A Guide to Aldurazyme® (laronidase) Billing and Reimbursement

Please see accompanying Full Prescribing Information, including Boxed Warning.
The following is provided for information purposes only and is not intended to substitute for the physician's independent diagnosis or treatment of each patient. Providers are responsible for the accuracy and validity of any claims, invoices, and related documentation submitted to payers. Physicians should contact the payer if they have any specific questions about coverage or payment. Any specific guidance or direction on the submission of claims offered by the payer supersede the codes listed below. Use of the following codes does not guarantee reimbursement.

INDICATIONS AND USAGE
ALDURAZYME® (laronidase) 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.

Important Safety 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.

Anaphylaxis and severe allergic 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 failure, respiratory distress, stridor, tachypnea, bronchospasm, obstructive airways disorder, hypoxia, hypotension, bradycardia, and urticaria. 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. 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 experienced initial severe reactions may require prolonged observation.

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.

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.

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 antihistamine use.

Caution should be exercised when administering ALDURAZYME to patients suspected to have or with a history of an 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 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.

Because of the potential for infusion reactions, patients should receive antipyretics and/or antihistamines prior to infusion. If an infusion-related reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms.

The most serious adverse reactions reported with ALDURAZYME treatment during clinical trials were anaphylactic and allergic reactions. In a 26-week, placebo-controlled clinical trial in patients 6 years and older, the most commonly reported infusion reactions regardless of treatment group were flushing, pyrexia, headache, and rash. Flushing occurred in 5% of patients (23%) receiving ALDURAZYME; the other reactions were less frequent. Less common infusion reactions included angioedema (including facial edema), hypotension, paresthesia, feeling hot or cold, hypoxia, tachycardia, vomiting, back pain, and cough. Other reported adverse reactions included bronchospasm, dyspnea, urticaria, and pruritus. In the open-label, uncontrolled extension phase of this clinical trial, the infusion reactions were similar, but also included abdominal pain or discomfort and intradermal reaction. Less commonly reported infusion reactions included nausea, diarrhea, feeling hot or cold, vomiting, pruritus, arthralgia and urticaria. Additional common adverse reactions included, back pain and musculoskeletal pain.

In an open-label, uncontrolled clinical trial in patients 6 years and younger who received ALDURAZYME treatment for up to 52 weeks, the most commonly reported severe adverse events (regardless of relationship) in patients 5 years and younger, were otitis media (20%), and central venous catheterization required for ALDURAZYME infusion (15%). The most commonly reported adverse reactions in patients 6 years and younger were infusion 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 commonly reported infusion reactions occurring in ≥5% of patients were pallor, tremor, respiratory distress, wheezing, crepitations (pulmonary), pruritus, and rash.

In postmarketing experience with ALDURAZYME, severe and serious infusion reactions have been reported, some of which were life-threatening, including anaphylactic shock. Adverse reactions resulting in death reported in postmarketing setting with ALDURAZYME treatment included cardio-respiratory arrest, respiratory failure, cardiac failure, and pneumonia. These events have been reported in MPS I patients with significant underlying disease. Additional common adverse reactions included erythema and cyanosis. There have been a small number of reports of extravasation in patients treated with ALDURAZYME. There have been no reports of tissue necrosis associated with extravasation. 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.

In clinical trials, 99 of 102 patients (97%) treated with ALDURAZYME were positive for IgG antibodies to ALDURAZYME. In the 2 trials of patients 6 years and older, 9 patients who experienced severe infusion reactions were tested for ALDURAZYME-specific IgG antibodies and complement activation. One of the nine patients had an anaphylactic reaction consisting of urticaria and acute obstruction and tested positive for both ALDURAZYME-specific IgG binding antibodies and complement activation. In the postmarketing setting, approximately 1% of patients experienced severe or serious infusion-allergic reactions and tested positive for IgE. Of these IgE-positive patients, some have discontinued treatment, but some have been successfully re-challenged. The clinical significance of antibodies to ALDURAZYME, including the potential for product neutralization, is not known.

