NOVARTIS

Chief Medical Office & Patient Safety

Omalizumab

IGE025

EU Safety Risk Management Plan

Active substance (INN or common name):	Omalizumab
Products concerned (brand names):	Xolair
Document status:	Final
Version number:	16.0
Data lock point for this RMP	31-Dec-2018
Data lock point for POLYP 1 and POLYP 2 studies (Nasal polyp indication)	11-March-2019
Date of final sign off	23-Oct-2019

Rationale for submitting an updated RMP:

The trigger for this EU RMP update is the submission of the dossier for a new indication, as Nasal polyps in adult patients (18 years and above) with inadequate response to intranasal corticosteroids.

Summary of significant changes in this RMP:

- A new indication, [redacted]
- Updates from two pivotal studies, POLYP 1 (GA39688) and POLYP 2 (GA39855).
- No change in safety risks.

Part	Major changes compared to RMP v 15.0
Part I	This section is updated with proposed indication and dosage details in EEA.
Part II	Section 2 is updated with epidemiology data of nasal polyp indication. Section 4 is updated with the cumulative exposure data. Section 6 is updated with cumulative post-authorization exposure data. Section 8 is updated with safety profile of omalizumab in target population of patients with nasal polyps.
Part III	No update.
Part IV	No update.
Part V	No update.
Part VI	Section 13 is updated with nasal polyp data.
Part VII	Annex 7 is updated with brief statistical description and supportive outputs for nasal polyp indication. Also, reference list is updated.

Other RMP versions under evaluation

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 15.0

Approved with procedure: EMEA/H/C/000606/II/0093

Date of approval (opinion date): 27/06/2019

QPPV Name: [redacted]

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

AA	Allergic Asthma
AAO	Allergic asthma patient population from open label studies
AAP	Allergic asthma patient population from placebo-controlled studies
ADR	Adverse Drug Reaction
AE	Adverse Event
ATA	Anti-Therapeutic Antibody
ATE	Arterial Thromboembolic Events
CDS	Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIU	Chronic Idiopathic Urticaria
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSS	Churg-Strauss syndrome
CSU	Chronic Spontaneous Urticaria
CU	Chronic Urticaria
CVD	Cerebrovascular Disorders
DVT	Deep vein thrombosis
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FESS	Functional endoscopic sinus surgery
GERD	Gastroesophageal reflux disease
GINA	Global Initiative for Asthma guidelines
HCP	Health Care Provider
HES	Hypereosinophilic syndrome
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard Ratio
ICS	Inhaled corticosteroids
IMS	Intercontinental Marketing Services
LABA	Long-acting inhaled beta2-agonist
LTRA	Leukotriene Receptor Antagonist
mAb	Monoclonal Antibody
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NP	Nasal polyps
NHIS	National Health Interview Survey
OCS	Oral Corticosteroid
PFS	Pre-Filled Syringe
PSUR	Periodic Safety Update Report
PTY	Patient treatment-years

QoL	Quality of life
RDBPC	Randomized, Double-Blind, Placebo-Controlled study
RMP	Risk Management Plan
RR	Rate Ratio
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SSS	Serum Sickness Syndrome
TIA	Transient Ischemic Attack
VCD	Vocal cord dysfunction
WHO	World health Organization

1 Part I: Products Overview

Table 1-1 Part I.1 - Product Overview

Active substance (INN or common name)	Omalizumab
Pharmacotherapeutic group (ATC Code)	R03DX05
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Xolair®
Marketing authorization procedure	Centralized Procedure
Brief description of the product	Chemical class: Humanized, recombinant anti-IgE mAb.
	Summary of mode of action: Omalizumab (Xolair®) is a unique humanized monoclonal antibody (mAb) that binds IgE at the same site as the high affinity IgE binding receptor (FcεRI), effectively acting as an IgE blocker, interrupting the allergic cascade.
	Important information about its composition: Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.
Hyperlink to the Product Information	[Current approved SmPC]
Indications in the EEA	Current: **Allergic Asthma (AA):** Xolair is indicated in adults, adolescents and children (6 to <12 years of age) for IgE (immunoglobulin E) mediated AA. • **Adults and adolescents (12 years of age and older):** Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent AA, who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (Forced Expiratory Volume in 1 second (FEV1) <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose ICS, plus a long-acting inhaled beta2-agonist (LABA). • **Children (6 to <12 years of age):** Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent AA who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented

	severe asthma exacerbations despite daily high-dose ICS, plus a LABA. **Chronic Spontaneous Urticaria (CSU):** Xolair is indicated as add-on therapy for the treatment of CSU in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.
	Proposed: [redacted]
Dosage in the EEA	**AA:** 75 mg to 600 mg according to body weight and baseline IgE levels (dosing table), administered subcutaneously every 2 or every 4 weeks. **CSU:** The recommended dose is 300 mg by SC injection every 4 weeks.
	Proposed: [redacted]
Pharmaceutical forms and strengths	Current: 75 mg and 150 mg powder and solvent for solution for injection; 75 mg and 150 mg solution for injection.
	Proposed (if applicable): not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indications and target population

2.1 Indication

Xolair is indicated in adults, adolescents and children (6 to <12 years of age) for IgE (immunoglobulin E) mediated Allergic Asthma (AA). It is also indicated as add-on therapy for the treatment of Chronic Spontaneous Urticaria (CSU) in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

2.1.1 Allergic Asthma

Incidence:

Studies in Europe estimated an annual incidence of 259 to 520 per 100,000 people. The annual incidence was increased in children <5 years (517 to 4,046 per 100,000 people).

In relation to symptom severity, a study conducted a worldwide survey and estimated that in Central/Eastern Europe 32% of the patients with Asthma had the severe type, and 19% the moderate type. In Western Europe, they reported that 18% had the severe type, while 19% the moderate type (Rabe et al 2004).

Prevalence:

Worldwide, asthma has been estimated to affect approximately 300 million individuals (Masoli et al 2004, GINA 2015). The global prevalence of asthma has been reported ranging from 1% to 18% of the population in different countries with different trends (increasing, decreasing, or stabilizing) in different countries (García-Marcos et al 2004, Teeratakulpisarn et al 2004, Carvajal-Urueña et al 2005, Ko et al 2005, Yan et al 2005). Approximately 15 million disability-adjusted life years due to asthma has been estimated by World Health Organization (WHO) in yearly basis which represents about 1% of the total global disease burden. Worldwide, WHO further estimated the total number of asthma-related deaths at 250,000 per year. There are insufficient data to determine the likely causes of the described variations in prevalence within and between populations. The European Community Respiratory Health Survey II (Janson et al 1997) has estimated the physician-diagnosed asthma prevalence in 33 centers of 13 countries among subjects aged 20-44 years.

Demographics of the population with Allergic Asthma – age, gender, racial and/or ethnic origin and risk factors for the disease:

The US NHIS, 2011 reported on age, gender and ethnicity distribution of asthma prevalence. Detailed asthma prevalence percent, overall, among children and adults and by gender and ethnicity groups in US NHIS, 2011 (CDC/NCHS 2012a and CDC/NCHS 2012b) are illustrated in the following table:

Table 2-1 Demographics of the population with Allergic Asthma– age, gender, racial and/or ethnic origin and risk factors for the disease

Characteristic	All ages	Children	Adults
	Total	Age <18	Age 18+
Total	8.5	9.5	8.2
Male	7.2	10.2	6.2
Female	9.7	8.8	10.0
White Non-Hispanic	8.2	7.8	8.4
Male	6.9	8.3	6.5
Female	9.6	7.3	10.1
Black Non-Hispanic	11.6	16.3	9.8
Male	10.7	18.9	7.2
Female	12.4	13.6	12.0
Other Non-Hispanic	8.4	9.1	8.1
Male	7.5	9.8	6.5
Female	9.3	8.5	9.6
Hispanic	7.3	9.6	6.0
Male	6.0	9.7	4.1
Female	8.6	9.5	8.0
Puerto Rican [a]	16.7	24.8	12.8
Male	12.7	21.6	8.6
Female	20.4	27.7	16.8
Mexican/ Mexican-American [a]	5.9	7.8	4.7

Characteristic	All ages	Children	Adults
	Total	Age <18	Age 18+
Male	5.3	8.1	3.7
Female	6.5	7.4	5.9

All relative standard errors are <30% unless otherwise indicated.
[a] As a subset of Hispanic.

Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms, some do both. The former include host factors, which are primarily genes predisposing to atopy or to airway hyper responsiveness, obesity, and sex. The latter are usually environmental factors and include diet, air pollution, tobacco smoke, occupational sensitizers, infections (predominantly viral) and allergens. The main allergens identified can be classified as indoor and outdoor allergens. Indoor allergens include domestic mites, furred animals (dogs, cats, and mice), cockroach allergen, fungi, moulds, and yeasts. Outdoor allergens include pollens, fungi, moulds and yeasts (GINA 2015).

The main existing treatment options:

The goal of asthma treatment is to achieve and maintain clinical control. Different therapeutic regimens are recommended depending on age groups, levels of control, and during acute asthma exacerbations. Medications to treat asthma can be classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. They include inhaled and systemic glucocorticosteroids, leukotriene modifiers, and LABA in combination with inhaled glucocorticosteroids, sustained release theophylline, cromones, and anti-IgE. More recently, anti-IL5 monoclonal antibodies have also become available for treatment of severe eosinophilic asthma. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms. They include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline, and short-acting oral β2-agonists (Reddel 2012).

Natural history of the indicated condition in the asthma patients including mortality and morbidity:

Similar to asthma prevalence, asthma mortality varied considerably from country to country over time. The following table has summarized asthma mortality by 3-year time periods 1970 to 1984 at rates per 100,000 subjects (averaged over 3-year periods for five to 34 year-old subjects) (Jackson et al 1988).

Table 2-2 Natural history of the indicated condition in the asthma patients including mortality and morbidity

Country (range - annual no. of deaths)	1970-1972	1973-1975	1976-1978	1979-1981	1982-1984	Percentage increase Between: 1976-1978 1979-1981 &1982-1984	
New Zealand (21-68)	1.93	1.38	2.86	3.63	2.67	-7	-28

Country (range - annual no. of deaths)	1970-1972	1973-1975	1976-1978	1979-1981	1982-1984	Percentage increase Between: 1976-1978 1979-1981 &1982-1984	
Singapore (6-24)	1.27	0.60	0.78	0.62	0.91	17	47
Australia (54-106)	1.18	1.13	0.91	0.97	1.09	20	12
Japan (180-532)	0.84	0.49	0.40	0.36	0.42	5	17
England/Wales (113-199)	0.82	0.59	0.60	0.76	0.86	43	13
West Germany (108-227)	0.44	0.51	0.66	0.82	0.83	26	1
Israel (0-8)	0.35	0.41	0.15	0.15	0.38	153	153
Finland (1-11)	0.32	0.26	0.24	0.13	0.16	-33	23
Sweden (8-25)	0.32	0.32	0.37	0.66	0.46	24	-30
Switzerland (5-13)	0.30	0.26	0.37	0.25	0.23	-38	-8
United States (183-408)	0.29	0.22	0.19	0.26	0.34	78	31
Netherlands (6-25)	0.21	0.24	0.18	0.25	0.30	67	20
Canada (21-62)	0.20	0.28	0.32	0.40	0.48	50	20
France (33-91)	0.20	0.20	0.25	0.25	0.29	16	16

Based on the US deaths report from 2011 CDC (CDC/NCHS 2012c), a total of 3,404 asthma-related deaths reported translated into an asthma-related mortality of 1.1 per 100,000 subjects. Detailed data on death rates by age and gender are provided in the table below:

Table 2-3 Asthma-related mortality by age and gender

	N	Death rates per 100,000 person
All ages	3,404	1.1
Under 1 year	6	-
1-4 years	31	0.2
5-14 years	119	0.3
15-24 years	132	0.3
25-34 years	210	0.5
35-44 years	303	0.7
45-54 years	571	1.3
55-64 years	513	1.4
65-74 years	374	1.7
75-84 years	498	3.8
85 years and over	647	11.8

Important co-morbidities:

Table 2-4 Co-morbidities found in the AA target population

Comorbidity	Prevalence among unexposed AA patients
Rhinitis	
– Allergic or non-allergic	>80%

Comorbidity	Prevalence among unexposed AA patients
– Chronic rhinosinusitis and sinusitis	>75%, 84% among severe asthmatics
Gastroesophageal reflux disease (GERD)	Abnormal esophageal pH 12% to 85% GERD 50% to 80%
Obesity	16% to 30% (BMI ≥30)
Obstructive Sleep Apnea	Data not available
Psychopathologies	Depression 13% to 14% Psychological dysfunction 20.4% Anxiety 21%
VCD and dysfunctional breathing	56% of the patients with VCD have asthma no specific data on the prevalence of VCD among asthmatics
COPD	3% to 30%
Smoking	20% to 27%
Infections	Recurrent respiratory infections 58.1%
– Viral	80% of the children, 41% to 78% of the adults
– Bacterial	Mycoplasma pneumonia and Chlamydia pneumonia most common, data on prevalence not available
– Fungal	Allergic broncho-pulmonary aspergillosis

Source : Bender et al 2007, Boutin-Forzano et al 2007, Boulet and Boulay 2011, Epstein et al 2000, Kuyucu et al 2006, Macri et al 2008, Ortega et al 2002, Schatz et al 2007, Ten Brinke et al 2005
COPD : Chronic Obstructive Pulmonary Disorder

2.1.2 Chronic Spontaneous Urticaria

Incidence:

To our knowledge, no published data regarding the incidence of CSU were identified.

Prevalence:

In a study in Thailand 450 case forms of patients with chronic urticaria (CU) from a single center between 2000 and 2004, was reviewed. Of the CU cases 75% were diagnosed as CSU (Kulthanan et al 2007). In a study in Spain among 5003 individuals, prevalence of CU was found to be 6 per 1000 (95% confidence interval (CI) 4-8). Considering 75% of CU cases are CSU prevalence of CSU would be 4.5 per 1000 (95% CI 3-6) (Gaig et al 2004). In Germany a questionnaire survey was conducted among 4093 inhabitants of Berlin, Germany. Prevalence of CU was found to be 8 per 1000 (95% CI 6-11). Considering 75% of CU cases are CSU prevalence of CSU would be 6 per 1000 (95% CI 4.5-8.25) (Zuberbier et al 2010a).

Demographics of the population with CSU – age, gender, racial and/or ethnic origin and risk factors for the disease:

From the available literature it appears that the female to male ratio for CSU varies from 2 to 3:1. Review shows that women suffer from CU as well as CSU nearly twice as often as men do. The peak age of CSU patients is between 20 and 40 years (Maurer et al 2011). In a study in Taiwan 62 CSU were assessed from 2005 to 2006. The female to male ratio was 2.1:1 with mean age of 31.8 yrs (Lee et al 2011).

In a study in Thailand among CU patients which included CSU, close to 74% of them were females. Average age was 36.7 years (Silpa-archa et al 2011). In another study in Taiwan, CSU was found more in females. Among all CSU patients (including male and female) 83% of them were aged less than 49 years (Yang et al 2005). In a questionnaire-based study in Germany, 70.3% of CU was female and the mean age was 42.8 years (Zuberbier et al 2010a).

Stress was found to be a risk factor for the development of CSU and CSU was found more in females (Yang et al 2005).

The main existing treatment options:

The goal of CSU treatment is management and alleviation of the symptoms of CSU through pharmacologic measures. Treatment should begin with a course of H_1-receptor antagonists, and H_2-receptor antagonists can be used as an add-on therapy. In patients who do not respond to H_1- or H_2-receptor antagonists, a short course of OCSs can also be used as needed. For patients who continue to remain unresponsive, doxepin (a tricyclic antidepressant with antihistaminic properties), anti-leukotriene (LTRA) therapy and intermittent courses of corticosteroids are helpful treatment options. Other less traditional, more experimental therapies may also be used, such as immunomodulatory agents, plasmapheresis treatment and IV immunoglobulins (Fromer 2008, Yasharpour and Randhawa 2011). In an insurance claims based study among CSU patients 67% used prescription antihistamines, 54% used OCSs, 24% used montelukast, and 9% used oral doxepin (Zazzali et al 2012). Sulfasalazine was also found to be a safe and successful treatment option for those who have not responded adequately to anti histamines. It was found to be steroid sparing in those who were steroid dependent (McGirt et al 2006).

