ALDURAZYME® (laronidase) injection, for intravenous use

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. (5.1)
- Appropriate medical support should be readily available when ALDURAZYME is administered. (5.1)
- 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. (5.2, 5.3)

INDICATIONS AND USAGE
ALDURAZYME® is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for adult and pediatric 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. (1)

DOSAGE FORMS AND STRENGTHS
Injection: 2.9 mg/5 mL (0.58 mg/mL) of laronidase in a single-dose vial (3).

DOSAGE AND ADMINISTRATION
The recommended dosage is 0.58 mg/kg of body weight administered once weekly as an intravenous infusion (2).

ADVERSE REACTIONS
Most common adverse reactions (≥10%) in patients:
- 6 months of age and older: injection reactions (erysipeloid, chills, blood pressure increased, tachycardia, and oxygen saturation decreased). (6.1)
- 6 years and older: rash, upper respiratory tract infection, injection site reaction, hyperreflexia, paresthesia, flushing, and poor venous access. (6.1)

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

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compatibility of diluted ALDURAZYME with glass containers.

1. Determine the number of vials to be diluted based on the patient’s weight and the recommended dose of 0.58 mg/kg, using the following equation:

Patient’s weight (kg) × 1 mL/kg of ALDURAZYME = Total number of mL of ALDURAZYME
Total number of mL of ALDURAZYME + 5 mL per Vial = Total number of Vials.

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

3. 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. Some turbidity may be present in the solution. Do not use if the solution is discolored or if there is particulate matter in the solution.

4. Withdraw and discard a volume of the 0.9% Sodium Chloride Injection, USP from the infusion bag, equal to the volume of ALDURAZYME concentrate to be added.

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

6. Slowly add the ALDURAZYME solution to the 0.9% Sodium Chloride Injection, USP using a filter needle to avoid agitation of the solutions. Do not use a filter needle.

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

8. The entire infusion volume (100 mL for patients weighing 20 kg or less and 250 mL for patients weighing greater than 20 kg) 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 1 and 2.

9. Administer the diluted ALDURAZYME solution to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2 µm in-line filter.

Table 1: Incremental Rates for 100 mL ALDURAZYME® Infusion (For use with Patients Weighing 20 kg or Less)

<table>
<thead>
<tr>
<th>Infusion Rate</th>
<th>Criteria for Increasing Infusion Rate</th>
</tr>
</thead>
</table>
| 2 mL/hour × 15 minutes (10 mcg/kg/hr) | Obtain vital signs, if stable then increase the rate to...
| 4 mL/hour × 15 minutes (20 mcg/kg/hr) | Obtain vital signs, if stable then increase the rate to...
| 8 mL/hour × 15 minutes (50 mcg/kg/hr) | Obtain vital signs, if stable then increase the rate to...
| 16 mL/hour × 15 minutes (100 mcg/kg/hr) | Obtain vital signs, if stable then increase the rate to...
| 32 mL/hour × 3 hours (200 mcg/kg/hr) | For the remainder of the infusion.

Table 2: Incremental Rates for 250 mL ALDURAZYME® Infusion (For use with Patients Weighing Greater than 20 kg)

<table>
<thead>
<tr>
<th>Infusion Rate</th>
<th>Criteria for Increasing Infusion Rate</th>
</tr>
</thead>
</table>
| 5 mL/hour × 15 minutes (10 mcg/kg/hr) | Obtain vital signs, if stable then increase the rate to...
| 10 mL/hour × 15 minutes (20 mcg/kg/hr) | Obtain vital signs, if stable then increase the rate to...
| 20 mL/hour × 15 minutes (50 mcg/kg/hr) | Obtain vital signs, if stable then increase the rate to...
| 40 mL/hour × 15 minutes (100 mcg/kg/hr) | Obtain vital signs, if stable then increase the rate to...
| 80 mL/hour × approximately 3 hours (200 mcg/kg/hr) | For the remainder of the infusion.

