Unit: Technical Assessment Unit

Public assessment report for biological products

Xolair 75 mg/0.5 ml and 150 mg/ml PFS

Administrative information:

Trade name of the medicinal product:	Xolair 75 mg/0.5ml Xolair 150 mg/1ml
INN (or common name) of the active substance(s):	OMALIZUMAB
Manufacturer of the finished product	Novartis Pharma Stein AG, Schaffhauserstrasse,4332 Stein - SWITZERLAND.
Marketing Authorization holder	Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4 – IRELAND.
Applied Indication(s):	Allergic Asthma Nasal polyps Chronic Spontaneous Urticaria
Pharmaceutical form(s) and strength(s):	Solution for injection in Pre-filled Syringe 75 mg/0.5ml and 150 mg/ml
Route of administration	S.C
Registration track	Fast Tracks
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

ATE: Arterial Thromboembolic Event
CCI: Container Closure integrity
CHO: Chinese Hamster Ovary
CSS: Churg Strauss Syndrome
CSS/HES: Churg Strauss Syndrome/Hypereosinophilic syndrome
CSU: Chronic Spontaneous Urticaria
FcεRI: High affinity IgE receptor
GLP: Good laboratory practice
HAHA: Human anti-human antibody
IgE: Immunoglobulin E
IV: Intravenous
MAHA: Mouse anti-human antibody
PFS: Pre-filled syringe
PK/PD: Pharmacokinetic/Pharmacodynamic

SC: Subcutaneous

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1. General introduction about the product including brief description of the Active Pharmaceutical Ingredient, its mode of action and indications

Omalizumab (Xolair®) is a recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Omalizumab inhibits the binding of circulating IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response and results in improved control of symptoms. Omalizumab is approved in the following indications: Allergic asthma, chronic spontaneous urticaria and nasal polyps.

It is available in two formulations, both in two strengths

- Powder and solvent for solution for injection: 150 mg.
- Solution for injection in a pre-filled syringe (PFS) with needle safety device (PFS-NSD): 75 mg/0.5 mL and 150 mg/1mL.

2. Quality aspects:

1.2.1 Introduction

As mentioned in the aforementioned section.

1.2.2 Drug Substance (Active ingredient)

- **General information**

-International non–proprietary name (INN): Omalizumab
- Omalizumab is a recombinant humanized monoclonal antibody with the IgE-binding characteristics of a murine anti-IgE antibody and the structural characteristics of a human IgG1-class antibody.

- **Physicochemical Characterization**

-The drug substance is an aqueous, colorless to pale yellow protein solution, stored as preformulated bulk containing 150 mg/mL omalizumab in histidine, M L-arginine HCl, polysorbate 20.

- **Biological characterization**

- The biological activity of Omalizumab is measured by the IgE receptor binding inhibition assay against an internal reference standard.

- **Manufacture, process controls and characterization:**
  - **Manufacturer**:

-The drug substance is manufactured & controlled at
Novartis Pharma S.A.S., Centre de Biotechnologie, 8 rue de l'Industrie, 68330 Huningue, France – FRANCE;
-Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., BioProduction Operations Singapore, 8 Tuas, Bay Lane, Singapore 636986, - SINGAPORE;

-The site complies with the GMP requirements.

- **Description of Manufacturing Process and Process Controls**

- The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.
- The DS is manufactured throgh the following: cell culture production process and purification process. The steps of each process are described in details.

- **Control of Materials**

- List of raw materials of Pharmacopoeial and In-House Standard with relevant COAs are provided.
- Information regarding the used cell line & cell banking is mentioned in detail in the MA file.
- Viral safety information for biologically-sourced materials is mentioned.
- Transmissible spongiform encephalopathies (TSE)/bovine spongiform encephalopathies (BSE) risk assessment and available certificates for relevant animal-derived materials are discussed.

- **Controls of Critical Steps and Intermediates**

- Critical process steps and critical process parameters are mentioned in the manufacturing process and process control flow chart
- The process controls selected for each critical manufacturing step and justification of the proposed acceptance criteria are provided.