Natural history of the indicated condition including mortality and morbidity:

A questionnaire based study was conducted among 89 CSU patients and 105 controls in United Kingdom (UK). CSU participants reported higher levels of alexithymia than the control group (Hunkin and Chang 2012).

In another study as well CSU patients exhibited high levels of psychological distress especially high levels of anxiety (Barbosa et al 2011) Depression was found to affect 60% of CSU patients (Yasharpour and Randhawa 2011). In another study in Turkey among 84 CSU patients and 75 controls with mean age 36.83±10.26 years 60% of them has psychiatric diagnosis. The most frequent diagnosis was depressive disorder (Ozkan et al 2007).

Important co-morbidities:

Table 2-5 Co-morbidities found in the CSU target population

Comorbidity	Prevalence among unexposed CSU patients
Rhinitis – Allergic or non-allergic	A cross sectional study was done among 6019 Chronic Idiopathic Urticaria (CIU) patients using insurance claims. Allergic rhinitis was diagnosed among 48% of them (Zazzali et al 2012). In another study in Thailand 18.7% of CIU patients had a family history of allergic rhinitis (Kulthanan et al 2007). In a study in Thailand 23.3% of CIU patients had a family history of allergic rhinitis (Silpa archa et al 2011)

Comorbidity	Prevalence among unexposed CSU patients
Psychopathologies	48% of CSU patients were diagnosed with one or more psychosomatic disorders. Most common were anxiety disorders followed by depressive and somatoform disorders (Staubach et al 2011)

Source : Zazzali et al 2012, Kulthanan et al 2007, Silpa archa et al 2011, Staubach et al 2011

2.1.3 Nasal Polyps

While nasal polyps (NPs) are observed in a variety of clinical conditions including cystic fibrosis and malignancy, they are more frequently associated with a subset of chronic rhinosinusitis aptly named chronic rhinosinusitis with nasal polyps (CRSwNP) (Stevens et al 2016). The epidemiology of NP and CRSwNP overlap and both are considered for the below description in adult population.

Incidence:

In Europe, the overall incidence of symptomatic NPs was estimated to be 0.627 per 1000 patient-years in Denmark (Larsen and Tos 2002), 0.86 and 0.39 per 1000 patient-years for males and females, respectively. The incidence increased with age, reaching peaks of 1.68 and 0.82 per 1000 patient-years for males and females, respectively in the age group 50–59 years (Larsen and Tos 2002). In the USA, the incidence of CRSwNP using real-world clinical practice data from 2007 to 2009 was assessed. The average incidence of CRSwNP was 0.83 (±0.13) per 1000 person-years (Tan et al 2013).

Prevalence:

In France, the prevalence of NPs in adults was reported as 2.11% (95% CI 1.83–2.39) increasing with age (Klossek et al 2005). In Sweden, the prevalence of NPs was 2.7% (95% CI 1.9-3.5) and NPs were more frequent in men (ratio of 2.2 in men to 1 in women) and the elderly (5% at ≥ 60 years of age) (Johansson et al 2003). In Southern Finland, the prevalence of NPs was estimated to 4.3% (95% CI 2.8-5.8%) with age standardized prevalence of 3.9% (Hedman et al 1999).

In the USA, NPs are estimated to occur in 1–4% of the US general population (Batra et al 2013; Settipane and Kaliner 2013; Steven et al 2016). In Korea, the prevalence of NP in adults (≥20 years) was reported as 2.5% and increased with age (We et al 2015). Similar results were published for CRSwNP (Won et al 2018; Ahn et al 2016).

Demographics of the population with NP or CRSwNP – age, gender, racial and/or ethnic origin and risk factors for the disease:

NP is a disease of middle age with the average age of onset being 42 years and the typical age of diagnosis ranging from 40–60 years (Grigoreas et al 2002; Johansson et al 2003). Males are more likely to have NP than females (Grigoreas et al 2002). Similar results were published for CRSwNP (Bohman et al 2018; Fokkens et al 2012; Ahn et al 2016).

A study examining CRSwNP patients undergoing sinus surgery at a tertiary care center found that females with CRSwNP had more severe disease than males (Stevens et al 2015). In this study, CRSwNP was diagnosed in 38% and 62% of females and males respectively. When

compared to males, females had significantly enhanced radiographic evidence of sinus disease, were more likely to be taking systemic corticosteroids at the time of sinus surgery, and more often required revision sinus surgeries (Stevens et al 2015).

The identified risk factors for NP or CRSwNP are gender (Bohman et al 2018, Ahn et al 2016, We et al 2015), age (Bohman et al 2018, Ahn et al 2016, We et al 2015), level of education (Ahn et al 2016, We et al 2015), asthma (Bohman et al 2018, Ahn et al 2016, Chen et al 2016, We et al 2015), obesity (Ahn et al 2016, We et al 2015) and thyroid cancer (We et al 2015).

The main existing treatment options:

Intranasal and systemic/oral corticosteroids remain the mainstay of treatment. However, many patients fail to achieve complete therapeutic benefit with these medications and resort to functional endoscopic sinus surgery (FESS) and other complex sinus surgery (Rimmer et al 2014, Fokkens et al. 2012). Although FESS and intranasal and oral corticosteroids are useful and often effective in reducing the size of nasal polyps, many patients do not respond sufficiently and/or polyps return rapidly after medication withdrawal or within months to years following surgery. In one study, almost 40% of patients who received daily intranasal corticosteroids (mometasone furoate) following FESS suffered a relapse within 6 months of the procedure (Stjarne et al 2009). In another study, almost 50% of the patients who received oral corticosteroids in combination with topical therapy suffered a relapse within 12 months of treatment (Cassano et al. 1996). Moreover, oral corticosteroids are associated with significant side effects (i.e. hypothalamic-pituitary-adrenal (HPA) axis suppression, unmasking of latent diabetes), and repeat surgical procedures become progressively more complex and riskier. Currently, in the EU, the only known approved pharmacotherapy for nasal polyps is intranasal corticosteroids (mometasone furoate, and/or budesonide). Because of these treatment limitations and given that quality of life (QoL) is considerably reduced in patients with CRSwNP, there remains an important unmet medical need for treatment options in these patients (Hulse et al. 2015).

Natural history of the indicated condition including mortality and morbidity:

Using a statewide population database in Canada, 27,005 patients diagnosed with chronic rhinosinusitis (CRS) between 1996 and 2012, were retrospectively identified. The risk of mortality was approximately 1.4 times greater in patients with NP (n=1643) compared to polyp-negative CRS patients (HR=1.38, 95%CI 1.09–1.77) (Alt et al 2017).

A review of existing published information (EPOS 2005-2012) has described NP as often associated with other important medical conditions such as asthma, allergy, sensitivity to aspirin, and other associated factors such as genes and environment. As well, CRSwNP is often associated with other important medical conditions such as acute rhinosinusitis, allergic rhinitis, chronic rhinitis, asthma, gastroesophageal reflux disease, and sleep apnea (Steven et al 2016). These conditions can also influence disease severity (Stevens et al 2016).

Important co-morbidities:

Table 2-6 Co-morbidities in the target population

Co/Pre-morbidity	Prevalence among CRSwNP or NP patients
Asthma	The clinical relationship between asthma and NP was previously established (Larsen 1997). Notably, 36% of the NP patients were asthmatic with a preponderance of asthma in women (46% vs 31% in male) (Collins et al 2002). The prevalence of asthma in CRSwNP patients ranged from 23.9% in primary care settings (Tan et al 2013) to 94% in tertiary academic respiratory hospital (Fountain et al 2013). A local study in Copenhagen estimated prevalence of asthma in CRSwNP patients (n=40) to 65% (Håkansson et al 2014). The association of asthma with CRSwNP or NPs was studied and estimated to be approximately 3 to 4 times (aOR: 3.7, 95% CI 1.9-7.0) (Hedman et al 1999) (aOR: 2.8, 95% CI 2.3–3.5) (Tan et al 2013).
Allergy	The prevalence of allergy in patients with NPs has been reported as varying from 10% (Delaney et al 1976), to 64% (English 1985; Fokkens et al 2007). An association was found between levels of both total and specific IgE and eosinophilic infiltration in nasal polyps (Bachert at al 2001). Food and drug sensitivities have been reported in 31% of patients with nasal polyposis and this was more common in men (43% vs. 24%) (Rugina et al 2002). Significant adjusted OR were also estimated comparing CRSwNP to all patients without chronic sinonasal disease consulting a primary care provider at Geisinger Clinic (Pennsylvania, USA) for pre-morbid allergic rhinitis (aOR: 2.6, 95% CI 2.2-3.1) and atopic dermatitis (aOR: 1.7, 95% CI 1.1-2.5) (Tan et al 2013).
Aspirin sensitivity	NP is associated with asthma, which can be severe and refractory, particularly in those patients with aspirin exacerbated respiratory disease (AERD). It is estimated that ~10% of patients with nasal polyps and 9% of patients with CRS have AERD (Rajan et al. 2015) but the true prevalence of this disease remains unknown (Stevens et al. 2016).
Other identified chronic pre-morbid conditions (Tan et al 2013)	Adjusted OR were calculated comparing CRSwNP to all patients without chronic sinonasal disease consulting a primary care provider at Geisinger Clinic (Pennsylvania, USA): Chronic rhinitis (aOR: 3.5, 95% CI 2.8-4.4), Sleep apnea (aOR: 2.2, 95% CI 1.4-3.5), GERD (aOR: 1.5, 95% CI 1.2–1.8).

Source : Stevens et al. 2016, Tan et al 2013, Fountain et al 2013, Hedman et al 1999, Håkansson et al 2014, Rajan et al 2015, Larsen 1997, Collins et al 2002, Delaney et al 1976, English 1985, Bachert et al 2001, Rugina et al 2002.

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Extensive pre-clinical testing has highlighted no evidence of any chronic adverse effects including no immune complex disorders, no risk of IgE-mediated mast cell activation responses such as anaphylaxis, and no effect on fertility or embryo-fetal and post-natal development. Carcinogenicity studies were not performed. There may be the potential for thrombocytopenia

at suprapharmacologic doses of omalizumab. Omalizumab caused a dose-related reduction in platelet counts and thrombocytopenia in both adult and juvenile non-human primates (macaques and chimpanzees), with juvenile cynomolgus monkeys (6-10 months old) more sensitive to the reduced platelet effects than adults. However, there has been no evidence of hemorrhage or thrombotic effects in any monkey (adult or juvenile) treated with omalizumab i.e., no evidence of bleeding or the presence of microthrombic platelet aggregation or activation, or disseminated intravascular coagulation.

In juvenile monkeys (n=56) (study numbers 00-188-1565 and 00-379-1560), the threshold serum concentration of omalizumab which caused a 50% decrease in circulating platelet levels was 400 µg/mL (1 in the 56 monkeys studied). The median trough concentration of omalizumab at steady-state in 579 pediatric patients (<12 years of age) from studies 10 and IA05 and from whom concentrations could be determined was dependent upon the baseline IgE. According to the dosing table, the omalizumab dose increases with baseline IgE. Patients with higher baseline IgE receive higher doses and, consequently, have higher omalizumab serum concentrations. The median trough concentration was 185 µg/mL (5th to 99th percentiles 96.1-374 µg/mL) in the highest group with >700 IU/mL of baseline IgE, and was lower in the other groups: 135 µg/mL, 77.4 µg/mL and 41.6 µg/mL in patients with baseline IgE levels of 500-700 IU/mL, 200-500 IU/mL and 30-200 IU/mL, respectively. Thus, the median trough concentrations achieved in children were between 2.2-fold and 9.6-fold lower than the threshold concentration in juvenile monkeys associated with a 50% drop in platelets. However, it cannot be ruled out that a few pediatric patients with high baseline IgE levels may experience omalizumab concentrations overlapping with the 400 µg/mL threshold concentration for platelet effects in monkeys.

The risk of clinically-significant effects on platelets in children is anticipated to be low. Functional thrombocytopenia (as measured by tail prick bleed times) was not evident in juvenile cynomolgus monkeys until platelet levels dropped below approximately 50,000 platelets/µL which was only observed at plasma concentrations greater than 1370 µg/ml. No pediatric patient came close to this plasma concentration. This level is also a generally accepted cut-off for allowing surgical procedures in both humans and non-human primates. In humans, clinically significant complications such as purpura, bleeding episodes, or reduction in hemoglobin usually occur when the platelet count is below 20,000 platelets/µL; hence, there is a further safety margin for these serious events occurring in children. We acknowledge a degree of uncertainty in the assumption that children behave like juvenile monkeys. However, a careful examination of the clinical data yielded no evidence that omalizumab treatment is associated with a significantly increased risk of clinically significant and sustained drops in platelet numbers or thrombocytopenia in pediatric patients.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including:	
Single and repeat-dose toxicity: Omalizumab was well tolerated in single dose studies with no mortalities or treatment related	Overall, omalizumab has been shown to have a well-tolerated non-clinical safety profile. With the exception of the reversible

Key Safety findings (from non-clinical studies)	Relevance to human usage
adverse findings up to 100 mg/kg in mice by IV bolus injection and up to 50 mg/kg (SC) or 200 mg/kg (IV) in monkeys. Omalizumab was well tolerated with no treatment-related mortalities or adverse findings up to 50 mg/kg for 4 weeks (weekly IV bolus injections) in mice or up to 5 mg/kg 3x weekly for 26 weeks (SC or IV injections) in monkeys. **Local tolerance:** Omalizumab did not cause hemolysis of human erythrocytes *in vitro*. There was no evidence of local irritation at concentrations of 125 mg/mL in rabbits (acute and repeated dose studies). In the 6 months study in cynomolgus monkeys a dose-related increase in the incidence and severity of acute hemorrhage and inflammation at the SC injection site was observed. **Reproductive and developmental toxicity:** Reproductive toxicology studies in cynomolgus monkeys have been conducted with omalizumab. No adverse effects observed in studies of male and female fertility with SC doses up to 75 mg/kg per week (at least 8-fold the maximum clinical dose in mg/kg over a 4-week period) of omalizumab and same dose levels did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing. Placental transfer of omalizumab resulted in fetal serum concentration of 33% of maternal levels and 0.15% of maternal serum level was observed in the milk. These results were anticipated as maternal-fetal transfer of Immunoglobulin G (IgGs) via FcRn is well documented, as is antibody transfer to neonates and infants via milk. At SC doses of 50 and 250 mg/kg omalizumab was well tolerated in juvenile cynomolgus monkeys but caused a reversible thrombocytopenia with accompanying decrease in platelets and prolongation of bleeding time. **Immune function:** Omalizumab did not have effects on immune function or on levels of immunoglobulins and *in vitro* omalizumab did not cause hemolysis of erythrocytes in whole human blood.	thrombocytopenia associated toxicity experienced only at high serum concentrations, there has been no evidence of toxicity of omalizumab in any nonclinical study conducted to date, including *in vitro* studies assessing hemolytic potential as well as tissue cross-reactivity, and *in vivo* studies assessing acute, chronic, or reproductive toxicity and local irritation at injection sites. Finally, there has been no safety issues associated with decreasing IgE to non-detectable levels in cynomolgus monkeys.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Cardiovascular & respiratory safety: Omalizumab produced no effects on blood pressure, heart rate, body temperature, respiration rate or electrocardiogram (ECG) intervals in cynomolgus monkeys at doses up to 5mg/kg 3 x weekly up to 6 months by IV and SC administration. Reversible dose dependent treatment-related decreases in platelets and in some cases thrombocytopenia with associated prolongation of bleeding time and focal hemorrhage in several organs was observed in juvenile monkeys after supra-pharmacological doses in juvenile cynomolgus monkeys at ≥15mg/kg and in adult cynomolgus monkeys at ≥30mg/kg.	
Other toxicity-related information or data	
Human and non-human primate tissue cross-reactivity: Tissue cross reactivity studies identified occasional specific staining in germinal centers of lymph nodes or Peyer's patches in monkeys but not in humans. These sporadic incidences of specific binding are presumed to result from IgE synthesis by lymphoid cells. Mechanistic studies on omalizumab-induced effects on platelets: Omalizumab caused a dose-related reduction in platelet counts & thrombocytopenia in both adult and juvenile non-human primates (macaques and chimpanzees), with juvenile cynomolgus monkeys (6-10 months old) more sensitive to the reduced platelet effects than adults. However, there has been no evidence of hemorrhage or thrombotic effects in any monkey (adult or juvenile) treated with omalizumab i.e., no evidence of bleeding or the presence of microthrombic platelet aggregation or activation, or disseminated intravascular coagulation.	