ALDURAZYME does not contain any preservatives; therefore, after dilution with saline, the infusion bags should be used immediately. If immediate use is not possible, the diluted solution should be stored refrigerated at 2°C to 8°C (36°F to 46°F) for up to 36 hours. Other than during infusion, room temperature storage of diluted solution is not recommended. Any unused product or waste material should be discarded and disposed of in accordance with local requirements.

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

5. DOSAGE FORMS AND STRENGTHS

Injection: 2.9 mg/mL (0.58 mg/mL) of laronidase as a colorless to pale yellow, clear to slightly opalescent solution in a single-dose vial

CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Hypersensitivity Reactions

Anaphylaxis and serious hypersensitivity reactions have been observed in patients during or up to 3 hours after ALDURAZYME infusions. Some of these reactions were life-threatening and included respiratory distress, stridor, tachypnea, bronchoospasm, obstructive airways disorder, hypoxia, hypotension, bradycardia, and urticaria. If anaphylactic or other serious hypersensitivity reactions occur, immediately discontinue the infusion of ALDURAZYME and initiate appropriate medical 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. Interventions have included resuscitation, mechanical ventilatory support, emergency tracheotomy, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and intravenous corticosteroids (see Adverse Reactions (6)).

Table 3: 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)

<table>
<thead>
<tr>
<th>MedDRA System Organ Class (SOC) MedDRA Preferred Term</th>
<th>(N=22) ALDURAZYME n (%)</th>
<th>(N=23) Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal opacity</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Face edema</td>
<td>2 (9)</td>
<td>0</td>
</tr>
</tbody>
</table>

In clinical studies and postmarketing safety experience with ALDURAZYME, approximately 1% of patients experienced severe or serious hypersensitivity 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 hypersensitivity 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.

The risks and benefits of re-administering ALDURAZYME following an anaphylactic or severe hypersensitivity reaction should be considered. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

Patients with an acute febrile or respiratory illness at the time of ALDURAZYME infusion may be at greater risk for infusion reactions. Careful consideration should be given to the patient’s clinical status prior to administration of ALDURAZYME and consider delaying ALDURAZYME infusion. One patient with asthma, 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.

Sleep apnea is common in MPS I patients. Evaluation of airway patency should be considered prior to initiation of treatment with ALDURAZYME. Patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments readily available during infusion in the event of an infusion reaction, or extreme drowsiness/sleep induced by anhistamine use.

5.3 Risk of Acute Cardiorespiratory Failure

Caution should be exercised when administering ALDURAZYME to patients susceptible to fluid overload, or patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusions. Appropriate medical support and monitoring measures should be readily available during ALDURAZYME infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient (see Adverse Reactions (6.3)).

6. ADVERSE REACTIONS

Serious and/or clinically significant adverse reactions described elsewhere in labeling include:

- Anaphylaxis and Hypersensitivity Reactions (see Warnings and Precautions (5.1))
- Acute Respiratory Complications Associated with Administration (see Warnings and Precautions (5.2))
- Risk of Acute Cardiorespiratory Failure (see Warnings and Precautions (5.3))
- Infusion Reactions (see Warnings and Precautions (6.4))

6.1 Clinical Trials Experience

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

The most serious adverse reactions reported with ALDURAZYME treatment during clinical trials were anaphylactic and hypersensitivity reactions. Most adverse reactions reported in clinical trials were considered disease-related and unrelated to study drug. The most common adverse reactions were infusion reactions. The frequency of infusion 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 reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, or with or without administering additional treatments including antihistamines, antipyrines, or both.

Clinical Trials in Patients 6 Years and Older

A 26-week, double-blind, placebo-controlled clinical study (Study 1) of ALDURAZYME was conducted in 45 patients with MPS I, ages 6 to 43 years old, gender evenly distributed (N=23 females and 22 males). Of these 45 patients, 1 was clinically assessed as having Hunter-Scheie, and 7 Scheie. Patients were randomized to receive either 0.58 mg/kg intravenously of ALDURAZYME per week for 26 weeks or placebo. All patients were treated with antipyrines and antihistamines prior to the infusions. Infusion reactions were reported in 32% (7 of 22) of ALDURAZYME-treated patients. The most commonly reported infusion reactions regardless of treatment group were flushing, pyrexia, headache, and rash. Flushing occurred in 5 patients (23%) receiving ALDURAZYME; the other reactions were less frequent. Less common infusion reactions included angioedema (including face edema), hypotension, paresthesia, feeling hot, hyperhidrosis, tachycardia, vomiting, back pain, and cough. Other reported adverse reactions included bronchoospasm, dyspnea, urticaria and pruritus.

