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.

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. It is also approved for treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients (18 years and above) with inadequate response to intranasal corticosteroids. It contains omalizumab as the active substance and it is given subcutaneously every 2 or every 4 weeks for AA and CRwNP (75 mg to 600 mg according to body weight and baseline IgE levels) and every 4 weeks for CSU (300 mg)

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

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.

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 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)

II.B: Summary of important risks

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

Table 1 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 2 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 3 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 4 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 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.

II.C: Post-authorization development plan

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.

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

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