Source: IB version 18

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Approximately [redacted] patients received omalizumab treatment in MAH/Genentech-Roche sponsored investigational clinical trials (CTs) cumulatively. Of these, approximately [redacted] patients received omalizumab treatment in the ongoing studies and [redacted] patients in the completed studies.

Estimates of the cumulative patient exposure for ongoing and completed studies, based upon actual exposure data from 79 completed interventional CTs in AA and 11 completed interventional CTs in CSU/CIU and the enrollment and randomization schemes for six ongoing interventional trials sponsored by Novartis/Genentech-Roche is provided in Table 4-1.

Table 4-1 Estimated subject exposure to omalizumab from completed clinical studies

Treatment	Allergic asthma**		CSU/CIU		Nasal Polyps	
	Number of subjects***	Exposure (PTY)	Number of subjects	Exposure (PTY)		
Completed studies						
Omalizumab						
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Healthy volunteers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No-treatment with omalizumab (Control)						
Patients§	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Healthy volunteers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo£	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXCELS						
Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control (switched to omalizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control (no-treatment with omalizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Includes patients and healthy volunteers, excludes Compassionate Use Program patients and patients from third party trials as of 31-Dec-2018 Exposure for asthma patients is counted up to the last dose. Exposure for CSU patients is counted up to the last dose plus dosing interval 2 or 4 weeks (wash out).
Study Q0709g, Q0716g and Q2569g were not included due to negligible Xolair exposure through nebulization.
Study CIGE025AQ4458g (X-PAND) was not included due to negligible Xolair exposure in the skin prick/intradermal test
Study CIGE025EFR02 (SUNRISE) was not included due to a single-arm and open label study
** includes subjects that have received Xolair and comparators during crossover studies.
*** Patients that received both Xolair and a comparator during a study (n=[redacted]) are counted only once (such as in a cross over studies)
In the EXCELS study, among [redacted] patients in the Non-Xolair cohort, [redacted] patients switched to omalizumab during the study. We do not have data on duration of exposure for [redacted] patients in control group.

§ Patients neither receiving omalizumab nor placebo as add-on treatment to standard of care treatment
£ Patients not receiving omalizumab but receiving placebo as add-on treatment to standard of care
CIU = chronic idiopathic urticaria, CSU = chronic spontaneous urticaria
Source: Annex 7, Study GA39688, Study GA39855.

Table 4-2 Duration of exposure to omalizumab (by indication)

Asthma		
Duration of exposure (at least)	**Subjects**	**Subject-time (years)**
≥ 1m		
≥ 3m		
≥ 6m		
≥ 12m		
Overall		
CSU/CIU		
Duration of exposure (at least)	**Subjects**	**Subject-time (years)**
≥ 1m		
≥ 3m		
≥ 6m		
≥ 12m		
≥ 1 day (Overall)		

- A subject is counted only once for each treatment group.
- Duration of exposure is the number of days between the first dose date and the last dose date + the dosing interval.
- Subject-time (years) = (sum of the duration of exposure over patients in days)/365.25.
- 1 Month = 30 days, 3 months = 91 days, 6 months = 182 days, 12 months = 365 days.

Source: Annex 7

An estimate of cumulative exposure to omalizumab by dose for CSU is provided in the Table 4-3.

Table 4-3 Exposure by dose

CSU/CIU		
Dose of exposure	**Subjects**	**Subject-time (years)**
Omalizumab 75mg		
Omalizumab 150mg		
Omalizumab 300mg		
Omalizumab 600mg		
All other Omalizumab*		
Placebo		
Total		

*These patients received omalizumab based on “asthma dosing table”.
Exposure by dose cannot be provided for AA
Source: Annex 7

An estimate of cumulative exposure to omalizumab by age and gender (by indication) for completed clinical trials is provided in Table 4-4.

Table 4-4 Exposure to omalizumab by age group and gender (by indication)

Asthma

Age group (years)	Male Subjects	Male Subject-time (years)	Female Subjects	Female Subject-time (years)
< 12				
≥ 12-≤ 17				
≥ 18-≤ 64				
≥ 65				
Total				

CSU/CIU

Age group (years)	Male Subjects	Male Subject-time (years)	Female Subjects	Female Subject-time (years)
<12				
12-≤ 17				
18-≤ 64				
≥ 65				
Total				

- A subject is counted only once for each treatment group.
- Duration of exposure is the number of days between the first dose date and the last dose date + the dosing interval.
- Subject-time (years) = (sum of the duration of exposure over patients in days)/365.25.

Source: Annex 7

An estimate of cumulative exposure to omalizumab by ethnic or racial origin (by indication) for completed clinical trials is provided in the Table 4-5.

Table 4-5 Exposure to omalizumab by ethnic or racial origin (by indication)

Asthma

Racial group	Subjects	Subject-time (years)
Black		
Caucasian		
Asian or Pacific Islander		
Other		
Unknown		
Total		

CSU/CIU

Racial group	Subjects	Subject-time (years)
Caucasian		
Black		
Asian or Pacific Islander		
Other		
Unknown		
Total		

- A subject is counted only once for each treatment group.

- Duration of exposure is the number of days between the first dose date and the last dose date + the dosing interval.
- Subject-time (years) = (sum of the duration of exposure over patients in days)/365.25.

Source: Annex 7

A pregnant women population has been studied through a non-interventional pregnancy registry (EXPECT-Q2952g). The cumulative exposure data from the EXPECT registry is presented in the Table 4-6.

Table 4-6 Exposure in special population: cumulative EXPECT data

	Subjects	Subject-time (days)
Pregnant women	[redacted]	[redacted]
Lactating women	[redacted]	[redacted]

End of Study: 4 January 2018
Source: EXPECT Pregnancy Registry

The numbers included in the table represent the final data presented in the Study Report. In total 309 pregnancies were enrolled in the registry however in the final analyses other indications that were not asthma, multiple pregnancies and retrospective cases were excluded. 154 women took Xolair while breastfeeding.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Exclusion criteria which will remain as contraindications			
Known ingredient hypersensitivity	Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab	No	Hypersensitivity to omalizumab or any component of the excipients listed in the prescribing information is a contraindication
Exclusion criteria which are NOT proposed to remain as contraindications			
Female of childbearing potential	In animal reproduction studies, no evidence of fetal harm was observed in cynomolgus monkeys with subcutaneous doses of omalizumab up to approximately 8 times the maximum recommended human dose (MRHD) of 8.75 mg/kg/week on mg/kg basis. IgG molecules are known to cross the placental barrier. Because animal reproduction studies are not always predictive of human response, female with child bearing potential were excluded from pivotal trials to avoid fetal malformation in pregnant women and to avoid potentially serious developmental adverse effects in newborns.	No	Pregnancy outcomes were considered as missing information until the data was available from EXPECT pregnancy registry. Based on data from EXPECT study this missing information is now well characterized and no safety risks were identified to the newborn and mother compared with a disease matched cohort.
Prior history of malignancy	Initial clinical studies at registration showed imbalance in new primary malignancies. A 5-year safety follow-up	No	Standard exclusion in clinical trials

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Exclusion criteria which will remain as contraindications			
Known ingredient hypersensitivity	Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab	No	Hypersensitivity to omalizumab or any component of the excipients listed in the prescribing information is a contraindication
Exclusion criteria which are NOT proposed to remain as contraindications			
	study (EXCELS) was required by the FDA.		
Known latex allergy (for planned exposure to Pre-Filled Syringe [PFS] only)	Potential risk of hypersensitivity due to theoretical possibility of residual latex allergens which may be transferred from the needle cap onto the syringe	No	This was already categorized as a potential risk in previous RMPs. Removed from the current version as this does not fulfil the definition of important potential risk according to Module GVP V revision 2

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reaction, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Children	In the AA indication, safety and efficacy in pediatric patients below the age of 6 have not been established and the use of omalizumab in this age-group is therefore not recommended. In the CSU indication, clinical studies to assess the safety and efficacy of omalizumab in patients younger than 12 years have not been conducted and the use of omalizumab in this age-group is therefore not recommended.
Elderly	There are limited data available on the use of omalizumab in patients older than 65 years but there is no evidence that elderly patients have a safety or efficacy profile that differs from younger adult patients.
Pregnancy	There are no adequate and well-controlled studies of omalizumab in pregnant women. IgG molecules are known to cross the placental barrier. Because animal reproduction studies are not always predictive of human response, all patients with child bearing potential were

Type of special population	Exposure
	excluded from pivotal trials to avoid fetal malformation in pregnant women and to avoid potentially serious developmental adverse effects in newborns. Reproduction studies in cynomolgus monkeys have been conducted with omalizumab. Subcutaneous doses up to 75 mg/kg per week (at least 8-fold the maximum clinical dose in mg/kg over a 4-week period) of omalizumab did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing. Although no clinically significant effects on platelets have been observed in patients, doses of omalizumab in excess of the clinical dose have been associated with age-dependent decreases in blood platelets in nonhuman primates, with a greater relative sensitivity in juvenile animals. In reproduction studies in cynomolgus monkeys, there was no clinical evidence of thrombocytopenia in neonatal monkeys from mothers treated with up to 75 mg/kg omalizumab; however, platelet counts were not measured in these offspring. Among all the AA Phase I/II/III studies, for patients who received omalizumab, intra-uterine death was reported in three patients during the clinical studies; none was considered drug-related. While the investigator reported intrauterine death, the definition of intrauterine refers to gestational age of 20 or more weeks; none of the cases were observed in that gestational age and are therefore considered to be spontaneous abortions rather than intra-uterine death cases. No cases of intra-uterine death have been reported in the CSU program. Studies suggest that the risk of spontaneous abortion, as well as other adverse pregnancy outcomes, is elevated in patients with asthma (Tata et al 2007). An analysis of spontaneous abortions in EXCELS study revealed that the rate of spontaneous abortions observed among Xolair-treated pregnant patients was 12%. The rate of spontaneous abortion among all pregnancies in the general US population is estimated to be 15% (Ventura et al 2012). Although the approach used to calculate the rate of spontaneous abortion for the EXCELS study was more conservative than the approach used to calculate the rate of spontaneous abortion in the general US population, the rates were similar. In the EXPECT pregnancy registry, outcomes from 250 prospectively enrolled women with asthma were included in the primary analysis population. Women in this population received Xolair for a median of 8.7 months during pregnancy (range: 1.0-9.9 months). The vast majority of women (98.4%) were exposed to Xolair during the first trimester of pregnancy and 82.6% were exposed in all three trimesters. Among the pregnancies in the EXPECT cohort used for comparison to a Quebec External Comparator Cohort (QECC) (women with moderate to severe asthma, excluding those with an elective termination or spontaneous abortion at <20 weeks gestational age), 99.1% (228/230) led to live births and 0.9% (2/230) ended in fetal death/stillbirth, similar to the 99.3% and 0.9%, respectively, found in QECC. Among singleton infants born to women with moderate to severe asthma, the prevalence of major congenital anomalies was 8.1% (18/223) of infants in

Type of special population	Exposure
	EXPECT, which was similar to the age-adjusted prevalence of major congenital anomalies in QECC (8.9%). The frequency of premature birth was higher in EXPECT than in QECC (15.0% vs. 11.3%), as was the proportion of infants with low birth weight (≤ 2.5 kg; 13.7% vs. 9.8%). The results for premature birth may reflect the underlying higher prevalence of premature birth in the United States (generally reported as 9.6%-12.8% in analyses conducted between 2006 and 2016) compared to that for Canada (7.8% in 2013; Martin and Osterman 2013; Statistics Canada 2016; Martin et al. 2017), and may also be related to the higher prevalence of obesity in EXPECT, a known risk factor for premature delivery (Kim et al. 2017). The frequency of infant infections identified in EXPECT was evaluated as an indirect measure of immune system development after exposure during pregnancy or through breastfeeding. The majority of 240 infants (77.5%) were breastfed. SAEs categorized as "infections and infestations" were similar in infants who were not breastfed,(11.4%). (16/154) in infants who were exposed to Xolair through breastfeeding (10.4%), and in infants who were breastfed without exposure to Xolair through breastfeeding (12.5%).
Breast feeding women	While omalizumab presence in human milk has not been studied, IgG is excreted in human milk and therefore it is expected that omalizumab will be present in human milk. The potential for omalizumab absorption or harm to the infant are unknown; caution should be exercised when administering omalizumab to a nursing woman. The excretion of omalizumab in milk was evaluated in female cynomolgus monkeys receiving SC doses of 75 mg/kg/week. Neonatal plasma levels of omalizumab after *in utero* exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of omalizumab were 0.15% of the maternal serum concentration.
Patients with renal and / or hepatic impairment	There are no pharmacokinetic (PK) or PD data in patients with renal or hepatic impairment. While no particular dose adjustment is recommended, omalizumab should be administered with caution in these patients.
Patients with a disease severity different from the inclusion criteria in the clinical trial population	Patients with moderate and severe asthma have been included in the pediatric, adolescent and adult clinical programs. In the CSU indication, patients aged 12-75 years with a confirmed diagnosis of CSU who are refractory to H1 antihistamine treatment have been studied in the Phase III clinical program. In one of the three Phase III studies, patients had to be refractory to H1 antihistamine treatment at up to four-times the approved dose in combination with a H2 blocker and/or a LTRA. In the nasal polyps clinical program, patients aged 18-75 years were assessed. These patients were considered difficult to treat, as evidenced by large bilateral nasal polyps, and who had inadequate response to intranasal corticosteroids.
Patients of different Age, Race/Ethnicity, Gender, Body Mass Index	The population PK of omalizumab was analyzed to evaluate the effects of demographic characteristics. Analyses of these data suggest that no dose adjustments are necessary for age (6-76 years), race, ethnicity, gender, or body mass index.

Source: Annex 7

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

The estimate of patient exposure by region, and formulation was calculated in patient-treatment-year (PTY), based on worldwide sales volume in kilogram (kg) of active substance (both as vials and pre-filled syringe formulations) sold cumulatively since launch of the product and the defined daily dose (DDD).

An estimate of patient exposure by age group, gender and indication was calculated based on Intercontinental Marketing Services (IMS) Health data. Information on omalizumab prescriptions was obtained from "IMS Medical Audit Database" for eight countries [Brazil, Canada, France, Germany, Italy, Japan, Spain, and USA]. Prescription data was collected for one to two consecutive workweeks per quarter, depending on prescribers (e.g. general practitioners, specialists) and then projected. The data collection methodology was the same for all countries except Japan, where the information was collected on a semester (Q2 & Q4) basis only. To provide a true representation of specialty prescribing habits, both prescription data from general practitioners and specialists in different regions (without hospital prescriptions) were included. In addition, information on hospital prescriptions was collected in Japan alone and analyzed separately. All omalizumab formulations were included.

6.1.2 Part II Module SV.1.2. Exposure

Estimate of patients exposure based on worldwide sales data

An estimate of patient exposure is calculated based on worldwide sales volume in kilograms of active substance sold during the reporting interval and the defined daily dose of 13.63 mg. The estimated interval exposure was approximately [redacted] Patient-Treatment-Years (PTY). The sales volume of omalizumab during the reporting interval was approximately [redacted] of active substance ([redacted] sold by Genentech-Roche representing [redacted] PTY for the USA, [redacted] sold by Novartis representing [redacted] PTY for the rest of the world).

Please note that Bolstran® sales data are included in the Novartis sales data for omalizumab (India).