Table 3 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.
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 body weight once weekly for up to 182 weeks. The most serious adverse reactions reported with ALDURAZYME in Studies 2 were anaphylactic and hypersensitivity reactions to infusions. A total of 102 patients (97%) treated with ALDURAZYME were positive for IgG antibodies. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed formation of antibodies to a polymorphic form of human α-L-iduronidase is not always considered along with the mother’s clinical need for ALDURAZYME and any potential adverse effects on the breastfed child from ALDURAZYME or from the underlying maternal condition. Lactating women with MPS I are encouraged to enroll in the MPS Registry. For more information, visit www.registryntx.com or call 1-800-745-4447 ext. 15500.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

An MPS I Registry has been established and pregnant women with MPS I should be encouraged to enroll in the registry to ensure the safety and effectiveness of ALDURAZYME in pediatric patients 6 to 18 years, and adults (see Adverse Reactions (6.1, 6.3)). Information can be found on the MPS Registry website at www.registryntx.com. Reported adverse experiences during pregnancy with ALDURAZYME use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. The nature and severity of infusion 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 infusion reactions in Study 3 were urticaria (13%), flushing (11%), chills (9%), abdominal pain or discomfort (9%), and injection site reaction (9%). Less commonly reported infusion reactions included nausea (7%), diarrhea (7%), feeling hot or cold (7%), vomiting (4%), pruritus (4%), arthralgia (4%), and urticaria (4%). Additional common adverse reactions included back pain and musculoskeletal pain.

Table 3: Summary of Adverse Reactions that Occurred in 2 Patients More in the Placebo Group than the ALDURAZYME Group in 2-WEEK Placebo-controlled Study (Study 1) (continued)

<table>
<thead>
<tr>
<th>MedDRA System Organ Class (SOC)</th>
<th>MedDRA Preferred Term</th>
<th>(N=22) ALDURAZYME n (%)</th>
<th>(N=23) Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravitational edema</td>
<td>2 (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2 (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>4 (18)</td>
<td>2 (9)</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty liver</td>
<td>1 (4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>2 (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7 (32)</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1 (4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>8 (36)</td>
<td>5 (22)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Poor venous access</td>
<td>3 (14)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

8.2 Lactation

Lactation Risk Summary
There are no available data on the presence of laronidase in human milk or the effects on milk production. No adverse effects have been reported in breastfed infants in a few postmarketing cases of ALDURAZYME use in lactating women. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ALDURAZYME and any potential adverse effects on the breastfed child from ALDURAZYME or from the underlying maternal condition. Lactating women with MPS I are encouraged to enroll in the MPS Registry. For more information, visit www.registryntx.com or call 1-800-745-4447 ext. 15500.

8.4 Pediatric Use

Pediatric 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 in children receiving 1.2 mg/kg body weight once weekly. No adverse effects were observed. In the adverse events reported in patients receiving 1.8 mg/kg body weight every other week were similar to the adverse events reported by patients treated with 0.58 mg/kg body weight once weekly.

11 DESCRIPTION

ALDURAZYME (laronidase) is a polysaccharide 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-iduronidohydrolase, EC 3.2.1.76) is a lysosomal hydrolase that catalyzes 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 and a polypeptide of approximately 5.5. The extractable volume of 5 mL from each vial contains 2.9 mg of 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 dose 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). Mucopolysaccharidoses (MPS I) is characterized by the deficiency of α-L-iduronidase, a lysosomal hydrolase which catalyzes the hydrolysis of terminal α-L-iduronate 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 GAG 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 larondase 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 (Cmax) 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 4.3 to 6.9 µg · hour/mL. The mean volume of distribution (Vd) ranged from 0.24 to 0.38 L/kg. Mean plasma clearance (CL) ranged from 1.7 to 2.7 mL/min/kg, and the mean elimination half-life (t1/2) ranged from 1.5 to 3.6 hours.

