HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALDURAZYME safely and effectively. See full prescribing information for ALDURAZYME.

ALDURAZYME (laronidase)
Solution for intravenous infusion only
Initial U.S. Approval: 2003

WARNING: RISK OF ANAPHYLAXIS.
See full prescribing information for complete boxed warning.
Life-threatening anaphylactic reactions have been observed in some patients during ALDURAZYME infusions. Therefore, appropriate medical support should be readily available when ALDURAZYME is administered. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions, and require additional monitoring.

----------RECENT MAJOR CHANGES----------
Boxed Warning (4/2008); Warnings and Precautions (5) (4/2008)

----------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 risk and benefits of treating mildly affected patients with 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 (1).

----------DOSAGE AND ADMINISTRATION----------
- 0.58 mg/kg of body weight administered once weekly as an intravenous (IV) infusion (2).

----------DOSAGE FORMS AND STRENGTHS----------
Solution for IV infusion: 2.9 mg/5 ml vial (3).

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Life-threatening anaphylactic reactions have been observed in some patients during or up to 3 hours after infusion. Patients with an acute illness at the time of infusion may be at greater risk for infusion-related reactions. Appropriate medical support should be available when ALDURAZYME is administered. If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion and initiate appropriate treatment, which may include ventilatory support, treatment with inhaled beta-adrenergic agonists, epinephrine, and IV corticosteroids (5.1).
- Pretreatment with antipyretics and/or antihistamines is recommended prior to the infusion to reduce the risk of infusion-related allergic reactions. If infusion-related reactions occur, decreasing the infusion rate, temporarily stopping the infusion, and/or administering additional antipyretics and/or antihistamines may ameliorate the symptoms (5.1).

----------ADVERSE REACTIONS----------
The most frequently occurring adverse reactions occurring in at least 10% of patients 6 years and older are rash, upper respiratory tract infection, injection site reaction, hyperreflexia, paresthesia, and vein disorder. The most commonly reported adverse reactions occurring in at least 10 % of patients less than 6 years of age were pyrexia, chills, increased blood pressure, tachycardia, and decreased oxygen saturation (6).

To report SUSPECTED ADVERSE REACTIONS, contact: Genzyme at 1-800-745-4447, or FDA at 1-800-FDA-1088 or go to www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------
A registry for pregnant women is available. Pregnant women with MPS I who are treated with ALDURAYZME should be encouraged to enroll in the MPS I Registry. For more information, visit www.MPSIregistry.com or call (800) 745-4447 (8.1).

See 17 for PATIENT COUNSELING INFORMATION.
Revised: X/200X

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF ANAPHYLAXIS.

Life-threatening anaphylactic reactions have been observed in some patients during ALDURAZYME® infusions. Therefore, appropriate medical support should be readily available when ALDURAZYME is administered. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions, and require additional monitoring.

1 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.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dosage regimen of ALDURAZYME is 0.58 mg/kg of body weight administered once weekly as an intravenous (IV) infusion. Pretreatment with antipyretics and/or antihistamines is recommended 60 minutes prior to the start of the infusion [*see Warnings and Precautions (5)*].

2.2 Instructions for Use

Prepare and use ALDURAZYME according to the following steps.

1. Each vial of ALDURAZYME provides 2.9 milligrams (mg) of laronidase in 5.0 milliliters (mL) of solution and is intended for single use only. Do not use the vial more than one time. The concentrated solution for infusion must be diluted with 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP using aseptic techniques. Prepare ALDURAZYME using PVC containers and administer with a PVC infusion set equipped with an in-line, low protein binding 0.2 micrometer (µm) filter. There is no information on the compatibility of diluted ALDURAZYME with glass containers.

2. The total volume of the infusion is determined by the patient's body weight. Patients with a body weight of 20 kg or less should receive a total volume of 100 mL. Patients with a body weight of greater than 20 kg should receive a total volume of 250 mL. Determine the number of vials to be diluted based on the individual patient's weight and the recommended dose of 0.58 mg/kg, using the following equation:

   [Patient's weight (kg) x 1 mL/kg of ALDURAZYME = Total # mL of ALDURAZYME, then
   Total # of mL of ALDURAZYME ÷ 5 mL per Vial = Total # of Vials].

3. Round up to the nearest whole vial. Remove the required number of vials from the refrigerator to allow them to reach room temperature. Do not heat or microwave vials.