The cumulative exposure from marketing experience based on region and formulation with data cut-off of 31-Dec-2018 is presented in the tables below:

Table 6-1 Cumulative exposure from marketing experience by region estimated using sales data

Region	Cumulative period		
	Sold volume (Kg)	Patient exposure (PTY)	Patient exposure (%)
USA	[redacted]	[redacted]	[redacted]
ROW*	[redacted]	[redacted]	[redacted]
EEA+Switzerland	[redacted]	[redacted]	[redacted]

Region	Cumulative period		
	Sold volume (Kg)	Patient exposure (PTY)	Patient exposure (%)
Canada	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Total	**5,688.81**	**1,143,490**[**]	**100**

EEA: European Economic Area; PTY: Patient-Treatment-Years; ROW: Rest of the World; USA: United States of America.
[*]ROW includes all countries except USA.
[**]Values are rounded-off
This table includes interval data obtained from Jul 2003 to Dec 2018.
Source of data: Worldwide sales volume

Table 6-2 Cumulative exposure from marketing experience in the EEA and Switzerland region estimated using sales data

Region	Cumulative period		
	Sold volume (Kg)	Patient exposure (PTY)	Patient exposure (%)
[redacted]	[redacted]	[redacted]	[redacted]

Region	Cumulative period		
	Sold volume (Kg)	Patient exposure (PTY)	Patient exposure (%)
[redacted]	[redacted]	[redacted]	[redacted]
Total	**1756.5**	**353068**	**100**

* Registered through centralized procedure

Table 6-3 Cumulative exposure from marketing experience by formulation estimated using sales data

Formulation	Cumulative period		
	Sold volume (Kg)	Patient exposure (PTY)	Patient exposure (%)
USA			
[redacted]	[redacted]	[redacted]	[redacted]
ROW*			
[redacted]	[redacted]	[redacted]	[redacted]
Total	**5,688.81**	**1,143,490****	**100**

PTY: Patient-Treatment-Years; ROW: Rest of the World; USA: United States of America

*ROW includes all countries except USA

**Values are rounded-off.

This table includes cumulative data obtained from Jul 2003 to Dec 2018.

#The values in the table are calculated by using formulae in excel. The sum up values may not match with the total as the figures are rounded off. Exact number is taken into consideration when calculating totals, which accounts for discrepancies (i.e. ± 1).

Source of data: Worldwide sales volume

Distribution by Age group and Gender

An estimate of patient exposure by age group, gender and indication was calculated based on IMS Health data from Q4 2017 - Q3 2018 which were available at the time of this report.

Information on omalizumab prescriptions was obtained from 'IMS Medical Audit Database' for nine countries (Argentina, Brazil, Canada, France, Germany, Italy, Japan, Spain and USA).

In order to estimate patient exposure by indication, age, gender and indication, the percentages calculated or extracted from IMS are applied to the cumulative post-marketing patient exposure calculated using worldwide sales data.

Table 6-4 Cumulative exposure (in PTY) by gender estimated using both sales and IMS data

Gender	Cumulative period	
	Percentage (%)	Exposure (PTY)
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]7
Not Reported	[redacted]	[redacted]
Total	**100%**	**1,143,490**

Table 6-5 Cumulative exposure (in PTY) by age group estimated using both sales and IMS data

Age group	Cumulative period	
	Percentage (%)	Exposure (PTY)
0 - 5 years	[redacted]	[redacted]
6 - 11 years	[redacted]	[redacted]
12 - 17 years	[redacted]	[redacted]
18 - 64 years	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]
Age unspecified	[redacted]	[redacted]
Total	**100%**	**1,143,490**

Source: IMS Medical Detailed Database

Table 6-6 Cumulative exposure (in PTY) by indication estimated using both sales and IMS data

Indication	Cumulative period	
	Percentage (%)	Exposure (PTY)
Asthma	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Other indications	[redacted]	[redacted]
Total	**100%**	**1,143,490**

Source: IMS Medical Detailed Database

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

The MAH is not aware of any misuse potential for omalizumab for illegal purposes.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

Not applicable, the RMP was already approved.

8.2 Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Omalizumab was safe and well-tolerated in the target population of patients with nasal polyps, and generally consistent with the established safety profile in patients with asthma or CSU. No new or unexpected safety signals were observed. There is no new important identified risk, important potential risk or missing information.

8.3 Part II SVII.3: Details of important identified risks, important potential risks, and missing information

All risks have been assessed based on available data from indications, AA and CSU with cut-off date of 31-Dec-2018 and NP with a cut-off date of 11-March-2019.

8.3.1 SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Anaphylaxis / anaphylactoid reactions

As an immunoglobulin, omalizumab is a protein, and so the possibility of hypersensitivity reactions, particularly immediate-type events such as anaphylactic/anaphylactoid reactions, and urticaria and other skin rashes must be considered.

Anaphylactic and anaphylactoid reactions were very rare in the clinical development programs. Urticaria and other skin rashes occurred at similar rates in the placebo and omalizumab groups. Adopting a conservative approach, however, the MAH has included a warning about anaphylactic reactions and hypersensitivity reactions in the SmPC. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement and either airway compromise, reduced blood pressure with or without associated symptoms, or both, and a temporal relationship with omalizumab administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. These search criteria were based on Sampson criteria (Sampson et al, 2006).

The same diagnostic criteria of anaphylaxis were used for the clinical database in children and adults (Sampson et al, 2006). Anaphylaxis was defined in two ways. In the first, the preferred terms (PTs) anaphylactic reaction and anaphylactoid reaction were used for identification. In the second, Sampson's criteria for anaphylaxis, were used (which includes anaphylaxis and anaphylactic reactions as terms of Category A (not shown in Table 8-1), respiratory related criteria as category B, skin related criteria as Category C, cardiac criteria as Category D and gastrointestinal criteria as Category E (not shown in Table 8-1) . Patients were defined as being

part of Group I or Group II, where Group I patients had at least one AE in Category C and one AE in Category B, and Group II patients had at least one AE in Category C and one AE in Category D. The temporal relationship between events was not considered when identifying patients with a cluster of events.

According to protocol criteria, events with these AEs may have been recorded as an adverse event of special interest (AESI), but not have met the Sampson criteria for anaphylaxis.

Table 8-1 Anaphylaxis categories (Sampson criteria)

Category B		**Category C**		**Category D**
Respiratory related		**Skin related**		**Cardiac related**
Acute respiratory failure	Nasal obstruction	Allergic edema	Injection site urticaria	Blood pressure decreased
Asthma	Oedema mouth	Angioedema	Lip edema / swelling	Blood pressure diastolic decreased
Bronchial oedema	Oropharyngeal spasm	Erythema	Nodular rash	Blood pressure systolic decreased
Bronchospasm	Oropharyngeal swelling	Eye edema	Ocular hyperaemia	Cardiac arrest
Cardio-respiratory distress	Respiratory arrest	Eye pruritus	Skin swelling	Cardio-respiratory arrest
Chest discomfort	Respiratory distress	Eye swelling	Swelling face	Cardiovascular insufficiency
Choking/choking sensation	Respiratory failure	Eyelid edema	Swelling	Hypotension
Circumoral oedema	Reversible airways obstruction	Face edema	Any PT including pruritus	Diastolic hypotension
Cough	Sensation of foreign body	Flushing	Any PT including rash	
Cyanosis	Sneezing	Periorbital edema	Any PT including urticaria	
Dyspnoea	Stridor			
Hyperventilation	Swollen tongue			
Irregular breathing	Tachypnoea			
Laryngeal dyspnoea	Throat tightness			
Laryngeal oedema	Tongue oedema			
Laryngospasm	Tracheal obstruction			
Laryngotracheal oedema	Tracheal oedema			
Mouth swelling	Upper airway obstruction			
	Wheezing			

Criteria based on: Sampson et al 2006; AE terms were categorized for pooling based on a Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Queries (SMQ) algorithmic search (MedDRA v18.1), PSUR21.

Category B: Respiratory; Category C: skin; Category D: cardiac

Clinical Trial data in AA and CSU patients:

Anaphylaxis in adolescent and adult patients (12 years old and older) with AA

In clinical trials from randomized, double-blind placebo controlled studies in AA, anaphylaxis /anaphylactoid reactions occurred at a similar rate in the omalizumab and placebo groups (Table 8-2).

Table 8-2 Analysis of potential and identified risk by risk factor and treatment - Anaphylaxis - anaphylactoid reactions

	Omalizumab N=3184 Exp=21.59 100PY n (IR/100 pyr) 95% CI	Control N=239 Exp=0.73 100PY n (IR/100 pyr) 95% CI	Placebo N=2921 Exp=19.60 100PY n (IR/100 pyr) 95% CI	Omalizumab vs Placebo IRR 95% CI	Omalizumab vs Placebo IRD 95% CI
Anaphylaxis - anaphylactoid reactions					
Patients with at least one AE	3 (0.14) (0.029,0.406)		5 (0.26) (0.083,0.595)	0.54 (0.085,2.800)	-0.12 (-0.389,0.157)
Maximum Severity					
Mild			1 (0.05) (0.001,0.284)		
Moderate	1 (0.05) (0.001,0.258)		2 (0.10) (0.012,0.369)	0.45 (0.008,8.721)	-0.06 (-0.224,0.112)
Severe	2 (0.09) (0.011,0.335)		2 (0.10) (0.012,0.369)	0.91 (0.066,12.527)	-0.01 (-0.200,0.182)
SAE	2 (0.09) (0.011,0.335)		2 (0.10) (0.012,0.369)	0.91 (0.066,12.527)	-0.01 (-0.200,0.182)
Adverse events with fatal outcome	-	-	-	-	-

Source: Annex 7

Based on the results from the retrospective case control study (XPAND), which was finalized in 2014 and reported in PSUR20 v2, the Core Data Sheet (CDS) and SmPC was updated in 2015 to include a statement “history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration”.

The retrospective observational study IGE025A2453 with title ‘Estimating the risk of anaphylaxis in patients prescribed omalizumab using a large retrospective claims database’, analyzed data from large claims databases from patients in the US. Results showed that anaphylactic reaction following omalizumab administration appears to be a relatively uncommon event. Anaphylaxis on a day of omalizumab injection was recorded in 18 of 6,148

patients, with an incidence of 0.29%. In a multivariable analysis, a prior history of other anaphylaxis and absence of both asthma and idiopathic urticaria were independently associated with a greater likelihood of anaphylaxis being specified on a day of a patient receiving omalizumab. These data must be interpreted in light of a number of significant limitations inherent in the claims database used in this analysis, such as: miscoding, lack of adjudication, lack of documentation for epinephrine administration, impossibility to distinguish event from medical history in some cases, and a pattern of events that suggested alternative diagnoses and/or were followed by multiple subsequent negative re-challenges. Some events might not have qualified as anaphylaxis based on Sampson criteria (Sampson et al, 2006) and/or might have been triggered by factors other than omalizumab. Most (14/18) patients continued to receive omalizumab following the index event. Given all the above limitations inherent in a claims-based database, the findings from the small numbers of patients in the current study must be interpreted with appropriate caution.

Anaphylaxis in the clinical pediatric (6 to less than 12 years old) program

In the pediatric AA clinical development program, there were no anaphylactic or anaphylactoid reactions to omalizumab. Even though few patients from the AAP (double-blind, placebo controlled AA studies), AAO (open-label, controlled and uncontrolled AA studies) and APC (double-blind placebo controlled in all indications) populations had AEs that are listed in the anaphylaxis categories shown in Table 8-1 and described in Section 8.3.1, no patient experienced multiple symptoms which met the Sampson criteria for anaphylactic reaction and was reported as such in the trials. In all the populations, urticaria and other skin rashes occurred at similar rates between the treatment groups.

Anaphylaxis in adolescents and adults in the CSU population:

The diagnosis of anaphylaxis in patients with CSU may be particularly challenging, since core components of anaphylaxis are also cardinal features of the disease. CSU is defined by the manifestation of daily, or almost daily, hives and itching without an obvious cause. Angioedema is also known to be a feature in approximately 28-50% of patients with CSU (Zuberbier et al (2010b)). These factors make it difficult to determine whether anaphylaxis has actually occurred, and if so, whether such events represent a reaction to omalizumab or are related, in part, to the patient's underlying CSU.

In the phase II/III clinical development program in CSU any patients with AEs that are listed in the anaphylaxis categories shown in Table 8-1 and described in Section 8.3.1 as part of Sampson criteria were adjudicated. No patient experienced multiple symptoms which met the Sampson criteria for anaphylactic reaction and was reported as such in the trials.

Anaphylaxis in adults (18 years and above) in the Nasal Polyps population:

No adjudicated anaphylaxis/anaphylactic reactions were identified from the pivotal studies.

Post marketing data in AA and CSU patients

Upon medical review of post-marketing data, no change in frequency, severity or in pattern of anaphylactic events was identified from 2003 until 31-Dec-2018. The overall reporting rate (i.e., in children, adolescents, adults and patients for whom the age was not reported) was low with 0.16 % using the Anaphylactic reaction SMQ (narrow) search criteria and remained stable over time (Table 8-3).

Table 8-3 Cases of anaphylaxis by age group (cases from Narrow Standardized MedDRA Query only)

Period (Year)	Young child (< six years)	Child (six to < 12 years)	Adolescent (12 to 17 years)	Adult 18 and older	Age unknown	Total	Patient-years**	RR/100 PTY
Pre-2003	0	0	0	4	0	4	0	0
2003	0	0	1	5	0	6	2,550	0.24
2004	0	0	3	17	4	24	18,690	0.13
2005	0	0	0	20	4	24	30,270	0.08
2006	0	0	3	21	3	27	40,890	0.07
2007	0	3	9	51	15	78	38,690	0.20
2008	2	2	9	56	13	82	41,730	0.20
2009	0	3	7	53	24	87	48,970	0.18
2010	0	0	3	63	13	79	57,100	0.14
2011	0	2	5	35	44	86	63,980	0.13
2012	1	4	7	54	32	98	68,990	0.14
2013	0	5	7	66	28	106	79,450	0.33
2014: Indication: Asthma, other and unknown								
	0	2	8	102	51	163	94,941	0.17
2014: Indication: CSU/CIU								
	0	0	1	21	12	34	2,935	1.16***
2015: Indication: Asthma, other and unknown								
	0	8	4	81	49	142	98,034	0.14
2015: Indication: CSU/CIU								
	1	0	4	42	9	56	17,300	0.32***
2016: Indication: Asthma, other and unknown								
	0	4	17	77	49	147	100,955	0.14
2016: Indication: CSU/CIU								
	0	2	4	51	10	67	35,379	0.19***
2017: Indication: Asthma, other and unknown								
	0	12	15	71	48	146	103,601	0.14
2017: Indication: CSU/CIU								
	0	0	4	51	14	69	50,567	0.14***
2018: Indication: Asthma, other and unknown								
	0	5	10	65	44	124	113,560	0.11
2018: Indication: CSU/CIU								
	0	0	6	76	17	99	56,342	0.18***
Total	**4**	**52**	**127**	**1,082**	**483**	**1,827**	**1,143,490**	**0.16**

*The total number of cases presented in the above table (n=1525) may be different from what was described in previous PSURs and cumulatively (n=1580) due to the receipt of follow-up information after their respective reporting interval of analysis

**For time periods prior to 2007, the patient exposure was calculated based on an average DDD of 10 mg. An analysis presented in PSUR covering period 01 Jan 2007 – 30 Jun 2007 comparing several approaches utilized in prior PSURs, resulted in the adaptation of the DDD to 13.63 mg for the calculation of exposure in patient-years

***Cases were not adjudicated; since core components of anaphylaxis such as urticaria and angioedema are also cardinal features of CSU/CIU these cases might not represent 'true' anaphylaxis cases

RR = Reporting rate

The majority of anaphylactic-type reactions have been reported to occur after the 1st dose with numbers decreasing with subsequent doses. Almost 70% of the anaphylaxis has been reported within the first three doses. As expected for an anaphylactic-type reaction (type I), events were reported to occur predominantly within the first two hours post-dosing with few reports occurring as far as > 36 hours post-dose. Almost 70% of the anaphylaxis has been reported within first two hours post-dosing.

