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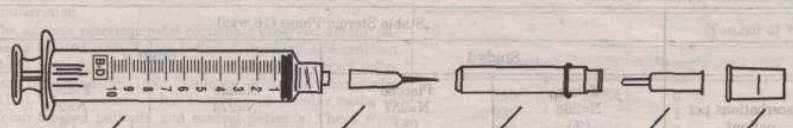
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The B-D® 10 cc Syringe with TwinPak™ Dual Cannula Device



Note: Do not discard the shield assembly.

2. Inject the entire contents of the syringe (10 mL) into the TNKase vial directing the diluent stream into the powder. Slight foaming upon reconstitution is not unusual; any large bubbles will dissipate if the product is allowed to stand undisturbed for several minutes.
3. Gently swirl until contents are completely dissolved. DO NOT SHAKE. The reconstituted preparation results in a colorless to pale yellow transparent solution containing TNKase at 5 mg/mL at a pH of approximately 7.3. The osmolality of this solution is approximately 290 mOsm/kg.
4. Determine the appropriate dose of TNKase (see Dose Information Table) and withdraw this volume (in milliliters) from the reconstituted vial with the syringe. **Any unused solution should be discarded.**
5. Once the appropriate dose of TNKase is drawn into the syringe, stand the shield vertically on a flat surface (with green side down) and passively recap the red hub cannula.
6. Remove the entire shield assembly, including the red hub cannula, by twisting counterclockwise. Note: The shield assembly also contains the clear-ended blunt plastic cannula; retain for split septum IV access.

Administration

1. The product should be visually inspected prior to administration for particulate matter and discoloration. TNKase may be administered as reconstituted at 5 mg/mL.
2. Precipitation may occur when TNKase is administered in an IV line containing dextrose. Dextrose-containing lines should be flushed with a saline-containing solution prior to and following single bolus administration of TNKase.
3. Reconstituted TNKase should be administered as a single IV bolus over 5 seconds.
4. Because TNKase contains no antibacterial preservatives, it should be reconstituted immediately before use. If the reconstituted TNKase is not used immediately, refrigerate the TNKase vial at 2–8°C (36–46°F) and use within 8 hours.
5. Although the supplied syringe is compatible with a conventional needle, this syringe is designed to be used with needleless IV systems. From the information below, follow the instructions applicable to the IV system in use.

Split septum IV system:	•Remove the green cap. •Attach the clear-ended blunt plastic cannula to the syringe. •Remove the shield and use the blunt plastic cannula to access the split septum injection port. •Because the blunt plastic cannula has two side ports, air or fluid expelled through the cannula will exit in two sideways directions; direct away from face or mucous membranes.
***Luer-Lok®* system:**	Connect syringe directly to IV port.
Conventional needle (not supplied in this kit):	Attach a large bore needle, e.g., 18 gauge, to the syringe's universal Luer-Lok®.

6. Dispose of the syringe, cannula, and shield per established procedures.

HOW SUPPLIED

TNKase is supplied as a sterile, lyophilized powder in a 50 mg vial under partial vacuum. Each 50 mg vial of TNKase is packaged with one 10 mL vial of Sterile Water for Injection, USP, for reconstitution, The B-D® 10 cc syringe with TwinPak™ Dual Cannula Device, and three alcohol prep pads. NDC 50242-038-61.

Stability and Storage

Store lyophilized TNKase at controlled room temperature not to exceed 30°C (86°F) or under refrigeration 2–8°C (36–46°F). Do not use beyond the expiration date stamped on the vial.

REFERENCES

1. ASSENT-2 Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet 1999;354:716-22.
2. Cannon CP, Gibson CM, McCabe CH, Adgey AAJ, Schweiger MJ, Sequeira RF, et al. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction. Results of the TIMI 10B trial. Circulation 1998;98:2805-14.
3. Van de Werf F, Cannon CP, Luyten A, Houbracken K, McCabe CH, Berioli S, et al. Safety assessment of a single bolus administration of TNK-tissue plasminogen activator in acute myocardial infarction: the ASSENT-1 trial. Am Heart J 1999;137:786-91.

