BOLSTRAN Injection (Omalizumab)

Composition

- **Active Substance**

Omalizumab is a humanized monoclonal antibody manufactured from a mammalian cell line. One vial of BOLSTRAN 150 mg delivers 150 mg of omalizumab. Reconstituted BOLSTRAN contains 125 mg/mL of omalizumab (150mg in 1.2mL).

- **Excipients**

  Powder vial: Sucrose, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20
  Solvent: Water for injection

Dosage Form

Powder vial and solvent for solution for injection

Pharmacology

- **Pharmacodynamics**

Omalizumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

Patients with Allergic Asthma

The allergic cascade is initiated when IgE bound to the high affinity IgE receptor, FcεRI, on the surface of mast cells and basophils is cross-linked by allergen. This results in the degranulation of these effector cells and the release of histamines, leukotrienes, cytokines and other mediators. These mediators are causally linked to the pathophysiology of allergic asthma including airway edema, smooth muscle contraction and altered cellular activity associated with the inflammatory process. They also contribute to the signs and symptoms of allergic disease such as bronchoconstriction, mucus production, wheezing, dyspnea, chest tightness, nasal congestion, sneezing, itchy, runny nose and itchy, watery eyes.

Omalizumab binds to IgE and prevents binding of IgE to FcεRI, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors. Furthermore, the in vitro histamine release from basophils isolated from BOLSTRAN® treated subjects was reduced by approximately 90% following stimulation with an allergen compared to pre-treatment values.

In clinical studies in asthma patients, free IgE levels in serum were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. Mean decrease in free IgE in serum was greater than 96% using recommended doses. Total IgE levels (i.e., bound and unbound) in serum increased after the first dose due to the
formation of omalizumab:IgE complexes which have a slower elimination rate compared with free IgE. At 16 weeks after the first dose, average serum total IgE levels were five-fold higher compared with pre-treatment levels when using standard assays. After discontinuation of BOLSTRAN® dosing, the BOLSTRAN® induced increase in total IgE and decrease in free IgE were reversible, with no observed rebound in IgE levels after drug washout. Total IgE levels did not return to pre-treatment levels for up to one year after discontinuation of BOLSTRAN®.

Pharmacokinetics

Absorption
After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg. Administration of BOLSTRAN® manufactured as a lyophilized or liquid formulation resulted in similar serum concentration-time profiles of omalizumab.

Distribution
In vitro, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than one million Daltons in molecular weight are not observed in vitro or in vivo. Tissue distribution studies in cynomolgus monkeys showed no specific uptake of 125I-omalizumab by any organ or tissue.

Elimination
Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the liver reticuloendothelial system (RES) and endothelial cells. Intact IgG is also excreted in bile. In studies with mice and monkeys, omalizumab:IgE complexes were eliminated by interactions with Fcγ receptors within the RES at rates that were generally faster than IgG clearance.

Indications

Allergic Asthma

Adults
Moderate to severe persistent allergic asthma, inadequately controlled with inhaled corticosteroids (ICS);

Children (12 years of age and older)
As add-on therapy to improve asthma control in children who have a positive skin test or in vitro reactivity to a perennial Aeroallergen and who have reduced lung function (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 inhaled corticosteroids, plus a long beta2-agonist.

Children (6 to < 12 years of age)
As add on therapy to improve asthma control in children with severe persistent allergic asthma 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 inhaled corticosteroids, plus a long beta2-agonist.

Chronic Spontaneous Urticaria

For adults and adolescents (12 years of age and above) with chronic spontaneous urticaria refractory to standard of care.

