ulcer	5	5	8	8	13	1	1
Gastric ulcer haemorrhage	8	8	0	0	8	0	0
Gastritis	5	5	13	13	18	0	0
Gastritis erosive	3	3	1	1	4	0	0
Gastritis haemorrhagic	1	1	1	1	2	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Gastroduodenal haemorrhage	2	2	0	0	2	0	0
Gastroduodenitis	1	1	0	0	1	0	0
Gastrointestinal disorder	2	2	10	10	12	0	0
Gastrointestinal erosion	1	1	0	0	1	0	0
Gastrointestinal haemorrhage	231	231	16	16	247	10	10
Gastrointestinal inflammation	1	1	0	0	1	0	0
Gastrointestinal pain	0	0	1	1	1	0	0
Gastrointestinal polyp haemorrhage	0	0	0	0	0	2	2
Gastrointestinal ulcer haemorrhage	2	2	0	0	2	0	0
Gastrooesophageal reflux disease	0	0	17	17	17	0	0
Gingival bleeding	7	7	48	48	55	1	1
Gingival blister	0	0	1	1	1	0	0
Gingival disorder	0	0	1	1	1	0	0
Gingival erythema	0	0	1	1	1	0	0
Gingival hyperplasia	0	0	1	1	1	0	0
Gingival pain	0	0	1	1	1	0	0
Gingival ulceration	0	0	1	1	1	0	0
Glossodynia	0	0	2	2	2	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Haematemesis	36	36	0	0	36	1	1
Haematochezia	15	15	21	21	36	6	6
Haemorrhagic erosive gastritis	2	2	0	0	2	0	0
Haemorrhoidal haemorrhage	3	3	11	11	14	0	0
Haemorrhoids	3	3	6	6	9	0	0
Hiatus hernia	2	2	2	2	4	0	0
Hyperchlorhydria	0	0	1	1	1	0	0
Hypoaesthesia oral	1	1	2	2	3	0	0
Ileus	1	1	0	0	1	0	0
Inflammatory bowel disease	1	1	0	0	1	0	0
Inguinal hernia	1	1	0	0	1	0	0
Intestinal haemorrhage	10	10	1	1	11	3	3
Intestinal ischaemia	2	2	0	0	2	0	0
Intestinal obstruction	3	3	0	0	3	0	0
Intestinal perforation	1	1	0	0	1	0	0
Intestinal polyp	1	1	1	1	2	0	0
Intestinal ulcer	1	1	0	0	1	0	0
Intra-abdominal haemorrhage	4	4	0	0	4	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Irritable bowel syndrome	0	0	3	3	3	0	0
Large intestinal haemorrhage	3	3	0	0	3	0	0
Large intestinal stenosis	1	1	0	0	1	0	0
Large intestinal ulcer	1	1	0	0	1	0	0
Large intestinal ulcer haemorrhage	1	1	1	1	2	0	0
Large intestine polyp	2	2	0	0	2	0	0
Lip dry	0	0	1	1	1	0	0
Lip exfoliation	0	0	1	1	1	0	0
Lip haemorrhage	0	0	1	1	1	1	1
Lip oedema	1	1	2	2	3	0	0
Lip swelling	3	3	11	11	14	1	1
Loose tooth	0	0	1	1	1	0	0
Lower gastrointestinal haemorrhage	5	5	0	0	5	0	0
Mallory-Weiss syndrome	1	1	0	0	1	0	0
Melaena	40	40	8	8	48	0	0
Mouth haemorrhage	1	1	14	14	15	2	2
Mouth swelling	1	1	2	2	3	0	0
Mouth ulceration	0	0	4	4	4	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Nausea	23	23	157	157	180	4	4
Oedema mouth	0	0	3	3	3	0	0
Oesophageal haemorrhage	3	3	0	0	3	0	0
Oesophageal pain	0	0	1	1	1	0	0
Oesophageal rupture	1	1	0	0	1	0	0
Oesophageal spasm	1	1	0	0	1	0	0
Oesophageal ulcer	2	2	0	0	2	0	0
Oesophageal varices haemorrhage	2	2	0	0	2	0	0
Oesophagitis	2	2	3	3	5	0	0
Oral discomfort	0	0	2	2	2	0	0
Oral mucosal blistering	0	0	1	1	1	0	0
Oral mucosal eruption	0	0	2	2	2	0	0
Oral pain	1	1	1	1	2	0	0
Pancreatic mass	1	1	0	0	1	0	0
Pancreatitis	4	4	1	1	5	0	0
Pancreatitis acute	1	1	0	0	1	0	0
Paraesthesia oral	0	0	2	2	2	0	0
Peptic ulcer haemorrhage	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Peritoneal haemorrhage	3	3	0	0	3	0	0
Proctalgia	1	1	0	0	1	0	0
Rectal haemorrhage	65	65	10	10	75	6	6
Rectal polyp	1	1	0	0	1	0	0
Rectal ulcer	1	1	0	0	1	0	0
Reflux gastritis	0	0	1	1	1	0	0
Retching	1	1	2	2	3	0	0
Retroperitoneal haematoma	4	4	0	0	4	0	0
Retroperitoneal haemorrhage	9	9	0	0	9	0	0
Saliva discolouration	0	0	1	1	1	0	0
Salivary hypersecretion	0	0	1	1	1	0	0
Small intestinal haemorrhage	3	3	0	0	3	0	0
Small intestine ulcer	1	1	0	0	1	0	0
Stomach mass	0	0	1	1	1	0	0
Stomatitis	1	1	0	0	1	0	0
Swollen tongue	5	5	2	2	7	1	1
Teething	0	0	1	1	1	0	0
Tongue disorder	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Tongue eruption	0	0	1	1	1	0	0
Tongue exfoliation	0	0	1	1	1	0	0
Tongue haemorrhage	1	1	1	1	2	0	0
Tongue oedema	2	2	1	1	3	0	0
Tooth discolouration	0	0	1	1	1	0	0
Tooth disorder	1	1	2	2	3	0	0
Tooth erosion	1	1	0	0	1	0	0
Tooth loss	1	1	1	1	2	0	0
Toothache	0	0	3	3	3	0	0
Umbilical hernia	0	0	1	1	1	0	0
Upper gastrointestinal haemorrhage	24	24	0	0	24	2	2
Vomiting	16	16	63	63	79	4	4
Hepatobiliary disorders	**39**	**39**	**11**	**11**	**50**	**1**	**1**
Acute hepatic failure	1	1	0	0	1	0	0
Cholecystitis	4	4	0	0	4	0	0
Cholelithiasis	4	4	0	0	4	0	0
Chronic hepatitis	1	1	0	0	1	0	0
Drug-induced liver injury							

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	1	1	0	0	1	0	0
Gallbladder disorder	4	4	1	1	5	0	0
Hepatic failure	2	2	0	0	2	0	0
Hepatic fibrosis	1	1	0	0	1	0	0
Hepatic function abnormal	3	3	1	1	4	0	0
Hepatic haemorrhage	1	1	0	0	1	0	0
Hepatic necrosis	1	1	0	0	1	0	0
Hepatic pain	0	0	1	1	1	0	0
Hepatic steatosis	0	0	1	1	1	0	0
Hepatitis	3	3	0	0	3	0	0
Hepatitis cholestatic	1	1	0	0	1	0	0
Hepatitis fulminant	1	1	0	0	1	0	0
Hepatitis toxic	3	3	0	0	3	0	0
Hepatocellular injury	1	1	1	1	2	0	0
Hepatomegaly	0	0	1	1	1	0	0
Hepatotoxicity	1	1	0	0	1	0	0
Hydrocholecystis	1	1	0	0	1	0	0
Ischaemic hepatitis	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Liver disorder	2	2	5	5	7	0	0
Liver injury	1	1	0	0	1	1	1
Perihepatic discomfort	1	1	0	0	1	0	0
Skin and subcutaneous tissue disorders	**210**	**210**	**844**	**844**	**1054**	**12**	**12**
Acne	0	0	2	2	2	0	0
Actinic keratosis	0	0	1	1	1	0	0
Alopecia	0	0	20	20	20	0	0
Angioedema	12	12	4	4	16	0	0
Blister	1	1	4	4	5	0	0
Blood blister	2	2	4	4	6	0	0
Circumoral oedema	1	1	0	0	1	0	0
Cold sweat	0	0	8	8	8	0	0
Dermal cyst	1	1	0	0	1	0	0
Dermatitis	2	2	2	2	4	0	0
Dermatitis allergic	5	5	16	16	21	0	0
Dermatitis atopic	1	1	0	0	1	0	0
Dermatitis bullous	1	1	0	0	1	0	0
Dermatitis exfoliative							

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	4	4	0	0	4	0	0
Diabetic foot	1	1	0	0	1	0	0
Diabetic ulcer	1	1	0	0	1	0	0
Drug eruption	4	4	6	6	10	0	0
Drug reaction with eosinophilia and systemic symptoms	1	1	0	0	1	0	0
Dry skin	1	1	7	7	8	0	0
Ecchymosis	7	7	37	37	44	1	1
Eczema	2	2	6	6	8	0	0
Eczema asteatotic	0	0	1	1	1	0	0
Erythema	6	6	27	27	33	0	0
Erythema multiforme	1	1	0	0	1	0	0
Exfoliative rash	1	1	1	1	2	0	0
Generalised erythema	2	2	1	1	3	0	0
Haemorrhage subcutaneous	4	4	25	25	29	0	0
Hair colour changes	0	0	1	1	1	0	0
Hyperhidrosis	3	3	17	17	20	0	0
Hyperkeratosis	0	0	2	2	2	0	0
Hypersensitivity vasculitis	2	2	0	0	2	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Lichenoid keratosis	0	0	1	1	1	0	0
Lividity	0	0	1	1	1	0	0
Macule	0	0	2	2	2	0	0
Miliaria	0	0	2	2	2	0	0
Night sweats	0	0	4	4	4	0	0
Palmar erythema	1	1	0	0	1	0	0
Petechiae	5	5	37	37	42	1	1
Photosensitivity reaction	0	0	3	3	3	0	0
Pigmentation disorder	0	0	3	3	3	0	0
Polymorphic light eruption	0	0	1	1	1	0	0
Pruritus	22	22	93	93	115	0	0
Pruritus allergic	1	1	0	0	1	0	0
Pruritus generalised	9	9	15	15	24	0	0
Pseudofolliculitis barbae	0	0	1	1	1	0	0
Psoriasis	0	0	1	1	1	0	0
Purpura	4	4	18	18	22	1	1
Pyoderma gangrenosum	1	1	0	0	1	0	0
Rash	41	41	244	244	285	6	6