TNKase™
(Tenecteplase)

Manufactured by:
Genentech, Inc. 4819900
1 DNA Way June 2000
South San Francisco, CA 94080-4990
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Shown in Product Identification Guide, page 313

XOLAIR® ℞

[zō'lār]
Omalizumab
For Subcutaneous Use

DESCRIPTION

Xolair (Omalizumab) is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149 kilodaltons. Xolair is produced by a Chinese hamster ovary cell suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Xolair is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with Sterile Water for Injection (SWFI), USP, and administered as a subcutaneous (SC) injection. A Xolair 75 mg vial contains 129.6 mg of Omalizumab, 93.1 mg sucrose, 1.8 mg L-histidine hydrochloride monohydrate, 1.2 mg L-histidine, and 0.3 mg polysorbate 20, and is designed to deliver 75 mg of Omalizumab in 0.6 mL after reconstitution with 0.9 mL SWFI, USP. A Xolair 150 mg vial contains 202.5 mg of Omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20, and is designed to deliver 150 mg of Omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

Xolair inhibits the binding of 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. Treatment with Xolair also reduces the number of FcεRI receptors on basophils in atopic patients.

Pharmacokinetics

After SC administration, Omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single SC dose in adult and adolescent patients with asthma, Omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7–8 days. The pharmacokinetics of Omalizumab are linear at doses greater than 0.5 mg/kg. Following multiple doses of Omalizumab, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose.

In vitro, Omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than 1 million daltons in molecular weight are not observed *in vitro* or *in vivo*. Tissue distribution studies in cynomolgus monkeys showed no specific uptake of ^{125}I-Omalizumab by any organ or tissue. The apparent volume of distribution in patients following SC administration was 78±32 mL/kg.

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. In asthma patients Omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4±1.1 mL/kg/day. In addition, doubling body weight approximately doubled apparent clearance.

Pharmacodynamics

In clinical studies, serum free IgE levels were reduced in a dose dependent manner within 1 hour following the first dose and maintained between doses. Mean serum free IgE decrease was greater than 96% using recommended doses. Serum total IgE levels (i.e., bound and unbound) 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 when using standard assays. After discontinuation of Xolair dosing, the Xolair-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 Xolair.

Special Populations

The population pharmacokinetics of Xolair were analyzed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for age (12–76 years), race, ethnicity, or gender.

CLINICAL STUDIES

The safety and efficacy of Xolair were evaluated in three randomized, double-blind, placebo-controlled, multicenter trials.

The trials enrolled patients 12 to 76 years old, with moderate to severe persistent (NHLBI criteria) asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. At screening, patients in Studies 1 and 2 had a forced expiratory volume in one second (FEV1) between 40% and 80% predicted, while in Study 3 there was no restriction on screening FEV1. All patients had a FEV1 improvement of at least 12% following beta-agonist administration. All patients were symptomatic and were being treated with inhaled corticosteroids (ICS) and short acting beta-agonists. In Study 3, long-acting beta-agonists were allowed. Study 3 patients were receiving at least 1000 µg/day fluticasone propionate and a subset was also receiving oral corticosteroids. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

Each study was comprised of a run-in period to achieve a stable conversion to a common ICS (beclomethasone dipropionate, for Studies 1 and 2; fluticasone propionate for Study 3), followed by randomization to Xolair or placebo. In Study 3, patients were stratified by use of ICS-only or ICS with concomitant use of oral steroids. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 weeks (Studies 1 and 2) or 16 weeks (Study 3) during which ICS (or oral steroid in Study 3 subset) dose reduction was attempted in a step-wise manner.

Xolair dosing was based on body weight and baseline serum total IgE concentration. All patients were required to have a baseline IgE between 30 and 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of Xolair or a matching volume of placebo over each 4-week period. The maximum Xolair dose per 4 weeks was 750 mg; patients who had a weight-IgE combination that yielded a dose greater than 750 mg were excluded from the studies. Patients who were to receive more than 300 mg within the 4-week period were administered half the total dose every 2 weeks.

The distribution of the number of asthma exacerbations per patient in each group during a study was analyzed separately for the stable steroid and steroid-reduction periods. In all three studies an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose.