Dosage And Administration

For subcutaneous administration only. Do not administer by the intravenous or intramuscular route.
The appropriate dose and dosing frequency of BOLSTRAN® is determined by baseline immunoglobulin E (IgE) (IU/mL), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements 75 to 600 mg of BOLSTRAN® in 1 to 4 injections may be needed for each administration. See Tables 1 for conversion chart and Tables 2 and 3 for the dose determination charts in children (6 years to less than 12 years of age) and in adults and adolescents (12 years of age and older). For doses of 225, 375 or 525 mg BOLSTRAN® 150 mg can be used in combination with BOLSTRAN® 75 mg. Patients whose baseline IgE levels or body weight in kilograms are outside the limits of the dosing table should not be given BOLSTRAN®.

### Table 1: Conversion from dose to number of vials, number of injections and total injection volume for each administration

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<thead>
<tr>
<th>Dose (mg)</th>
<th>Number of vials</th>
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<th>Total injection volume (mL)</th>
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*0.6 mL = maximum delivered volume per vial (BOLSTRAN® 75 mg).

1.2 mL = maximum delivered volume per vial (BOLSTRAN® 150 mg).

or use 0.6 mL from a 150 mg vial.
Dosage for Chronic Spontaneous Urticaria

The recommended dose is 300 mg by subcutaneous injection every four weeks. Some patients may achieve control of their symptoms with a dose of 150 mg every four weeks.

Duration of use

In clinical trials, there were reductions in asthma exacerbation events and rescue medication use with improvements in symptom scores during the first 16 weeks of treatment. At least 12 weeks of treatment is required to adequately assess whether a patient is responding to BOLSTRAN®.

BOLSTRAN® is intended for long-term treatment. Discontinuation generally results in a return to elevated free IgE levels and associated symptoms. Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during BOLSTRAN® treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than one year should be based on serum IgE levels obtained at the initial dose determination. Total serum IgE levels may be re-tested for dose determination if treatment with BOLSTRAN® has been interrupted for one year or more. Doses should be adjusted for significant changes in body weight.
**Contraindications**

Hypersensitivity to omalizumab or to any of the excipients

**Warnings And Precautions**

### Allergic Reactions

As with any protein, local or systemic allergic reactions, including anaphylaxis, may occur when taking omalizumab. Therefore, medications for the treatment of anaphylactic reactions should be available for immediate use following administration of BOLSTRAN®. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. Anaphylactic reactions were rare in clinical trials.

In post-marketing experience, anaphylaxis and anaphylactoid reactions have been reported following the first or subsequent administrations of BOLSTRAN®. Although most of these reactions occurred within 2 hours, some occurred beyond 2 hours. As with all recombinant DNA derived humanized monoclonal antibodies patients may in rare cases develop antibodies to omalizumab.

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have rarely been seen in patients treated with humanized monoclonal antibodies including omalizumab. 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/arthralgia, 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.

### Parasitic Infections

IgE may be involved in the immunological response to some 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 omalizumab, although the course, severity, and response to treatment of infection were unaltered. The helminth infection rate in the overall clinical program, 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 traveling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of BOLSTRAN® should be considered.

### General

BOLSTRAN® is not indicated for the treatment of acute asthma exacerbations, acute bronchospasm or status asthmaticus. BOLSTRAN® has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions.

BOLSTRAN® has not been adequately studied in atopic dermatitis, allergic rhinitis or food allergy. BOLSTRAN® therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or those with pre-existing renal or hepatic impairment. Caution should be exercised when administering BOLSTRAN® in these patient populations.

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

*Advice to handler*

For subcutaneous administration only. Do not administer by the intravenous or intramuscular route.
Drug Interactions

Cytochrome P450 enzymes, efflux pumps and protein binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions. No formal drug or vaccine interaction studies have been performed with BOLSTRAN®.

There is no pharmacological reason to expect that commonly prescribed medications used in the treatment of asthma or CSU will interact with omalizumab.

Allergic Asthma

In clinical studies BOLSTRAN® was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta2-agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of BOLSTRAN® was altered with these other commonly used asthma medications. Limited data are available on the use of BOLSTRAN® in combination with specific immunotherapy (hypo-sensitization therapy).