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Rash erythematous	3	3	8	8	11	0	0
Rash generalised	9	9	29	29	38	0	0
Rash macular	0	0	1	1	1	0	0
Rash maculo-papular	6	6	8	8	14	0	0
Rash morbilliform	0	0	1	1	1	0	0
Rash papular	0	0	2	2	2	0	0
Rash pruritic	7	7	23	23	30	0	0
Rash scarlatiniform	1	1	0	0	1	0	0
Rash vesicular	0	0	2	2	2	0	0
Rosacea	0	0	1	1	1	0	0
Scar pain	0	0	1	1	1	0	0
Skin atrophy	0	0	1	1	1	0	0
Skin burning sensation	1	1	1	1	2	0	0
Skin depigmentation	0	0	1	1	1	0	0
Skin discolouration	2	2	44	44	46	0	0
Skin disorder	0	0	5	5	5	0	0
Skin exfoliation	2	2	13	13	15	0	0
Skin fissures	0	0	1	1	1	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Skin fragility	0	0	1	1	1	0	0
Skin haemorrhage	5	5	14	14	19	1	1
Skin hyperpigmentation	0	0	1	1	1	0	0
Skin irritation	0	0	2	2	2	0	0
Skin odour abnormal	0	0	2	2	2	0	0
Skin plaque	0	0	1	1	1	0	0
Skin reaction	0	0	4	4	4	0	0
Skin swelling	0	0	1	1	1	0	0
Skin ulcer	0	0	1	1	1	0	0
Skin warm	0	0	1	1	1	0	0
Skin wrinkling	0	0	1	1	1	0	0
Stevens-Johnson syndrome	2	2	0	0	2	0	0
Swelling face	4	4	8	8	12	1	1
Telangiectasia	2	2	0	0	2	0	0
Toxic skin eruption	4	4	0	0	4	0	0
Urticaria	12	12	44	44	56	1	1
Urticaria chronic	0	0	2	2	2	0	0
Urticaria papular	0	0	1	1	1	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Musculoskeletal and connective tissue disorders	**109**	**109**	**258**	**258**	**367**	**2**	**2**
Arthralgia	8	8	29	29	37	0	0
Arthritis	1	1	6	6	7	0	0
Arthropathy	1	1	1	1	2	0	0
Back pain	8	8	28	28	36	0	0
Bone disorder	0	0	1	1	1	0	0
Bone pain	0	0	2	2	2	0	0
Bursitis	0	0	1	1	1	0	0
CREST syndrome	1	1	0	0	1	0	0
Connective tissue disorder	1	1	0	0	1	0	0
Costochondritis	0	0	1	1	1	0	0
Eosinophilic fasciitis	1	1	0	0	1	0	0
Fistula	2	2	1	1	3	0	0
Flank pain	1	1	1	1	2	0	0
Gouty arthritis	0	0	1	1	1	0	0
Groin pain	0	0	1	1	1	0	0
Haemarthrosis	3	3	6	6	9	0	0
Intervertebral disc disorder	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Intervertebral disc protrusion	2	2	1	1	3	0	0
Joint swelling	4	4	12	12	16	0	0
Kyphosis	1	1	0	0	1	0	0
Limb discomfort	0	0	4	4	4	0	0
Mobility decreased	0	0	3	3	3	0	0
Muscle atrophy	1	1	1	1	2	0	0
Muscle haemorrhage	6	6	3	3	9	0	0
Muscle spasms	3	3	19	19	22	0	0
Muscle twitching	0	0	1	1	1	0	0
Muscular weakness	7	7	15	15	22	0	0
Musculoskeletal chest pain	0	0	1	1	1	0	0
Musculoskeletal discomfort	2	2	4	4	6	0	0
Musculoskeletal disorder	0	0	4	4	4	0	0
Musculoskeletal pain	1	1	5	5	6	0	0
Musculoskeletal stiffness	2	2	1	1	3	0	0
Myalgia	8	8	38	38	46	0	0
Myopathy	2	2	0	0	2	0	0
Myositis	1	1	2	2	3	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Neck pain	0	0	5	5	5	0	0
Osteoarthritis	0	0	5	5	5	0	0
Osteochondrosis	1	1	0	0	1	0	0
Osteopenia	0	0	1	1	1	0	0
Osteoporosis	0	0	4	4	4	0	0
Pain in extremity	16	16	37	37	53	2	2
Pain in jaw	1	1	2	2	3	0	0
Polyarthritis	1	1	1	1	2	0	0
Polymyalgia rheumatica	0	0	1	1	1	0	0
Rhabdomyolysis	21	21	0	0	21	0	0
Rheumatic disorder	1	1	1	1	2	0	0
Rheumatoid arthritis	0	0	1	1	1	0	0
Soft tissue necrosis	1	1	0	0	1	0	0
Spinal pain	0	0	2	2	2	0	0
Synovial cyst	0	0	1	1	1	0	0
Systemic lupus erythematosus	0	0	1	1	1	0	0
Tendonitis	0	0	1	1	1	0	0
Wrist deformity	0	0	1	1	1	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Renal and urinary disorders	**211**	**211**	**116**	**116**	**327**	7	7
Anuria	3	3	0	0	3	0	0
Azotaemia	1	1	0	0	1	0	0
Bladder discomfort	0	0	1	1	1	0	0
Bladder tamponade	1	1	1	1	2	0	0
Calculus urinary	1	1	0	0	1	0	0
Chromaturia	1	1	2	2	3	1	1
Cystitis haemorrhagic	4	4	1	1	5	0	0
Cystitis interstitial	1	1	1	1	2	0	0
Dysuria	2	2	5	5	7	0	0
Enuresis	0	0	2	2	2	0	0
Focal segmental glomerulosclerosis	0	0	1	1	1	0	0
Glycosuria	1	1	0	0	1	0	0
Haematinuria	1	1	0	0	1	0	0
Haematuria	53	53	64	64	117	2	2
Haemorrhage urinary tract	9	9	6	6	15	1	1
Incontinence	1	1	0	0	1	0	0
Leukocyturia	0	0	1	1	1	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Loss of bladder sensation	0	0	1	1	1	0	0
Micturition urgency	1	1	0	0	1	0	0
Nephrolithiasis	1	1	1	1	2	0	0
Nephropathy	1	1	1	1	2	0	0
Nephropathy toxic	3	3	1	1	4	0	0
Nephrotic syndrome	2	2	0	0	2	0	0
Oliguria	0	0	1	1	1	0	0
Pollakiuria	0	0	3	3	3	0	0
Proteinuria	1	1	1	1	2	0	0
Renal artery stenosis	2	2	0	0	2	0	0
Renal colic	2	2	0	0	2	0	0
Renal cyst	3	3	0	0	3	0	0
Renal cyst haemorrhage	1	1	0	0	1	0	0
Renal disorder	5	5	2	2	7	0	0
Renal embolism	1	1	0	0	1	0	0
Renal failure	26	26	3	3	29	0	0
Renal failure acute	30	30	0	0	30	0	0
Renal haemorrhage	2	2	0	0	2	1	1

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Renal impairment	13	13	4	4	17	0	0
Renal injury	2	2	0	0	2	0	0
Renal mass	1	1	0	0	1	0	0
Renal pain	0	0	1	1	1	0	0
Renal tubular necrosis	2	2	0	0	2	0	0
Renal vein thrombosis	1	1	0	0	1	0	0
Stress urinary incontinence	0	0	1	1	1	0	0
Tubulointerstitial nephritis	1	1	0	0	1	0	0
Urate nephropathy	0	0	1	1	1	0	0
Urethral haemorrhage	2	2	1	1	3	0	0
Urethral pain	1	1	0	0	1	0	0
Urethral perforation	1	1	0	0	1	0	0
Urethritis noninfective	1	1	0	0	1	0	0
Urge incontinence	1	1	0	0	1	0	0
Urinary bladder haemorrhage	17	17	1	1	18	2	2
Urinary incontinence	2	2	3	3	5	0	0
Urinary retention	4	4	1	1	5	0	0
Urine flow decreased	0	0	1	1	1	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Urine odour abnormal	0	0	1	1	1	0	0
Urogenital haemorrhage	2	2	2	2	4	0	0
Pregnancy, puerperium and perinatal conditions	**1**	**1**	**0**	**0**	**1**	**0**	**0**
Cephalhaematoma	1	1	0	0	1	0	0
Reproductive system and breast disorders	**28**	**28**	**47**	**47**	**75**	**3**	**3**
Benign prostatic hyperplasia	1	1	4	4	5	0	0
Breast discomfort	0	0	1	1	1	0	0
Breast disorder female	0	0	1	1	1	0	0
Breast enlargement	0	0	1	1	1	0	0
Breast haematoma	0	0	1	1	1	0	0
Breast mass	1	1	0	0	1	0	0
Breast pain	0	0	1	1	1	0	0
Breast swelling	0	0	1	1	1	0	0
Erectile dysfunction	0	0	2	2	2	0	0
Erection increased	0	0	1	1	1	0	0
Genital haemorrhage	1	1	0	0	1	0	0
Gynaecomastia	1	1	3	3	4	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Haematospermia	0	0	4	4	4	0	0
Male genital tract fistula	0	0	1	1	1	0	0
Menorrhagia	3	3	11	11	14	1	1
Menstrual disorder	0	0	1	1	1	0	0
Metrorrhagia	2	2	0	0	2	0	0
Organic erectile dysfunction	0	0	1	1	1	0	0
Penile haemorrhage	1	1	1	1	2	1	1
Prostatic haemorrhage	1	1	0	0	1	0	0
Prostatomegaly	5	5	1	1	6	0	0
Scrotal oedema	1	1	0	0	1	0	0
Testicular haemorrhage	0	0	1	1	1	0	0
Uterine disorder	1	1	0	0	1	0	0
Uterine haemorrhage	2	2	2	2	4	1	1
Vaginal disorder	0	0	1	1	1	0	0
Vaginal haemorrhage	5	5	5	5	10	0	0
Vulvovaginal burning sensation	1	1	0	0	1	0	0
Vulvovaginal dryness	0	0	1	1	1	0	0
Vulvovaginal pain	1	1	1	1	2	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Vulvovaginal pruritus	1	1	0	0	1	0	0
Congenital, familial and genetic disorders	**2**	**2**	**1**	**1**	**3**	**0**	**0**
Epidermolysis	1	1	0	0	1	0	0
Gastrointestinal malformation	1	1	0	0	1	0	0
Multiple lentigines syndrome	0	0	1	1	1	0	0
General disorders and administration site conditions	**923**	**923**	**888**	**888**	**1811**	77	77
Abasia	3	3	1	1	4	0	0
Adverse drug reaction	1	1	13	13	14	3	3
Adverse event	10	10	52	52	62	0	0
Adverse reaction	1	1	2	2	3	0	0
Apparent death	3	3	0	0	3	0	0
Application site haemorrhage	1	1	1	1	2	0	0
Arterial restenosis	14	14	1	1	15	0	0
Asthenia	12	12	62	62	74	1	1
Atrophy	1	1	0	0	1	0	0
Brain death	6	6	0	0	6	0	0
Catheter site bruise	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Catheter site haematoma	2	2	1	1	3	0	0
Catheter site haemorrhage	7	7	3	3	10	0	0
Chest discomfort	10	10	38	38	48	2	2
Chest pain	83	83	85	85	168	9	9
Chills	0	0	3	3	3	0	0
Condition aggravated	11	11	2	2	13	0	0
Coronary artery restenosis	20	20	0	0	20	0	0
Crying	0	0	4	4	4	0	0
Death	131	131	0	0	131	51	51
Device dislocation	1	1	0	0	1	0	0
Device malfunction	2	2	0	0	2	0	0
Device material issue	1	1	0	0	1	0	0
Device occlusion	55	55	1	1	56	1	1
Diapedesis	0	0	1	1	1	0	0
Discomfort	4	4	20	20	24	0	0
Disease progression	1	1	0	0	1	0	0
Drug effect decreased	3	3	0	0	3	0	0
Drug effect delayed	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Drug effect incomplete	0	0	2	2	2	1	1
Drug ineffective	29	29	30	30	59	2	2
Drug ineffective for unapproved indication	0	0	3	3	3	0	0
Drug interaction	54	54	27	27	81	0	0
Drug intolerance	0	0	22	22	22	1	1
Drug resistance	1	1	2	2	3	0	0
Drug therapeutic incompatibility	1	1	0	0	1	0	0
Drug tolerance decreased	0	0	1	1	1	0	0
Drug withdrawal syndrome	0	0	1	1	1	0	0
Effusion	2	2	1	1	3	0	0
Exercise tolerance decreased	1	1	4	4	5	0	0
Extravasation	0	0	3	3	3	0	0
Face oedema	0	0	3	3	3	0	0
Facial pain	0	0	2	2	2	0	0
Fatigue	25	25	138	138	163	1	1
Feeling abnormal	5	5	46	46	51	0	0
Feeling cold	3	3	3	3	6	0	0
Feeling hot	0	0	8	8	8	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Feeling jittery	0	0	2	2	2	0	0
Feeling of body temperature change	0	0	1	1	1	0	0
Fibrosis	1	1	0	0	1	0	0
Food interaction	0	0	1	1	1	0	0
Gait disturbance	7	7	27	27	34	0	0
General physical health deterioration	4	4	2	2	6	0	0
Generalised oedema	0	0	2	2	2	0	0
Gravitational oedema	1	1	0	0	1	0	0
Hernia	1	1	1	1	2	0	0
Hypothermia	0	0	1	1	1	0	0
Ill-defined disorder	0	0	2	2	2	0	0
Impaired healing	2	2	1	1	3	0	0
Implant site fibrosis	1	1	0	0	1	0	0
Implant site haemorrhage	2	2	1	1	3	0	0
Implant site pain	0	0	1	1	1	0	0
Induration	0	0	1	1	1	0	0
Inflammation	2	2	2	2	4	0	0
Influenza like illness	0	0	3	3	3	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Infusion site haemorrhage	0	0	1	1	1	0	0
Injection site bruising	1	1	0	0	1	0	0
Injection site haematoma	2	2	4	4	6	0	0
Injection site haemorrhage	2	2	4	4	6	0	0
Injection site joint effusion	0	0	1	1	1	0	0
Injection site mass	0	0	1	1	1	0	0
Injection site nodule	0	0	1	1	1	0	0
Injection site pain	0	0	2	2	2	0	0
Local swelling	1	1	0	0	1	0	0
Localised oedema	0	0	2	2	2	0	0
Malaise	27	27	111	111	138	0	0
Mass	0	0	3	3	3	0	0
Medical device complication	1	1	0	0	1	0	0
Multi-organ failure	15	15	0	0	15	0	0
No adverse event	0	0	1	1	1	0	0
No therapeutic response	1	1	2	2	3	0	0
Nodule	0	0	3	3	3	0	0
Non-cardiac chest pain	0	0	2	2	2	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Oedema	3	3	11	11	14	0	0
Oedema mucosal	1	1	0	0	1	0	0
Oedema peripheral	4	4	9	9	13	0	0
Pain	9	9	41	41	50	0	0
Patient-device incompatibility	1	1	0	0	1	0	0
Peripheral swelling	9	9	19	19	28	0	0
Polyp	3	3	0	0	3	0	0
Potentiating drug interaction	2	2	0	0	2	0	0
Product odour abnormal	0	0	1	1	1	0	0
Puncture site discharge	0	0	1	1	1	0	0
Puncture site haemorrhage	1	1	2	2	3	0	0
Pyrexia	5	5	10	10	15	1	1
Rebound effect	0	0	1	1	1	0	0
Sluggishness	0	0	1	1	1	0	0
Stent malfunction	0	0	1	1	1	0	0
Submandibular mass	0	0	1	1	1	0	0
Sudden cardiac death	1	1	0	0	1	0	0
Sudden death	4	4	0	0	4	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Suprapubic pain	1	1	0	0	1	0	0
Swelling	1	1	11	11	12	0	0
Systemic inflammatory response syndrome	1	1	0	0	1	0	0
Temperature intolerance	0	0	1	1	1	0	0
Terminal state	1	1	0	0	1	0	0
Therapeutic response changed	0	0	2	2	2	0	0
Therapeutic response decreased	1	1	0	0	1	0	0
Therapeutic response increased	1	1	0	0	1	0	0
Thrombosis in device	288	288	0	0	288	0	0
Ulcer	3	3	0	0	3	0	0
Ulcer haemorrhage	5	5	2	2	7	2	2
Unevaluable event	1	1	0	0	1	0	0
Vessel puncture site haematoma	1	1	1	1	2	1	1
Vessel puncture site haemorrhage	0	0	0	0	0	1	1
Investigations	**318**	**318**	**537**	**537**	**855**	**8**	**8**
Activated partial thromboplastin time abnormal	1	1	0	0	1	0	0
Activated partial thromboplastin time prolonged	1	1	1	1	2	0	0
Alanine aminotransferase increased							