In both Studies 1 and 2 the number of exacerbations per patient was reduced in patients treated with Xolair compared with placebo (Table 1). In Study 3 the number of exacerbations in patients treated with Xolair was similar to that in placebo-treated patients (Table 2). The absence of an observed treatment effect in Study 3 may be related to differences in the patient population compared with Studies 1 and 2, study sample size, or other factors. In all three studies most exacerbations were managed in the out-patient setting and the majority were treated with systemic steroids. Hospitalization rates were not significantly different between Xolair and placebo-treated patients; however, the overall hospitalization rate was small. Among those patients who experienced an exacerbation, the distribution of exacerbation severity was similar between treatment groups.

[See table 1 at top of next page]
[See table 2 on next page]

In all three of the studies, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV1 >80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

In Studies 1 and 2 measures of airflow (FEV1) and asthma symptoms were evaluated (Table 3). The clinical relevance of the treatment-associated differences is unknown.

[See table 3 on next page]

Continued on next page

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Xolair—Cont.

Results from the stable steroid phase of Study 2 and the steroid reduction phases of both Studies 1 and 2 were similar to those presented in Table 3.

INDICATIONS AND USAGE

Xolair (Omalizumab) is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

CONTRAINDICATIONS

Xolair should not be administered to patients who have experienced a severe hypersensitivity reaction to Xolair (see WARNINGS: Anaphylaxis).

WARNINGS

Malignancy

Malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known (see ADVERSE REACTIONS: Malignancy).

Anaphylaxis

Anaphylaxis has occurred within 2 hours of the first or subsequent administration of Xolair in 3 (<0.1%) patients without other identifiable allergic triggers. These events included urticaria and throat and/or tongue edema (see ADVERSE REACTIONS). Patients should be observed after injection of Xolair, and medications for the treatment of severe hypersensitivity reactions including anaphylaxis should be available. If a severe hypersensitivity reaction to Xolair occurs, therapy should be discontinued (see CONTRAINDICATIONS).

PRECAUTIONS

General

Xolair has not been shown to alleviate asthma exacerbations acutely and should not be used for the treatment of acute bronchospasm or status asthmaticus.

Corticosteroid Reduction

Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of Xolair therapy. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

Information for Patients

Patients receiving Xolair should be told not to decrease the dose of, or stop taking any other asthma medications unless otherwise instructed by their physician. Patients should be told that they may not see immediate improvement in their asthma after beginning Xolair therapy.

Laboratory Tests

Serum total IgE levels increase following administration of Xolair due to formation of Xolair:IgE complexes (see CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION). Elevated serum total IgE levels may persist for up to 1 year following discontinuation of Xolair. Serum total IgE levels obtained less than 1 year following discontinuation may not reflect steady state free IgE levels and should not be used to reassess the dosing regimen.

Drug Interactions

No formal drug interaction studies have been performed with Xolair. The concomitant use of Xolair and allergen immunotherapy has not been evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed in animals to evaluate the carcinogenic potential of Xolair.

No evidence of mutagenic activity was observed in Ames tests using six different strains of bacteria with and without metabolic activation at Omalizumab concentrations up to 5000 µg/mL.

The effects of Omalizumab on male and female fertility have been assessed in cynomolgus monkey studies. Administration of Omalizumab at doses up to and including 75 mg/kg/week did not elicit reproductive toxicity in male cynomolgus monkeys and did not inhibit reproductive capability, including implantation, in female cynomolgus monkeys. These doses provide a 2- to 16-fold safety factor based on total dose and 2- to 5-fold safety factor based on AUC over the range of adult clinical doses.

Pregnancy (Category B)

Reproduction studies in cynomolgus monkeys have been conducted with Omalizumab. Subcutaneous doses up to 75 mg/kg (12-fold the maximum clinical dose) 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.

IgG molecules are known to cross the placental barrier. There are no adequate and well-controlled studies of Xolair in pregnant women. Because animal reproduction studies are not always predictive of human response, Xolair should be used during pregnancy only if clearly needed.