Adverse events should be reported promptly to Genzyme Medical Information at 800-745-4447, option 2 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

ALDURAZYME is available by prescription only. To learn more, please see the accompanying Full Prescribing Information including Boxed Warning. Visit www.ALDURAZYME.com or contact Genzyme at 1-800-745-4447, option 2.
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Questions? Contact Sanofi Genzyme Support Services at 1-800-745-4447 or 1-617-768-9000 (option 3). Your Call, Our Commitment. Please see accompanying full Prescribing Information including Boxed Warning.
Introduction

MPS I is a rare, inherited disorder caused by a deficiency of the lysosomal enzyme α-L-iduronidase. This deficiency leads to systemic accumulation of glycosaminoglycans (GAG). The accumulation of GAG can result in widespread tissue and organ dysfunction. Aldurazyme® (laronidase) works by replacing the missing or deficient lysosomal enzyme, which reduces the accumulation of GAG as measured by urinary GAG excretion. The relationship of urinary GAG to other measures of clinical response has not been established.

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.

Sanofi Genzyme is committed to working with providers, as well as public and private payers, to help ensure access to treatment for patients for whom Aldurazyme is medically necessary. This guide is designed to help you understand coverage, coding and reimbursement for Aldurazyme. Providers are responsible for determining reimbursement and insurance issues related to their patients. Sanofi Genzyme is not responsible for failure of a provider to obtain reimbursement.

If you still have questions after reviewing this guide, please contact Sanofi Genzyme Support Services at 1-800-745-4447 or 1-617-768-9000 (option 3) to speak with a Sanofi Genzyme Case Manager. Sanofi Genzyme Support Services is staffed by Case Managers with expertise in reimbursement, insurance, case management, and the healthcare delivery system, and can help guide physicians and their patients through the reimbursement process.

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.
Aldurazyme® (laronidase) Support Services

Sanofi Genzyme Case Managers

Sanofi Genzyme assigns individual Case Managers who provide free and confidential care coordination and support services to patients living with MPS I disease. Our Case Managers have over 25 years of expertise in insurance coverage, reimbursement, and billing issues for enzyme replacement therapies. Sanofi Genzyme Case Managers can work with physicians and their staff to help coordinate access to treatment with Aldurazyme® (laronidase).

Reimbursement Support

With experience navigating the billing and reimbursement process for Aldurazyme under many types of insurers and plans, Sanofi Genzyme Case Managers can assist healthcare professionals with the reimbursement process by offering:

- Insurance consultations to review, understand, and verify a patient’s coverage for treatment
- Information on billing to support physicians and office staff
- Assistance in obtaining prior authorizations and through the entire coverage approval process
- Assistance in preparing correspondence to third-party payers
- Help educating insurance companies on MPS I disease
- Assistance with billing and claims issues, including appeal process if coverage is denied

A Sanofi Genzyme Case Manager is only a phone call away from providing personalized assistance to your patients.

1-800-745-4447, Option 3
Monday - Friday, 8:00AM to 6:00PM ET

Information you or your patients provide will always be kept confidential.
Support for your Patients

By working with a Sanofi Genzyme Case Manager, your patients will receive comprehensive case management and one-on-one support personalized to their individual needs.

- Information about treatment with Aldurazyme® (laronidase), and related insurance coverage
- Educational materials about MPS I disease
- Access to other Sanofi Genzyme resources
- Help for insured, underinsured, and uninsured patients with identifying new coverage or alternative funding resources
- Confidential coordination and exchange of information between patients, their healthcare providers, insurers, and others

Sanofi Genzyme Co-Pay Assistance Program

The Sanofi Genzyme Co-Pay Assistance Program can help eligible patients who are prescribed treatment with Aldurazyme® (laronidase) with their drug-related out-of-pocket expenses, including co-pays, co-insurance, and deductibles regardless of financial status.

Please have your patients call their Sanofi Genzyme Case Manager or visit www.aldurazyme.com/copay for more information about the Sanofi Genzyme Co-Pay Assistance Program, including current eligibility criteria, eligible expenses, program benefits and the application process. Sanofi Genzyme reserves the right to make eligibility determinations, to set program benefit maximums, to monitor participation, and to modify or discontinue the program at any time.

Product Information

To learn more about Aldurazyme® (laronidase), please visit www.aldurazyme.com and please see enclosed Full Prescribing Information including Boxed Warning in Appendix E.