Table 8-4 Important identified risk: Anaphylaxis / anaphylactoid reactions (Other details)

Anaphylaxis / anaphylactoid reactions	Details
Potential mechanisms	Direct or indirect effects on mast or basophil cells.
Evidence sources and strength of evidence	Current evidence is based on a pooled clinical study database of AA and CSU with 16,249 patients, 2 pooled NP studies with 135 patients and 1,143,490 PTY exposure from post-marketing scenario and on the review of total of 6,604 cases reported as anaphylaxis to the company safety database.
Characterization of the risk	Refer to the Table 8-2 and Table 8-3 above.
Risk factors and risk groups	Patients with previous history of anaphylaxis, children, atopic individuals and asthmatics.
Preventability	Outreach and education to caregivers and patients on signs and symptoms of anaphylaxis, and the need to get immediate treatment.
Impact on the benefit-risk balance of the product	Although rare, anaphylaxis can be life threatening and requiring emergency care. This safety concern has a high impact on the benefit-risk balance of omalizumab. However, the benefit-risk balance remains positive for omalizumab for the treatment of AA and CSU.
Public health impact	Unknown at this time, however, based on incidences in the safety databases, the potential for significant public health impact is low.

Important identified risk: Churg Strauss Syndrome/Hypereosinophilic syndrome

Churg Strauss Syndrome (CSS) is a rare disease. It is now renamed as Eosinophilic Granulomatosis with Polyangiitis (EGPA).

The diagnostic criteria included in the definition of CSS vary depending on the agreements reached by different medical associations. For classification purposes, according to the American college of Rheumatology (ACR), a patient shall be said to have CSS if at least four of these six criteria (asthma; eosinophilia >10%; neuropathy, mono or poly; pulmonary infiltrates, non-fixed; paranasal sinus abnormality; extravascular eosinophils) are positive. The presence of any 4 or more of the 6 criteria yields a sensitivity of 85% and a specificity of 99.7% (Masi et al 1990).

Clinical Trial Data in AA and CSU

CSS/HES in adolescent and adult patients (12 years old and older) with AA:

There have been six cases of CSS/HES in the Omalizumab group and four cases of CSS/HES in the placebo group of the clinical trial program in AA (Table 8-5).

Table 8-5 Analysis of potential and identified risk by risk factor and treatment - Churg Strauss Syndrome - Hypereosinophilic syndrome

	Omalizumab N=3184 Exp=21.59 100PY n (IR/100 pyr) 95% CI	Control N=239 Exp=0.73 100PY n (IR/100 pyr) 95% CI	Placebo N=2921 Exp=19.60 100PY n (IR/100 pyr) 95% CI	Omalizumab vs Placebo IRR 95% CI	Omalizumab vs Placebo IRD 95% CI
Churg Strauss Syndrome - Hypereosinophilic syndrome					
Patients with at least one AE	6 (0.28) (0.102,0.605)		4 (0.20) (0.056,0.523)	1.36 (0.323,6.562)	0.07 (-0.225,0.373)
Maximum Severity					
Mild	3 (0.14) (0.029,0.406)		1 (0.05) (0.001,0.284)	2.72 (0.219,143.003)	0.09 (-0.098,0.274)
Moderate	1 (0.05) (0.001,0.258)		3 (0.15) (0.032,0.447)	0.30 (0.006,3.770)	-0.11 (-0.302,0.089)
Severe	2 (0.09) (0.011,0.335)				0.09 (-0.036,0.221)
SAE	-	-	-	-	-
Adverse events with fatal outcome	-	-	-	-	-

Source: Annex 7

Churg Strauss syndrome/ Hypereosinophilic syndrome in the clinical pediatric (6 to less than 12 years old) program:

There have been 5 cases of CSS/HES in the Omalizumab group and 3 cases of CSS/HES in the pediatric program (AAP) (Table 8-6)

No cases of CSS have been reported in the Phase III CSU program.

Churg Strauss Syndrome/Hypereosinophilic syndrome in adults (18 years and above) with NP:

There were no confirmed events of Churg Strauss syndrome or hypereosinophilic syndrome identified from the pivotal studies.

Table 8-6 Important identified risk: Churg Strauss Syndrome/Hypereosinophilic syndrome (Other details)

Churg Strauss Syndrome/Hypereosinophilic syndrome	Details
Potential mechanisms	Unknown
Evidence sources and strength of evidence	All cases of CSS/HES were reported in the post-marketing setting. Current evidence is based on a pooled clinical study database of AA and CSU with 16,249 patients, 2 pooled NP studies with 135 patients and 1,143,490PTY exposure from post-marketing scenario and the review of 597 cases of CSS reported to the company safety database with RR of 0.52 cases per 1,000 PTY.
Characterization of the risk	No cases of CSS related to omalizumab have been reported in the AA or CSU development programs. There have been 6 cases of CSS/HES in the omalizumab group and 4 cases of CSS/HES in the placebo group of the adolescent and adult clinical trial program in AA; While there have been 5 cases of CSS/HES in the omalizumab group and 3 cases of CSS/HES in the placebo group of the pediatric program (AAP) in AA. In post-marketing setting, the cumulative reporting rate is 0.52 cases per 1,000 PTY and remained stable over time.
Risk factors and risk groups	Unknown
Preventability	Unknown
Impact on the benefit-risk balance of the product	This safety concern has a low impact on the benefit-risk balance of omalizumab based on low incidence, the low impact on public health and mostly non-severe cases.
Public health impact	Unknown at this time, however, based on incidences in the safety databases, the potential for significant public health impact is very low.

Important potential risk: Arterial thromboembolic events

Arterial thromboembolic events and treatment of allergic asthma with omalizumab:

Arterial Thromboembolic Events (ATEs) were identified as an important potential risk in the RMP, based on a numerical imbalance observed from an interim report of the EXCELS study (primary population = controlled trials data set) for adults.

An externally adjudicated, pooled analysis of RDBPC trials was submitted to the FDA to better quantify and qualify the risk. ATEs have also been observed in post-marketing setting. During the reporting period of PSUR 16 two clinical sources provided information to support the assessment of ATE:

- The EXCELS study, which provides a longer term assessment of ATE in 7,836 patients (5,007 in the omalizumab treatment group and 2,829 in the control group).
- The pooled clinical trial analysis which provides the highest level of evidence from RDBPC study. Twenty-five core clinical studies plus two extension studies were included with an overall population of 6,237 of whom there were 3,342 omalizumab-exposed patients.

Results of these analyses are described below:

EXCELS

The rates (per 1,000 person-years) of adjudicated study-emergent ATE SAEs, the number of patients with adjudicated study-emergent ATE SAEs, and the rates of ATE SAEs excluding deaths that were not classified as myocardial infarction, unstable angina, ischemic stroke or TIA are presented in Table 8-7. The omalizumab cohort demonstrated a higher rate of study-emergent ATE SAEs than the non-omalizumab cohort.

Table 8-7 Rates of adjudicated study emergent Arterial Thromboembolic Events Serious Adverse Event (event and patient rates): safety evaluable patients

	Non-Xolair cohort [a] (n=2829)	Xolair cohort [b] (n=5007)	Difference in rates (95% CI)	Ratio of rates (95% CI)
Person-years at risk for an ATE SAE	9,962.6	15,286.4		
Number of ATE SAEs	51	115		
Observed ATE SAE rate per 1000 person-years (95% CI)	5.12 (3.81, 6.73)	7.52 (6.21,9.03)	2.40 (0.16, 4.62)	1.47 (1.02, 2.18)
Number of Patients with ATE SAE	46	101		
Observed ATE SAE rate per 1000 person-years (95% CI)	4.62 (3.38, 6.16)	6.61 (5.38,8.03)	1.99 (0.11, 3.80)	1.43 (1.02, 2.06)
Number of ATE SAEs (excluding non-ATE deaths)	32	91		
Observed ATE SAE (excluding non-ATE deaths) rate per 1000 person-years (95% CI)	3.21 (2.20, 4.53)	5.95 (4.79,7.31)	2.74 (0.74, 4.68)	1.85 (1.16, 3.09)

[a] All non−omalizumab or omalizumab cohort patients prior to any change in baseline omalizumab treatment status.

[b] After initiation of treatment with omalizumab for non−omalizumab cohort patients or >6 months after last omalizumab dose for omalizumab cohort patients.

Note: The upper limit of the 95% CI will be reported as infinity (∞) when >2.5% of the bootstrap samples have undefined ratios.

Note: Person−years at risk is defined as time (in years) from Study Day 0 to the earliest of the following events: completion of the study, death, initiation of omalizumab treatment (non−omalizumab patients), discontinuation of omalizumab + 6 months (omalizumab patients), or the last completed study visit date (discontinued patients). For patients who change omalizumab treatment status, person−years at risk after treatment change is calculated from omalizumab start date (non−omalizumab patients) or end date + 6 months (omalizumab patients) to the earliest of the previously−mentioned events

In the Cox proportional hazards analysis without adjusting any confounding factors, the unadjusted hazard ratio (HR) was 1.47 (95% CI: 1.04, 2.08). The adjusted HR, which controlled for potential confounders, was 1.32 (95% CI: 0.91, 1.91). The existence of a treatment by age interaction was evaluated; no evidence of such an interaction was found.

Despite adjustment for measured confounding factors, a numerical imbalance in ATE rates was observed. Although there was no consistent evidence of an association between omalizumab

use and risk of ATEs, the confidence intervals were wide and could not definitively exclude an elevated risk.

Pooled Randomized Clinical Trials

The population, which was derived from 25 core clinical studies plus two extension studies, consisted of 6,237 patients, of whom 3,342 were exposed to omalizumab. More than 70% of the population was from AA studies and studies in this population accounted for the greatest proportion of observation time.

Table 8-8 Numbers of patients in each analysis population

Analysis population	Omalizumab	Placebo
Allergic asthma	2,409	2,320
Other indications	933	575
All studies	3,342	2,895

Table 8-9 Observation time in each analysis population

Analysis population	Omalizumab	Placebo
Allergic asthma	1,555.9	1,463.7
Other indications	300.7	217.7
All studies	1,856.6	1,681.3

-Observation time expressed in patient-years

For most analyses, the AA and all studies populations were comparable, in most circumstances providing the same number of events and consequently slightly higher incidences in the AA population. Baseline characteristics of patients were well-matched between the omalizumab and placebo groups. A prior history of cardiovascular disease was found in 4.8% of patients allocated to omalizumab (all studies) compared with 4.6% for placebo. There were no major imbalances between omalizumab and placebo groups in β-agonist or systemic corticosteroid use in any analysis population. The median duration of treatment was 182 days in the AA studies.

After identification of potential agreed events of interest for the primary outcome of SAEs or death, there were 79 cases sent for adjudication: these included 6 fatal events. A further 272 non-serious AEs were also sent for external adjudication to the independent external adjudication panel and assessed in the secondary endpoints.

The primary analysis was performed on SAEs and on deaths from the Case Report Form discontinuation page. Table 8-10 shows nine events that were positively adjudicated cardiovascular events. Cardiovascular death, myocardial infarction, unstable angina, stroke and TIA were aggregated into the ATE category. No event in the other indications population was adjudicated to any cardiovascular outcome so the AA and the all studies populations featured the same number of cardiovascular events.

Table 8-10 Primary analysis: number of patients with cardiovascular events (All studies population)

Event	Omalizumab (N=3342)	Placebo(N=2895)
All ATEs	5	4
Cardiovascular death	0	3
Myocardial infarction	2	0
Unstable angina	1	1
Stroke	1	0
TIA	1	0
Other cardiovascular outcomes		
Arrhythmia	1	8
Heart failure	1	0
Pulmonary hypertension	0	1
Pulmonary embolus (PE)/deep vein thrombosis (DVT)	1	2

In the All studies population, the rates of ATE were similar between the omalizumab and placebo groups.

The ATE rates/1000 patient-years, the difference in rates and the RRs relating to the comparison of the omalizumab to the placebo groups are shown in the Table 8-11.

Table 8-11 Primary analysis: rate of Arterial Thromboembolic Events (deaths and SAEs) by population

	Omalizumab	Placebo	Difference in rates (95% CI)	Ratio of rates (95% CI)
All studies population				
Patient years	1855.81	1680.46		
No. of ATEs	5	4		
ATE rate / 1,000 patient-year PTYs (95% CI)	2.69 (0.88,6.28)	2.38 (0.65,6.08)	0.31 (-4.18, 4.61)	1.13 (0.24, 5.71)
Allergic asthma population				
Patient years	1555.12	1462.79		
No. of ATEs	5	4		
ATE rate / 1,000 patient-years (95% CI)	3.22 (1.04,7.49)	2.73 (0.75,6.99)	0.48 (-4.7,5.58)	1.18 (0.25, 5.94)

Observation time is censored at the time of the first event

Table 8-12 Primary analysis: rates of other cardiovascular events (deaths and SAEs: All studies population)

	Events per 1000 patient-years			
	Omalizumab (N=3342)	Placebo (N=2895)	Difference in Rates (95% CI)	Ratio of Rates (95% CI)
Cardiovascular death	0.00	1.78	-1.78 (-5.68, 1.11)	0.00 (0.00, 1.55)
Myocardial infarction	1.08	0.00	1.08 (-1.90, 4.34)	Undefined
Stroke	0.54	0.00	0.54 (-2.35, 3.50)	Undefined

	Events per 1000 patient-years			
	Omalizumab (N=3342)	Placebo (N=2895)	Difference in Rates (95% CI)	Ratio of Rates (95% CI)
TIA	0.54	0.00	0.54 (-2.35, 3.49)	Undefined
Unstable angina	0.54	0.60	-0.06 (-3.36, 2.95)	0.91 (0.01, 71.09)
Arrhythmia	0.54	4.77	-4.23 (-9.27, -0.32)	0.11 (0.00, 0.84)
Heart failure	0.54	0.00	0.54 (-2.35, 3.50)	Undefined
Pulmonary hypertension	0.00	0.59	-0.59 (-3.86, 2.04)	0.00 (0.00, 17.20)
PE/DVT	0.54	1.19	-0.65 (-4.29, 2.47)	0.45 (0.01, 8.70)

The most common arrhythmia events of interest were atrial fibrillation and cardiac arrest, the latter two PTs occurring only in the placebo group; the only SAE PT adjudicated to arrhythmia in the omalizumab group was a single case of pneumonia.

Secondary analyses that included all AEs (i.e. included but were not limited to SAEs) identified a greater number of events but showed similar risk differences and risk ratios to the primary analysis, with no evidence of increased ATE risk with omalizumab treatment.

In summary, in the primary analysis, the total number of positively adjudicated serious ATE events was small: 5 events following omalizumab treatment compared with 4 following placebo, in a database of over 6000 patients with an observation time of over 3500 PTYs. The risk ratio for the primary analysis is not significantly increased and with wide confidence intervals (1.13, 95% CI: 0.24, 5.71).

Arterial thromboembolic events and treatment of CSU with omalizumab:

In the Phase III CSU program, there were four patients who reported events considered a possible arterial thromboembolic event, including two patients in the placebo, and one patient in the omalizumab 150 mg group and one in the omalizumab 300 mg group.

Rate difference to placebo (95% CI) for ATE events, in events per 100 patient-years, was −0.56 (-1.875, 0.754) for the omalizumab group.

Arterial thromboembolic events in adults (18 years and above) with Nasal Polyps:

An SAE of myocardial infarction was identified in one patient in the placebo arm of Study GA39855. No other arterial thrombotic events were identified from the pivotal studies.

Table 8-13 Important potential risk: Arterial thromboembolic events (Other details)

Arterial thromboembolic events	Details
Potential mechanisms	No potential mechanism was identified in preclinical studies.
Evidence sources and strength of evidence	Current evidence is based on a pooled clinical study database of AA and CSU with16,249 patients, 2 pooled NP studies with 135 patients and , 1,143,490 PTY exposure from post-marketing scenario and on the review of total of 1,251 ATE cases reported to the company safety database.