Nursing Mothers

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 1.5% of maternal blood concentration. While Xolair presence in human milk has not been studied, IgG is excreted in human milk and therefore it is expected that Xolair will be present in human milk. The potential for Xolair absorption or harm to the infant are unknown; caution should be exercised when administering Xolair to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric Use

In clinical trials 134 patients 65 years of age or older were treated with Xolair. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

ADVERSE REACTIONS

The most serious adverse reactions occurring in clinical studies with Xolair are malignancies and anaphylaxis (see WARNINGS). The observed incidence of malignancy among Xolair-treated patients (0.5%) was numerically higher than

Table 1
Frequency of Asthma Exacerbations per Patient by Phase in Studies 1 and 2

	Stable Steroid Phase (16 wks)			
	Study 1		Study 2	
Exacerbations per patient	Xolair N=268 (%)	Placebo N=257 (%)	Xolair N=274 (%)	Placebo N=272 (%)
0	85.8	76.7	87.6	69.9
1	11.9	16.7	11.3	25.0
≥2	2.2	6.6	1.1	5.1
p-Value	0.005		<0.001	
Mean number exacerbations/patient	0.2	0.3	0.1	0.4
	Steroid Reduction Phase (12 wks)			
Exacerbations per patient	Xolair N=268 (%)	Placebo N=257 (%)	Xolair N=274 (%)	Placebo N=272 (%)
0	78.7	67.7	83.9	70.2
1	19.0	28.4	14.2	26.1
≥2	2.2	3.9	1.8	3.7
p-Value	0.004		<0.001	
Mean number exacerbations/patient	0.2	0.4	0.2	0.3

Table 2
Percentage of Patients with Asthma Exacerbations by Subgroup and Phase in Study 3

	Stable Steroid Phase (16 wks)			
	Inhaled Only		Oral+Inhaled	
	Xolair N=126	Placebo N=120	Xolair N=50	Placebo N=45
% Patients with ≥1 exacerbations	15.9	15.0	32.0	22.2
Difference (95% CI)	0.9 (−9.7, 13.7)		9.8 (−10.5, 31.4)	
	Steroid Reduction Phase (16 wks)			
	Xolair N=126	Placebo N=120	Xolair N=50	Placebo N=45
% Patients with ≥1 exacerbations	22.2	26.7	42.0	42.2
Difference (95% CI)	−4.4 (−17.6, 7.4)		−0.2 (−22.4, 20.1)	

Table 3
Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Study 1

	Xolair N=268[a]		Placebo N=257[a]	
Endpoint	Mean Baseline	Median Change (Baseline to Wk 16)	Mean Baseline	Median Change (Baseline to Wk 16)
Total asthma symptom score	4.3	−1.5[b]	4.2	−1.1[b]
Nocturnal asthma score	1.2	−0.4[b]	1.1	−0.2[b]
Daytime asthma score	2.3	−0.9[b]	2.3	−0.6[b]
FEV1 % predicted	68	3[b]	68	0[b]

Asthma symptom scale: total score from 0 (least) to 9 (most); nocturnal and daytime scores from 0 (least) to 4 (most symptoms).
[a] Number of patients available for analysis ranges 255–258 in the Xolair group and 238–239 in the placebo group.
[b] Comparison of Xolair versus placebo ($p<0.05$).

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among patients in control groups (0.2%). Anaphylactic reactions were rare but temporally associated with Xolair administration.

The adverse reactions most commonly observed among patients treated with Xolair included injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in Xolair-treated patients and control patients. These were also the most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse reaction).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in medical practice.

The data described above reflect Xolair exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo.

Table 4 shows adverse events that occurred ≥ 1% more frequently in patients receiving Xolair than in those receiving placebo in the placebo-controlled asthma studies. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events and are described following Table 4.

Table 4
Adverse Events ≥1% More Frequent in Xolair-Treated Patients

Adverse event	Xolair n=738 (%)	Placebo n=717 (%)
Body as a whole		
Pain	7	5
Fatigue	3	2
Musculoskeletal system		
Arthralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
Nervous system		
Dizziness	3	2
Skin and appendages		
Pruritus	2	1
Dermatitis	2	1
Special senses		
Earache	2	1

Age (among patients under age 65), race, and gender did not appear to affect the between group differences in the rates of adverse events.