4. Before withdrawing the ALDURAZYME from the vial, visually inspect each vial for particulate matter and discoloration. The ALDURAZYME solution should be clear to slightly opalescent and colorless to pale yellow. A few translucent particles may be present. Do not use if the solution is discolored or if there is particulate matter in the solution.

5. Using *Table 1* as a guide, prepare an infusion bag of 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP. Remove and discard a volume of 0.9% Sodium Chloride Injection, USP equal to the volume of Albumin (Human) to be added to the infusion bag. Add the appropriate volume of Albumin (Human) to the infusion bag and gently rotate the infusion bag to ensure proper distribution of the Albumin.

Table 1: Amount of Albumin (Human) Required in Infusion Solution

Total Volume of ALDURAZYME Infusion	Volume of Albumin (Human) [5% solution] to be Added	Volume of Albumin (Human) [25% solution] to be Added
100 mL	2 mL	0.4 mL
250 mL	5 mL	1 mL

6. Withdraw and discard a volume of the 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP from the infusion bag, equal to the volume of ALDURAZYME concentrate to be added.

7. Slowly withdraw the calculated volume of ALDURAZYME from the appropriate number of vials using caution to avoid excessive agitation. Do not use a filter needle, as this may cause agitation. Agitation may denature ALDURAZYME, rendering it biologically inactive.

8. Slowly add the ALDURAZYME solution to the 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP using care to avoid agitation of the solutions. Do not use a filter needle.

9. Gently rotate the infusion bag to ensure proper distribution of ALDURAZYME. Do not shake the solution.

10. The entire infusion volume (100 mL for patients weighing 20 kg or less and 250 mL for patients weighing 20 kg or greater) should be delivered over approximately 3 to 4 hours. The initial infusion rate of 10 µg/kg/hr may be incrementally increased every 15 minutes during the first hour, as tolerated, until a maximum infusion rate of 200 µg/kg/hr is reached. The maximum rate is then maintained for the remainder of the infusion (2-3 hours), as outlined in *Tables 2 and 3*.

Table 2: Incremental Rates for 100 mL ALDURAZYME Infusion (For use with Patients Weighing 20 kg or Less)

Infusion Rate	Criteria for Increasing Infusion Rate
2 mL/hr x 15 minutes (10 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
4 mL/hr x 15 minutes (20 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
8 mL/hr x 15 minutes (50 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
16 mL/hr x 15 minutes (100 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
32 mL/hr x ~3 hours (200 µg/kg/hr)	For the remainder of the infusion.

Table 3: Incremental Rates for 250 mL ALDURAZYME Infusion (For use with Patients Weighing 20 kg or Greater)

Infusion Rate	Criteria for Increasing Infusion Rate
5 mL/hr x 15 minutes (10 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
10 mL/hr x 15 minutes (20 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
20 mL/hr x 15 minutes (50 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
40 mL/hr x 15 minutes (100 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
80 mL/hr x ~3 hours (200 µg/kg/hr)	For the remainder of the infusion.

ALDURAZYME must not be mixed with other medicinal products in the same infusion. The compatibility of ALDURAZYME in solution with other products has not been evaluated.

3. DOSAGE FORMS AND STRENGTHS

ALDURAZYME is supplied as a sterile solution in clear Type I glass 5 mL vials (2.9 mg laronidase per 5 mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Allergic Reactions [see *Boxed Warning*]

Life-threatening anaphylactic reactions have been observed in some patients during or up to 3 hours after ALDURAZYME infusions. Reactions have included respiratory failure, respiratory distress, stridor, tachypnea, bronchospasm, airway obstruction, hypoxia, hypotension, bradycardia, and urticaria. Interventions have included resuscitation, mechanical ventilatory support, emergency tracheotomy, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and IV corticosteroids.

In clinical studies and postmarketing safety experience with ALDURAZYME, approximately 1% of patients experienced severe or serious allergic reactions. In patients with MPS I, pre-existing upper airway obstruction may have contributed to the severity of some reactions. Due to the potential for severe allergic reactions, appropriate medical support should be readily available when ALDURAZYME is administered. Because of the potential for recurrent reactions, some patients who experience initial severe reactions may require prolonged observation.

