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XOLAIR CSU - safety profile - HCP

Prescribing information

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Xolair® (omalizumab) safety profile

Please refer to the Xolair Summary of Product Characteristics (SmPC) for full information on safety, warnings and precautions, special populations, drug interactions and other important considerations.[1]

Indications:[1]

Xolair is 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.

The recommended dose of Xolair in patients with chronic spontaneous urticaria is 300 mg

by subcutaneous injection every four weeks.[1]

Xolair has additional therapeutic indications, special warnings and precautions and safety information. Please refer to the Xolair Summary of Product Characteristics (SmPC) for the full therapeutic indication.[1]

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma, chronic rhinosinusitis with nasal polyps (CRSwNP) or chronic spontaneous urticaria. Prescribers are advised to periodically reassess the need for continued therapy.

Summary of safety profile for CSU

The safety and tolerability of Xolair were investigated with doses of 75 mg, 150 mg and 300 mg every four weeks* in 975 CSU patients, 242 of whom received placebo. Overall, 733 patients were treated with Xolair for up to 12 weeks and 490 patients for up to 24 weeks. Of those, 412 patients were treated for up to 12 weeks and 333 patients were treated for up to 24 weeks at the 300 mg dose.[1]

*The recommended dose of Xolair in patients with CSU is 300 mg by subcutaneous injection every 4 weeks.

- Tabulated list of adverse reactions for CSU

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The adverse reactions (events occurring in ≥1% of patients in any treatment group and ≥2% more frequently in any Xolair treatment group than with placebo (after medical review)) are reported with 300 mg in three pooled Phase III studies.[1]

The adverse reactions are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions listed first. The corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from the available data).[1]

Adverse reactions are from pooled CSU safety database (Day 1 to

Week 24) at 300 mg Xolair[1]

12-week study	Xolair studies 1, 2 and 3 pooled		Frequency category
	Placebo N=242	300 mg N=412	
Infections and infestations			
Sinusitis	5 (2.1%)	20 (4.9%)	Common
Nervous system disorders			
Headache	7 (2.9%)	25 (6.1%)	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (0.4%)	12 (2.9%)	Common
General disorders and administration site conditions			
Injection site reaction*	2 (0.8%)	11 (2.7%)	Common
24-week study	**Xolair studies 1 and 3 pooled**		**Frequency category**
	Placebo N=163	**300 mg N=333**	
Infections and infestations			
Upper respiratory tract infection	5 (3.1%)	19 (5.7%)	Common

Adapted from Xolair® (omalizumab) Summary of Product Characteristics.[1]

*Despite not showing a 2% difference from placebo, injection site reactions were included as all cases were assessed causally related to study treatment. In a 48-week study, 81 CSU patients received Xolair 300 mg every 4 weeks. The safety profile of long-term use was similar to the safety profile observed in 24-week studies in CSU.[1]

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Anaphylaxis[1]

Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%.

Arterial thromboembolic events[1]

In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. The definition of the composite endpoint ATE included stroke, transient ischaemic 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 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% confidence interval 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% confidence interval 0.24–5.71).

Platelets[1]
In clinical trials few patients had platelet counts below the lower limit of the normal laboratory range. Isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

Parasitic infections[1]
In allergic patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight numerical increase in infection rate with Xolair that was not statistically significant. The course, severity and response to treatment of infections were unaltered.

Systemic lupus erythematosus[1]
Clinical trial and post-marketing cases of systemic lupus erythematosus have been reported in patients with moderate-to-severe asthma and CSU. The pathogenesis of SLE is not well understood.

For immune system disorder, please see the ‘Special warnings and precautions for use’ section.

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Hypersensitivity to the active substance (omalizumab) or to any of the following:[1]

- Arginine hydrochloride
- Histidine hydrochloride monohydrate
- Histidine
- Polysorbate 20
- Water for injections

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Image

Traceability[1]

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Image

General[1]
Xolair is not indicated for the treatment of acute asthma exacerbations, acute bronchospasm or status asthmaticus.

Xolair has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Xolair is not indicated for the treatment of these conditions.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment. Caution should be exercised when administering Xolair in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of Xolair therapy in allergic asthma or CRSwNP is not recommended. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

Image

Allergic reactions type I[1]
Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking Xolair, even after a long duration of treatment. However, most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair, but some started beyond 2 hours and even beyond 24 hours after the injection. The majority of anaphylactic reactions occurred within the first 3 doses of Xolair. Therefore, the first 3 doses must be administered either by or under the supervision of a healthcare professional. A history of anaphylaxis unrelated to Xolair may be a risk factor for anaphylaxis following Xolair administration. Therefore, for patients with a known history of anaphylaxis, Xolair must be administered by a healthcare professional, who should always have medicinal products for the treatment of anaphylactic reactions available for immediate use following administration of Xolair. If an anaphylactic or other serious allergic reaction occurs, administration of Xolair must be discontinued immediately, and appropriate therapy initiated. Patients should be informed that such reactions are possible, and prompt medical attention should be sought if allergic reactions occur.

Antibodies to Xolair have been detected in a low number of patients in clinical trials. The clinical relevance of anti-Xolair antibodies is not well understood.

Image

Serum sickness[1]
Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including Xolair. The suggested pathophysiological mechanism includes immune-complex formation and deposition due to development of antibodies against Xolair. The onset has typically been 1–5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgias, rash (urticaria or other forms), fever and lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder, and patients should be advised to report any suspected symptoms.