Injection Site Reactions

Injection site reactions of any severity occurred at a rate of 45% in Xolair-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection-site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group (12% versus 9%).

The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

Immunogenicity

Low titers of antibodies to Xolair were detected in approximately 1/1723 (<0.1%) of patients treated with Xolair. The data reflect the percentage of patients whose test results were considered positive for antibodies to Xolair in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence of antibodies to other products may be misleading.

Table 7
Number of Vials, Number of Injections and Total Injection Volumes for Asthma

Dose (mg)	Number of Vials: 75 mg[a]	Number of Vials: 150 mg[b]	Number of Injections	Total Volume Injected (mL)
150	0	1	1	1.2
225	1	1	2	1.8
300	0	2	2	2.4
375	1	2	3	3.0

[a] 0.6 mL maximum delivered volume per vial.
[b] 1.2 mL maximum delivered volume per vial.

Allergic symptoms, including urticaria, dermatitis, and pruritus were observed in patients treated with Xolair. There were also 3 cases of anaphylaxis observed within 2 hours of Xolair administration in which there were no other identifiable allergic triggers (see WARNINGS: Anaphylaxis).

OVERDOSAGE

The maximum tolerated dose of Xolair has not been determined. Single intravenous doses of up to 4000 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, which was not associated with toxicities.

DOSAGE AND ADMINISTRATION

Xolair (Omalizumab) 150 to 375 mg is administered SC every 2 or 4 weeks. Because the solution is slightly viscous, the injection may take 5-10 seconds to administer. Doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts below (Table 5 and Table 6) for appropriate dose assignment. Doses of more than 150 mg are divided among more than one injection site to limit injections to not more than 150 mg per site.

Table 5
ADMINISTRATION EVERY 4 WEEKS
Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 4 Weeks for Adults and Adolescents (12 Years of Age and Older) with Asthma

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg) 30–60	> 60–70	> 70–90	> 90–150
≥ 30–100	150	150	150	300
> 100–200	300	300	300	
> 200–300	300			
> 300–400	SEE TABLE 6			
> 400–500				
> 500–600				

Table 6
ADMINISTRATION EVERY 2 WEEKS
Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 2 Weeks for Adults and Adolescents (12 Years of Age and Older) with Asthma

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg) 30–60	> 60–70	> 70–90	> 90–150
≥ 30–100	SEE TABLE 5			
> 100–200				225
> 200–300		225	225	300
> 300–400	225	225	300	
> 400–500	300	300	375	
> 500–600	300	375	DO NOT DOSE	
> 600–700	375			

Dosing Adjustments

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 Xolair treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than 1 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 Xolair has been interrupted for one year or more.

Doses should be adjusted for significant changes in body weight. (See Table 5 and Table 6.)

Preparation for Administration

Xolair for SC administration should be prepared using SWFI, USP, ONLY.

Xolair is for single use only and contains no preservatives. The solution should be used for SC administration within 8 hours following reconstitution when stored in the vial at 2–8°C (36–46°F), or within 4 hours of reconstitution when stored at room temperature.

The lyophilized product takes 15–20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent and may have a few small bubbles or foam around the edge of the vial. The reconstituted product is somewhat viscous; in order to obtain the full 0.6 mL (75 mg) or 1.2 mL (150 mg) dose, ALL OF THE PRODUCT MUST BE WITHDRAWN from the vial before expelling any air or excess solution from the syringe.

• For Xolair 75 mg vial:

STEP 1: Draw 0.9 mL of SWFI, USP into a 3-cc syringe equipped with a 1-inch, 18-gauge needle.

STEP 2: Place the vial upright on a flat surface and using standard aseptic technique, insert the needle and inject the SWFI, USP directly onto the product.

STEP 3: Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.

STEP 4: After completing STEP 3, gently swirl the vial for 5–10 seconds approximately every 5 minutes in order to dissolve any remaining solids. There should be no visible gel-like particles in the solution. Do not use if foreign particles are present.