- **Process Validation**

-The Critical Process Parameters and Critical Control Parameters of the manufacturing process were identified and validated.
- All critical manufacturing processes were validated by taking three consistency runs at commercial scale.
-Validation protocols and reports are attached to the MA file illustrating the details of the batches used.

- **Manufacturing Process Development**

- The developmental history of the manufacturing process is sufficiently describing the whole changes made to the DS manufacturing process with proper justification.
- Detailed description for each step development is mentioned in the MA file.

- Relevant information on DS batches manufactured during development, such as the batch number (and subsequential drug product batch numbers), manufacturing date, scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, are presented.

- **Characterization**

- Omalizumab's structure is well characterized confirming its expected IgG1 architecture and cell-specific glycosylation.

Biological Characterization

- Product- and process-related variants are thoroughly analyzed and controlled. These variants have minimal or no impact on potency, with consistent levels across lots.

- **Specification**

-The tests performed on the drug substance comply with the requirements of ICH Q6B guideline, USP, Ph. Eur, and In-house practices.
- Detailed SOPs are provided with their validation report.
-The identity, purity, potency, physicochemical properties & microbiology of DS are tested.

- **Batch analysis**

-The consistency in manufacturing process of Omalizumab DS was observed in all the batches manufactured at the commercial manufacturing sites
-Batch analysis for commercial batches of Omalizumab DS have complied with test specification ensuring the consistency of the manufacturing process.

- **Reference Standards or Materials**

-The information provided regarding reference standards was sufficient, with the applicant submitting testing, specifications, and qualification protocols for both primary and working standards. These were accompanied by their certificates of analysis (COAs) and traceability to the primary standard, along with extensive characterizations.

- **Container closure system**

- Omalizumab bulk DS is stored in suitable tanks for the recommended conditions until further processing to final drug product.
Omalizumab utilizes mobile, freeze/thaw tanks for the storage and transfer of bulk material. The tanks are constructed of suitable materials that provide Xolair DS with protection from light and allow long term storage at the recommended conditions.

- **Stability of drug substance**

Based on available stability data

- ✓ **Approved Shelf Life:**
  As predetermined in the stability data
- ✓ **Approved Storage Conditions:**

the recommended conditions

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

- Xolair solution for injection in pre-filled syringe is a sterile, single use, preservative-free, clear to slightly opalescent, colorless to pale brownish-yellow solution for injection.
- The drug product composition has been fully detailed, including the active substance and accompanying excipients along with their respective functions.
-The container closure system consists of a Type I syringe glass barrel, equipped with a staked stainless-steel needle, a rubber plunger stopper and a rigid needle shield, which are assembled with a needle safety device.

Pharmaceutical Development

- **Components of drug product**

- Omalizumab 15% DS is a recombinant humanized monoclonal antibody of the IgG1/kappa isotype directed against human IgE, containing the IgE binding characteristics of a murine anti-IgE antibody.

Formulation Development

-The formulation development of Xolair drug products started with the development of the 150 mg lyophilisate presentation, followed by the development of the 75 mg/0.5 mL and 150 mg/1.0 mL solution for injection in pre-filled syringe presentations.
-The primary packaging of the new presentations was slightly adapted compared to the initially commercialized Xolair 75 mg/0.5 mL and 150 mg/1.0 mL solution for injection in pre-filled syringe presentations. Additionally, bulk pre-filled syringes of the new presentations will be manufactured at a different site from the existing commercial pre-filled syringe products.

- **Manufacturing Process Development**

- During process development the following attributes were investigated to evaluate and confirm the program for thawing and homogenization:
• Time for thawing of drug substance
• Stability of drug substance during thawing and homogenization
• Homogeneity of drug substance
- It was further confirmed by the process validation campaign which was also used to manufacture the registration stability batches.
- Sufficient studies were performed to define and evaluate the filling process for Xolair solution for injection bulk PFS.