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	3	3	7	7	10	0	0
Amphetamines positive	0	0	1	1	1	0	0
Amylase increased	0	0	1	1	1	0	0
Antineutrophil cytoplasmic antibody positive	1	1	0	0	1	0	0
Arteriogram coronary abnormal	1	1	0	0	1	0	0
Aspartate aminotransferase increased	1	1	6	6	7	0	0
Bleeding time prolonged	1	1	9	9	10	3	3
Blood alkaline phosphatase increased	0	0	1	1	1	0	0
Blood bilirubin increased	2	2	0	0	2	0	0
Blood cholesterol abnormal	0	0	5	5	5	0	0
Blood cholesterol decreased	0	0	5	5	5	0	0
Blood cholesterol increased	0	0	45	45	45	0	0
Blood count abnormal	1	1	0	0	1	0	0
Blood creatine increased	0	0	4	4	4	0	0
Blood creatine phosphokinase increased	5	5	6	6	11	0	0
Blood creatinine increased	17	17	26	26	43	0	0
Blood gases abnormal	1	1	0	0	1	0	0
Blood glucose abnormal	0	0	1	1	1	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Blood glucose decreased	0	0	4	4	4	0	0
Blood glucose fluctuation	1	1	2	2	3	0	0
Blood glucose increased	4	4	15	15	19	0	0
Blood insulin increased	0	0	1	1	1	0	0
Blood iron decreased	1	1	2	2	3	0	0
Blood lactate dehydrogenase increased	1	1	0	0	1	0	0
Blood potassium decreased	0	0	1	1	1	0	0
Blood potassium increased	0	0	3	3	3	0	0
Blood pressure abnormal	1	1	5	5	6	0	0
Blood pressure decreased	10	10	4	4	14	0	0
Blood pressure immeasurable	1	1	0	0	1	0	0
Blood pressure increased	9	9	20	20	29	1	1
Blood pressure systolic decreased	1	1	0	0	1	0	0
Blood pressure systolic increased	0	0	3	3	3	0	0
Blood test abnormal	0	0	3	3	3	0	0
Blood testosterone decreased	0	0	2	2	2	0	0
Blood thyroid stimulating hormone increased	0	0	1	1	1	0	0
Blood triglycerides decreased	0	0	1	1	1	0	0

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System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Blood triglycerides increased	1	1	12	12	13	0	0
Blood urea abnormal	0	0	1	1	1	0	0
Blood urea increased	1	1	3	3	4	0	0
Blood uric acid increased	2	2	11	11	13	0	0
Blood urine present	9	9	14	14	23	3	3
Body height decreased	0	0	2	2	2	0	0
Body mass index increased	0	0	1	1	1	0	0
Body temperature decreased	1	1	0	0	1	0	0
Body temperature increased	0	0	1	1	1	0	0
Bone density decreased	0	0	1	1	1	0	0
Brain natriuretic peptide increased	1	1	0	0	1	0	0
Breath sounds abnormal	0	0	1	1	1	0	0
C-reactive protein increased	2	2	4	4	6	0	0
CSF glucose increased	1	1	0	0	1	0	0
CSF protein increased	1	1	0	0	1	0	0
CSF white blood cell count increased	1	1	0	0	1	0	0
Cardiac imaging procedure abnormal	1	1	0	0	1	0	0
Cardiac murmur	1	1	0	0	1	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Cardiac stress test abnormal	1	1	1	1	2	0	0
Catheterisation cardiac abnormal	0	0	0	0	0	1	1
Chest X-ray abnormal	1	1	0	0	1	0	0
Coagulation test abnormal	1	1	1	1	2	0	0
Coagulation time prolonged	1	1	1	1	2	0	0
Coma scale abnormal	1	1	0	0	1	0	0
Creatinine renal clearance decreased	2	2	0	0	2	0	0
Creatinine renal clearance increased	0	0	2	2	2	0	0
Culture stool positive	1	1	0	0	1	0	0
Drug level below therapeutic	0	0	1	1	1	0	0
Drug level changed	0	0	1	1	1	0	0
Drug level increased	2	2	1	1	3	0	0
Drug screen false positive	0	0	1	1	1	0	0
Ejection fraction decreased	6	6	2	2	8	0	0
Electrocardiogram PR prolongation	2	2	0	0	2	0	0
Electrocardiogram QT prolonged	4	4	0	0	4	0	0
Electrocardiogram ST segment abnormal	1	1	0	0	1	0	0
Electrocardiogram ST segment depression	1	1	0	0	1	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Electrocardiogram ST segment elevation	7	7	1	1	8	0	0
Electrocardiogram T wave inversion	1	1	0	0	1	0	0
Electrocardiogram abnormal	26	26	6	6	32	0	0
Electrocardiogram change	1	1	0	0	1	0	0
Electrocardiogram repolarisation abnormality	1	1	0	0	1	0	0
Enzyme activity abnormal	1	1	0	0	1	0	0
Enzyme level increased	2	2	0	0	2	0	0
Eosinophil count increased	0	0	2	2	2	0	0
Exercise test abnormal	1	1	1	1	2	0	0
Full blood count decreased	1	1	0	0	1	0	0
Gamma-glutamyltransferase increased	0	0	4	4	4	0	0
Gastric pH increased	0	0	1	1	1	0	0
General physical condition abnormal	0	0	1	1	1	0	0
Glomerular filtration rate decreased	1	1	1	1	2	0	0
Glycosylated haemoglobin increased	0	0	2	2	2	0	0
Haematocrit decreased	11	11	4	4	15	0	0
Haematocrit increased	0	0	1	1	1	0	0
Haemoglobin abnormal	4	4	0	0	4	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Haemoglobin decreased	51	51	17	17	68	0	0
Haemoglobin increased	0	0	1	1	1	0	0
Heart rate abnormal	1	1	1	1	2	0	0
Heart rate decreased	7	7	10	10	17	0	0
Heart rate increased	5	5	20	20	25	0	0
Heart rate irregular	1	1	5	5	6	0	0
Hepatic enzyme abnormal	0	0	2	2	2	0	0
Hepatic enzyme increased	7	7	11	11	18	0	0
High density lipoprotein increased	0	0	1	1	1	0	0
Inflammatory marker increased	1	1	0	0	1	0	0
International normalised ratio increased	3	3	3	3	6	0	0
Intra-abdominal pressure increased	0	0	1	1	1	0	0
Intraocular pressure increased	0	0	1	1	1	0	0
Investigation abnormal	0	0	1	1	1	0	0
Laboratory test abnormal	0	0	1	1	1	0	0
Lipids increased	0	0	1	1	1	0	0
Liver function test abnormal	6	6	9	9	15	0	0
Low density lipoprotein decreased	0	0	1	1	1	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Low density lipoprotein increased	0	0	2	2	2	0	0
Medication residue present	0	0	4	4	4	0	0
Myocardial necrosis marker increased	2	2	1	1	3	0	0
Occult blood positive	2	2	0	0	2	0	0
Oxygen saturation decreased	4	4	2	2	6	0	0
Plasma viscosity decreased	0	0	2	2	2	0	0
Platelet aggregation abnormal	0	0	4	4	4	0	0
Platelet aggregation decreased	0	0	2	2	2	0	0
Platelet aggregation increased	1	1	1	1	2	0	0
Platelet count decreased	15	15	11	11	26	0	0
Platelet count increased	4	4	8	8	12	0	0
Platelet function test abnormal	2	2	5	5	7	0	0
Pneumocystis test positive	1	1	0	0	1	0	0
Prostatic specific antigen abnormal	1	1	0	0	1	0	0
Prostatic specific antigen increased	1	1	1	1	2	0	0
Protein C decreased	0	0	1	1	1	0	0
Prothrombin time prolonged	2	2	1	1	3	0	0
Pulmonary function test decreased	0	0	1	1	1	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Pulse abnormal	0	0	1	1	1	0	0
Red blood cell count decreased	1	1	1	1	2	0	0
Red blood cell count increased	0	0	1	1	1	0	0
Red blood cell sedimentation rate increased	0	0	1	1	1	0	0
Red cell distribution width increased	0	0	1	1	1	0	0
Respiratory rate increased	0	0	2	2	2	0	0
Serum ferritin decreased	0	0	2	2	2	0	0
Serum ferritin increased	0	0	2	2	2	0	0
Spermatozoa abnormal	0	0	1	1	1	0	0
Staphylococcus test positive	0	0	1	1	1	0	0
Thyroid function test abnormal	0	0	2	2	2	0	0
Transaminases increased	6	6	5	5	11	0	0
Troponin increased	6	6	3	3	9	0	0
Urine output decreased	1	1	0	0	1	0	0
Vitamin D decreased	0	0	3	3	3	0	0
Volume blood decreased	1	1	0	0	1	0	0
Waist circumference increased	0	0	1	1	1	0	0
Weight decreased	12	12	79	79	91	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Weight increased	5	5	23	23	28	0	0
White blood cell count decreased	0	0	2	2	2	0	0
White blood cell count increased	2	2	3	3	5	0	0
Injury, poisoning and procedural complications	**326**	**326**	**394**	**394**	**720**	**11**	**11**
Accident	1	1	0	0	1	0	0
Accidental overdose	2	2	0	0	2	0	0
Alcohol poisoning	0	0	1	1	1	0	0
Anastomotic ulcer haemorrhage	1	1	0	0	1	0	0
Ankle fracture	2	2	0	0	2	0	0
Arterial injury	1	1	0	0	1	0	0
Arthropod bite	0	0	2	2	2	0	0
Arthropod sting	0	0	1	1	1	0	0
Brain herniation	4	4	0	0	4	0	0
Burn oesophageal	0	0	1	1	1	0	0
Circumstance or information capable of leading to medication error	3	3	7	7	10	0	0
Clavicle fracture	0	0	1	1	1	0	0
Contrast media reaction	1	1	0	0	1	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Contusion	18	18	193	193	211	5	5
Coronary artery reocclusion	1	1	0	0	1	0	0
Counterfeit drug administered	0	0	1	1	1	0	0
Craniocerebral injury	2	2	0	0	2	0	0
Drug administration error	0	0	2	2	2	0	0
Drug dispensing error	1	1	0	0	1	0	0
Drug dose omission	57	57	77	77	134	0	0
Drug prescribing error	2	2	4	4	6	0	0
Endotracheal intubation complication	1	1	0	0	1	0	0
Expired product administered	1	1	1	1	2	0	0
Extra dose administered	2	2	2	2	4	0	0
Extradural haematoma	2	2	0	0	2	0	0
Eye contusion	0	0	1	1	1	0	0
Face injury	1	1	2	2	3	0	0
Fall	35	35	16	16	51	0	0
Feeding tube complication	1	1	0	0	1	0	0
Femoral neck fracture	1	1	0	0	1	0	0
Femur fracture	1	1	0	0	1	0	0