Arterial thromboembolic events	**Details**
Characterization of the risk:	In AA controlled clinical trials and during interim analyses of an observational study (EXCELS), a numerical imbalance of ATEs was observed. ATE included stroke, transient ischemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patients' years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% CI 0.91 to 1.91). In a separate analysis of pooled clinical trials including all randomized double-blind, placebo-controlled clinical trials of 8 or more weeks duration, the rate of ATE per 1000 patient years was 2.69. In the Phase III CSU program rate difference between omalizumab and placebo (95% CI) for ATE events, in events per 100 patient-years, was −0.56 (-1.875, 0.754). Refer to the Table 8-11 and Table 8-12 above.
Risk factors and risk groups	No specific group identified.
Preventability	Unknown.
Impact on the benefit-risk balance of the product	This safety concern has a low impact on the benefit-risk balance of omalizumab considering no causal association has been established with Xolair. However, if causality get established based on future data, it may have high impact considering the nature and severity of the disease.
Public health impact	Unknown at this time, however, based on incidences in the safety databases, the potential for significant public health impact is very low.

Important potential risk: Malignant neoplasms in adults and adolescents 12 years old or older:

During initial clinical development in adults and adolescents 12 years of age and older, there was a numerical imbalance in cancers arising in the active treatment group, compared with the control group. The number of observed cases was uncommon (<1/100) in both the active and the control group. Of note, the original potential risk was based on an imbalance in numbers of malignancy seen within all the studies at the time of submission, not simply the RDBPC trials. Many of the malignancies were in the open label studies. At the point of submission (2003) there were 9/1,536 cases of malignancy in the omalizumab group and 4/1,124 cases in the placebo group, with a RR of 1.65 with wide CI. Results were re-assessed in 2006 with the submission to the Japanese heath authority and the numbers then had 9/2,134 cases on omalizumab and 6/1,715 cases in the placebo group, with a RR of 1.20. On re-assessment in 2010 when the clinical trial data base was double the original size there were 14/3,382 cases in the omalizumab group and 11/2,473 cases in the placebo group with a RR of 0.93 and CI of 0.39 and 2.27.

In Dec-2012, the final EXCELS study report became available. In addition, an externally adjudicated, pooled analysis of all double-blind, randomized, placebo controlled RDBPC trials was conducted. Data from EXCELS and the pooled analysis were included in the PSUR 16.

The incidence of malignancy in patients with asthma from a meta-analysis of 16 case-control and cohort clinical studies found a pooled incidence ratio for cancer incidence in asthma from 1.03 (95% CI: 0.93, 1.14), with a range from 0.90, 1.27 (Tennis et al 2005).

As reported in RMP 9.2, two clinical sources provided evidence to support the assessment for malignancy:

- The pooled clinical trial analysis which provides the highest level of evidence from RDBPC. Thirty-two (32) RDBPC trials which included a total of 7,432 patients, of whom 4,254 were exposed to Xolair (the clinical trial patient population is doubled from the time of original US submission in 2003).
- The EXCELS study, which provides a long-term assessment of malignancy in 7,836 patients (5,007 in the omalizumab treatment group and 2,829 in the control group).

In the pooled clinical trials analysis, when adjusted for observation time, the rates of primary malignancy were 4.14 events per 1,000 patient-years for omalizumab and 4.45 events per 1,000 patient years for placebo, with a RR of 0.93 (95% CI: 0.39, 2.27). The primary malignancies identified in patients enrolled in RDBPC trials were of varying histological type and occurred in a number of different organ systems with no cluster of histologies.

Results from EXCELS indicated that the incidence rates of primary malignancies (per 1000 patient-years) were similar among Xolair-treated and non-Xolair-treated patients, with a RR (Xolair to non-Xolair cohort) of 0.84 (95% CI: 0.62, 1.13).

In conclusion, neither the pooled clinical trial analysis nor the EXCELS study support a relationship between omalizumab treatment and malignancy risk.

One case each of malignant melanoma in situ and skin neoplasm excision were reported in omalizumab group, in the Phase III CSU program.

This was Patient [redacted], a [redacted] who was in the omalizumab 300 mg group in Study Q4883g. This patient was diagnosed with malignant melanoma in situ (Stage 0) on the scalp on Day 121 (last dose administered on Day 59). Upon further investigation, the patient reported to the investigator that the lesion was present 4 months prior to enrolling in the study. The investigator assessed the event as serious and not related to the study drug. One patient in the placebo group in Study Q4881g, Patient [redacted], a [redacted], had an SAE of severe cervical dysplasia, which occurred during the follow-up period. This event was not suspected to be related to study medication. This event was subsequently identified as cervical adenocarcinoma in situ post database lock.

Malignant neoplasms in adults (18 years and above) with Nasal Polyps:

A non-serious adverse event of squamous cell carcinoma was reported in a patient in the placebo arm of Study GA39688. No action was taken with the study medication and the event was ongoing. No other malignancy events were identified from the pivotal studies.

Table 8-14 Important potential risk: Malignant neoplasms in adults and adolescents ≥ 12 years of age (Other details)

Malignant neoplasms in adults and adolescents ≥ 12 years of age	**Details**
Potential mechanisms	No potential mechanism identified in preclinical studies.
Evidence sources and strength of evidence	Current evidence is based on a pooled clinical study database of AA and CSU with 16,249 patients, 2 pooled NP studies with 135 patients and, 1,143,490 PTY exposure from post-marketing scenario and on the review of total of 2,014 post-marketing malignancy cases (in adult and adolescents) reported to the company safety database.
Characterization of the risk:	In the pooled clinical trials analysis, when adjusted for observation time, the rates of primary malignancy were 4.14 events per 1,000 patient-years for omalizumab and 4.45 events per 1,000 patient years for placebo, with a RR of 0.93 (95% CI: 0.39, 2.27). These results do not support an association between use of omalizumab and increased malignancy risk, a conclusion supported by data from the EXCELS study: In EXCELS, incidence RR of primary malignancies (Xolair to non-Xolair cohort) was 0.84 (95% CI: 0.62, 1.13). In the Phase III CSU program, there was one case in placebo and two in the omalizumab 300 mg group with pre-existing history. In post-marketing setting, the cumulative reporting rate is 1.76/1000 PTY and remained stable over time.
Risk factors and risk groups	No specific group identified.
Preventability	Unknown.
Impact on the benefit-risk balance of the product	This safety concern has a low impact on the benefit-risk balance of omalizumab considering no causal association has been established with Xolair. However, if causality get established based on future data, it may have high impact considering the nature and severity of the disease.
Public health impact	Unknown at this time, however, based on incidences in the safety databases, the potential for significant public health impact is very low.

Important potential risk: Malignant neoplasms (children 6 to less than 12 years old)

Table 8-15 Important potential risk: Malignant neoplasms (children 6 to less than 12 years old)

Malignant neoplasms (children 6 to less than 12 years old)	**Details**
Potential mechanisms	No potential mechanism identified in preclinical studies
Evidence sources and strength of evidence	Current evidence is based on a pooled clinical study database of AA and CSU with 16,249 patients, 2 pooled NP studies with 135 patients and, 1,143,490 PTY exposure from post-marketing scenario and the review of five cases of malignancies in children six to less than 12 years of age reported to

Malignant neoplasms (children 6 to less than 12 years old)	Details
	the company safety database with RR of 0.004 cases per 1000 PTY in the post marketing setting.
Characterization of the risk:	No cases of malignancy in patients treated with omalizumab were reported in any pediatric clinical trials in AA. There was no pediatric (6-<12) population studied in the CSU and NP clinical trial program. Post-marketing setting: There was five cases cumulatively until 31-Dec-2018 and causal association with Xolair could not be established.
Risk factors and risk groups	No specific group identified.
Preventability	Unknown.
Impact on the benefit-risk balance of the product	This safety concern has a low impact on the benefit-risk balance of omalizumab considering no causal association has been established with Xolair. However, if causality get established based on future data, it may have high impact considering the nature and severity of the disease.
Public health impact	Unknown at this time, however, based on incidences in the safety databases, the potential for significant public health impact is very low

8.3.2 SVII.3.2. Presentation of the missing information

None.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	Anaphylaxis/anaphylactoid reactions Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)
Important potential risks	Arterial Thromboembolic Events (ATEs) Malignant neoplasms in adults and adolescents ≥ 12 years of age Malignant neoplasms (children 6 to less than 12 years old)

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up questionnaires

Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concern specified below. Targeted follow-

ups with specific checklist are applicable only for serious adverse events for the below mentioned risks:

- Anaphylaxis/anaphylactoid reactions
- Arterial Thromboembolic Events (ATEs)
- Malignant neoplasms in adults and adolescents ≥ 12 years of age and Malignant neoplasms (children 6 to less than 12 years old)

Other forms of routine pharmacovigilance activities:

Anaphylaxis:

Expedited reporting to the EMA (and to other countries as per local regulations) of all cases of serious anaphylaxis, anaphylactoid reactions, or a combination of individual symptoms meeting accepted diagnostic criteria and assessed as related to omalizumab.

A safety analysis of anaphylactic reaction cases reported in the home use setting of omalizumab will be performed and included in each PSUR on periodic basis. The data on patient/caregiver training collected from anaphylactic reaction ICSRs (through targeted Follow-up checklist), will also be provided in the PSURs.

Follow up of all case reports for omalizumab:

The minimum desired case information for omalizumab includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with GVP VI.

10.2 Part III.2. Additional pharmacovigilance activities

There are no additional pharmacovigilance activities planned.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Not applicable.

11 Part IV: Plans for post-authorization efficacy studies

Not applicable.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Identified risks	

Safety concern	Routine risk minimization activities
Anaphylaxis/anaphylactoid reactions	**Routine risk communication** SmPC sections - 4.2, 4.4 and 4.8. PL sections - 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.2 and 4.4 – These two sections were updated to reflect the risk minimization measures for anaphylaxis applicable for home use – appropriate patient selection criteria to choose low risk patients for anaphylaxis, training etc. PL Sections 2 and 4 – PL has been updated with more guidance for patients to recognise early symptoms of severe allergic reactions including anaphylaxis and how to manage this risk. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription.
Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)	**Routine risk communication:** SmPC sections - 4.4 and 4.8. PL sections - 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 - Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids. In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy. *In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy. Discontinuation of omalizumab should be considered in all severe cases with the above mentioned immune system disorders.* **Other routine risk minimization measures beyond the Product Information:** Legal Status: Prescription only medicine. Medicinal product subject to restricted medical prescription.
Potential risks	
Arterial Thromboembolic Events (ATEs)	**Routine risk communication:** SmPC section - 4.8 (This is not an adverse drug reaction (ADR). The available data from the pooled CT database and observational study has been summarized) PL sections - None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Legal Status: Prescription only medicine. Medicinal product subject to restricted medical prescription.
Malignant neoplasms in adults and adolescents ≥ 12 years of age	**Routine risk communication:** SmPC sections - None PL sections - None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal Status: Prescription only medicine. Medicinal product subject to restricted medical prescription.
Malignant neoplasms (children 6 to less than 12 years old)	**Routine risk communication:** SmPC sections - None PL sections - None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal Status: Prescription only medicine. Medicinal product subject to restricted medical prescription.

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified risks		
Anaphylaxis/anaphylactoid reactions	Routine risk minimization measures: SmPC sections – 4.2, 4.4 and 4.8. PL sections - 2 and 4 Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. -Expedited reporting to the EMA (and to other countries as per local regulations) of all cases of serious anaphylaxis, anaphylactoid reactions, or a combination of individual symptoms meeting accepted diagnostic criteria and assessed as related to omalizumab.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None.	Additional pharmacovigilance activities: None.
Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)	Routine risk minimization measures: SmPC sections - 4.4 and 4.8. PL sections - 2 and 4 Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
	Additional risk minimization measures: None.	
Important potential risks		
Arterial Thromboembolic Events (ATEs)	Routine risk minimization measures: SmPC section - 4.8 (This is not an ADR. The available data from the pooled CT database and observational study has been summarized) PL sections - None Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. Additional pharmacovigilance activities: None.
	Additional risk minimization measures: None.	
Malignant neoplasms in adults and adolescents ≥ 12 years of age	Routine risk minimization measures: SmPC sections – None. PL sections – None. Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. Additional pharmacovigilance activities: None.
	Additional risk minimization measures: None.	

Safety concern	Risk minimization measures	Pharmacovigilance activities
Malignant neoplasms (children 6 to less than 12 years old)	Routine risk minimization measures: SmPC sections - None PL sections - None Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. Additional pharmacovigilance activities: None.

13 Part VI: Summary of the risk management plan for Omalizumab

This is a summary of the RMP for Xolair. The RMP details important risks of Xolair, how these risks can be minimized, and how more information will be obtained about Xolair's risks and uncertainties (missing information).

Xolair's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Xolair should be used.

This summary of the RMP Xolair should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xolair's RMP.

13.1 Part VI: I. The medicine and what it is used for

Xolair is authorized in adults, adolescents and children (6 to <12 years of age) for IgE (immunoglobulin E) mediated Allergic Asthma. It is also authorized as add-on therapy for the treatment of Chronic Spontaneous Urticaria (CSU) in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment. [redacted] It contains omalizumab as the active substance and it is given subcutaneously every 2 or every 4 weeks for AA (75 mg to 600 mg according to body weight and baseline IgE levels), every 4 weeks for CSU (300 mg) and every 2 or every 4 weeks for nasal polyps (75 mg to 600 mg according to body weight and baseline IgE levels).

Further information about the evaluation of Xolair benefits can be found in Xolair's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link:

https://www.ema.europa.eu/documents/overview/xolair-epar-summarypublic_en.pdf

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Xolair, together with measures to minimize such risks and the proposed studies for learning more about Xolair's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Xolair is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Xolair are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Xolair. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Anaphylaxis/anaphylactoid reactions Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)
Important potential risks	Arterial Thromboembolic Events (ATEs) Malignant neoplasms in adults and adolescents ≥ 12 years of age Malignant neoplasms (children 6 to less than 12 years old)

13.2.2 Part VI - II B: Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 13-2 Important identified risk: Anaphylaxis/anaphylactoid reactions

Evidence for linking the risk to the medicine	Although incidences of anaphylaxis/anaphylactoid reactions in omalizumab clinical trials are rare, based on post-marketing experience a causal association between omalizumab and Anaphylaxis/anaphylactoid reactions has been established. In post-marketing reports, the frequency of anaphylaxis in patients exposed to Xolair use was estimated to be 0.2% based on a total number of anaphylactic reactions observed from an estimated exposure of over 500,000 patient years (SmPC). The post-marketing reporting rate remained stable over time and mostly ranged between 0.1-0.2/100 PTY.
Risk factors and risk groups	Patients with previous history of anaphylaxis, children, atopic individuals and asthmatics.
Risk minimization measures	**Routine risk minimization measures:** Routine risk minimization measures: SmPC sections – 4.2, 4.4 and 4.8. PL sections - 2 and 4 Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Table 13-3 Important identified risk: Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)

Evidence for linking the risk to the medicine	In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy. No cases of CSS/HES was reported in clinical trials. All cases of CSS were reported in the post-marketing setting and the RR is 0.48/1000 PTY.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** SmPC sections - 4.4 and 4.8. PL sections - 2 and 4 Legal Status: Prescription only medicine. Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Table 13-4 Important potential risk: Arterial Thromboembolic Events (ATEs)

Evidence for linking the risk to the medicine	A causal association between omalizumab and ATE events has not been established. In controlled clinical trials and during interim analyses of an observational study (EXCELS), a numerical imbalance of ATE was observed. In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patient years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% CI 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% CI 0.24-5.71).
Risk factors and risk groups	No specific group identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC section - 4.8 (This is not an ADR. The available data from the pooled CT database and observational study has been summarized) PL sections – None Legal Status: Prescription only medicine. Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None.
Additional pharmacovigilance activities.	**Additional pharmacovigilance activities:** None.

Table 13-5 Important potential risk: Malignant neoplasms in adults and adolescents ≥ 12 years of age

Evidence for linking the risk to the medicine	A causal association between omalizumab and malignancies in adults and adolescents ≥ 12 years of age has not been established. In the pooled clinical trials analysis, when adjusted for observation time, the rates of primary malignancy were 4.14 events per 1,000 patient-years for omalizumab and 4.45 events per 1,000 patient years for placebo, with a RR of 0.93 (95% CI: 0.39, 2.27). These results do not support an association between use of omalizumab and increased malignancy risk, a conclusion supported by data from the EXCELS study: In EXCELS, incidence RR of primary malignancies (Xolair to non-Xolair cohort) was 0.84 (95% CI: 0.62, 1.13).
Risk factors and risk groups	No specific group identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections - None PL sections - None Legal Status: Prescription only medicine. Medicinal product subject to restricted medical prescription.