Updates to this Guide

This guide is reviewed and updated periodically. As reimbursement information is subject to continuing changes, please contact a Sanofi Genzyme Case Manager for the most up-to-date information.
Aldurazyme® (LARONIDASE) Coverage

Private Payers

Aldurazyme® treatment is covered by many private payers; however, individual patients’ insurance benefits will vary. A patient’s insurance coverage should be understood before treatment is initiated so that problems obtaining reimbursement may be minimized. Important points related to private payers include:

- Managed care plans may require a referral from the patient’s primary care provider (PCP) to a specialist.

Private payers may require the following:

- Prior authorization to establish medical necessity for Aldurazyme®.
- Periodic reauthorization or recertification for continued treatment.
- Letter of Intent to Treat. See the example in Appendix A, page 11.
- Statement of Medical Necessity. See the example in Appendix B, page 13.

NOTE

- If the patient’s private insurer denies coverage, an appeal process may be initiated.
- Sanofi Genzyme Case Managers are available to assist patients and work with their physicians through this process.
Medicare Part B

Medicare Part B coverage is determined by the local Medicare Part B carrier. Medicare will not prior authorize, so the patient’s coverage policy should be understood before treatment is initiated. Treatment with Aldurazyme® (laronidase) will need to be considered medically necessary in order to be covered under the Medicare program. Aldurazyme® is generally covered by Medicare Part B when it is administered and billed as incident to a physician’s services. This means that in order for it to be reimbursed, Aldurazyme® and all associated supplies and services must be purchased by the physician or hospital. Medicare Part B does not reimburse for Aldurazyme® when it is administered in a home setting.

NOTE

- Confirm the patient’s eligibility under Medicare Part B prior to ordering Aldurazyme®.

Medicare Managed Care (Medicare Part C)

In general, Medicare Managed Care plans work like commercial managed care plans and may require prior authorization. While different plans have different guidelines, Medicare Managed Care plans are required by Medicare to provide at a minimum, the same level of benefits available under the traditional fee for service Medicare program. Therefore, when the local Medicare B carrier covers Aldurazyme®, the Medicare Managed Care Plan must also cover the Aldurazyme®, although prior authorization and other medical management approaches may be required by the managed care plan.
**Medicare Part D Prescription Drug Coverage**

Aldurazyme\textsuperscript{®} (laronidase) may be on formulary under the patient’s Prescription Drug Plan (PDP) or Medicare Advantage Prescription Drug (MA-PD). The patient’s out of pocket (OOP) costs will vary depending upon plan coverage. Due to the complexity and variability of Medicare Part D prescription drug coverage, contact the PDP, MA-PD or a Sanofi Genzyme Case Manager for further information.

**NOTE**

Medicare Part D reimburses the PDP or MA-PD pharmacy for drug.

**Medicaid**

Medicaid eligibility and benefit plans vary from state-to-state, so the program’s coverage policy should be understood before treatment is initiated. Usually, treatment with Aldurazyme\textsuperscript{®} will need to be considered medically necessary in order to be covered under the Medicaid program. Depending on the state, initial treatment with Aldurazyme\textsuperscript{®} may require prior approval by the state Medicaid program. For information on Medicaid coverage for Aldurazyme \textsuperscript{®} in your state, contact your local Medicaid office or a Sanofi Genzyme Case Manager.
Medicaid agencies may require the following:

- Prior authorization to establish medical necessity for Aldurazyme® (laronidase).
- Periodic reauthorization or recertification for continued treatment.
- Letter of Intent to Treat. See the example in Appendix A, page 11.
- Statement of Medical Necessity. See the example in Appendix B, page 13.

**NOTE**

- Medicaid regularly updates patient eligibility. Therefore, prior to each patient encounter, physicians should verify eligibility and coverage.
- If Medicaid denies coverage, an appeal process may be initiated. Sanofi Genzyme Case Managers are available to assist patients and work with their physicians through this process.

**Medicaid Managed Care**

Many states require Medicaid patients to be enrolled in Medicaid Managed Care plans. These plans vary considerably from state-to-state, and have different documentation and coverage requirements. For example, referrals for treatment with Aldurazyme® may need to be in place in order for the patient to receive treatment by anyone other than the patient’s primary care provider. For information on Medicaid coverage for Aldurazyme® in your state, contact the Medicaid Managed Care plan or a Sanofi Genzyme Case Manager.
Aldurazyme® (LARONIDASE) Reimbursement

Obtaining reimbursement for Aldurazyme® varies by payer and setting.