Note: Some vials may take longer than 20 minutes to dissolve completely. If this is the case, repeat STEP 4 until there are no visible gel-like particles in the solution. It is acceptable to have small bubbles or foam around the edge of the vial. Do not use if the contents of the vial do not dissolve completely by 40 minutes.

STEP 5: Invert the vial for 15 seconds in order to allow the solution to drain toward the stopper. Using a new 3-cc syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.

STEP 6: Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

STEP 7: Expel air, large bubbles, and any excess solution in order to obtain the required 0.6 mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, the injection may take 5–10 seconds to administer.

• For Xolair 150 mg vial:

STEP 1: Draw 1.4 mL of SWFI, USP into a 3-cc syringe equipped with a 1-inch, 18-gauge needle.

STEP 2: Place the vial upright on a flat surface and using standard aseptic technique, insert the needle and inject the SWFI, USP directly onto the product.

STEP 3: Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.

STEP 4: After completing STEP 3, gently swirl the vial for 5–10 seconds approximately every 5 minutes in order to dissolve any remaining solids. There should be no visible gel-like particles in the solution. Do not use if foreign particles are present.

Note: Some vials may take longer than 20 minutes to dissolve completely. If this is the case, repeat STEP 4 until there are no visible gel-like particles in the solution. It is acceptable to have small bubbles or foam around the edge of the vial. Do not use if the contents of the vial do not dissolve completely by 40 minutes.

STEP 5: Invert the vial for 15 seconds in order to allow the solution to drain toward the stopper. Using a new 3-cc syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.

STEP 6: Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

STEP 7: Expel air, large bubbles, and any excess solution in order to obtain the required 1.2 mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, the injection may take 5–10 seconds to administer.

A 75 mg vial delivers 0.6 mL (75 mg) of Xolair. A 150 mg vial delivers 1.2 mL (150 mg) of Xolair (see Table 7).

[See table 7 above]

Continued on next page

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Xolair—Cont.

Stability and Storage
Xolair should be shipped at controlled ambient temperature (≤30°C [≤86°F]). Xolair should be stored under refrigerated conditions 2–8°C (36–46°F). Do not use beyond the expiration date stamped on carton.
Xolair is for single-use only and contains no preservatives. The solution may be used for SC administration within 8 hours following reconstitution when stored in the vial at 2–8°C (36–46°F), or within 4 hours of reconstitution when stored at room temperature.
Reconstituted Xolair vials should be protected from direct sunlight.

HOW SUPPLIED
Xolair (Omalizumab) is supplied as a lyophilized sterile powder in a single-use 5 cc vial.
The 75 mg vial configuration is designed to deliver 75 mg of Xolair upon reconstitution with 0.9 mL SWFI, USP. Each 75 mg carton contains one single-use vial of Xolair (Omalizumab) NDC 50242-042-01.
The 150 mg vial configuration is designed to deliver 150 mg of Xolair upon reconstitution with 1.4 mL SWFI, USP. Each 150 mg carton contains one single-use vial of Xolair (Omalizumab). NDC 50242-040-62.
XOLAIR®
Omalizumab
For Subcutaneous Use
Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990 (4821002)
FDA Approval Date: February 2004
Code Revision Date: September 2004
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Jointly marketed by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
Shown in Product Identification Guide, page 313