	Additional risk minimization measures: None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Table 13-6 Important potential risk: Malignant neoplasms (children 6 to less than 12 years old)

Evidence for linking the risk to the medicine	A causal association between omalizumab and malignancies in children 6 to less than 12 years old has not been established. No cases of malignancy in patients treated with omalizumab were reported in any pediatric clinical trials. There were limited number of cases reported in the post-marketing setting and causal association with omalizumab could not be established in those cases.
Risk factors and risk groups	No specific group identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections - None PL sections - None Legal Status: Prescription only medicine. Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

13.2.2.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Xolair.

13.2.2.2 II.C.2. Other studies in post-authorization development plan

There are no other studies in post-authorization development plan of Xolair.

14 Part VII: Annexes

Annex 1 – EudraVigilance Interface

Available in electronic format only.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study program

There are no planned or ongoing studies included in the pharmacovigilance plan.

Table 14-1 Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
EXCELS (Q2948g) An Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma Category 3	The primary objective was to compare the long-term clinical safety profile of patients with moderate-to-severe persistent asthma and a positive skin test or in vitro reactivity to an aeroallergen who have been treated with Xolair with the profile of similar patients who have not been treated with Xolair. The secondary objective was to assess the clinical benefit of Xolair in patients with moderate- to-severe persistent asthma, as determined by measures of asthma control, work productivity and activity impairment, and healthcare use over time.	Malignant neoplasms	Submission date: 20 December 2012
EXPECT (Q2952g) (Protocol available upon request) Category 3	The primary objective is to evaluate pregnancy outcomes, including live births, elective terminations, fetal deaths/stillbirths, and congenital anomalies in women exposed to Xolair within 8 weeks prior to conception or at any time during pregnancy. Secondary objectives are to estimate the	Pregnancy outcome	Final report – Q3 2018 [EXPECT CSR]

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
	incidence of spontaneous fetal loss, premature births, and low birth weight infants in addition to monitoring the safety of newborn infants exposed to Xolair prenatally or both prenatally and via breast milk.		
(IGE025A1402) Long-term safety (3 year study duration) of omalizumab in the Japanese Population Category 4	To collect safety and efficacy data on long-term use of the product in actual medical practice, to understand any related issues, and to examine Xolair's suppressive effects on exacerbation of asthma. The results would be used for documents for the reexamination application submitted to the Ministry of Health, Labour and Welfare (MHLW).	Anaphylaxis/ anaphylactoid reactions. Serum Sickness Syndrome (SSS) / Serum Sickness Like Disease (SSLD). Antibody formation to omalizumab. Churg Strauss Syndrome / Hypereosinophilic Syndrome. Thrombocytopenia. Arterial Thromboembolic Events (ATEs). Malignant neoplasms (Adult and adolescent patients ≥ 12 years old). Malignant neoplasms in children 6 to less than 12 years old.	Submission date: 20 July 2017
(X-PAND) Q4458g Pharmacosurveillance data repository of patients with and without history of anaphylactic reactions subsequent to Xolair dosing Category 4	A post-marketing commitment with the Food and Drug Administration (FDA) with the following primary objectives: to establish a repository of data from subjects having anaphylactic reactions subsequent to omalizumab dosing (cases); to obtain data	Anaphylaxis. Antibody formation to omalizumab	Submission date : 24 September 2015

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
	from a group of subjects who have not had a hypersensitivity reaction subsequent to receiving omalizumab (controls); to evaluate the association between the presence of anti-therapeutic antibodies of the IgG or IgE isotype and the risk of anaphylactic reactions among subjects with prior omalizumab exposure; and to establish a DNA sample repository from anaphylaxis case subjects and controls. An optional skin testing sub-study was implemented to evaluate the frequency of positive skin reactions to active omalizumab and omalizumab excipients (placebo omalizumab) in subjects with a history of omalizumab exposure prior to a hypersensitivity reaction, as well as in subjects exposed to omalizumab who have not had a hypersensitivity reaction.		
(IGE025B1301E1) A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled AA despite	The primary objective was to assess the long-term safety and tolerability of omalizumab as add-on therapy in Japanese pediatric patients with inadequately	Anaphylaxis/ anaphylactoid reactions. Serum Sickness Syndrome (SSS) / Serum Sickness Like Disease (SSLD). Antibody formation to omalizumab.	Submission date : 24 June 2014

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
current recommended treatment Category 4	controlled allergic asthma despite current recommended treatment	Churg Strauss Syndrome / Hypereosinophilic Syndrome. Thrombocytopenia. Arterial Thromboembolic Events (ATEs). Malignant neoplasms (Adult and adolescent patients ≥ 12 years old). Malignant neoplasms in children 6 to less than 12 years old.	

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this first or updated version of the RMP.

Not applicable.

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

Not applicable.

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.

Table 14-2 Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority

Study number, Study name (version number)	Procedure number in which protocol was approved
Category 1 and 2 studies in PV plan that were approved	
Not applicable	
Category 3 studies in PV plan that were not requested to be reviewed (Protocols are available upon request)	
EXPECT (Q2952g) Category 3	Not applicable
EXCELS (Q2948g) Category 3	Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

The targeted follow-up forms have to be used for the follow up of cases for the following risks:

- Anaphylaxis/anaphylactoid reactions
- Arterial Thromboembolic Events (ATEs)
- Malignant neoplasms (children 6 to less than 12 years old) and Malignant neoplasms in adults and adolescents ≥ 12 years of age

Targeted Follow-up Checklist for Xolair (Omalizumab) - Hypersensitivity including Anaphylaxis (Version 1.1/ October 2018)

In addition to collecting routine information for this adverse event reported to Novartis as 'Anaphylaxis' following the use of Xolair, please ensure the following additional information is provided and/or confirmed.

Administration of Xolair:

1. Where was Xolair administered immediately prior to the adverse event? :

   ☐ In the Home setting [Home setting includes: Self-injection (patient gave himself the medication) at home or elsewhere or by a lay caregiver (spouse, parent or others) at home or elsewhere]

   ☐ In the Office setting [Office setting includes a doctor's office, hospital/clinic, or by a Health Care Professional (includes doctor, nurse, physician's assistant etc.) at the patient's home or a Health Care Professional's office]

   ☐ Unknown
2. How many times has the patient received Xolair prior to the adverse event? ☐_____ (*indicate number*) ☐ Unknown
3. In case Xolair has been administered at Home, did the patient receive Xolair at least three times in an Office setting? ☐ **Yes** ☐ **No**
4. If **No,** were the first 3 doses of medication given by a doctor, nurse or other health care professional in another location (not in a doctor's office)? ☐ **Yes** ☐ **No**
5. If Xolair is now administered at Home, was the patient/caregiver trained/explained on how to recognize the signs and symptoms of severe allergic reactions including Anaphylaxis? ☐ **Yes** ☐ **No**

Event Description:

Was a type I hypersensitivity and/or anaphylaxis/anaphylactoid reaction noted in the patient?

☐ **Yes**

☐ **No**

☐ **Unknown**

Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Asthma/Wheezing

☐ Hyperventilation

☐ Erythema/Flushing edema/Spasm/Swelling
☐ Chest discomfort
☐ Urticaria/Rash
☐ Mouth/Circumoral (excluding lips)
☐ Upper airway obstruction/Choking
☐ Papules
☐ Tongue
☐ Sensation of foreign body/Upper
☐ Fixed eruption
☐ Oropharyngealairway obstruction/Choking
☐ Itching
☐ Laryngeal
☐ Stridor
☐ Edema/Swelling
☐ Tracheal
☐ Cough or sneezing
☐ Allergic
☐ Bronchial
☐ Eye/Eyelid
☐ Respiratory arrest
☐ Cardiac arrest
☐ Skin
☐ Respiratory distress/failure
☐ Heart failure
☐ Other *(please specify)*
☐ Dyspnea
☐ Hypotension (systolic and/or diastolic)
☐ None of the above

<u>Diagnostic Tests</u>: Check all that apply and specify dates, results and if possible, include copies of test results

☐ Laboratory tests including full blood count/Coombs'

☐ Skin biopsy Test/LFTs/Complement as appropriate

☐ Skin allergy tests

☐ IgE levels

☐ Drug sensitivity lymphocyte test

☐ Bone marrow aspiration

☐ Antibodies to drug detected

☐ None of the above

Patient History:

Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**

☐ Allergic asthma

☐ Previous drug hypersensitivity reaction *(please specify)*

☐ Allergic rhinitis

☐ Alcohol abuse

☐ Atopic dermatitis

☐ Drug abuse

☐ Food allergies, including colorants (dyes) and preservatives

☐ Recent pregnancy

☐ Urticaria

☐ Allergens *(please specify)*

☐ Rash

☐ Family history of allergies *(please specify)*

☐ Viral infection

☐ Malignancies

☐ Bacterial infection

☐ Autoimmune disease

☐ Foreign travel

☐ Other relevant history *(please specify)*

☐ Photosensitivity

☐ Other infections (e.g. fungal, protozoal) *(please specify)*

☐ None of the above

Has the patient taken/received any of the following (in reasonably close proximity to the event)? **Check all that apply**

☐ Recent blood/Serum/Blood-product transfusion

☐ Vaccination

☐ Injectable or oral antibiotics

☐ NSAIDS

☐ Narcotic analgesics

☐ Local anesthetics

☐ Hormones (ACTH/insulin/calcitonin)

☐ Herbals/alternative medicine/vitamin supplements *(please specify)*

☐ Neuromuscular blockers

☐ Chemotherapy

☐ None of the above

Targeted Follow-up Checklist - Arterial Thromboembolic Events (ATEs)

Cardiac Conduction Abnormalities (Version 2/ November 2015)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Palpitations

☐ Lightheadedness/ dizziness/near-syncope

☐ Shortness of breath

☐ Fatigue

☐ Fainting/syncope

☐ Chest pressure or pain

☐ None of the above

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates and results**

☐ Additional ECGs

☐ Holter monitor/ECG telemetry

☐ Exercise stress test

☐ Electrophysiology study

☐ Potassium level

☐ None of the above

Patient History:

Did the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**

☐ Heart attack/Myocardial infarction

☐ Cardiomyopathy

☐ Myocarditis

☐ Cardiac surgery

☐ Congenital heart condition *(please specify)*

☐ Hypothyroidism

☐ Other relevant history *(please specify)*

☐ Stroke / Brain tumor / CNS disease -Please specify

☐ Recent strenuous athletic training

☐ Vasovagal episode

☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply**

☐ Antiarrhythmics (e.g. flecainide, propafenone,

☐ Cholinomimetics (e.g. donepezil) verapamil)

☐ Antidepressants/Antipsychotics (e.g. tricyclic

☐ Beta-blockersantidepressants)

☐ Digitalis

☐ None of the above

Ischemic Heart Disease/Myocardial Infarction (Version 3.0/April 2017)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Palpitations
☐ Lightheadedness/ dizziness/near-syncope
☐ Shortness of breath
☐ Fatigue
☐ Fainting/syncope
☐ Chest pressure or pain
☐ None of the above

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates and results**

☐ Additional ECGs
☐ Holter monitor/ECG telemetry
☐ Exercise stress test
☐ Electrophysiology study
☐ Potassium level
☐ None of the above

Patient History:

Did the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**

☐ Heart attack/Myocardial infarction
☐ Cardiomyopathy
☐ Myocarditis
☐ Cardiac surgery
☐ Congenital heart condition *(please specify)*
☐ Hypothyroidism
☐ Other relevant history *(please specify)*
☐ Stroke / Brain tumor / CNS disease -Please specify
☐ Recent strenuous athletic training
☐ Vasovagal episode
☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply**

☐ Antiarrhythmics (e.g. flecainide, propafenone,

☐ Cholinomimetics (e.g. donepezil) verapamil)

☐ Antidepressants/Antipsychotics (e.g. tricyclic

☐ Beta-blockersantidepressants)

☐ Digitalis

☐ None of the above

Stroke (Version 4.0/April 2017)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

Did the patient present with any of the following signs or symptoms? Check all that apply

☐ Sensory deficit

☐ Difficulty swallowing

☐ Motor deficit (e.g. paralysis, paresis)

☐ Headache (severe or of abrupt onset)

☐ Difficulty speaking/Expressive aphasia

☐ Unexplained change in the pattern of headaches

☐ Difficulty understanding when spoken to/Receptive aphasia

☐ Confusion

☐ Unexplained dizziness

☐ Disorientation to place, time, person

☐ Blurred or poor vision in one or both eyes

☐ Unconsciousness

☐ Loss of balance or coordination

☐ Dysarthria

☐ Difficulty walking or an unexplained fall

☐ Cerebral topographical localization *(please specify)*

☐ Other *(please specify)*

☐ None of the above

What type of stroke(s) was/were reported? (*please specify,* e.g., ischemic, hemorrhagic, TIA):

_____

_____

_____

Were any of the following diagnostic tests performed? Check all that apply and please specify which test(s), dates and results

☐ Electroencephalogram (EEG)

☐ Electrocardiogram (ECG)

☐ Imaging studies (i.e. CT scan, MRI scan, magnetic resonance angiography)

☐ Blood or urine tests

☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

Did the patient have a history of any of the following prior to the start of the suspect drug? Check all that apply

☐ Cerebral Vascular Attacks or Transient Ischemic Attacks

☐ Hypertension *(please explain)*

☐ Diabetes

☐ Cardiovascular disease including cardiac arrhythmias,

☐ Hyperlipidaemia rheumatic heart disease, or recent myocardial infarction (MI)

☐ Hypercoaguable disease/disorder (e.g. polycythaemia *(please explain)*, sickle cell anemia, dysproteinemia)

☐ Peripheral vascular disease

☐ Head injury

☐ Smoking

☐ Drug abuse (i.e. cocaine, amphetamines, heroin)

☐ Migraine

☐ Malignancy or neoplasm

☐ None of the above

Was the patient taking any of the following drugs? Check all that apply

☐ Ergotamines

☐ Antihypertensive agents

☐ Lipid lowering agents

☐ Anticoagulants

☐ Oral contraceptives/Hormone therapy

☐ None of the above

Sudden Death or Unexplained Death (Version 2/November 2015)

In addition to collecting routine information for this SAE, please ensure the following additional information is provided and/or confirmed.

Event Description:

Autopsy performed: ☐ **Yes** (Please provide cause of death if available) ☐ No

_____
_____

If patient was hospitalized, please provide relevant information

_____
_____

_____
_____

If the death was witnessed, were any symptoms or signs noted (convulsions, mouth foaming, incontinence, confusion, etc.)

_____
_____

_____
_____

If the death was not witnessed, when was the patient last seen alive; please include any information about the health of the patient on that date.

_____
_____

_____
_____

If resuscitation was attempted please describe the initial response to treatment if applicable.

_____
_____

_____
_____

If death certificate was issued, please summarize primary and secondary cause(s) of death.

Primary:

Secondary:

What was the initial cardiac rhythm noted? (e.g. ventricular fibrillation, Torsade de Pointes, etc.)

_____
_____

Were any of the following diagnostic tests performed? **Check all that apply and specify the test, date and result**

☐ Relevant cardiac investigations during life (e.g. stress ECG, angiogram, ECG, Holter monitor, etc.)

☐ Relevant CNS investigations (e.g. investigations for epilepsy)

☐ Recent blood tests (electrolytes, enzymes)

☐ Additional relevant post-mortem findings

☐ None of the above

Patient History:

Does the patient have a history of any of the following? **Check all that apply**

☐ Congenital heart disease

☐ Hypertrophic obstructive cardiomyopathy

☐ Alcohol abuse

☐ Cardiac disease (e.g. angina,

☐ Valvular heart disease

☐ Drugs of abuse CAD, myocardial infarction)

☐ Family history of sudden death

☐ Unexplained syncope

☐ Major surgery (e.g. heart, abdomen)*(please specify)*

☐ Arrhythmias, palpitations

☐ Epilepsy/Seizures

☐ Thromboembolic or hemorrhagic

☐ Thyrotoxicosis

☐ Myocarditisevents including CVA, TIA
☐ Diabetes
☐ Wolff-Parkinson-White syndrome
☐ Malignancies
☐ Asthma
☐ Attempted suicide
☐ Psychiatric disease
☐ Severe vomiting, diarrhea
☐ Hypertension
☐ Morbid obesity
☐ Oral contraceptives

Has the patient recently taken any of the following? **Check all that apply**

☐ Antiarrhythmics (e.g. quinidine, amiodarone)
☐ Beta blockers
☐ QT prolonging medication (antihistamine, antibiotics etc.)
☐ Digoxin
☐ Chemotherapy
☐ None of the above

Targeted Follow-up Checklist - Malignancy (Version 2.0)

AER:	
Site No:	
Patient ID/Initials:	
Patient Gender:	❑ M❑ F

Local Case ID:	
Patient Date of Birth (dd-MMM-yyyy):	

Malignancy has been observed in some patients treated with Xolair.