Most patients who received once weekly infusions of ALDURAZYME in Study 1 developed antibodies to GAG in lysosomes. The pharmacokinetics of larondase were evaluated 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 also not been established [see Clinical Studies (14)].

13 NONCLINICAL TOXICITY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies to assess the mutagenic and carcinogenic potential of ALDURAZYME have not been conducted. Larondase in intravenous doses up to 3.6 mg/kg (6.2 times the recommended human dose) was found to have no effect on the fertility and reproductive performance of male and female rats.

14 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 daily. After 26 weeks of treatment, 16 patients continued to receive 0.58 mg/kg of body weight once daily for an additional 26 weeks. All patients were treated with antipyretics and antihistamines prior to each infusion.

The primary efficacy outcome assessments were percent predicted FVC and 6-Minute Walk Distance (6MWD) measured at baseline and at each study visit. The difference in percent predicted FVC and 6-Minute Walk Distance from Baseline to Week 26 was compared between groups using a repeated measures analysis of variance. The results of the analysis of variance for percent predicted FVC and 6-Minute Walk Distance from Baseline to Week 26 between groups are summarized in Table 4.

Table 4: Primary Efficacy Outcomes in the Placebo-controlled Study (Study 1)

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>ALDURAZYME (N=22) Mean ± s.d.</th>
<th>Placebo (N=23) Mean ± s.d.</th>
<th>Difference in Change From Baseline to Week 26 Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment Baseline FVC (%)</td>
<td>48 ± 15</td>
<td>54 ± 16</td>
<td>4 (median 2 [0.4, 7], p=0.02)</td>
</tr>
<tr>
<td>6-Minute Walk Distance (meters)</td>
<td>319 ± 131</td>
<td>367 ± 114</td>
<td>-3 ± 7</td>
</tr>
</tbody>
</table>

*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 placebo-treated patients. 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, controlled 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.

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. At 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.

16 HOW SUPPLIED/STORAGE AND HANDLING
ALDURAZYME is supplied as a sterile colorless to pale yellow, clear to slightly opalescent solution in single-use 5 mL vials, containing 2.3 mg/mL of ALDURAZYME. The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic flip-off cap.

NDC 58468-3070-1, 5 mL vial
Rete proximal of ALDURAZYME at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light. This product contains no preservatives.

17 PATIENT COUNSELING INFORMATION
Anaphylaxis, Hypersensitivity and Infusion Reactions
Inform the patient or caregiver that hypersensitivity reactions, including life-threatening anaphylaxis, and infusion reactions may occur with ALDURAZYME treatment. Advise the patient or caregiver to report immediately to a healthcare provider if signs or symptoms of a hypersensitivity or infusion reaction occur during infusion of ALDURAZYME. Hypersensitivity reactions may also occur up to 3 hours following an infusion of ALDURAZYME [see Warnings and Precautions (5.1, 5.4)].

Cardiac and Respiratory Adverse Reactions
Advise the patient or caregiver to report immediately to a healthcare provider if signs or symptoms of cardiac or respiratory decompensation occur during or following an infusion [see Warnings and Precautions (5.2, 5.5)].

Informed patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep to have these treatments readily available during infusion or extreme drowsiness/sleep induced by antihistamine use.

Registry
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. The MPS I Registry also monitors the effects of Alurzyrene on pregnant women, lactating women, and infants. 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.registrynt.com or by calling 1-800-745-4447 ext. 15500.

ALDURAZYME is manufactured by:
BioMarin Pharmaceutical Inc.
Novato, CA 94949

US License Number 1649
ALDURAZYME is distributed by:
Genzyme Corporation
Cambridge, MA 02142
1-800-745-4447 (phone)

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