Patients with an acute illness at the time of ALDURAZYME infusion may be at greater risk for infusion-related reactions. Careful consideration should be given to the patient's clinical status prior to administration of ALDURAZYME. One patient with acute bronchitis and hypoxia experienced increased tachypnea during the first ALDURAZYME infusion that resolved without intervention. The patient's respiratory symptoms returned within 30 minutes of completing the infusion and responded to bronchodilator therapy. Approximately 6 hours after the infusion, the patient experienced coughing, then respiratory arrest, and died.

Patients should receive antipyretics and/or antihistamines prior to infusion [*see Adverse Reactions (6); Dosage and Administration (2.1)*]. If an infusion-related reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administering additional antipyretics and/or antihistamines may ameliorate the symptoms [*see Adverse Reactions (6)*].

If anaphylactic or other severe allergic 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 an anaphylactic or severe allergic reaction should be considered. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Studies

The most serious adverse reactions reported with ALDURAZYME treatment during clinical studies were anaphylactic and allergic reactions [*see Boxed Warning and Warnings and Precautions (5)*]. Most adverse events reported in clinical studies were considered disease-related and unrelated to study drug. The most common adverse reactions were infusion-related reactions. The frequency of infusion-related reactions decreased over time with continued use of Aldurazyme, and the majority of reactions were classified as being mild to moderate in severity. Most infusion-related reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administering additional antipyretics and/or antihistamines [*see Warnings and Precautions (5)*].

6.1.1 Clinical Studies in Patients 6 Years and Older

In a 26-week, double-blind, placebo-controlled clinical study (Study 1) of ALDURAZYME in 45 patients with MPS I, ages 6 to 43 years old, in which all patients were treated with antipyretics and antihistamines prior to the infusions, infusion-related reactions were reported in 32% (7 of 22) of ALDURAZYME treated patients. The most commonly reported infusion-related reactions were flushing, fever, headache and rash. Flushing occurred in 5 patients (23%) receiving ALDURAZYME; the other reactions were less frequent. Less common infusion-related reactions included cough, bronchospasm, dyspnea, urticaria, angioedema, and pruritus.

The data (*Table 4*) described below reflect exposure to 0.58 mg/kg of ALDURAZYME for 26 weeks in Study 1. The population in Study 1 was evenly distributed for gender (N=23 females and 22 males). Of these 45 patients, 1 was clinically assessed as having Hurler form, 37 Hurler-Scheie, and 7 Scheie.

Because clinical studies are conducted under widely varying conditions, the adverse reaction rates cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in patients in clinical practice.

Table 4 enumerates adverse reactions and selected laboratory abnormalities that occurred during the placebo-controlled study (Study 1) that were reported in at least 2 patients more in the ALDURAZYME group than in the placebo group.

Table 4: Summary of Adverse Reactions that Occurred in 2 Patients More in the ALDURAZYME Group than in the Placebo Group in the 26-Week Placebo-controlled Study (Study 1)*

Adverse Event	ALDURAZYME (N=22) n (%)	Placebo (N=23) n (%)
Respiratory System		
Upper respiratory tract infection	7 (32)	4 (17)
Body as a Whole		
Chest pain	2 (9)	0
Nervous System		
Hyperreflexia	3 (14)	0
Paresthesia	3 (14)	1 (4)
Skin and Appendages		
Rash	8 (36)	5 (22)
Resistance Mechanism		
Abscess	2 (9)	0
Liver and Biliary System		
Bilirubinemia	2 (9)	0
Vascular		
Vein disorder	3 (14)	1 (4)
Urinary System		
Facial edema	2 (9)	0
Cardiovascular, General		
Hypotension	2 (9)	0
Dependent edema	2 (9)	0
Vision		
Corneal opacity	2 (9)	0
Application Site		
Injection site pain	2 (9)	0
Injection site reaction	4 (18)	2 (9)
Platelet, Bleeding and Clotting		
Thrombocytopenia	2 (9)	0

*Reported adverse reactions were classified using WHOART terminology.