Image

Churg–Strauss syndrome and hypereosinophilic syndrome[1]
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 Xolair, 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.

Image

Parasitic (helminth) infections[1]
IgE may be involved in the immunological response to some helminth infections. In patients at chronic high risk of helminth infection, a placebo-controlled trial in allergic patients

showed a slight increase in infection rate with Xolair, although the course, severity and response to treatment of infection were unaltered. The helminth infection rate in the overall clinical programme, which was not designed to detect such infections, was less than 1 in 1,000 patients. However, caution may be warranted in patients at high risk of helminth infection, in particular when travelling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of Xolair should be considered.

Image

Latex-sensitive individuals[1]

The removable needle cap of this pre-filled syringe contains a derivative of natural rubber latex. No natural rubber latex has to date been detected in the removable needle cap. Nevertheless, the use of Xolair solution for injection in pre-filled syringe in latex-sensitive individuals has not been studied and thus there is a potential risk for hypersensitivity reactions which cannot be completely ruled out.

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If clinically needed, the use of Xolair may be considered during pregnancy.

- A moderate amount of data on pregnant women (between 300 and 1,000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foetal/neonatal toxicity

- A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to Xolair showed the prevalence of major congenital anomalies was similar (8.1% vs 8.9%) between EXPECT and disease-matched (moderate and severe asthma) patients

- The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design

- Xolair crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity; therefore, care should be taken when prescribing in pregnancy

- Xolair has been associated with age-dependent decreases in blood platelets in non-human primates with a greater relative sensitivity in juvenile animals

Image

If clinically needed, the use of Xolair may be considered in breastfeeding.

- Immunoglobulins G are present in human milk and it is therefore expected that Xolair will be present in human milk. Available data in non-human primates have shown excretion of Xolair into milk

- Data from the EXPECT study including 154 infants who had been exposed to Xolair during pregnancy and through breastfeeding did not indicate adverse effects in the breastfed infant

    - The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design

- Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breastfed newborns/infants are anticipated

Image

- There are no human fertility data for Xolair

- In specifically designed non-clinical fertility studies in non-human primates, including mating studies, no impairment of male or female fertility was observed following repeated dosing with Xolair up to 75 mg/kg

- No genotoxic effects were observed in a separate non-clinical genotoxicity study

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ASTERIA I:[2]

- The most common adverse events observed in the Xolair group were nasopharyngitis, headache, sinusitis, bronchitis, urticaria, arthralgia, and oropharyngeal pain. **The majority of AEs were mild or moderate in intensity**

ASTERIA II:[3]

- During the 28-week study period, there were reports of nine SAEs, with five reported in the group receiving 300 mg of Xolair (6%), and two in the placebo group (3%)

- **The percentages of patients with at least one adverse event were similar across the treatment groups**: 61% in the placebo group vs 65% in those receiving 300 mg of Xolair

GLACIAL:[4]

- During the 40-week study period (24-week treatment and 16-week follow-up period), **the incidence and severity of AEs and SAEs were similar between Xolair and placebo recipients, with no new Xolair safety issues identified**

- In Xolair and placebo recipients, the percentages of patients experiencing at least 1 AE, AEs reported as suspected to be caused by study drug, and serious AEs were 83.7% versus 78.3%, 11.1% versus 13.3%, and 7.1% versus 6.0%, respectively

Pooled safety analysis across three Phase III trials:[2–4]

	ASTERIA I[2]		ASTERIA II*[3]		GLACIAL†[4]	
	Placebo	**300 mg**	**Placebo**	**300 mg**	**Placebo**	**300 mg**
Number of patients	80	81	79	79	83	252
Any AE	53 (66.3%)	57 (70.4%)	48 (60.8%)	51 (64.6%)	65 (78.3%)	211 (83.7)
Severe AE	8 (10.0%)	13 (16.0%)	7 (8.9%)	6 (7.6%)	NR	NR
Serious AE (SAE)	5 (6.3%)	2 (2.5%)	2 (2.5%)	5 (6.3%)	5 (6.0%)	18 (7.1%)
AE leading to treatment withdrawal	7 (8.8%)	2 (2.5%)	-	-	1 (1.2%)	3 (1.2%)
AE suspected to be caused by study drug	4 (5.0%)	14 (17.3%)	3 (3.8%)	7 (8.9%)	11 (13.3%)	28 (11.1%)
Deaths	0	0	0	0	0	0
Anaphylaxis	0	0	0	0	0	0

Adapted from Saini S, et al. 2015,[2] Maurer M, et al. 2013[3] and Kaplan A, et al. 2013.[4]

*Incidence of AEs observed across duration of study including treatment period and follow-up = 28 weeks.[3]
†Incidence of AEs observed across duration of study including treatment period and follow-up = 40 weeks.[4]

AE, adverse event; ATE, arterial thromboembolic events; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; DLQI, dermatology life quality index; IgE, immunoglobulin E; NR, not reached; SAE, serious adverse event; SLE, systemic lupus erythematosus; SmPC, summary of product characteristics.

References

1. Xolair® (omalizumab) Summary of Product Characteristics.

2. Saini S, et al. *J Invest Dermatol* 2015;135(1):67–75 (and supplementary appendix).

3. Maurer M, et al. *N Engl J Med* 2013;368(10):924–935 (and supplementary appendix).

4. Kaplan A, et al. *J Allergy Clin Immunol* 2013;132(1):101–109.

Xolair® (omalizumab) efficacy

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See more details

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report, or alternatively email medinfo.uk@novartis.com or call 01276 698370.