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	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Fracture	0	0	1	1	1	0	0
Fractured coccyx	1	1	0	0	1	0	0
Gastrointestinal injury	1	1	0	0	1	0	0
Graft overgrowth	1	1	0	0	1	0	0
Graft thrombosis	1	1	0	0	1	0	0
Gun shot wound	1	1	0	0	1	0	0
Head injury	5	5	1	1	6	0	0
Heat exhaustion	0	0	1	1	1	0	0
Heat stroke	1	1	0	0	1	0	0
Hepatic haematoma	2	2	0	0	2	0	0
Hip fracture	2	2	0	0	2	0	0
Inappropriate schedule of drug administration	1	1	5	5	6	0	0
Incision site haemorrhage	1	1	0	0	1	0	0
Incorrect dosage administered	0	0	1	1	1	0	0
Incorrect dose administered	2	2	11	11	13	0	0
Injury	2	2	2	2	4	0	0
Joint dislocation	1	1	0	0	1	0	0
Joint injury	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Labelled drug-drug interaction medication error	1	1	0	0	1	0	0
Laceration	0	0	3	3	3	0	0
Limb injury	2	2	4	4	6	0	0
Lower limb fracture	2	2	0	0	2	0	0
Medication error	2	2	4	4	6	0	0
Meniscus injury	1	1	0	0	1	0	0
Multiple fractures	1	1	1	1	2	0	0
Multiple injuries	2	2	0	0	2	0	0
Muscle strain	0	0	1	1	1	0	0
Overdose	2	2	1	1	3	0	0
Periorbital contusion	1	1	1	1	2	0	0
Periorbital haematoma	1	1	0	0	1	0	0
Post procedural complication	2	2	0	0	2	0	0
Post procedural haematoma	4	4	1	1	5	0	0
Post procedural haemorrhage	32	32	6	6	38	1	1
Post procedural stroke	1	1	0	0	1	0	0
Post procedural swelling	1	1	0	0	1	0	0
Postoperative wound complication	0	0	0	0	0	1	1

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Procedural anxiety	0	0	1	1	1	0	0
Procedural haemorrhage	16	16	0	0	16	1	1
Renal haematoma	1	1	0	0	1	0	0
Reocclusion	2	2	0	0	2	0	0
Road traffic accident	3	3	1	1	4	1	1
Sciatic nerve injury	1	1	0	0	1	0	0
Scratch	0	0	2	2	2	0	0
Scrotal haematoma	0	0	1	1	1	0	0
Skeletal injury	1	1	0	0	1	0	0
Skin abrasion	0	0	2	2	2	0	0
Skull fracture	1	1	0	0	1	0	0
Spinal fracture	3	3	0	0	3	0	0
Splenic haematoma	1	1	0	0	1	0	0
Splenic rupture	1	1	0	0	1	0	0
Subcutaneous haematoma	4	4	13	13	17	0	0
Subdural haematoma	30	30	0	0	30	0	0
Subdural haemorrhage	12	12	0	0	12	0	0
Sunburn	0	0	1	1	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Tendon rupture	1	1	1	1	2	0	0
Testicular injury	1	1	0	0	1	0	0
Tooth fracture	0	0	2	2	2	0	0
Toxicity to various agents	1	1	0	0	1	0	0
Tracheal injury	1	1	0	0	1	0	0
Traumatic haematoma	1	1	0	0	1	0	0
Traumatic haemorrhage	3	3	2	2	5	1	1
Traumatic intracranial haemorrhage	1	1	0	0	1	0	0
Traumatic lung injury	1	1	0	0	1	0	0
Upper limb fracture	1	1	0	0	1	0	0
Urethral injury	2	2	0	0	2	0	0
Vascular graft occlusion	6	6	0	0	6	0	0
Vascular pseudoaneurysm	5	5	0	0	5	0	0
Wound	1	1	2	2	3	0	0
Wound haemorrhage	4	4	6	6	10	1	1
Wound secretion	1	1	1	1	2	0	0
Wrong drug administered	2	2	0	0	2	0	0
Wrong technique in drug usage process	0	0	2	2	2	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

System Organ Class Preferred Term	Spontaneous, including regulatory authority and literature				Total Spontaneous	Non-interventional post-marketing study	
	Serious		Non-serious			Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Surgical and medical procedures	**53**	**53**	**405**	**405**	**458**	**1**	**1**
Intentional product misuse	34	34	106	106	140	1	1
Off label use	6	6	281	281	287	0	0
Oral surgery	0	0	1	1	1	0	0
Product used for unknown indication	0	0	1	1	1	0	0
Surgery	0	0	1	1	1	0	0
Therapy cessation	13	13	14	14	27	0	0
Weight loss diet	0	0	1	1	1	0	0
Social circumstances	**5**	**5**	**21**	**21**	**26**	**0**	**0**
Activities of daily living impaired	3	3	12	12	15	0	0
Disability	1	1	0	0	1	0	0
Impaired driving ability	0	0	1	1	1	0	0
Impaired work ability	0	0	1	1	1	0	0
Refusal of treatment by patient	0	0	1	1	1	0	0
Stress at work	0	0	1	1	1	0	0
Treatment noncompliance	0	0	5	5	5	0	0
Walking disability	1	1	0	0	1	0	0

Table 2 - Number of Adverse Reactions by Term from Post Marketing Sources

Listing of MedDRA SOCs in the Internationally Agreed Order

MedDRA Version : 17.1

Infections and infestations
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Blood and lymphatic system disorders
Immune system disorders
Endocrine disorders
Metabolism and nutrition disorders
Psychiatric disorders
Nervous system disorders
Eye disorders
Ear and labyrinth disorders
Cardiac disorders
Vascular disorders
Respiratory, thoracic and mediastinal disorders
Gastrointestinal disorders
Hepatobiliary disorders
Skin and subcutaneous tissue disorders
Musculoskeletal and connective tissue disorders
Renal and urinary disorders
Pregnancy, puerperium and perinatal conditions
Reproductive system and breast disorders
Congenital, familial and genetic disorders
General disorders and administration site conditions
Investigations
Injury, poisoning and procedural complications
Surgical and medical procedures
Social circumstances

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Addendum to the Clinical Overview Appendix 4

Medicinal Product(s)	Ticagrelor
Period covered	3 December 2010 to 8 November 2014
Date	16 January 2015

Appendix 4

History of Pharmacovigilance Inspections

Table 1 History of pharmacovigilance inspections for ticagrelor

Date(s) of inspection	Inspecting regulatory authority(ies)	Site(s) inspected	Type of inspection	List of products concerned (if product-specific inspection)	Impact
Jun 2011	OGYI (National Institute of Pharmacy, Hungary)	AZ Hungary	Pharmacovigilance	All	The inspection findings had no impact on the benefit-risk of AstraZeneca products
Jan 2012	Health Canada	AZ Canada	Pharmacovigilance	All	No findings
Feb 2012	SUKL (Czech Republic)	AZ Czech Republic	Pharmacovigilance	All	The inspection findings had no impact on the benefit-risk of AstraZeneca products
Jun 2012	US FDA	AZ USA	Risk Evaluation and Mitigation Strategy (REMS)	Caprelsa	No findings
Jun 2012	Austrian Health Authority	AZ Austria	GXP/Pharmacovigilance	All	No findings applicable
Sep 2012	US FDA	AZ USA	Pharmacovigilance	All	No findings
Dec 2012	Osaka Prefectural (Japan)	AZ Japan	GVP/GQP	Bydureon	The inspection findings had no impact on the benefit-risk of AstraZeneca products
Dec 2012 – Jan 2013	MPA Sweden	AZ Sweden AZ Hungary TCS (Outsource case handler) Hungary	Pharmacovigilance	All	The inspection findings had no impact on the benefit-risk of AstraZeneca products
Apr 2013	DHMA Denmark	AZ Denmark	Pharmacovigilance	All	The inspection findings had no impact on the benefit-risk of AstraZeneca products
Apr 2013	Bulgarian Drug Agency	AZ Bulgaria	Pharmacovigilance	All	No findings

Table 1 History of pharmacovigilance inspections for ticagrelor

Date(s) of inspection	Inspecting regulatory authority(ies)	Site(s) inspected	Type of inspection	List of products concerned (if product-specific inspection)	Impact
Apr 2013	US FDA	AZ Wilmington USA	REMS	Brillinta	No findings
Aug 2013	Polish Regulatory Authority (URPL)	AZ Poland	Pharmacovigilance	All	The inspection findings had no impact on the benefit-risk of AstraZeneca products
Aug 2013	Swiss Health Authority (SwissMedic)	AZ Switzerland	Pharmacovigilance	All	The inspection findings had no impact on the benefit-risk of AstraZeneca products
Oct 2013	Venezuelan Regulatory Authority	AZ Venezuela	Pharmacovigilance	All	No findings
Oct 2013	MHRA UK	AZ UK TCS (outsource case handler) Mumbai	Pharmacovigilance	All	The inspection findings had no impact on the benefit-risk of AstraZeneca products

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Addendum to the Clinical Overview Appendix 5

Medicinal Product(s)	Ticagrelor
Period covered	3 December 2010 to 8 November 2014
Date	16 January 2015

Appendix 5

Listing of Post-approval Studies

Table 1 Listing of all non-interventional studies with the primary aim of post-authorisation safety monitoring

Study #	Status	Study title	Study objective	Country	# of pts	Study length	FSI / LSO (actual/ planned)	CSR (actual/ planned)	Required by RA (eg, EU, US, other)
D5130N00010	Ongoing	A pharmaco-epidemiological study to examine patient characteristics, drug utilisation pattern, and crude incidence rates of selected outcomes in new users of ticagrelor, clopidogrel, and prasugrel in Swedish registries	Provide a detailed patient description and to estimate crude incidence rates of selected outcomes in patients who for the first time are prescribed ticagrelor, clopidogrel, and prasugrel, respectively. Use of prasugrel is expected to be low in the study period.	Sweden[a]	~6000[a]	1.5 years[a]	Actual FSI 2Q 2011 (1 month after market availability) Data collection continue 1.5 years after market availability	Planned QIV 2015	EU
D5130L00019	Ongoing	A Post Marketing Surveillance to evaluate the safety and efficacy of Brilinta in Korea	To evaluate safety and efficacy of Brilinta under actual clinical practice	South Korea	1818 (actual); 3000 (planned)	6 years	Actual FSI 30 April 2013 Planned LSO 1Q 2017	Planned QIV 2017	South Korea
D5130C00087	Ongoing	A multicenter, single arm, open label, Phase IV study to evaluate safety and to describe the incidence of major cardiovascular events of ticagrelor in Chinese patients with ACS	To describe the safety and tolerability of ticagrelor, by assessment of the bleeding events and other SAEs during 1 year follow up	China	2000 (actual)	2 years	Actual FSI 26 June 2013 Planned LSO Sep 2015	Planned QI 2016	China

Table 1 Listing of all non-interventional studies with the primary aim of post-authorisation safety monitoring

Study #	Status	Study title	Study objective	Country	# of pts	Study length	FSI / LSO (actual/ planned)	CSR (actual/ planned)	Required by RA (eg, EU, US, other)
D5137R00007 Non-interventional data base study	Planned	SPACE-AA: Secondary Prevention of acute Coronary Events with Antiplatelet Agents: a cohort study in the SNIIRAM database	To estimate in real life the one-year incidence of death, hospitalisation for ACS, hospitalisation for other atherothrombotic events and hospitalisation for major bleeding during secondary prevention of ACS with ticagrelor and other antiplatelet agents.	France	150 000	24 months	2015-Q3 (planned data extraction)/ 2015-Q4 (statistical analysis)	Planned 2Q2016	Health Authority HAS (French RA) and CEPS/DGS
D5137L00001 Non-interventional	Ongoing	AReMIS: PGRx study on prevention of cardiovascular events by antiplatelet agents after acute coronary syndrome	To compare the relative risk of new myocardial infarction in patients with a history of acute coronary syndrome, using ticagrelor, or clopidogrel or prasugrel (if applicable) or none of these treatments, where aspirin is considered a co-variate.	France	3750	30 months	Actual FSI 15 October 2013 Planned LSO 2015	Planned 30 March 2016	Health Authority HAS (French RA) and CEPS/DGS

[a] Following CHMP response to the second annual report for the DUS (FUM008), this study will be conducted in Sweden rather than the UK. Due to this change, approval of the revised protocol by EMA, endorsed by CHMP, was approved 29 July 2013.

ACS Acute coronary syndrome; CHMP Committee for Medicinal Products for Human Use; CSR Clinical study report; EMA European Medicines Agency; EU European Union; FSI First Subject In; LSO Last Subject Out; PGRx Pharmacoepidemiologic General Research Extension database; RA Regulatory Authority; US United States.

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Addendum to the Clinical Overview Appendix 6	
Medicinal Product(s)	Ticagrelor
Period covered	3 December 2010 to 8 November 2014
Date	16 January 2015

Appendix 6

Proposed Changes to the Summary of Product Characteristics

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 90 mg ticagrelor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Round, biconvex, yellow tablets marked with '90' above 'T' on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Brilique, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

For further information, please refer to section 5.1.

4.2 Posology and method of administration

Posology
Brilique treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily.

Patients taking Brilique should also take ASA daily, unless specifically contraindicated. Following an initial dose of ASA, Brilique should be used with a maintenance dose of ASA of 75-150 mg (see section 5.1).

Treatment is recommended for up to 12 months unless discontinuation of Brilique is clinically indicated (see section 5.1). Experience beyond 12 months is limited.