- **Microbiological Attributes**

- Xolair is sterile products which do not contain a microbial preservative and supplied as single dose product.

- Xolair is manufactured using standard aseptic processes, and the aseptic manufacturing processes have been validated by media fill runs.
-The integrity of the sterile final products is routinely evaluated using pharmacopeial methods for sterility and bacterial endotoxins at release and during stability.
- **Compatibility**
- Compatibility of Omalizumab with its excipients has been shown during stability of the initially commercialized Xolair 75 mg/0.5 mL and 150 mg/1.0 mL solution for injection in PFS presentations.

- Stability data of the newly developed Xolair 150 mg/1.0 mL, 75 mg/0.5 mL solution for injection in PFS presentations further substantiate compatibility of Omalizumab active ingredient with excipients as well as the compatibility of the DP solution with the primary packaging materials of the newly developed presentations are well illustrated

Manufacture of the drug product:
Description of manufacturing process and process controls along with manufacturers and responsibilities.

- **Manufacture**:

- Manufacturer and batch release site of the finished product is Novartis Pharma Stein AG, Schaffhauserstrasse,4332 Stein – SWITZERLAND.

- Xolair 150 mg/1.0 mL and 75 mg/0.5 mL solution for injection in PFS DP are produced using standard manufacturing steps, such as thawing and homogenization of drug substance, bioburden reduction and in-line sterile filtration, aseptic filling and stoppering of syringes.

- A flow diagram is clearly presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted are identified. A narrative description of the manufacturing process, including packaging, which represents the sequence of steps undertaken are provided.

- **Control of critical steps and intermediates**

-Tests and acceptance criteria for critical manufacturing steps are clearly identified, with defined action and acceptance limits.

- **Process validation and / or evaluation**

-The process validation comprised nine consecutive bulk PFS batches of Xolair 150 mg/1.0 mL, 75 mg/0.5 mL solution for injection, with three batches per strength.
- The information provided in the study report support the current manufacturing process proposed for commercial use, including IPCs results and data from relevant manufacturing batches to demonstrate consistency in yield and production, and degree of purity.

- **Product specification:**

- Specifications proposed for release and stability testing of the finished product comply with current ICH guidelines Q6B /USP/Eur.Ph.
- Detailed SOPs validation protocols & reports are provided for the in-house methods
The provided Certificates of Analysis (CoAs) comply with the stated specifications.
- Justification of the drug product specifications at the release and during stability studies are provided.

- **Reference Standards or Materials.**

-The reference standard used for release and stability testing of Xolair 150 mg/1.0 mL and 75 mg/0.5 mL solution for injection in PFS is the same as the reference standard used for Omalizumab 15% DS. For details reference is made to DS section 'Reference Standards or Materials'.

- **Container closure system**

- The primary packaging of Xolair 150 mg/1.0 mL, 75 mg/0.5 mL solution for injection in pre-filled syringe contains the following components:
• A type I glass syringe barrel, equipped with a staked stainless-steel needle were the needle is fixed to the syringe barrel with an adhesive
• A rubber plunger stopper
• A rigid needle shield composed of a needle shield covered by a rigid shell
The syringe glass barrel contains the drug product solution.

- **Stability of the drug product**

-Based on available stability data,

- ✓ **approved Shelf Life:**
  18 months
- ✓ **approved Storage Conditions:**
- ✓ Store in a refrigerator (2-8°C)
- ✓ Do not freeze
- ✓ Store in the original package to protect from light
- ✓ The product may be kept for a total of 48 hours at 25^{O}C

3.Non–clinical aspect:

- Omalizumab is a recombinant humanized anti-IgE monoclonal antibody that is used as a therapeutic agent for the treatment of patients with allergic asthma mediated by overproduction of allergen-specific IgE. IgE can bind to the high affinity IgE receptor (FcεRI) on the surface of mast cells and basophils and trigger the allergic cascade (including histamine release) following cross-linking by allergens.