**Private Payers, Medicare Managed Care and Medicaid Managed Care**

**Physician Office**
- Reimbursement for office-administered drugs is often based on Average Wholesale Price (AWP), or Average Sales Price (ASP).
- Reimbursement for services varies, depending on the negotiated rate between the provider and insurance company or the insurance company’s fee schedule.

**Hospital Outpatient**
- Reimbursement varies depending on the negotiated rate between the hospital and insurance company or the insurance company’s fee schedule.

**Medicare Part B**

**Physician Office**
- The Medicare allowable amount for Aldurazyme® is Average Sales Price (ASP) plus 6%. Rates are updated quarterly.
- Medicare covers 80% of the allowable amount, and the beneficiary or their supplemental policy is responsible for the remaining 20%.
- Reimbursement for physician services is based upon the Medicare Physician Fee Schedule (MPFS).

**Hospital Outpatient**
- The Medicare allowable amount for Aldurazyme® is Average Sales price (ASP) plus 6%. Rates are updated quarterly.
- Medicare covers 80% of the allowable amount, and the beneficiary or their supplemental policy is responsible for the remaining 20% balance; however, in this site of service, the patient’s 20% coinsurance liability is limited to the current year’s Part A deductible dollar amount [Section 1833(t)(8)(C) of the Social Security Act].
  - Medicare pays 80% of the allowable amount plus any additional amount remaining on the beneficiary’s 20% coinsurance when the limitation on the coinsurance applies [Section 1833(t)(4)(C)].
- Reimbursement for services is based upon the Ambulatory Payment Classification (APC).

**Medicaid Fee for Service**

**Physician Office and Hospital Outpatient Setting**
- Reimbursement varies from state-to-state.
- For more information, contact your local Medicaid Office.
Aldurzyme® (laronidase) Billing Codes

The following is provided for information purposes only and is not intended to substitute for the physician’s independent diagnosis or treatment of each patient. Providers are responsible for the accuracy and validity of any claims, invoices, and related documentation submitted to payers. Physicians should contact the payer if they have any specific questions about coverage or payment. Any specific guidance or direction on the submission of claims offered by the payer supersedes the codes listed below. Use of the following codes does not guarantee reimbursement.

| ICD-10-CM | E 76.01 Hurler Syndrome  
E 76.02 Hurler Scheie Syndrome  
E 76.03 Scheie Syndrome |
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>NDC</td>
<td>58468-0070-1  2.9 mg laronidase per 5 mL</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J1931  Aldurzyme® - injection, laronidase, 0.1 mg</td>
</tr>
</tbody>
</table>
| CPT-4     | 96365  Intravenous infusion therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour  
96366  Each additional hour. (List separately in addition to primary procedure code, 96365). |
| Revenue   | 260  General IV therapy service  
261  Infusion pump  
258  IV solutions  
636  Drugs and biologicals requiring a HCPCS Code |

**NOTE**

- Since third party payers evaluate treatment based on medical necessity, expected outcome, and cost, they generally require documentation of diagnosis and clinical symptoms of MPS I. Refer to the Statement of Medical Necessity sample in the back of this guide (Appendix B). This information may need to be submitted with the claim; for specific requirements check with the payer or contact a Sanofi Genzyme Case Manager.

- The treating physician should request written confirmation of coverage from the third party payer prior to initiation of enzyme replacement therapy. Sanofi Genzyme Case Managers can assist in obtaining written authorization for Aldurzyme® treatment.
Coding Glossary of Terms

ICD-10-CM (International Classification of Diseases, 10th Edition, clinical modification)
ICD-10-CM is a revision to the ICD-9-CM system used by physicians and hospitals to classify and code all diagnoses. These codes used by hospitals and physicians are recognized by all insurers. Official use of the ICD-10-CM system in the U.S. started on October 1, 2015.

NDC (National Drug Code)
NDCs are codes that identify FDA-approved drugs. The NDC identifies the manufacturer, product, and package size. NDCs are used primarily by retail pharmacies.

HCPCS (Healthcare Common Procedure Coding System)
HCPCS codes are assigned by CMS (Center for Medicare and Medicaid Services) and are used by Medicare and most private payers to describe products administered in the physician office or hospital setting.