In patients with Acute Coronary Syndromes (ACS), premature discontinuation with any antiplatelet therapy, including Brilique, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.

Lapses in therapy should also be avoided. A patient who misses a dose of Brilique should take only one 90 mg tablet (their next dose) at its scheduled time.

Patients treated with clopidogrel can be directly switched to Brilique if needed (see section 5.1). Switching from prasugrel to Brilique has not been investigated.

Special populations

Older people
No dose adjustment is required in elderly (see section 5.2).

Patients with renal impairment
No dose adjustment is necessary for patients with renal impairment (see section 5.2). No information is available concerning treatment of patients on renal dialysis and therefore Brilique is not recommended in these patients.

Patients with hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment. Brilique has not been studied in patients with moderate or severe hepatic impairment. Its use in patients with moderate to severe hepatic impairment is therefore contraindicated (see section 4.3, 4.4 and 5.2).

Paediatric population
The safety and efficacy of Brilique in children below the age of 18 in the approved adult indication has not been established. No data are available (see section 5.1 and 5.2).

Method of administration
For oral use. Brilique can be administered with or without food. For patients who are unable to swallow the tablet(s) whole, Brilique tablets (90 mg and 2x90 mg) can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.8).
- Active pathological bleeding.
- History of intracranial haemorrhage (see section 4.8).
- Moderate to severe hepatic impairment (see section 4.2, 4.4 and 5.2).
- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Bleeding risk
In the phase 3 pivotal trial (PLATO [PLATelet Inhibition and Patient Outcomes], 18,624 patients) key exclusion criteria included an increased risk for bleeding, clinically important thrombocytopenia or anaemia, previous intracranial bleed, gastrointestinal bleed within the past 6 months or major surgery within the past 30 days. Patients with acute coronary syndromes treated with Brilique and ASA showed an increased risk of non-CABG major bleeding and also more generally in bleeds requiring medical attention i.e. Major + Minor PLATO bleeds, but not Fatal or Life-threatening bleeds (see section 4.8).

Therefore, the use of Brilique in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. If clinically indicated, Brilique should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding). The use of Brilique is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage, and in patients with moderate to severe hepatic impairment (see section 4.3).

- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours of Brilique dosing.

No data exist with Brilique regarding a haemostatic benefit of platelet transfusions; circulating Brilique may inhibit transfused platelets. Since co-administration of Brilique with desmopressin did not decrease template-bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events (see section 4.5).
Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may increase haemostasis. Brilique may be resumed after the cause of bleeding has been identified and controlled.

Surgery
Patients should be advised to inform physicians and dentists that they are taking Brilique before any surgery is scheduled and before any new medicinal product is taken.

In PLATO patients undergoing coronary artery bypass grafting (CABG), Brilique had more bleeding than clopidogrel when stopped within 1 day prior to surgery but a similar rate of major bleeds compared to clopidogrel after stopping therapy 2 or more days before surgery (see section 4.8). If a patient is to undergo elective surgery and antiplatelet effect is not desired, Brilique should be discontinued 7 days prior to surgery (see section 5.1).

Patients at risk for bradycardic events
Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) were excluded from the main PLATO study evaluating the safety and efficacy of Brilique. Therefore, due to the limited clinical experience, Brilique should be used with caution in these patients (see section 5.1).

In addition, caution should be exercised when administering Brilique concomitantly with medicinal products known to induce bradycardia. However no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more medicinal products known to induce bradycardia (e.g., 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin) (see section 4.5).

During the Holter substudy in PLATO, more patients had ventricular pauses $\geq$3 seconds with ticagrelor than with clopidogrel during the acute phase of their ACS. The increase in Holter-detected ventricular pauses with ticagrelor was higher in patients with chronic heart failure (CHF) than in the overall study population during the acute phase of ACS, but not at one month with ticagrelor or compared to clopidogrel. There were no adverse clinical consequences associated with this imbalance (including syncope or pacemaker insertion) in this patient population (see section 5.1).

Dyspnoea
Dyspnoea was reported by 13.8% of patients treated with Brilique and by 7.8% of patients treated with clopidogrel. In 2.2% of patients, investigators considered the dyspnoea causally related to treatment with Brilique. It is usually mild to moderate in intensity and often resolves without need for treatment discontinuation. Patients with asthma/COPD may have an increased absolute risk of experiencing dyspnoea with Brilique (see section 4.8). Ticagrelor should be used with caution in patients with history of asthma and/or COPD. The mechanism has not been elucidated. If a patient reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with Brilique should be stopped.

Creatinine elevations
Creatinine levels may increase during treatment with Brilique (see section 4.8). The mechanism has not been elucidated. Renal function should be checked after one month and thereafter according to

routine medical practice, paying special attention to patients ≥ 75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an ARB.

Uric acid increase
In PLATO study, patients on ticagrelor had a higher risk of hyperuricaemia than those patients receiving clopidogrel (see section 4.8). Caution should be exercised when administering ticagrelor to patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acid nephropathy is discouraged.

Other
Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of Brilique and high maintenance dose ASA (>300 mg) is not recommended (see section 5.1).

Co-administration of Brilique with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated (see section 4.3 and 4.5). Co-administration may lead to a substantial increase in Brilique exposure (see section 4.5).

Co-administration of ticagrelor with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine and phenobarbital) is discouraged, as co-administration may lead to a decrease in exposure and efficacy of ticagrelor (see section 4.5).

Co-administration of Brilique and CYP3A4 substrates with narrow therapeutic indices (i.e., cisapride and ergot alkaloids) is not recommended, as ticagrelor may increase the exposure to these medicinal products (see section 4.5). The concomitant use of Brilique with doses of simvastatin or lovastatin greater than 40 mg is not recommended (see section 4.5).

Close clinical and laboratory monitoring is recommended when giving digoxin concomitantly with Brilique (see section 4.5).

No data are available on concomitant use of Brilique with verapamil and quinidine, drugs that are potent P-glycoprotein (P-gp) inhibitors and moderate CYP3A4 inhibitors which may increase ticagrelor exposure. If the association cannot be avoided, their concomitant use should be made with caution (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. Ticagrelor is also a P-glycoprotein (P-gp) substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates.

Effects of other medicinal products on Brilique

Medicinal products metabolised by CYP3A4
CYP3A4 inhibitors

- Strong CYP3A4 inhibitors – Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir, and atazanavir) would be expected to have similar effects and their concomitant use with Brilique is contraindicated (see section 4.3 and 4.4).

- Moderate CYP3A4 inhibitors – Co-administration of diltiazem with ticagrelor increased the ticagrelor C_{max} by 69% and AUC to 2.7 fold and decreased the active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other

moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin and fluconazole) would be expected to have a similar effect and can as well be co-administered with Brilique.

CYP3A inducers
Co-administration of rifampicin with ticagrelor decreased ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46%, respectively. Other CYP3A inducers (e.g., phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to Brilique as well. Co-administration of ticagrelor with potent CYP3A inducers may decrease exposure and efficacy of ticagrelor (see section 4.4).

Cyclosporine (P-gp and CYP3A inhibitor)
Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and C_{max} was decreased by 15% in the presence of cyclosporine.

No data are available on concomitant use of Brilique with other drugs that also are potent P-glycoprotein (P-gp) inhibitors and moderate CYP3A4 inhibitors (e.g. verapamil, quinidine) that also may increase ticagrelor exposure. If the association cannot be avoided, their concomitant use should be made with caution (see section 4.4).

Others
Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and ASA or desmopressin did not have any effect on the pharmacokinetics of ticagrelor or the active metabolite or on ADP-induced platelet aggregation compared with ticagrelor alone. If clinically indicated, medicinal products that alter haemostasis should be used with caution in combination with Brilique (see section 4.4).

A 2-fold increase of ticagrelor exposure was observed after daily consumption of large quantities of grapefruit juice (3x 200ml). This magnitude of increased exposure is not expected to be clinically relevant to most patients.

Effects of Brilique on other medicinal products

Medicinal products metabolised by CYP3A4

- *Simvastatin* – Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3 fold. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse effects of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. Brilique may have similar effect on lovastatin. The concomitant use of Brilique with doses of simvastatin or lovastatin greater than 40 mg is not recommended (see section 4.4).
- *Atorvastatin* - Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.
- A similar effect on other statins metabolised by CYP3A4 cannot be excluded. Patients in PLATO receiving ticagrelor took a variety of statins, with no concern of an association with statin safety among the 93% of the PLATO cohort taking these medicinal products.

Ticagrelor is a mild CYP3A4 inhibitor. Co-administration of Brilique and CYP3A4 substrates with narrow therapeutic indices (i.e., cisapride or ergot alkaloids) is not recommended, as ticagrelor may increase the exposure to these medicinal products (see section 4.4).

Medicinal products metabolised by CYP2C9
Co-administration of Brilique with tolbutamide resulted in no change in the plasma levels of either medicinal product, which suggest that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of medicinal products like warfarin and tolbutamide.

Oral contraceptives
Co-administration of Brilique and levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure approximately 20% but did not alter the pharmacokinetics of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with Brilique.

P-glycoprotein (P-gp) substrates (including digoxin, cyclosporine)
Concomitant administration of Brilique increased the digoxin C_{max} by 75% and AUC by 28%. The mean trough digoxin levels were increased about 30% with ticagrelor co-administration with some individual maximum increases to 2 fold. In the presence of digoxin, the C_{max} and AUC of ticagrelor and its active metabolite were not affected. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicinal products like digoxin concomitantly with Brilique (see section 4.4).

There was no effect of ticagrelor on cyclosporine blood levels. Effect of ticagrelor on other P-gp substrates has not been studied.

Other concomitant therapy

Medicinal products known to induce bradycardia
Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering Brilique concomitantly with medicinal products known to induce bradycardia (see section 4.4). However no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more medicinal products known to induce bradycardia (e.g., 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

In the PLATO study, Brilique was commonly administered with ASA, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions for long-term and also heparin, low molecular weight heparin and intravenous GpIIb/IIIa inhibitors for short durations (see section 5.1). No evidence of clinically significant adverse interactions with these medicinal products was observed.

Co-administration of Brilique with heparin, enoxaparin or desmopressin had no effect on activated partial thromboplastin time (aPTT), activated coagulation time (ACT) or factor Xa assays. However, due to potential pharmacodynamic interactions, caution should be exercised with the concomitant administration of Brilique with medicinal products known to alter haemostasis (see section 4.4).

Due to reports of cutaneous bleeding abnormalities with SSRIs (e.g., paroxetine, sertraline and citalopram), caution is advised when administering SSRIs with Brilique as this may increase the risk of bleeding.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during Brilique therapy.

Pregnancy
There are no or limited amount of data from the use of ticagrelor in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Brilique is not recommended during pregnancy.

Breastfeeding

Available pharmacodynamic/toxicological data in animals have shown excretion of ticagrelor and its active metabolites in milk (see section 5.3). A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Brilique therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
Ticagrelor had no effect on male or female fertility in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of Brilique on the ability to drive and use machines have been performed. Brilique is expected to have no or negligible influence on the ability to drive and use machines. During treatment for acute coronary syndromes, dizziness has been reported. Therefore, patients who experience dizziness should be cautious while driving or using machines.

4.8 Undesirable effects

Summary of the safety profile
The safety of Brilique in patients with acute coronary syndromes (UA, NSTEMI and STEMI) was evaluated in the pivotal large phase 3 PLATO ([PLATelet Inhibition and Patient Outcomes] study, 18,624 patients), which compared patients treated with Brilique (loading dose of 180 mg of Brilique and a maintenance dose of 90 mg twice daily) to patients treated with clopidogrel (300-600 mg loading dose followed by 75 mg once daily maintenance dose) both given in combination with acetylsalicylic acid (ASA) and other standard therapies.

The most commonly reported adverse reactions in patients treated with ticagrelor were dyspnoea, contusion and epistaxis and these reactions occurred at higher rates than in the clopidogrel treatment group.

Tabulated list of adverse reactions
The following adverse reactions have been identified following studies or have been reported in post-marketing experience with Brilique (Table 1).

Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following conventions: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Table 1 – Adverse reactions by frequency and System Organ Class (SOC)

Common	**Uncommon**	**Rare**
System Organ Class *Metabolism and nutrition disorders*		
		Hyperuricaemia[a]
Psychiatric disorders		
		Confusion
Nervous system disorders		
	Intracranial haemorrhage (including fatal)[b, ##], Dizziness, Headache	Paraesthesia
Eye disorders		
	Eye haemorrhage (intraocular, conjunctival, retinal)	
Ear and labyrinth disorders		

Table 1 – Adverse reactions by frequency and System Organ Class (SOC)		
Common	**Uncommon**	**Rare**
		Ear haemorrhage, Vertigo
Respiratory, thoracic and mediastinal disorders		
Dyspnoea[c], Epistaxis	Haemoptysis	
Gastrointestinal disorders		
Gastrointestinal haemorrhage[d]	Haematemesis, Gastrointestinal ulcer haemorrhage[e], Haemorrhoidal haemorrhage, Gastritis, Oral haemorrhage (including gingival bleeding), Vomiting, Diarrhoea, Abdominal pain, Nausea, Dyspepsia	Retroperitoneal haemorrhage, Constipation
Skin and subcutaneous tissue disorders		
Subcutaneous or dermal bleeding[f], Bruising[g]	Rash, Pruritus	
Musculoskeletal and connective tissue disorders		
		Haemarthrosis[#]
Renal and urinary disorders		
	Haemorrhage urinary tract[h]	
Reproductive system and breast disorders		
	Vaginal bleeding (including metrorrhagia)	
Investigations		
		Blood creatinine increased
Injury, poisoning and procedural complications		
Procedural site haemorrhage[i]	Post procedural haemorrhage, Haemorrhage	Wound haemorrhage, Traumatic haemorrhage
Immune system disorders		
	Hypersensitivity including angioedema	

Multiple related adverse reaction terms have been grouped together in the table and include medical terms as described below:

[a] Hyperuricaemia, Blood uric acid increased

[b] Cerebral haemorrhage, Haemorrhage intracranial, Haemorrhagic stroke,

[c] Dyspnoea, Dyspnoea exertional, Dyspnoea at rest, Nocturnal dyspnoea

[d] Gastrointestinal haemorrhage, Rectal haemorrhage, Intestinal haemorrhage, Melaena, Occult blood

[e] Gastrointestinal ulcer haemorrhage, Gastric ulcer haemorrhage, Duodenal ulcer haemorrhage, Peptic ulcer haemorrhage

[f] Subcutaneous haematoma, Skin haemorrhage, Haemorrhage subcutaneous, Petechiae

[g] Contusion, Haematoma, Ecchymosis, Increased tendency to bruise, Traumatic haematoma

[h] Haematuria, Blood urine present, Haemorrhage urinary tract

[i] Vessel puncture site haemorrhage, Vessel puncture site haematoma, Injection site haemorrhage, Puncture site haemorrhage, Catheter site haemorrhage

[#] There were no reported ADRs of haemarthrosis reported in the ticagrelor arm (n=9235) of the PLATO study, the frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate (based on 3/X, where X represents the total sample size e.g. 9235). This is calculated as 3/9235 which equates to a frequency category of 'rare'

[##] Fatal intracranial bleedings have been reported during post-marketing

Description of selected adverse reactions

Bleeding

Overall outcome of bleeding rates in the PLATO study are shown in Table 2.

Table 2 –Kaplan-Meier estimate of bleeding rates by treatment

	Brilique (%/year) N=9235	Clopidogrel (%/year) N=9186	*P*
PLATO Total Major	11.6	11.2	0.4336
PLATO Major Fatal/Life-Threatening	5.8	5.8	0.6988
Non-CABG PLATO Major	4.5	3.8	0.0264
Non-Procedural PLATO Major	3.1	2.3	0.0058
PLATO Total Major + Minor	16.1	14.6	0.0084
Non-Procedural PLATO Major + Minor	5.9	4.3	<0.0001
TIMI-defined Major	7.9	7.7	0.5669
TIMI-defined Major + Minor	11.4	10.9	0.3272

Bleeding category definitions:
Major Fatal/Life-threatening Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or ≥4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolaemic shock or severe hypotension requiring pressors or surgery.
Major Other: Clinically apparent with 30-50 g/l decrease in haemoglobin or 2-3 red cell units transfused; or significantly disabling.
Minor Bleed: Requires medical intervention to stop or treat bleeding.
TIMI Major Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or intracranial haemorrhage.
TIMI Minor Bleed: Clinically apparent with 30-50 g/l decrease in haemoglobin.

Brilique and clopidogrel did not differ in rates of PLATO Major Fatal/Life-threatening bleeding, PLATO total Major bleeding, TIMI Major bleeding, or TIMI Minor bleeding (Table 2). However, more PLATO combined Major + Minor bleeding occurred with ticagrelor compared with clopidogrel. Few patients in PLATO had fatal bleeds: 20 (0.2%) for ticagrelor and 23 (0.3%) for clopidogrel (see section 4.4).

Age, sex, weight, race, geographic region, concurrent conditions, concomitant therapy, and medical history, including a previous stroke or transient ischaemic attack, all did not predict either overall or non-procedural PLATO Major bleeding. Thus no particular group was identified at risk for any subset of bleeding.

CABG-related bleeding: In PLATO, 42% of the 1584 patients (12% of cohort) who underwent coronary artery bypass graft (CABG) surgery had a PLATO Major Fatal/Life-threatening bleeding with no difference between treatment groups. Fatal CABG bleeding occurred in 6 patients in each treatment group (see section 4.4).

Non-CABG related bleeding and non-procedural related bleeding: Brilique and clopidogrel did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening bleeding, but PLATO-defined Total Major, TIMI Major, and TIMI Major + Minor bleeding were more common with ticagrelor. Similarly, when removing all procedure related bleeds, more bleeding occurred with ticagrelor than with clopidogrel (Table 2). Discontinuation of treatment due to non-procedural bleeding was more common for ticagrelor (2.9%) than for clopidogrel (1.2%; p<0.001).

Intracranial bleeding: There were more intracranial non-procedural bleeds with ticagrelor (n=27 bleeds in 26 patients, 0.3%) than with clopidogrel (n=14 bleeds, 0.2%), of which 11 bleeds with ticagrelor and 1 with clopidogrel were fatal. There was no difference in overall fatal bleeds.

Dyspnoea
Dyspnoea, a sensation of breathlessness, is reported by patients treated with Brilique. Dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal and nocturnal dyspnoea), when combined, was reported by 13.8% of patients treated with ticagrelor and by 7.8% of patients treated with clopidogrel. In 2.2% of patients taking ticagrelor and by 0.6% taking clopidogrel investigators considered the dyspnoea causally related to treatment in the PLATO study and few were serious (0.14% ticagrelor; 0.02% clopidogrel), (see section 4.4). Most

reported symptoms of dyspnoea were mild to moderate in intensity, and most were reported as a single episode early after starting treatment.

Compared with clopidogrel, patients with asthma/COPD treated with ticagrelor may have an increased risk of experiencing non-serious dyspnoea (3.29% ticagrelor versus 0.53% clopidogrel) and serious dyspnoea (0.38% ticagrelor versus 0.00% clopidogrel). In absolute terms, this risk was higher than in the overall PLATO population. Ticagrelor should be used with caution in patients with history of asthma and/or COPD (see section 4.4).

About 30% of episodes resolved within 7 days. PLATO included patients with baseline congestive heart failure, chronic obstructive pulmonary disease, or asthma; these patients, and the elderly, were more likely to report dyspnoea. For Brilique, 0.9% of patients discontinued study drug because of dyspnoea compared with 0.1% taking clopidogrel. The higher incidence of dyspnoea with Brilique is not associated with new or worsening heart or lung disease (see section 4.4). Brilique does not affect tests of pulmonary function.

Investigations
Creatinine elevations: In PLATO, serum creatinine concentration significantly increased by >30% in 25.5% of patients receiving ticagrelor compared to 21.3% of patients receiving clopidogrel and by >50% in 8.3% of patients receiving ticagrelor compared to 6.7% of patients receiving clopidogrel. Creatinine elevations by >50% were more pronounced in patients > 75 years (ticagrelor 13.6% versus clopidogrel 8.8%), in patients with severe renal impairment at baseline (ticagrelor 17.8% versus clopidogrel 12.5%) and in patients receiving concomitant treatment with ARBs (ticagrelor 11.2% versus clopidogrel 7.1%). Within these subgroups renal-related serious adverse events and adverse events leading to discontinuation of study drug were similar between treatment groups. The totality of renal AEs reported were 4.9% for ticagrelor vs. 3.8% for clopidogrel, however a similar percent of patients reported events considered by the investigators as causally related to treatment; 54 (0.6%) for ticagrelor and 43 (0.5%) for clopidogrel.

Uric acid elevations: In PLATO, serum uric acid concentration increased to more than upper limit of normal in 22% of patients receiving ticagrelor compared to 13% of patients receiving clopidogrel. Mean serum uric acid concentration increased approximately 15% with ticagrelor compared to approximately 7.5% with clopidogrel and after treatment was stopped, decreased to approximately 7% on ticagrelor but with no decrease observed for clopidogrel. The hyperuricaemia AEs reported were 0.5% for ticagrelor vs. 0.2% for clopidogrel. Of these AEs 0.05% for ticagrelor vs. 0.02% for clopidogrel were considered causally related by investigators. For gouty arthritis, the AEs reported were 0.2% for ticagrelor vs 0.1% for clopidogrel; none of these adverse events were assessed as causally related by investigators.

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

Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse reactions which may occur with overdose include dyspnoea and ventricular pauses (see section 4.8).

In the event of overdose, observe for these potential adverse reactions and consider ECG monitoring

There is currently no known antidote to reverse the effects of Brilique, and Brilique is not expected to be dialysable (see section 4.4). Treatment of overdose should follow local standard medical practice.

The expected effect of excessive Brilique dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs appropriate supportive measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin, ATC code: B01AC24

Mechanism of action
Brilique contains ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)- mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as death, myocardial infarction or stroke.

Ticagrelor, also increases local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter -1 (ENT-1).

Ticagrelor has been documented to augment the following adenosine-induced effects in healthy subjects and in patients with ACS: vasodilation (measured by coronary blood flow increases in healthy volunteers and ACS patients~~, headache~~), inhibition of platelet function (in human whole blood *in vitro*) and dyspnoea. However, a link between the observed increases in adenosine and clinical outcomes (e.g.: morbidity-mortality) has not been clearly elucidated.
Pharmacodynamic effects
Onset of Action
In patients with stable coronary artery disease on ASA, ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean Inhibition of Platelet Aggregation (IPA) for ticagrelor at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA effect of 89% by 2-4 hours post dose, and maintained between 2-8 hours. 90% of patients had final extent IPA >70% by 2 hours post dose.

Offset of Action
If a CABG procedure is planned, ticagrelor bleeding risk is increased compared to clopidogrel when discontinued within less than 96 hours prior to procedure.

Switching data
Switching from clopidogrel to ticagrelor results in an absolute IPA increase of 26.4% and switching from ticagrelor to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to ticagrelor without any interruption of antiplatelet effect (see section 4.2).

Clinical efficacy and safety
The PLATO study included 18,624 patients who presented within 24 hours of onset of symptoms of unstable angina (UA), non ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI), and were initially managed medically, or with percutaneous coronary intervention (PCI), or with coronary artery bypass grafting (CABG) (see section 4.1).

On a background of daily ASA, ticagrelor 90 mg twice daily showed superiority to 75 mg daily clopidogrel in preventing the composite endpoint of cardiovascular [CV] death, myocardial infarction [MI], or stroke, with the difference driven by CV death and MI. Patients received a 300 mg loading dose of clopidogrel (600 mg possible if having PCI) or 180 mg of ticagrelor.

The result appeared early (absolute risk reduction [ARR] 0.6% and Relative Risk Reduction [RRR] of 12% at 30 days), with a constant treatment effect over the entire 12 month period, yielding ARR 1.9% per year with RRR of 16%. This suggests it is appropriate to treat patients with ticagrelor for up to 12 months (see section 4.2). Treating 54 ACS patients with ticagrelor instead of clopidogrel will prevent 1 atherothrombotic event; treating 91 will prevent 1 CV death (see Figure 1 and Table 3).

The treatment effect of ticagrelor over clopidogrel appears consistent across many subgroups, including weight; sex; medical history of diabetes mellitus, transient ischaemic attack or non-haemorrhagic stroke, or revascularisation; concomitant therapies including heparins, GpIIb/IIIa inhibitors and proton pump inhibitors (see section 4.5); final index event diagnosis (STEMI, NSTEMI, or UA); and, treatment pathway intended at randomisation (invasive or medical).

A weakly significant treatment interaction was observed with region whereby the HR for the primary endpoint favours ticagrelor in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045). Exploratory analyses suggest a possible association with ASA dose such that reduced efficacy was observed with ticagrelor with increasing ASA doses. Chronic daily ASA doses to accompany Brilique should be 75-150 mg (see section 4.2 and 4.4).

Figure 1 shows the estimate of the risk to the first occurrence of any event in the composite efficacy endpoint.