- **Pharmacology:** These results provided a proof of concept for the ability of omalizumab to ameliorate an allergic response in vivo.
- **Secondary Pharmacodynamic:** no specific secondary pharmacodynamic studies with omalizumab.
- **Safety Pharmacology:** no separate safety pharmacology studies were performed for omalizumab.
- **Pharmacodynamic Drug Interaction**: Nonclinical drug interaction studies were not performed with omalizumab
- **Pharmacokinetics:** The pharmacokinetic parameters following the SC dose of Omalizumab were similar to those of the IV dose.
- **Toxicology** The safety of omalizumab has been studied in the cynomolgus monkey. Acute and chronic administration of omalizumab was well tolerated in non-human primates, with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4 to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute hemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.
  -Pharmacokinetics after repeated administration and toxicokinetics were comparable to the kinetics after single dose administration.
  -Omalizumab was not mutagenic in the Ames test at concentrations up to 5000 µg/mL. Based on the ICH Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (S6), a full battery of genotoxicity studies was not required.
  -Standard rodent carcinogenicity studies were not conducted, since omalizumab does not bind rodent IgE. There were no incidences of tumors in 3 separate 6-month studies in cynomolgus monkeys.
  -SC administration of omalizumab, at doses up to 75 mg/kg once weekly for 6 weeks (to cover the period of spermatogenesis) did not elicit reproductive toxicity in males. The same doses were administered to females for 13 weeks (three menstrual cycles) before mating, during the mating period (maximum of two menstrual cycles) and during early pregnancy (up to Day 25 of gestation). Omalizumab did not elicit reproductive toxicity in female Cynomolgus monkeys.
  -Administration of omalizumab to pregnant monkeys during organogenesis (gestational Days 20 to 50) at doses of 0, 3, 15 and 75 mg/kg did not elicit maternal toxicity, embryotoxicity or teratogenicity.
  -There was no evidence of late gestational maternal or offspring toxicity. Omalizumab was observed in amniotic fluid (~3.3% of maternal serum levels), milk (~0.154%), and fetal (~33%) and neonatal (~33%) serum.

  - **Overall conclusion:** based on the review of the submitted studies, Xolair is accepted from the preclinical point of view.

4.Clinical aspect:

<u>Phase II study</u>

- Omalizumab exposure in treated subjects was generally comparable for both lyophilized and aged liquid omalizumab formulations. Reduction in free IgE and increase in total IgE compared with baseline were similar in subjects treated with lyophilized and aged liquid omalizumab.
- The study demonstrated that both the aged liquid and lyophilized omalizumab formulations resulted in an increase in allergen PC15 at Week 16. However, when tested for superiority compared with placebo, the lyophilized omalizumab group achieved a statistically significant increase in allergen PC15 while the liquid omalizumab group did not. Similar results were found for the two-point slope ratio. Based on these results, aged liquid omalizumab did not meet the criteria of comparability as specified in the Statistical Analysis Plan.
- The lyophilized and aged liquid forms of omalizumab were well tolerated and most adverse events were related to upper and lower airways inflammation, generally mild or moderate in severity, and were consistent with events observed in prior studies of omalizumab as claimed by the applicant.

Phase III studies:

- No patients had an immune response (determined by a positive HAHA test result) to the liquid formulation of omalizumab, indicating no evidence for gross effect in immunogenicity for the liquid formulation in this study.
- Pharmacokinetic and pharmacodynamic results demonstrated that exposure was achieved resulting in low free IgE and elevated total IgE concentration as expected. The concentration of free IgE was low and similar for both dosing schedules.
- The frequency of AEs was consistent with previous studies as claimed by the applicant. The majority of AEs were mild or moderate in severity, and not suspected to be study drug related. The most commonly reported AEs during the treatment and follow-up periods were asthma and sinusitis. No patients discontinued due to asthma exacerbation during the treatment period.