CPT (Current Procedural Terminology)
CPT Codes are used by physicians and hospitals to designate the procedures performed.

Revenue Codes
Revenue Codes are used by hospitals to classify services by category, and typically are required by payers when billing infusions in the hospital setting.
Appendix A

Sample Letter of Intent to Treat

THIS IS A MODEL LETTER - PLEASE CUSTOMIZE FOR YOUR PATIENT

[Date]
[Contact Name] [Insurance Company] [Street Address]
[City], [State] [Zip]

Patient Name: [Patient Name]
Subscriber ID#: [ID Number]
Group#: [Group Number]

Subject: Intent to Treat with Aldurazyme® (laronidase) Solution for intravenous infusion only

Dear [Contact Name]:

I am writing on behalf of my patient, [Patient Name] who has been diagnosed with Mucopolysaccharidosis I disease (MPS I) whom I plan to treat with Aldurazyme, an enzyme replacement therapy. 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.

Important Safety 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.

Anaphylaxis and severe allergic 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 failure, respiratory distress, stridor, tachypnea, bronchospasm, obstructive airways disorder, hypoxia, hypotension, bradycardia, and urticaria. 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. 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 post marketing 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. 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.

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.

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 antihistamine use.
Caution should be exercised when administering ALDURAZYME to patients susceptible to fluid overload or patients with an 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. Because of the potential for infusion reactions, patients should receive antipyretics and/or antihistamines prior to infusion. If an infusion-related reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms.

The most serious adverse reactions reported with ALDURAZYME treatment during clinical trials were anaphylactic and allergic reactions.

In a 26-week, placebo-controlled clinical trial in patients 6 years and older, 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 bronchospasm, dyspnea, urticaria, and pruritus. In the open-label, uncontrolled extension phase of this clinical trial, the infusion reactions were similar, but also included abdominal pain or discomfort and injection site reaction. Less commonly reported infusion reactions included nausea, diarrhea, feeling hot or cold, vomiting, pruritus, arthralgia and urticaria. Additional common adverse reactions included, back pain and musculoskeletal pain.

In an open-label, uncontrolled clinical trial in patients 6 years and younger who received ALDURAZYME treatment for up to 52 weeks, the most commonly reported serious adverse events (regardless of relationship) in patients 6 years and younger, were otitis media (20%), and central venous catheterization required for ALDURAZYME infusion (15%). The most commonly reported adverse reactions in patients 6 years and younger who received infusions were infusion 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 commonly reported infusion reactions occurring in 5% of patients were pallor, tremor, respiratory distress, wheezing, crepitations (pulmonary), pruritus, and rash.

In post marketing experience with ALDURAZYME, severe and serious infusion reactions have been reported, some of which were life-threatening, including anaphylactic shock. Adverse reactions resulting in death reported in the post marketing setting with ALDURAZYME treatment included cardio-respiratory arrest, respiratory failure, cardiac failure, and pneumonia. These events have been reported in MPS I patients with significant underlying disease. Additional common adverse reactions included erythema and cyanosis. There have been a small number of reports of extravasation in patients treated with ALDURAZYME. There have been no reports of tissue necrosis associated with extravasation. 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.

In clinical trials, 99 of 102 patients (97%) treated with ALDURAZYME were positive for IgG antibodies to ALDURAZYME. In the 2 trials of patients 6 years and older, 9 patients who experienced severe infusion reactions were tested for ALDURAZYME-specific IgE antibodies and complement activation. 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. In the post marketing setting, approximately 1% of patients experienced severe or serious infusion allergic reactions and tested positive for IgE. Of these IgE-positive patients, some have discontinued treatment, but some have been successfully re-challenged. The clinical significance of antibodies to ALDURAZYME, including the potential for product neutralization, is not known. Adverse events should be reported promptly to Genzyme Medical Information at 800-745-4447, option 2 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Please see enclosed full Prescribing Information including Boxed Warning

Documentation Enclosed
The attached Statement of Medical Necessity contains information pertaining to [Patient Name]’s clinical history, diagnosis and signs and symptoms - demonstrating that the use of Aldurazyme is medically indicated for treatment of [his/her] MPS I disease. Initially, my prescribed dosing regimen will be [ ] mg per kilogram administered [ ] per week.