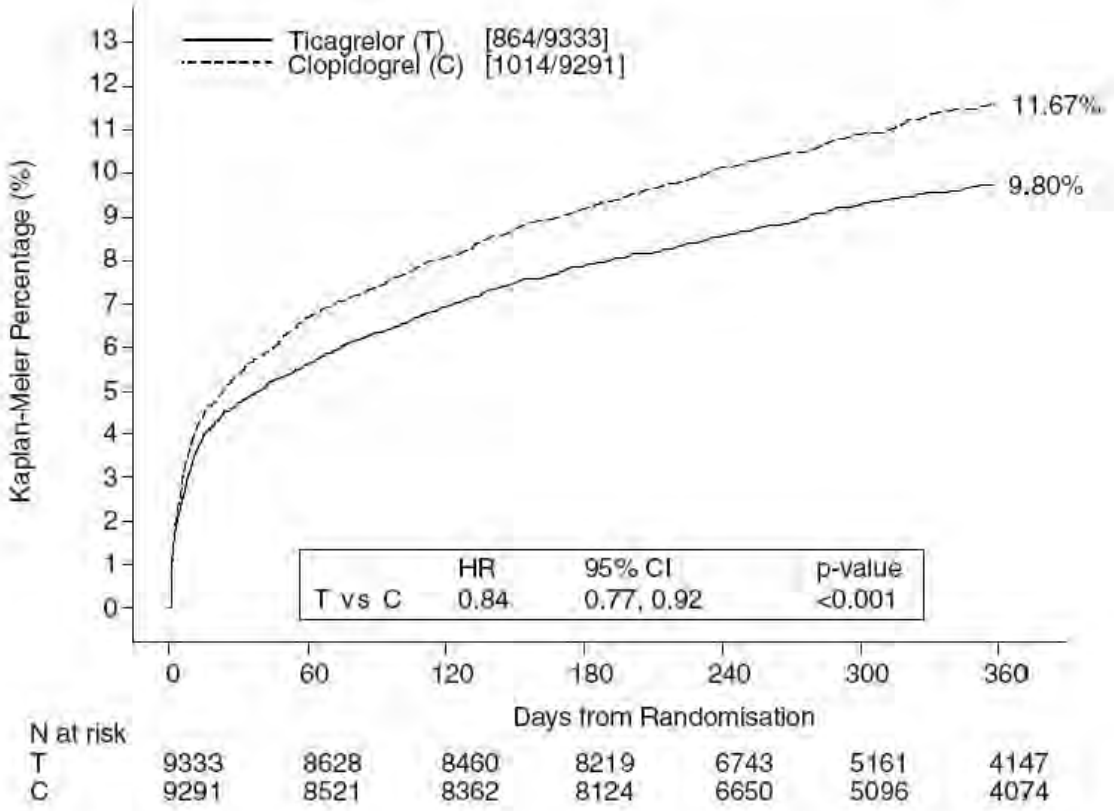

Figure 1 – Time to first occurrence of CV death, MI and Stroke (PLATO)

Brilique reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population (Table 3).

Table 3 -Outcome Events in PLATO

	Brilique (% patients with event) N=9333	Clopidogrel (% patients with event) N=9291	ARR[a] (%/yr)	RRR[a] (%) (95% CI)	*P*
CV death, MI (excl. silent MI) or stroke	9.3	10.9	1.9	16 (8, 23)	0.0003
Invasive intent	8.5	10.0	1.7	16 (6, 25)	0.0025
Medical intent	11.3	13.2	2.3	15 (0.3, 27)	0.0444[d]
CV death	3.8	4.8	1.1	21 (9, 31)	0.0013
MI (excl. silent MI)[b]	5.4	6.4	1.1	16 (5, 25)	0.0045
Stroke	1.3	1.1	-0.2	-17 (-52, 9)	0.2249
All cause mortality, MI (excl. silent MI), or stroke	9.7	11.5	2.1	16 (8, 23)	0.0001
CV death, total MI, stroke, SRI, RI, TIA, or other ATE[c]	13.8	15.7	2.1	12 (5, 19)	0.0006
All-cause mortality	4.3	5.4	1.4	22 (11, 31)	0.0003[d]
Definite stent thrombosis	1.2	1.7	0.6	32 (8, 49)	0.0123[d]

[a]ARR = absolute risk reduction; RRR = relative risk reduction = (1-Hazard ratio) x 100%. A negative RRR indicates a relative risk increase.
[b]excluding silent myocardial infarction.
[c]SRI = serious recurrent ischaemia; RI = recurrent ischaemia; TIA = transient ischaemic attack; ATE = arterial thrombotic event. Total MI includes silent MI, with date of event set to date when discovered.
[d]nominal significance value; all others are formally statistically significant by pre-defined hierarchical testing.

Holter Substudy

To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3000 patients, of whom approximately 2000 had recordings both in the acute phase of their ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. More patients had ventricular pauses with ticagrelor (6.0%) than with clopidogrel (3.5%) in the acute phase; and 2.2% and 1.6% respectively after 1 month (see section 4.4). The increase in ventricular pauses in the acute phase of ACS was more pronounced in ticagrelor patients with history of CHF (9.2% versus 5.4% in patients without CHF history; for clopidogrel patients, 4.0% in those with versus 3.6% in those without CHF history) This imbalance did not occur at one month: 2.0% versus 2.1% for ticagrelor patients with and without CHF history respectively; and 3.8% versus 1.4% with clopidogrel. There were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

PLATO genetic substudy

CYP2C19 and ABCB1 genotyping of 10,285 patients in PLATO provided associations of genotype groups with PLATO outcomes. The superiority of ticagrelor over clopidogrel in reducing major CV events was not significantly affected by patient CYP2C19 or ABCB1 genotype. Similar to the overall PLATO study, total PLATO Major bleeding did not differ between ticagrelor and clopidogrel, regardless of CYP2C19 or ABCB1 genotype. Non-CABG PLATO Major bleeding was increased with ticagrelor compared clopidogrel in patients with one or more CYP2C19 loss of function alleles, but similar to clopidogrel in patients with no loss of function allele.

Combined efficacy and safety composite

A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined 'Total Major' bleeding) indicates that the benefit in efficacy of Brilique compared to clopidogrel is not offset by the major bleeding events (ARR 1.4%, RRR 8%, HR 0.92; p=0.0257) over 12 months after ACS.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Brilique in all subsets of the paediatric population in the granted indication (see section 4.2 and 5.2).

5.2 Pharmacokinetic properties

Ticagrelor demonstrates linear pharmacokinetics and exposure to ticagrelor and the active metabolite (AR-C124910XX) are approximately dose proportional up to 1260 mg.

Absorption
Absorption of ticagrelor is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median t_{max} of approximately 2.5 hours. Following oral administration of ticagrelor 90 mg under fasted conditions, C_{max} is 529 ng/ml and AUC is 3451 ng*h/ml. The metabolite parent ratios are 0.28 for C_{max} and 0.42 for AUC.

The mean absolute bioavailability of ticagrelor was estimated to be 36%. Ingestion of a high-fat meal resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max} but had no effect on ticagrelor C_{max} or the AUC of the active metabolite. These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food. Ticagrelor as well as the active metabolite are P-gp substrates.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, has a comparable bioavailability to whole tablets with regards to AUC and C_{max} for ticagrelor and the active metabolite. Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

Distribution
The steady state volume of distribution of ticagrelor is 87.5 l. Ticagrelor and the active metabolite is extensively bound to human plasma protein (>99.0%).

Biotransformation
CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition.

The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet $P2Y_{12}$ ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

Elimination
The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is most likely via biliary secretion. The mean $t_{1/2}$ was approximately 7 hours for ticagrelor and 8.5 hours for the active metabolite.

Special populations

Older people
Higher exposures to ticagrelor (approximately 25% for both C_{max} and AUC) and the active metabolite were observed in elderly (≥ 75years) ACS patients compared to younger patients by the population pharmacokinetic analysis. These differences are not considered clinically significant (see section 4.2).

Paediatric
Ticagrelor has not been evaluated in a paediatric population (see section 4.2 and 5.1).

Gender
Higher exposures to ticagrelor and the active metabolite were observed in women compared to men. These differences are not considered clinically significant.

Renal impairment
Exposure to ticagrelor was approximately 20% lower and exposure to the active metabolite was approximately 17% higher in patients with severe renal impairment (creatinine clearance <30 ml/min) compared to subjects with normal renal function (see section 4.2).

Hepatic impairment
C_{max} and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively (see section 4.2). Ticagrelor has not been studied in patients with moderate or severe hepatic impairment and its use in these patients is contraindicated (see section 4.3 and 4.4).

Ethnicity
Patients of Asian descent have a 39% higher mean bioavailability compared to Caucasian patients. Patients self-identified as Black had an 18% lower bioavailability of ticagrelor compared to Caucasian patients. In clinical pharmacology studies, the exposure (C_{max} and AUC) to ticagrelor in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians.

5.3 Preclinical safety data

Preclinical data for ticagrelor and its major metabolite have not demonstrated unacceptable risk for adverse effects for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxic potential.

Gastrointestinal irritation was observed in several animal species at clinical relevant exposure levels (see section 4.8).

In female rats, ticagrelor at high dose showed an increased incidence of uterine tumours (adenocarcinomas) and an increased incidence of hepatic adenomas. The mechanism for uterine tumours is likely hormonal imbalance which can lead to tumours in rats. The mechanism for the hepatic adenomas is likely due to a rodent-specific enzyme induction in the liver. Thus, the carcinogenicity findings are considered unlikely to be relevant for humans.

In rats minor developmental anomalies were seen at a maternal toxic dose (safety margin of 5.1). In rabbits a slight delay in hepatic maturity and skeletal development was seen in foetuses from dams at high dose without showing maternal toxicity (safety margin of 4.5).

Studies in rats and rabbits have shown reproductive toxicity, with slightly reduced maternal body weight gain and reduced neonatal viability and birth weight, with delayed growth. Ticagrelor produced irregular cycles (mostly extended cycles) in female rats, but did not affect overall fertility in male and female rats. Pharmacokinetic studies performed with radio-labeled ticagrelor have shown that the parent compound and its metabolites are excreted in the milk of rats (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Mannitol (E421)
Dibasic calcium phosphate

Magnesium stearate (E470b)
Sodium starch glycolate
Hydroxypropyl-cellulose (E463)

Coating
Talc
Titanium dioxide (E171)
Ferric oxide yellow (E172)
Polyethylene-glycol 400
Hypromellose (E464)

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

- PVC-PVDC/Al transparent blister (with sun/moon symbols) of 10 tablets; cartons of 60 tablets (6 blisters) and 180 tablets (18 blisters).
- PVC-PVDC/Al transparent calendar blister (with sun/moon symbols) of 14 tablets; cartons of 14 tablets (1 blister), 56 tablets (4 blisters), and 168 tablets (12 blisters).
- PVC-PVDC/Al perforated unit dose transparent blister of 10 tablets; cartons of 100x1 tablets (10 blisters).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85
Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/655/001-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 December 2010

10. DATE OF REVISION OF THE TEXT

~~07/2014~~
Xx/2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

or

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield, Cheshire, SK10 2NA
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 90 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg film-coated tablets
ticagrelor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 90 mg ticagrelor

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
56 film-coated tablets
60 film-coated tablets
100x1 film-coated tablets
168 film-coated tablets
180 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

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

AstraZeneca AB
S-151 85
Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/655/001 60 film-coated tablets
EU/1/10/655/002 180 film-coated tablets
EU/1/10/655/003 14 film-coated tablets
EU/1/10/655/004 56 film-coated tablets
EU/1/10/655/005 168 film-coated tablets
EU/1/10/655/006 100x1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

brilique 90 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED UNIT DOSE BLISTER (100X1 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg tablets
ticagrelor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (10 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg tablets
ticagrelor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Sun/Moon symbol

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTER (14 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg tablets
ticagrelor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon Tue Wed Thu Fri Sat Sun
Sun/Moon symbol

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Brilique 90 mg film-coated tablets
ticagrelor

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 Brilique is and what it is used for

What Brilique is
Brilique contains the active substance called ticagrelor. This belongs to a group of medicines called anti-platelet medicines.

How Brilique works
Brilique affects cells called 'platelets' (also called thrombocytes). These very small blood cells help stop bleeding by clumping together to plug tiny holes in blood vessels that are cut or damaged.

However, platelets can also form clots inside diseased blood vessels in the heart and brain. This can be very dangerous because:
- the clot can cut off the blood supply completely - this can cause a heart attack (myocardial infarction) or stroke, or
- the clot can partly block the blood vessels to the heart - this reduces the blood flow to the heart and can cause chest pain which comes and goes (called 'unstable angina').

Brilique helps stop the clumping of platelets. This reduces the chance of a blood clot forming that can reduce blood flow.

What Brilique is used for
Brilique is to be used in adults only. You have been given Brilique because you have had:
- a heart attack, or
- unstable angina (angina or chest pain that is not well controlled).

Brilique reduces the chances of you having another heart attack or a stroke or of dying from a disease related to your heart or blood vessels.

2. What you need to know before you take Brilique

Do not take Brilique if:

- You are allergic (hypersensitive) to ticagrelor or any of the other ingredients of Brilique (listed in section 6).
- You are bleeding now or have bled recently inside your body, such as bleeding in your stomach or gut from an ulcer.
- You have moderate to severe liver disease
- You are taking any of the following medicines: ketoconazole (used to treat fungal infections), clarithromycin (used to treat bacterial infections), nefazodone (an antidepressant), ritonavir and atazanavir (used to treat HIV infection and AIDS).
- You have had a stroke caused by bleeding in the brain.