By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Reporter Information
Name of reporter completing this form **(if other than addressee, provide contact information below)**:

Reporter Information	
Health Care Provider? ❑ Yes ❑ No-Specify:	
Phone number:	Fax number:
Email address:	

Details of treatment with Xolair				
Indication	Route	Dosing Regimen & Frequency of Dosing	Start Date	Stop Date or On going
				❑ On going
				❑ On going
				❑ On going

Details of Patient weight and IgE levels prior to treatment with Xolair		
Date	Patient weight	Patient serum IgE level

Diagnosis of Malignancy			
Clinical Diagnosis:	Stage of Malignancy Event:		ICD-10 code:
Histology of Malignancy Event	Histological confirmation?	❑ Yes ❑ No ❑ Unknown	
	Histology grading:	❑ Grade 0 ❑ Grade I ❑ Grade II ❑ Grade III ❑ Grade IV	
	Histology findings:		
Cytology of Malignancy Event	Cytological confirmation?	❑ Yes ❑ No ❑ Unknown	
	Cytological grading:	❑ Grade 0 ❑ Grade I ❑ Grade II ❑ Grade III ❑ Grade IV	
	Cytological findings:		
Nature of Malignancy	Is this a primary malignancy?		❑ Yes ❑ No ❑ Unknown
	Is this a secondary malignancy (cancer following a previously treated malignant neoplasm, but not considered a metastasis of the initial neoplasm)?		❑ Yes ❑ No ❑ Unknown **If yes,** specify:
	Is tumor a recurrence of a tumor existing before treatment with Xolair (omalizumab) (disease progression)?		❑ Yes ❑ No ❑ Unknown **If yes,** specify:
	If tumor is a recurrence, is recurrence confirmed by a pathologist?		❑ Yes ❑ No ❑ Unknown
Relevant Cancer Biomarkers?	❑ Yes ❑ No ❑ Unknown		

Diagnosis of Malignancy	
	If yes, specify:

List any immunosuppressants and/or chemotherapy medications and/or radiation therapy the patient has received IN THE PAST						
Drug Name (generic or trade name)	Indication	Route	Total # of cycles received by time of event onset	Dosing Regimen & Frequency of Dosing	Start Date	Stop Date or On going
						❑ On going
						❑ On going
						❑ On going
						❑ On going
						❑ On going

List any immunosuppressants and/or chemotherapy medications and/or radiation therapy the patient was receiving AT THE TIME OF EVENT ONSET						
Drug Name (generic or trade name)	Indication	Route	Total # of cycles received by time of event onset	Dosing Regimen & Frequency of Dosing	Start Date	Stop Date or On going
						❑ On going
						❑ On going
						❑ On going
						❑ On going

Relevant Medical History				
History of immunodeficiency?	❑ Yes	❑ No	❑ Unknown	Specify:
History of autoimmune disease?	❑ Yes	❑ No	❑ Unknown	Specify:
History of recurrent infections?	❑ Yes	❑ No	❑ Unknown	Specify:
History of opportunistic infections?	❑ Yes	❑ No	❑ Unknown	Specify:
History of previous malignancy?	❑ Yes	❑ No	❑ Unknown	Specify:
Family history of malignancy?	❑ Yes	❑ No	❑ Unknown	Specify:
History of smoking?	❑ Yes	❑ No	❑ Unknown	Specify:
History of alcohol use?	❑ Yes	❑ No	❑ Unknown	Specify:
	❑ Yes	❑ No	❑ Unknown	Specify:
	❑ Yes	❑ No	❑ Unknown	Specify:

History of exposure to other known carcinogens? (e.g. Excessive ultraviolet radiation [sunlight or PUVA/UVB] if malignancy is skin cancer), etc.	❑ Yes	❑ No	❑ Unknown	Specify:
Other relevant medical history – specify:				

Treatment for Malignancy		
Did patient refuse treatment for malignancy?		
❑ Yes	❑ No- please provide treatment details in the table(s) below	❑ Unknown

Surgical Treatment for the Malignancy (planned or completed)		
Type of Surgery	Date of Surgery:	
	❑ Date completed:	❑ Planned
	❑ Date completed:	❑ Planned
	❑ Date completed:	❑ Planned

Chemotherapy/Radiation treatment or other treatment for the malignancy (planned, on-going or completed):				
Drug Name	Dosing Regimen and Frequency	Status of Treatment		
		❑ Date completed:	❑ Planned	❑ On going
		❑ Date completed:	❑ Planned	❑ On going
		❑ Date completed:	❑ Planned	❑ On going
		❑ Date completed:	❑ Planned	❑ On going
		❑ Date completed:	❑ Planned	❑ On going
		❑ Date completed:	❑ Planned	❑ On going
		❑ Date completed:	❑ Planned	❑ On going

Outcome of Malignancy					
Was patient sent to hospice care? ❑ Yes ❑ No					
Current status of malignancy?					
❑ Complete remission	❑ Partial remission	❑ Stable	❑ Regression	❑ Progressive disease	❑ Fatal outcome- date of death:

Autopsy Data		
If applicable, please provide the following information: ❑ Not applicable		
If the patient has expired, was an autopsy performed?		
❑ Yes –please provide autopsy results including cause of death	❑ No	❑ Unknown

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Brief Statistical Description and Supportive Outputs

The [Brief Statistical Description portion and Supportive Outputs of Annex 7] is presented separately.

MedDRA Search terms for spontaneous post-marketing data

Table 14-3 MedDRA Search terms for spontaneous post-marketing data

Safety Concern	MedDRA Term
Important Identified Risk	
Anaphylaxis - anaphylactoid reactions	• Anaphylactic reaction (SMQ narrow) • Anaphylactic/anaphylactoid shock conditions (SMQ narrow)
Churg Strauss Syndrome - Hypereosinophilic syndrome	• Eosinophilic disorders (HLT) • Vascular inflammations (HLGT)
Important Potential Risk	
Arterial Thromboembolic Events	• Haemorrhagic central nervous system vascular conditions (SMQ) • Ischaemic central nervous system vascular conditions (SMQ) • Myocardial infarction (SMQ broad) • Other ischaemic heart disease (SMQ broad) • Cardiac death (PT) • Hemiparesis (PT) • Hemiplegia (PT) • Sudden cardiac death (PT) • Sudden death (PT)
Malignant neoplasms	• Malignancies (SMQ broad)

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Annex 8 – Summary of changes to the risk management plan over time

Table 14-4 Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
1.0	EMEA/H/C/000606/II/007 30-May-2007 (EC decision)	Initial RMP Safety concerns and additional PVA and RMA Safety concerns Important Identified risks: • Anaphylaxis / anaphylactoid reactions • Malignancies Important Potential risks: • Serum sickness syndrome / influenza like syndrome • Antibody formation • Churg Strauss Syndrome / HES • Thrombocytopenia • Parasitic (helminth) infections Missing information: • Pregnancy outcomes Additional Pharmacovigilance activities (PVA) Post-marketing commitment from FDA: EXCELS study (An epidemiologic study of Xolair (omalizumab) evaluating clinical effectiveness and long-term safety in patients with moderate to severe asthma). Pregnancy registry (EXPECT) started September 2006 Human-anti-human antibody (HAHA) /anti-therapeutic antibody (ATA) testing when requested by HCP Post-authorization efficacy plan: NA Additional Risk minimization activities (RMA): Routine risk minimization measures such as information about risks included in the SmPC. No additional RMA proposed.
2.0	EMEA/H/C/000606/X0014 10-Feb-2009 (EC decision)	Safety concerns No changes from the previous version Pharmacovigilance Plan: No changes made to version 1.0 Post-authorization efficacy plan: NA Additional Risk minimization measures: None
3.0	EMEA/H/C/000606/II/018 27-July-2009	The format of version 3.0 was updated from version 2.0 in order to fully comply with the EMA Guideline on Risk Management Systems for Medicinal Products for Human Use Safety concerns Off-label added as an important potential risk The important identified risk of 'Malignancies' was split into two risks: • Malignant neoplasms (in adult and adolescent patients ≥ 12 years old) was retained as an identified risk.

Version	Approval date Procedure	Change
		• Malignant neoplasms in children (in pediatric patients 6 to < 12 years old) qualified as a potential risk due to absence of any signal in the pediatric clinical program and the interim data from the EXCELS Study. Pharmacovigilance Plan: No changes made to the previous version. Post-authorization efficacy plan: NA Additional Risk minimization measures: None
4.0	v4.0 EMEA/H/C/000606/II/018 v4.1 EMEA/H/C/000606/II/019 v4.2 EMEA/H/C/000606/II/019 25-Jan-2010 (EC decision)	Safety concerns Serum sickness was changed from an important potential risk to an important identified risk Pharmacovigilance Plan: Targeted follow-up with the use of event-specific questionnaires for the risks of Anaphylaxis and Malignancies, Expedited reporting to the EMEA of all cases of anaphylaxis, anaphylactoid reactions, or a combination of individual symptoms meeting accepted diagnostic criteria (Sampson's criteria) and assessed as related to omalizumab. Post-authorization efficacy plan: NA Additional Risk minimization measures: None
5.0	EMEA/H/C/000606/II/021 12-Nov-2010 (EC decision)	Safety concerns A new important potential risk -Cerebro-vascular disorders (CVDs) was added. Pharmacovigilance Plan: Targeted follow-up with the use of an event-specific questionnaire for the risk of CVD Post-authorization efficacy plan: N/A Additional Risk minimization measures: None
6.0	EMEA/H/C/606 RMP 6.1 21-Jul-2011 (CHMP adoption)	Safety concerns The former important potential risk "CVDs" was replaced by the new important potential risk "Arterial Thromboembolic Events (ATEs)". The important potential risk of "Antibody formation to omalizumab" has been escalated to become an important identified risk. Pharmacovigilance Plan: Targeted follow up with the use of a questionnaire / checklist for the risk of ATEs. Post-authorization efficacy plan: NA Additional Risk minimization measures: None
7.0	EMEA/H/C/606 RMP 7 17-Nov-2011 (CHMP adoption)	Safety concerns Former important potential risk of 'parasitic (helminth) infection' was removed from the RMP Pharmacovigilance Plan: No change from the previous version Post-authorization efficacy plan: NA

Version	Approval date Procedure	Change
		Additional Risk minimization measures: None
8.0	11-Jul-2013 EMEA/H/C/0606/PSU/037	Safety concerns Important potential risks CSS/ HES and Thrombocytopenia upgraded to important identified risks Pharmacovigilance Plan: EXCELS study removed due to its completion. Three additional studies added to the PV Plan: Pharmacosurveillance data repository of patients with and without history of anaphylactic reactions subsequent to Xolair dosing (X-PAND) Special Drug Use Observational Study of Xolair Subcutaneous Injection for Bronchial Asthma in Japan (CIGE025A1402) A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled allergic asthma despite current recommended treatment (CIGE025B1301E1). Post-authorization efficacy plan: NA Additional Risk minimization measures: None
8.1	17-Jul-2013 EMEA/H/C/606/II/0046 28/02/2014 (EC decision)	Safety concerns Important Identified risk 'Malignant neoplasms in adults and adolescents ≥ 12 years of age' downgraded to an important potential risk. Pharmacovigilance Plan: No change from the previous version Post-authorization efficacy plan: NA Additional Risk minimization measures: None
9.0	28-Feb-2014 EMEA/H/C/606/II/48	Included data that is specific to the proposed chronic spontaneous urticaria (CSU) indication. Safety concerns No change from the previous version Pharmacovigilance Plan: No change from the previous version Post-authorization efficacy plan: NA Additional Risk minimization measures: None
10.0	09-Jul-2015 EMEA/H/C/PSUSA/00002214/201412	Safety concerns The inclusion of a new important potential risk 'Hypersensitivity reactions in latex-sensitive individuals treated with PFS'. Pharmacovigilance Plan: XPAND Study and Study CIGE025B1301E1 removed due to completion. Post-authorization efficacy plan: NA Additional Risk minimization measures: None
11.0	29-April-2016 EMEA/H/C/000606/IB/0077/G	Safety concerns No changes as compared to the previous version Pharmacovigilance Plan

Version	Approval date Procedure	Change
		Updated milestones of study CIGE025A1402 and the EXPECT study, listed in the pharmacovigilance plan Post-authorization efficacy plan: NA Additional Risk minimization measures: None
12.0	14-June-2018 EMEA/H/C/000606/IB/0088	Reassessment of safety concerns as per the definition of 'important risk' in the revised GVP V revision 2. Safety concerns Important Identified risks: "Serum Sickness Syndrome (SSS) / Serum Sickness Like Disease (SSLD)", "Antibody formation to omalizumab", and "Thrombocytopenia" are removed from the list of safety concerns. Important potential Risk: "Off label use" and Hypersensitivity reactions in latex-sensitive individuals treated with PFS are removed from the list of safety concerns. Pharmacovigilance Plan: ATA testing when requested by HCP was removed. Post-authorization efficacy plan NA Additional Risk minimization measures None
13.0	20-Jul-2018 EMEA/H/C/000606/II/0092	Home Use submission for Xolair for the formulation solution for injection in pre filled syringe (PFS) and update on risk minimization measure for anaphylaxis in the context of home use. Safety concerns None. Pharmacovigilance Plan: None. Post-authorization efficacy plan NA. Additional Risk minimization measures None.
14.0	Under Evaluation EMEA/H/C/000606/II/XXX 24-Sep-2018	This version of RMP is updated on completion of a category 3 study-EXPECT Pregnancy Registry which is an RMP commitment. Safety concerns: "Pregnancy Outcomes" is no longer considered missing information in the RMP as no new safety risks were identified from EXPECT pregnancy registry that would necessitate additional PV or risk minimization measures. Pharmacovigilance Plan: Expect pregnancy registry removed since completed. Post-authorization efficacy plan NA. Additional Risk minimization measures None.

Version	Approval date Procedure	Change
13.1	18-Oct-2018 EMEA/H/C/000606/II/0092	RMP update to address the questions from the updated preliminary assessment report for procedure EMEA/H/C/000606/II/0092 Safety concerns None. Pharmacovigilance Plan: Clarification on how to assess if patients displaying anaphylaxis under home use settings were adequately trained. Post-authorization efficacy plan NA. Additional Risk minimization measures None.
15.0	04-Feb-2019 EMEA/H/C/000606/II/0093	This EU RMP is a consolidated version of parallel procedures. It combines the two RMPs as follows: **Version 13.1:** Dossier in support of home use (self-administration or administration by a lay care giver) for Xolair, solution for injection in a pre-filled syringe (PFS) including an update of the risk minimization measures for anaphylaxis. **Version 14.0:** Completion of a category 3 PASS study - EXPECT Pregnancy Registry which is an RMP commitment. Safety concerns “Pregnancy Outcomes” is no longer considered missing information in the RMP as no new safety risks were identified from EXPECT pregnancy registry that would necessitate additional PV or risk minimization measures. Pharmacovigilance Plan: Clarification on how to assess if patients displaying anaphylaxis under home use settings were adequately trained. Expect pregnancy registry removed since completed. Post-authorization efficacy plan NA. Additional Risk minimization measures None.
16.0	23-Oct-2019	The trigger for this EU RMP update is the submission of the dossier for a new indication, as Nasal polyps in adult patients (18 years and above) with inadequate response to intranasal corticosteroids. Safety concerns None. Pharmacovigilance Plan: None. Post-authorization efficacy plan NA. Additional Risk minimization measures None.