Action Requested
Please send verification of [Patient Name]’s insurance coverage for enzyme replacement therapy with Aldurazyme as soon as possible. If you have any questions pertaining to [Patient Name]’s clinical history and/or my treatment plan, please call me at [Phone Number].

Thank you for your immediate attention to this request. Sincerely,

[Physician Name]

Enclosure: Statement of Medical Necessity
Cc: [Patient Name/Legal Guardian]
## Appendix B

### Sample Statement of Medical Necessity

**STATEMENT OF MEDICAL NECESSITY**  
FOR THE TREATMENT OF MUCOPOLYSACCHARIDOSIS I DISEASE

<table>
<thead>
<tr>
<th>Patient Information</th>
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<tr>
<td>Parent/Legal Guardian Name (If applicable)</td>
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<table>
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<tr>
<td>Policy Number</td>
<td>Group Number</td>
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<td>Insurance Phone</td>
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<table>
<thead>
<tr>
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<tr>
<td>Mucopolysaccharidosis I (MPS I)</td>
<td></td>
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<tr>
<td>ICD-9-CM</td>
<td>□ 277.5 MPS I</td>
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<tr>
<td>ICD-10-CM*</td>
<td>□ E76.01 Hurler Syndrome □ E76.02 Hurler Scheie Syndrome □ E76.03 Scheie Syndrome</td>
</tr>
<tr>
<td>Method of diagnosis: Enzyme Assay Activity</td>
<td>□ leukocytes □ plasma □ skin fibroblasts</td>
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<td>Urinary GAG</td>
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<td>Lab performing Diagnosis</td>
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<td>Height</td>
<td>Inches</td>
</tr>
<tr>
<td>Head Circumference</td>
<td>Inches</td>
</tr>
<tr>
<td>Symptoms consistent with MPS I (Please List)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Recommendation</th>
<th></th>
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<tbody>
<tr>
<td>Dose</td>
<td>mg/kg</td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>Therapy Start Date</td>
<td>Frequency of follow-up evaluation</td>
</tr>
<tr>
<td>Please list any additional treatment information:</td>
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<table>
<thead>
<tr>
<th>Physician Authorization</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I certify that the above-indicated therapy is medically necessary, and the information provided is accurate to the best of my knowledge</td>
<td></td>
</tr>
<tr>
<td>Physician Name (printed)</td>
<td>Date</td>
</tr>
<tr>
<td>Address</td>
<td>City</td>
</tr>
<tr>
<td>Phone</td>
<td>Fax</td>
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<tr>
<td>Physician’s Signature</td>
<td>Medical License #</td>
</tr>
<tr>
<td>State Issued</td>
<td></td>
</tr>
</tbody>
</table>

ICD-10-CM* for dates of service starting on October 1, 2015

Statement of Medical Necessity GZUS.ALDU.15.09.2509(1)

Call Sanofi Genzyme to request a copy of this form.
Appendix C

Sample CMS-1450 (UB-04) Claim Form

DISCLAIMER: This is a reference sheet only. It is NOT inclusive of all applicable codes that may be reported on a UB-04 claim form. The inclusion of codes listed is not intended to suggest or imply that such codes reflect appropriate diagnoses for any particular patient. To ensure appropriate documentation and coding, Providers should contact their billing/finance department.

Field 46: Note the appropriate amount of drug provided in units; Example: multiples of 0.1 mg for Aldurazyme

General IV therapy:
- 96365 Intravenous IV therapy, prophylaxis, or diagnosis (specify substance or drug); initial up to 1 hr
- 96366 Each additional hour (list separately in addition to primary procedure code, 96365)

Fields 42 and 43: Enter appropriate revenue code and description of service; Example:
- 0636 for drugs that require detailed coding
- 0260 for IV therapy

Enter appropriate ICD-10-CM diagnosis code as reflected in the patient’s medical record
Example:
- E76.01 (Hurler)
- E76.02 (Hurler Scheie)
- E76.03 (Scheie)

Questions? Contact Sanofi Genzyme Support Services at 1-800-745-4447 or 1-617-768-9000 (option 3). Your Call, Our Commitment. Please see accompanying full Prescribing Information including Boxed Warning.
Appendix D

Sample CMS 1500 (02-12) Claim Form

Box 21: Complete the indicator field to reflect diagnosis code reported: ICD-10-CM

Box 24D: Enter the appropriate HCPCS codes:

- Drugs: J1931 for Aldurazyme, 0.1 mg
- General IV Therapy: 96365 Intravenous infusion therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
- 96366 Each additional hour (list separately in addition to primary procedure code, 96365)
Appendix E

Full Prescribing Information

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.