Do not take Brilique if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Brilique.

Warnings and precautions
Check with your doctor, pharmacist or dentist before taking Brilique if:
- You have an increased risk of bleeding because of:
  - a recent serious injury
  - recent surgery (including dental work)
  - you have a condition that affects blood clotting
  - recent bleeding from your stomach or gut (such as a stomach ulcer or colon 'polyps')
- You are due to have surgery (including dental work) at any time while taking Brilique. This is because of the increased risk of bleeding. Your doctor may want you to stop taking Brilique 7 days prior to surgery.
- Your heart rate is abnormally low (usually lower than 60 beats per minute) and you do not already have in place a device that paces your heart (pacemaker).
- You have asthma or other lung problem or breathing difficulties.
- You have had a blood test that showed more than the usual amount of uric acid

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or dentist before taking Brilique.

Children
Brilique is not recommended for children and adolescents under 18 years.

Other medicines and Brilique
Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines that you buy without a prescription, dietary supplements and herbal remedies. This is because Brilique can affect the way some medicines work and some medicines can have an effect on Brilique.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- more than 40 mg daily of either simvastatin or lovastatin (medicines used to treat high cholesterol)
- rifampicin (an antibiotic), phenytoin, carbamazepine and phenobarbital (used to control seizures), digoxin (used to treat heart failure), cyclosporine (used to lessen your body's defenses), quinidine and diltiazem (used to treat abnormal heart rhythms), beta blockers and verapamil (used to treat high blood pressure).

In particular, tell your doctor or pharmacist if you are taking any of the following medicines that increase your risk of bleeding:
- 'oral anticoagulants' often referred to as 'blood thinners' which include warfarin.
- non-steroidal anti-inflammatory drugs (abbreviated as NSAIDs) often taken as pain killers such as ibuprofen and naproxen.
- selective serotonin reuptake inhibitors (abbreviated as SSRIs) taken as antidepressants such as paroxetine, sertraline and citalopram
- other medicines such as ketoconazole (used to treat fungal infections), clarithromycin (used to treat bacterial infections), nefazodone, (an antidepressant), ritonavir and atazanavir (used to

treat HIV infection and AIDS), cisapride (used to treat heartburn), ergot alkaloids (used to treat migraines and headaches).

Also tell your doctor that because you are taking Brilique, you may have an increased risk of bleeding if your doctor gives you fibrinolytics, often called 'clot dissolvers', such as streptokinase or alteplase.

Brilique with food and drink
You can take Brilique with or without food.

Pregnancy and breast-feeding
It is not recommended to use Brilique if you are pregnant or may become pregnant. Women should use appropriate contraceptive measures to avoid pregnancy while taking this medicine.
Talk to your doctor before taking Brilique if you are breast-feeding. Your doctor will discuss with you the benefits and risks of taking Brilique during this time.

Ask your doctor or pharmacist for advice before taking any medicine, if you are pregnant or breast-feeding.

Driving and using machines
Brilique is not likely to affect your ability to drive or use machines. If you feel dizzy while taking Brilique, be careful while driving or using machines.

3. How to take Brilique

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- The starting dose is two tablets at the same time (loading dose of 180 mg). This dose will usually be given to you in the hospital.
- After this starting dose, the usual dose is one tablet of 90 mg twice a day for up to 12 months unless your doctor tells you differently. Take Brilique around the same time everyday (for example, one tablet in the morning and one in the evening).

Your doctor will usually also tell you to take acetylsalicylic acid. This is a substance present in many medicines used to prevent blood clotting. Your doctor will tell you how much to take (usually between 75-150 mg daily).

How to take Brilique
- You can take the tablet with or without food.
- You can check when you last took a tablet of Brilique by looking on the blister. There is a sun (for the morning) and a moon (for the evening). This will tell you whether you have taken the dose.

If you have trouble swallowing the tablet(s)
If you have trouble swallowing the tablet(s) you can crush them and mix with water as follows:
- Crush the tablet(s) to a fine powder
- Pour the powder into half a glass of water
- Stir and drink immediately
- To make sure there is no medicine left, rinse the empty glass with another half a glass of water and drink it

If you take more Brilique than you should
If you take more Brilique than you should, talk to a doctor or go to hospital straight away. Take the medicine pack with you. You may be at increased risk of bleeding.

If you forget to take Brilique

- If you forget to take a dose, just take your next dose as normal.
- Do not take a double dose (two doses at the same time) to make up for the forgotten dose.

If you stop taking Brilique

Do not stop taking Brilique without talking to your doctor. Take Brilique on a regular basis and for as long as your doctor keeps prescribing it. If you stop taking Brilique, it may increase your chances of having another heart attack or stroke or dying from a disease related to your heart or blood vessels.

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. The following side effects may happen with this medicine:

See a doctor straight away if you notice any of the following – you may need urgent medical treatment:

- **Signs of a stroke such as:**
  - sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body (uncommon)
  - sudden confusion, difficulty speaking or understanding others (uncommon)
  - sudden difficulty in walking or loss of balance or co-ordination (uncommon)
  - suddenly feeling dizzy or sudden severe headache with no known cause (uncommon)

  These are signs of a kind of stroke caused by bleeding into the brain.

- **Bleeding** – some bleeding is common. However, severe bleeding is uncommon, but can be life threatening. Bleeding of many different kinds can be increased, for example:
  - nosebleed (common)
  - blood in your urine (uncommon)
  - black stools or blood in your stools (common)
  - blood in your eye (uncommon)
  - coughing up or bringing up blood (uncommon)
  - vaginal bleeding that is heavier, or happens at different times, to your normal period (menstrual) bleeding (uncommon)
  - bleeding after surgery or from cuts and wounds that is more than normal (common)
  - bleeding from your stomach lining (ulcer) (uncommon).
  - bleeding gums (uncommon)
  - blood in your ear (rare)
  - internal bleeding (rare)
  - bleeding into joints causing painful swelling (rare)

Discuss with your doctor if you notice any of the following:

- **Feeling short of breath** - this is common. It might be due to your heart disease or another cause, or it might be a side effect of Brilique. If your feeling of shortness of breath gets worse or lasts a long time, tell your doctor. Your doctor will decide if it needs treatment or further investigations.

Other possible side effects

Common (affects 1 to 10 users in 100)

- Bruising

Uncommon (affects 1 to 10 users in 1,000)

- Allergic reaction – a rash, itching, or a swollen face or swollen lips/tongue may be signs of an allergic reaction (see section 2: What you need to know before you take Brilique).
- Headache
- Feeling dizzy or like the room is spinning
- Abdominal pain
- Diarrhoea or indigestion
- Feeling or being sick
- Rash
- Itching
- Inflamed stomach (gastritis)

Rare (affects 1 to 10 users in 10,000)
- Constipation
- A tingling feeling
- Confusion

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 Brilique

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 blister and carton after EXP. The expiry date refers to the last day of that month.
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 Brilique contains
- The active substance is ticagrelor. Each film-coated tablet contains 90 mg of ticagrelor.

- The other ingredients are:
  Tablet core: mannitol (E421), dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl-cellulose (E463), magnesium stearate (E470b)

  Tablet film coating: hypromellose (E464), titanium dioxide (E171), talc, polyethylene-glycol 400, and ferric oxide yellow (E172).

What Brilique looks like and contents of the pack
Film-coated tablet (tablet): The tablets are round, biconvex, yellow, film-coated marked with a "90" above "T" on one side.

Brilique is available in:
- standard blisters (with sun/moon symbols) in cartons of 60 and 180 tablets
- calendar blisters (with sun/moon symbols) in cartons of 14, 56 and 168 tablets
- perforated blisters in a carton of 100x1 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
AstraZeneca AB
S-151 85
Södertälje
Sweden

Manufacturer:
AstraZeneca AB
Gärtunavägen
SE-151 85
Södertälje
Sweden

Manufacturer:
AstraZeneca UK Limited
Silk Road Business Park
Macclesfield, Cheshire, SK10 2NA
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in ~~07~~xx/201~~4~~5

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

AstraZeneca

Addendum to the Clinical Overview Appendix 7	
Medicinal Product(s)	Ticagrelor
Period covered	3 December 2010 to 8 November 2014
Date	16 January 2015

Appendix 7

Clinical Justification Document for Proposed Changes to the Summary of Product Characteristics

AstraZeneca

Justification document

Drug Substance	Brilique (ticagrelor)
Edition Number	1
Date	12 January 2015

Clinical Justification Document for Change to Brilique (Ticagrelor) Summary of Product Characteristics (SmPC) Wording

Signature: [redacted]

12/1 2015

Date
(Day Month Year)

CLINICAL JUSTIFICATION FOR CHANGE TO BRILIQUE (TICAGRELOR) SMPC WORDING

With procedure EMEA/H/C/001241/II/0021 (CHMP opinion 24 July 2014) the product information for Brilique (ticagrelor) was updated. A new paragraph was added to Section 5.1, referring to the mechanism of action by which ticagrelor increases endogenous levels of adenosine. A mistake was noted during subsequent review of the approved wording, and AstraZeneca now would like to correct this mistake.

It is proposed to delete the word "headache" from Section 5.1 since available evidence does not support that ticagrelor augments adenosine-induced headache. The current wording in Section 5.1 is provided below, with the error highlighted and struck out:

> ***5.1 Pharmacodynamic properties***
>
> *Ticagrelor, also increases local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter -1 (ENT-1).*
>
> *Ticagrelor has been documented to augment the following adenosine-induced effects in healthy subjects and in patients with ACS: vasodilation (measured by coronary blood flow increases in healthy volunteers and ACS patients~~; headache~~), inhibition of platelet function (in human whole blood in vitro) and dyspnoea. However, a link between the observed increases in adenosine and clinical outcomes (e.g.: morbidity-mortality) has not been clearly elucidated.*

The evidence supporting the inclusion of the new information is derived from studies of coronary blood flow during adenosine infusion in healthy volunteers (Wittfeldt et al 2013) and in ACS patients (Alexopoulos et al 2013). The study published by Wittfeldt et al is an AstraZeneca sponsored study (Study D5130C00067), with full Clinical Study Report available. Below is an excerpt of the reported adverse events in the System Organ Class "Nervous System Disorders" (see Table 1). There was no increased reporting of headache for ticagrelor compared with placebo in this study. In the publication of Alexopolous there is no indication that headache was more common in patients given ticagrelor versus prasugrel during infusion of adenosine. There is thus no support for the statement that ticagrelor has been documented to augment headache following administration of adenosine.

AstraZeneca acknowledges the comment made by a CHMP member in the updated draft final assessment report, received on 18 July 2014 (p13), which refers to a potential contribution of the adenosine effect on headache in relation to treatment with ticagrelor:

"In this regard, headache should be included as a potential effect of adenosine-mediated effects, which is consistent with "headache" reported in Section 4.8 of Brilique, as well as in the SmPC of Adenocor (adenosine)" (http://www.medicines.org.uk/emc/medicine/6727/SPC/Adenocor/).

Headache is, as noted, already reported in Section 4.8 as an uncommon adverse reaction for ticagrelor, and it is the view of AstraZeneca that there is no support to mention headache in relation to adenosine in Section 5.1 of the SmPC.

Table 1 **Number (%) of subjects who had at least one adverse event, by preferred term, arranged by system organ class (Safety analysis set)**

SYSTEM ORGAN CLASS/ Preferred term	Pre-dose ticagrelor	Pre-dose Placebo	Ticagrelor	Placebo	Ticagrelor + theophylline	Placebo + theophylline	Overall
	N = 39	N = 40	N = 39	N = 40	N = 39	N = 40	N = 40
NERVOUS SYSTEM DISORDERS	8 (20.5)	14 (35.0)	12 (30.8)	12 (30.0)	4 (10.3)	9 (22.5)	22 (55.0)
Headache	4 (10.3)	10 (25.0)	7 (17.9)	9 (22.5)	2 (5.1)	7 (17.5)	14 (35.0)
Paraesthesia	3 (7.7)	3 (7.5)	2 (5.1)	3 (7.5)	2 (5.1)	2 (5.0)	5 (12.5)
Dizziness	0	0	2 (5.1)	0	0	0	2 (5.0)
Dysgeusia	1 (2.6)	0	1 (2.6)	0	0	0	1 (2.5)
Head discomfort	1 (2.6)	1 (2.5)	1 (2.6)	0	0	0	1 (2.5)

Data source: Table 9 of the Study D5130C00067 Clinical Study Report.

REFERENCES

Alexopoulos et al 2013
Alexopoulos D, Moulias A, Koutsogiannis N, Xanthopoulou I, Kahhavas A, Mavronasiou E, et al. Differential effect of ticagrelor versus prasugrel on coronary blood flow velocity in patients with non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention. An exploratory study. Circ Cardiovasc Interv 2013;6:277-83.

Wittfeldt et al 2013
Wittfeldt A, Emanuelsson H, Brandrup-Wognsen G, van Giezen JJ, Jonasson J, Nylander S, et al. Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans. JACC 2013;61:723-8.