Chronic Spontaneous Urticaria (CSU)

In clinical studies in CSU BOLSTRAN® was used in conjunction with antihistamines (anti-H1, anti-H2) and leukotriene receptor antagonists (LTRAs). There was no evidence that the safety of omalizumab was altered when used with these medicinal products relative to its known safety profile in allergic asthma. In addition, a population pharmacokinetic analysis showed no relevant effect of H2 antihistamines and LTRAs on omalizumab pharmacokinetics.

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, BOLSTRAN® should only be used during pregnancy if clearly needed.

Lactation

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 BOLSTRAN® to a nursing woman.

Renal or Hepatic Impairment

There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of omalizumab. Because omalizumab clearance at clinical doses is dominated by IgG clearance process, including degradation in the reticular endothelial system (RES) it is unlikely to be altered by renal or hepatic impairment. While no particular dose adjustment is recommended, BOLSTRAN® should be administered with caution in these patients.

Pediatric Patients

In allergic asthma, safety and efficacy in pediatric patients below the age of 6 have not been established and use of BOLSTRAN® in such patients is therefore not recommended.

In chronic spontaneous urticaria, safety and efficacy in pediatric patients below the age of 12 years have not been established.

Geriatric Patients

There are limited data available on the use of BOLSTRAN® in patients older than 65 years but there is no evidence that elderly patients require a different dosage from younger adult patients.
Undesirable Effects

Allergic Asthma
During clinical studies with adult and adolescent patients 12 years of age and older, the most commonly reported adverse reactions were injection site reactions, including injection site pain, swelling, erythema, pruritus, and headaches. In clinical studies with patients 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the events were mild or moderate in severity. Adverse reactions from the clinical studies listed were infections and infestations, pharyngitis, rare parasitic infections, immune system disorders, rare anaphylactic reaction and other allergic conditions, anti-therapeutic antibody development, nervous system disorders, headache, dizziness, somnolence, paresthesia, syncope, vascular disorders postural hypotension, flushing, coughing, allergic bronchospasm, rare laryngoedema, common abdominal pain upper, nausea, diarrhea, dyspeptic signs and symptoms, uncommon urticaria, rash, pruritus, photosensitivity, rare angioedema, very common pyrexia. Common injection site reactions such as pain, erythema, pruritus, swelling. Uncommon weight increase, fatigue, swelling arms, influenza-like illness.

Listing of adverse reactions from post-marketing spontaneous reports. The following reactions have been identified through spontaneous reporting.

Immune system disorders: Anaphylaxis and anaphylactoid reactions have been reported following the first or subsequent administrations, serum sickness.

Skin and subcutaneous disorders: Alopecia.

Blood and lymphatic system disorders: Idiopathic severe thrombocytopenia.

Respiratory, thoracic and mediastinal disorders: Allergic granulomatous angiitis (i.e. Churg Strauss syndrome).

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia, joint swelling.

Overdosage

No case of overdose has been reported. Maximum tolerated dose of BOLSTRAN® has not been determined. Single intravenous doses up to 4,000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period and this dose did not result in any untoward acute effects.

Incompatibilities

Powder vial and solvent for solution for injection: BOLSTRAN® should not be mixed with any medication or diluents other than sterile water for injection.

Shelf Life

Powder and solvent for solution for injection: 48 months

Storage

BOLSTRAN® must be stored in a refrigerated condition at 2°C–8°C. Do not freeze. In order to protect from light, store in the original package. The shelf life includes potential temperature excursions. BOLSTRAN® must not be used after the date marked “EXP” on the pack. BOLSTRAN® must be kept out of the reach and sight of children.
Packaging Information

Pack of 1 powder vial of BOLSTRAN (Omalizumab) 150 mg and 1 ampoule of solvent for solution for injection.

Reference

India pack insert dtd 7 Dec 2015 (same as current approved Xolair PI based on the IPL dtd 13 Mar 2014).
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BOLSTRAN Injection

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