Genzyme Corporation
500 KENDALL STREET
CAMBRIDGE, MA 02142

Direct Inquiries to:
(800) 745-4447
(617) 768-9000

ALDURAZYME® ℞
[al-dər'ə-zīm]
(laronidase)
Solution for Intravenous Infusion Only

DESCRIPTION
ALDURAZYME® (laronidase) is a polymorphic variant of the human enzyme, α-L-iduronidase that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. α-L-iduronidase (glycosaminoglycan α-L-iduronohydrolase, EC 3.2.1.76) is a lysosomal hydrolase that catalyses the hydrolysis of terminal α-L-iduronic acid residues of dermatan sulfate and heparan sulfate.
Laronidase is a glycoprotein with a molecular weight of approximately 83 kD. The predicted amino acid sequence of the recombinant form, as well as the nucleotide sequence that encodes it, are identical to a polymorphic form of human α-L-iduronidase. The recombinant protein is comprised of 628 amino acids after cleavage of the N-terminus and contains 6 N-linked oligosaccharide modification sites. Two oligosaccharide chains terminate in mannose-6-phosphate sugars. ALDURAZYME has a specific activity of approximately 172 U/mg.
ALDURAZYME, for intravenous infusion, is supplied as a sterile, nonpyrogenic, colorless to pale yellow, clear to slightly opalescent solution that must be diluted prior to administration in 0.9% Sodium Chloride Injection, USP containing 0.1% Albumin (Human). The solution in each vial contains a nominal laronidase concentration of 0.58 mg/mL and a pH of approximately 5.5. The extractable volume of 5.0 mL from each vial provides 2.9 mg laronidase, 43.9 mg sodium chloride, 63.5 mg sodium phosphate monobasic monohydrate, 10.7 mg sodium phosphate dibasic heptahydrate, and 0.05 mg polysorbate 80. ALDURAZYME does not contain preservatives; vials are for single use only.

CLINICAL PHARMACOLOGY
Mechanism of Action
Mucopolysaccharide storage disorders are caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG). Mucopolysaccharidosis I (MPS I) is characterized by the deficiency of α-L-iduronidase, a lysosomal hydrolase which catalyses the hydrolysis of terminal α-L-iduronic acid residues of dermatan sulfate and heparan sulfate. Reduced or absent α-L-iduronidase activity results in the accumulation of the GAG substrates, dermatan sulfate and heparan sulfate, throughout the body and leads to widespread cellular, tissue, and organ dysfunction.
The rationale of ALDURAZYME therapy in MPS I is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of GAG. ALDURAZYME uptake by cells into lysosomes is most likely mediated by the mannose-6-phosphate-terminated oligosaccharide chains of laronidase binding to specific mannose-6-phosphate receptors.
Because many proteins in the blood are restricted from entry into the central nervous system by the blood brain barrier, effects of intravenously administered ALDURAZYME on cells within the central nervous system (CNS) cannot be inferred from activity in sites outside the CNS. The ability of ALDURAZYME to cross the blood brain barrier has not been evaluated in animal models or in clinical trials.
Pharmacokinetics
The pharmacokinetics of laronidase were evaluated in 12 patients with MPS I who received 0.58 mg/kg of ALDURAZYME as a 4 hour infusion. After the 1st, 12th and 26th weekly infusions, the mean maximum plasma concentrations (C_{max}) ranged from 1.2 to 1.7 mcg/mL for the 3 time points. The mean area under the plasma concentration-time curve (AUC_∞) ranged from 4.5 to 6.9 mcg•hour/mL. The mean volume of distribution (V_s) ranged from 0.24 to 0.6 L/kg. Mean plasma clearance (CL) ranged from 1.7 to 2.7 mL/min/kg, and the mean elimination half-life ($t_{1/2}$) ranged from 1.5 to 3.6 hours.
Effects of Antibodies
Most patients who received once-weekly infusions of ALDURAZYME developed antibodies to laronidase by week 12. Between weeks 1 and 12, increases in plasma clearance of laronidase were observed in some patients which appeared to be proportional to the antibody titer. At week 26, plasma clearance of laronidase was comparable to that at week 1, in spite of the continued and, in some cases, increased titers of antibodies.