Phase IV studies:

- Treatment with omalizumab resulted in a reduction in asthma exacerbations requiring systemic steroids or hospitalization in the 90-day period beginning on the first day of each participant's school year.
- The PFS formulation of omalizumab was **generally well-tolerated**. Non-serious AEs were generally mild to moderate in intensity. No AEs were life-threatening

- **Clinical Pharmacology conclusion:**
  - Bioequivalence of omalizumab was demonstrated for both the comparison of the non-aged liquid omalizumab or aged liquid omalizumab in PFS vs the lyophilized omalizumab. Concentration time profiles of free and total IgE were similar for all three formulations.

- The liquid formulation has demonstrated similar PK properties to the lyophilized formulation and achieves comparable reduction in serum free IgE, a PD marker for omalizumab efficacy.
-The PFS formulation is considered to be more convenient to use as reconstitution before each use is not required.

➢ **Clinical Efficacy conclusion:**

- On the basis of demonstrated bioequivalence between the new liquid formulation and the marketed lyophilizate formulation, it is expected and therefore considered that the solution for injection and the authorized lyophilizate formulation **have the same efficacy.**

➢ **Clinical Safety conclusion:**

- Results from the bioequivalence studies did not indicate new or unexpected adverse events following single doses of Xolair solution for injection compared to the authorized lyophilizate formulation.
- A cumulative analysis of all available data does not suggest a differentiated safety profile for the PFS formulation compared to the lyophilized formulation of omalizumab.
- Post- marketing surveillance of Xolair solution in pre-filled syringe from January 2011 until December 2014 retrieved a total of 179 cases in 10 risk categories showed that no case was reported with a 'fatal' outcome, 3 life-threatening cases were reported (2 cases of anaphylaxis (assessed as suspected to be related to omalizumab and 1 case of ATE (assessed as not suspected to be related to omalizumab),) and 3 cases of **Serum Sickness Syndrome/Serum Sickness-Like Disease (one case assessed as suspected to omalizumab and the other 2 cases with no reported causality).**
- 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 (Important identified risk)**. Additionally, in other 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. Hence, routine risk minimization measures of anaphylaxis should be considered especially in risk groups (**patients with previous history of anaphylaxis, children, atopic individuals and asthmatics).**
- **Similarly,** in rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and CSS. These events are commonly associated with the reduction of oral corticosteroid therapy. No cases of CSS/HES were reported in clinical trials. All cases of CSS were reported in the post-marketing setting, so **routine risk minimization measures should be considered.**

➢ **Clinical Immunogenicity conclusion:**

- From study (CIGE025C2303) that aimed to assess the safety and **immunogenicity** of omalizumab liquid administered subcutaneously in a pre-filled safety syringe (75 mg/0.5ml or 150 mg/ml): **No patients had a positive HAHA test result for the liquid formulation, indicating no evidence for gross effect in immunogenicity for the liquid formulation**, this

conclusion can be supported by the results of other submitted studies that proved absence of any positive HAHAs or specific immunoreactivity with omalizumab.

- **Benefit/ Risk discussion:** In conclusion the overall benefit/risk of Xolair 75 mg/0.5 ml solution for injection in prefilled syringe and Xolair 150 mg/ml solution for injection in prefilled syringe is favorable in the treatment of Allergic Asthma, Nasal Polyps and Chronic Spontaneous Urticaria (CSU).

5.General Conclusion and Recommendations if any:

- **Recommendations:**

1- Any updated PSUR should be submitted to Pharmacovigilance administration in EDA.

2- Submission of the pregnancy registry (EXPECT), an omalizumab prospective pregnancy registry study, which was a post-marketing commitment to the US Food and Drug Administration (FDA) designed to evaluate health outcomes, including the incidence of congenital anomalies, in pregnant women and their infants.

3- Submission of the (EXCELS) study, (An Epidemiologic Study of Xolair (Omalizumab): Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma). A causal association has not been established between omalizumab and two important potential risk: ATE events and malignancies in adults and adolescents ≥ 12 years of age, where the results from the pooled clinical trials analysis were supported by data from the EXCELS study. As a result, information has been added about these potential risks to the drug label.