All 45 patients who completed the placebo-controlled study (Study 1) continued treatment in an open-label, uncontrolled extension study (Study 2). All patients received ALDURAZYME 0.58 mg/kg of body weight once weekly for up to 182 weeks. The most serious adverse reactions reported with ALDURAZYME infusions in Study 2 were anaphylactic and allergic reactions [*see Warnings and Precautions (5)*]. The most common adverse reactions requiring intervention were infusion-related reactions reported in 49% (22 of 45) of patients treated with ALDURAZYME. The most commonly reported infusion-related reactions included rash (13%), flushing (11%), fever (11%), headache (9%), abdominal pain (9%), and injection site reaction (9%). Less commonly reported infusion-related reactions included diarrhea (7%), nausea (7%), temperature changed sensation (7%), vomiting (4%), and hypotension (4%). The most common adverse events (regardless of relationship) included rhinitis, headache, fever, cough, pharyngitis, nausea, pain, arthralgia, diarrhea, vomiting, skeletal pain, upper respiratory infection, abdominal pain, back pain, and rash.

6.1.2 Clinical Studies in Patients 6 Years and Younger

Study 3 was a 52-week open-label, uncontrolled study of 20 MPS I patients, ages 6 months to 5 years old (at enrollment). Sixteen patients were clinically assessed as having the Hurler form, and 4 had the Hurler-Scheie form. All 20 patients received ALDURAZYME at 0.58 mg/kg of body weight once weekly for 26 weeks and up to 52 weeks. All patients were treated with antipyretics and antihistamines prior to the infusions.

The most commonly reported serious adverse events (regardless of relationship) reported with ALDURAZYME infusions in Study 3 were otitis media (20%), and venous catheterization required for ALDURAYZME infusion (15%).

The nature and severity of infusion-related reactions were similar between the older and less severely affected patients in Studies 1 and 2, and the younger, more severely affected patients in Study 3. The most commonly reported adverse reactions in Study 3 were infusion-related reactions reported in 35% (7 of 20) of patients and included pyrexia (30%), chills (20%), blood pressure increased (10%), tachycardia (10%), and oxygen saturation decreased (10%). Other infusion-related reactions occurring in ≥ 5% of patients were pallor, tremor, respiratory distress, wheezing, crepitations (pulmonary), pruritis, and rash.

Other commonly reported adverse events were cough, diarrhea, vomiting, rhinorrhea, rhinitis, and otorrhea.

6.2 Immunogenicity

In clinical studies, 99 of 102 patients (97%) treated with ALDURAZYME were positive for IgG antibodies to ALDURAZYME. The clinical significance of antibodies to ALDURAZYME, including the potential for product neutralization, is not known. Potential for antibody neutralization of cellular uptake has not been assessed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to ALDURAZYME using an enzyme-linked immunosorbent assay (ELISA) for ALDURAZYME-specific IgG binding antibodies reported as titers (57 patients) or optical density units per uL (OD/uL) (42 patients), and confirmed by radio-immunoprecipitation (RIP). The relationship of ALDURAZYME antibody concentration in titer units and OD/uL units has not been established.

Nine patients in Study 1 and Study 2, collectively, who experienced severe infusion-related reactions were tested for ALDURAZYME-specific IgE antibodies and complement activation. IgE testing was performed by ELISA, and complement activation was measured by the Quidel Enzyme Immunoassay. One of the nine patients had an anaphylactic reaction consisting of urticaria and airway obstruction and tested positive for both ALDURAZYME-specific IgE binding antibodies and complement activation [*see Warnings and Precautions (5)*]. None of the patients in the open-label clinical study of patients 5 years old or younger (Study 3) tested positive for IgE.

Other allergic reactions were also seen in patients receiving ALDURAZYME [*see Adverse Reactions (6)*].

In the postmarketing setting, approximately 1% of patients experienced severe or serious infusion-related allergic reactions and tested positive for IgE [*see Warnings and Precautions (5)*]. Of these IgE-positive patients, some have discontinued treatment, but some have been successfully re-challenged. The clinical significance of IgE antibodies has not been established.

As with all the therapeutic proteins, there is potential for immunogenicity. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ALDURAZYME with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

In postmarketing experience with ALDURAZYME, severe and serious infusion-related reactions have been reported, some of which were life-threatening [*see Boxed Warning and Warnings and Precautions (5)*].

The most common adverse reactions (using MedDRA terminology) included chills, vomiting, nausea, arthralgia, diarrhea, tachycardia, abdominal pain, blood pressure increased, and oxygen saturation decreased. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

No formal drug interaction studies were performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

A developmental toxicity study has been performed in rats at doses up to 6.2 times the human dose and has revealed no evidence of impaired fertility or harm to the fetus due to ALDURAZYME. However, there are no adequate and well-controlled studies of ALDURAZYME in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pregnant women with MPS I who are treated with ALDURAZYME should be encouraged to enroll in the MPS I Registry. For more information, visit www.MPSIregistry.com or call (800) 745-4447 [*see Patient Counseling Information (17)*].