CLINICAL STUDIES
ALDURAZYME was studied in a randomized, placebo-controlled clinical trial of 45 MPS I patients of whom 1 patient was clinically assessed as having the Hurler form, 37 Hurler-Scheie, and 7 Scheie. All patients had a baseline forced vital capacity (FVC) less than or equal to 77% of predicted. Patients received ALDURAZYME at 0.58 mg/kg or placebo once-weekly for 26 weeks. All patients were treated with antipyretics and antihistamines prior to each infusion. The primary efficacy outcome assessments were FVC and distance walked in 6 minutes (6-minute walk test, 6MWT). After 26 weeks, patients treated with ALDURAZYME showed improvement in FVC and in 6MWT compared to placebo-treated patients (see **Table 1**).
[See table 1 above]
Evaluations of bioactivity were changes in liver size and urinary GAG levels. Liver size and urinary GAG levels decreased in patients treated with ALDURAZYME compared to patients treated with placebo. No subject in the group receiving ALDURAZYME reached the normal range for urinary GAG levels during this 6-month study.
All 45 patients received open-label ALDURAZYME for 36 weeks following the double-blind period. Maintenance of mean FVC and an additional increase in mean 6MWT distance were observed compared to the start of the open-label period among patients who were initially randomized to and then continued to receive ALDURAZYME. Among patients who had been initially randomized to placebo, improvements from baseline in mean FVC and 6MWT distance were observed compared to the start of the open-label period.

Table 1: Primary Efficacy Outcomes

		ALDURAZYME N = 22	Placebo N = 23
Forced Vital Capacity (percent of predicted normal)			
Baseline	Mean ± s.d.	48 ± 15	54 ± 16
Week 26	Mean ± s.d.	50 ± 17	51 ± 13
Change from baseline to week 26	Mean ± s.d.	1 ± 7	-3 ± 7
	Median	1	-1
Difference between groups	Mean	4	
	Median (95% CI)	2 (0.4, 7) p=0.02*	
6-Minute Walk Distance (meters)			
Baseline	Mean ± s.d.	319 ± 131	367 ± 114
Week 26	Mean ± s.d.	339 ± 127	348 ± 129
Change from baseline to week 26	Mean ± s.d.	20 ± 69	-18 ± 67
	Median	28	-11
Difference between groups	Mean	38	
	Median (95% CI)	39 (-2, 79) p=0.07*	

* By Wilcoxon Rank Sum Test

INDICATIONS AND USAGE
ALDURAZYME is indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established.
ALDURAZYME has been shown to improve pulmonary function and walking capacity. ALDURAZYME has not been evaluated for effects on the central nervous system manifestations of the disorder.

CONTRAINDICATIONS
There are no known contraindications to the use of ALDURAZYME.

WARNINGS
Hypersensitivity Reactions
Patients treated with ALDURAZYME may develop infusion-related hypersensitivity reactions (see **ADVERSE REACTIONS**). In the clinical studies, one patient developed an anaphylactic reaction approximately three hours after the initiation of the infusion. The reaction consisted of urticaria and airway obstruction. Resuscitation required an emergency tracheostomy. This patient's pre-existing MPS I related upper airway obstruction may have contributed to the severity of this reaction (see **ADVERSE REACTIONS**: ***Infusion-Related Reactions*** and ***Immunogenicity***).
Some infusion-related reactions may be ameliorated by slowing the rate of infusion or treatment with additional antipyretics and/or antihistamines. If severe hypersensitivity or anaphylactic reactions occur, immediately discontinue the infusion of ALDURAZYME and initiate appropriate treatment. Caution should be exercised if epinephrine is being considered for use in patients with MPS I due to the increased prevalence of coronary artery disease in these patients.
The risks and benefits of re-administering ALDURAZYME following a severe hypersensitivity or anaphylactic reaction should be considered. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

PRECAUTIONS
General
Patients should receive antipyretics and/or antihistamines prior to infusion (see **WARNINGS** and **ADVERSE REACTIONS**). If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of additional *antipyretics and/or antihistamines* may ameliorate the symptoms.
Information for Patients
Patients should be informed that a registry for MPS I patients has been established in order to better understand the variability and progression of MPS I disease, and to continue to monitor and evaluate treatments. Patients should be encouraged to participate and advised that their participation may involve long-term follow-up. Information regarding the registry program may be found at www.MPSIregistry.com or by calling (800) 745-4447.
Drug Interactions
No formal drug interaction studies have been conducted.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies to assess the mutagenic and carcinogenic potential of ALDURAZYME have not been conducted.
Reproductive studies in rats have not demonstrated impairment of fertility (see **PRECAUTIONS**: **Pregnancy**).
Pregnancy: Category B
Reproduction studies have been performed in male and female rats at doses up to 6.2 times the human dose and have

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