8.2 Labor and Delivery

There is no information on the effect of ALDURAZYME during labor and delivery. Pregnant women with MPS I who are treated with ALDURAZYME should be encouraged to enroll in the MPS I Registry [*see Patient Counseling Information (17)*].

8.3 Nursing Mothers

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ALDURAZYME is administered to a nursing woman.

Nursing mothers with MPS I who are treated with ALDURAZYME should be encouraged to enroll in the MPS I Registry [*see Patient Counseling Information (17)*].

8.4 Pediatric Use

The safety and effectiveness of ALDURAZYME was assessed in a 52-week, open-label, uncontrolled clinical study in 20 patients with MPS I, ages 6 months to 5 years old, and was found to be similar to the safety and effectiveness of ALDURAZYME in pediatric patients 6 to 18 years, and adults [*see Adverse Reactions (6) and Clinical Studies (14)*].

8.5 Geriatric Use

Clinical studies of ALDURAZYME did not include patients aged 65 and over. It is not known whether they respond differently from younger patients.

10 OVERDOSAGE

There have been no reports of overdose with ALDURAZYME. In clinical studies, a small number of patients received doses up to 1.2 mg/kg body weight once weekly or 1.8 mg/kg body weight every other week**.** Adverse events reported in patients receiving 1.2 mg/kg body weight once weekly or 1.8 mg/kg body weight every other week were similar to the adverse reactions reported by patients treated with 0.58 mg/kg body weight once weekly.

11 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 IV 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.

12 CLINICAL PHARMACOLOGY

12.1 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 (CNS) by the blood brain barrier, effects of intravenously administered ALDURAZYME on cells within the 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 studies.

12.2 Pharmacodynamics

The pharmacodynamic effect of ALDURAZYME was assessed by reductions in urinary GAG levels. The responsiveness of urinary GAG to dosage alterations of ALDURAZYME is unknown, and the relationship of urinary GAG to other measures of clinical response has also not been established [*see Clinical Studies (14)*].

12.3 Pharmacokinetics

The pharmacokinetics of laronidase were evaluated in 6 year old or older patients (N = 10 to 12) with MPS I who received 0.58 mg/kg of body weight once weekly of ALDURAZYME as a 4-hour infusion in the placebo-controlled clinical study (Study 1). After the 1st, 12th, and 26th weekly infusions, the mean maximum plasma concentrations (C_{max}) ranged from 1.2 to 1.7 µg/mL for the 3 time points. The mean area under the plasma concentration-time curve (AUC_{∞}) ranged from 4.5 to 6.9 µg • hour/mL. The mean volume of distribution (V_z) 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.

Most patients who received once weekly infusions of ALDURAZYME in Study 1 developed antibodies to laronidase by Week 12. Between Weeks 1 and 12, increases in the plasma clearance of laronidase were observed in some patients and 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.

The pharmacokinetics of ALDURAZYME have not been established in patients 6 years and younger.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess the mutagenic and carcinogenic potential of laronidase have not been conducted.

Laronidase at IV doses up to 3.6 mg/kg (6.2 times the human dose) was found to have no effect on the fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

The safety and efficacy of ALDURAZYME were assessed in three clinical studies.

14.1 Clinical Studies in Patients 6 Years and Older

Study 1 was a randomized, double-blind, placebo-controlled study in 45 patients with MPS I, ages 6 to 43 years old, including 1 patient with the Hurler form, 37 patients with Hurler-Scheie form, and 7 patients with Scheie form of MPS I. All patients had a baseline percent predicted forced vital capacity (FVC) less than or equal to 77%. Patients received ALDURAZYME at 0.58 mg/kg of body weight once weekly 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 percent predicted FVC and distance walked in 6 minutes (6-minute walk test). After 26 weeks, patients treated with ALDURAZYME showed improvement in percent predicted FVC and in 6-minute walk test compared to placebo-treated patients (*see Table 5*).

Table 5: Primary Efficacy Outcomes in the Placebo-controlled Study (Study 1)

		ALDURAZYME (N = 22)	**Placebo (N = 23)**
Forced Vital Capacity (percent of predicted normal)			
Pre-treatment 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 in Change from Baseline to Week 26 Between Groups	Mean	4	
	Median (95% CI)	2 (0.4, 7), p=0.02*	
6-Minute Walk Distance (meters)			
Pre-treatment 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 in Change from Baseline to Week 26 Between Groups	Mean	38	
	Median (95% CI)	39 (-2, 79), p=0.07*	

* By Wilcoxon Rank Sum Test

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 patient in the group receiving ALDURAZYME reached the normal range for urinary GAG levels during this 6-month study.

Study 2 was a 182-week, open-label, uncontrolled extension study of all 45 patients who completed Study 1. Patients received ALDURAZYME at 0.58 mg/kg body weight once weekly. For patients treated with ALDURAZYME, the mean increase in 6-minute walk test distance was maintained for an additional 182 weeks through completion of Study 2.

At the end of Study 2, the decrease in mean urinary GAG was similar to the decrease in urinary GAG reported in ALDURAZYME treated patients at the end of Study 1. The relationship of urinary GAG to other measures of clinical response has not been established [*see Clinical Pharmacology (12.2)*].

14.2 Clinical Studies in Patients 6 Years and Younger

Study 3 was a 52-week, open-label, uncontrolled clinical study in 20 patients with MPS I, ages 6 months to 5 years old (at enrollment), including 16 patients (80%) with the Hurler form and 4 patients (20%) with the Hurler-Scheie form. All 20 patients received ALDURAZYME at 0.58 mg/kg of body weight once weekly for 26 weeks. After 26 weeks of treatment, 16 patients continued to receive 0.58 mg/kg of body weight once weekly through Week 52, and 4 patients received 1.16 mg/kg of body weight once weekly from Week 26 through Week 52.

Reduction in mean urinary GAG was demonstrated at Week 13 and was maintained through Week 52. No patient receiving ALDURAZYME reached the normal range for urinary GAG levels during this 52-week study. Changes in urinary GAG levels in children 6 years and younger were similar to changes reported in older patients in Studies 1 and 2 (6 through 43 years old). The relationship of urinary GAG to other measures of clinical response has not been established [*see Clinical Pharmacology (12.2)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

ALDURAZYME is supplied as a sterile solution in clear Type I glass 5 mL vials (2.9 mg laronidase per 5 mL). The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic flip-off cap.

NDC 58468-0070-1, 5 mL vial

Refrigerate vials of ALDURAZYME at 2° to 8°C (36° to 46°F). DO NOT FREEZE OR SHAKE. DO NOT USE ALDURAZYME after the expiration date on the vial. This product contains no preservatives.

The diluted solution should be used immediately. If immediate use is not possible, the diluted solution should be stored for up to 36 hours refrigerated at 2° to 8°C (36° to 46°F). Room temperature storage of diluted solution is not recommended.

ALDURAZYME does not contain any preservatives; therefore, after dilution with saline in the infusion bags, any unused product or waste material should be discarded and disposed of in accordance with local requirements.

ALDURAZYME must not be mixed with other medicinal products in the same infusion.

The compatibility of ALDURAZYME in solution with other products has not been evaluated.

17 PATIENT COUNSELING INFORMATION

Patients should be counseled that allergic reactions may occur during ALDURAZYME treatment, including life-threatening anaphylaxis. Premedication and reduction of infusion rate may alleviate those allergic reactions associated with the infusion. The appropriate length of post-infusion monitoring is to be determined by the treating physician based on the individual patient's clinical status and infusion history. [*see Warnings and Precautions (5)*].

Patients should be advised to report any adverse reactions experienced while on ALDURAZYME treatment.

It is unknown how ALDURAZYME affects women during pregnancy, labor and delivery or while nursing, as no adequate and well controlled clinical studies have been conducted in these patient populations [*see Use in Specific Populations (8)*].

The full benefits of ALDURAZYME may not be evident for several months to years of treatment. To maintain treatment benefit, ALDURAZYME should be administered on a weekly basis as indicated.

Patients should be informed that a registry for MPS I patients has been established in order to better understand the MPS I disease, and to track clinical outcomes of patients with MPS I over time. Patients should be encouraged to participate, and advised that their participation is voluntary and may involve long-term follow-up. Information regarding the registry program may be found at www.MPSIregistry.com or by calling (800) 745-4447.

ALDURAZYME is manufactured by:

BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

US License Number 1649

ALDURAZYME is distributed by:

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142

1-800-745-4447 (phone)