INDICATIONS AND USAGE
ALDURAZYME is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme 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 (1).

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

DOSE FORMS AND STRENGTHS
Solution: 2.9 mg/5 mL vial (3).

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
• Anaphylaxis and Allergic Reactions: Life-threatening anaphylactic reactions have been observed in some patients during ALDURAZYME infusion and up to 3 hours after infusion. Appropriate medical support and monitoring measures should be readily 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).

• Risk of Acute Respiratory Complications: Patients with acute febrile or respiratory illness at the time of ALDURAZYME infusion may be at greater risk for infusion reactions. Consider delaying ALDURAZYME infusion. Sleep apnea is common in MPS I patients. Evaluation of airway patency should be considered prior to initiation of treatment with ALDURAZYME. Appropriate respiratory support should be available during infusion (5.2).

• Risk of Acute Cardio-respiratory Failure: Caution should be exercised when administering ALDURAZYME to patients susceptible to fluid overload. Consider a decreased total infusion volume and infusion rate when administering ALDURAZYME to these patients. Appropriate medical monitoring and support measures should be available during infusion (2.2, 5.3).

• Infusion Reactions: Pretreatment is recommended prior to the infusion to reduce the risk of infusion reactions and may include antihistamines, antipyretics, or both. If infusion reactions occur, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms (5.4).

ADVERSE REACTIONS
The most commonly reported infusion reactions occurring in at least 10% of patients 6 months of age and older were pyrexia, chills, blood pressure increased, tachycardia, and oxygen saturation decreased (6). 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, flushing, and poor venous access.

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 should be encouraged to enroll in the MPS I Registry. For more information, visit www.MPSregistry.com or call (800) 745-4447 (8.1).

See 17 for PATIENT COUNSELING INFORMATION. Revised: 04/2013

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: RISK OF ANAPHYLAXIS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dose
2.2 Instructions for Use
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Anaphylaxis and Allergic Reactions
5.2 Acute Respiratory Complications Associated with Administration
5.3 Risk of Acute Cardiorespiratory Failure
5.4 Infusion Reactions
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
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8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
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10 OVERDOSE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
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12.2 Pharmacodynamics
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14 CLINICAL STUDIES
14.1 Clinical Studies in Patients 6 Years and Older
14.2 Clinical Studies in Patients 6 Years and Younger
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the Full Prescribing Information are not listed.
**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® (laronidase) 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 is recommended 60 minutes prior to the start of the infusion and may include antihistamines, antipyretics, or both [see Warnings and Precautions (5)].

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 0.9% Sodium Chloride Injection, USP to a final volume of 100 mL or 250 mL, using aseptic techniques. The final 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 greater than 20 kg should receive a total volume of 250 mL [see Dosage and Administration (2.2)]. For patients with underlying cardiac or respiratory compromise and weighing up to 30 kg, physicians may consider diluting ALDURAZYME in a volume of 100 mL and administering at a decreased infusion rate [see Warnings and Precautions (5.3) and Adverse Reactions (6.3)].

2.2 Instructions for Use

Prepare and use ALDURAZYME according to the following steps. Use aseptic techniques. Prepare ALDURAZYME using low-protein-binding containers and administer with a low-protein-binding infusion set equipped with a low-protein-binding 0.2 µm in-line filter. There is no information on the 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) x 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 vial. 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 translucency 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 caution 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 care to avoid agitating 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>
<thead>
<tr>
<th>Infusion Rate</th>
<th>Criteria for Increasing Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mL/hr x 15 minutes (10 µg/kg/hr)</td>
<td>Obtain vital signs, if stable then increase the rate to…</td>
</tr>
<tr>
<td>4 mL/hr x 15 minutes (20 µg/kg/hr)</td>
<td>Obtain vital signs, if stable then increase the rate to…</td>
</tr>
<tr>
<td>8 mL/hr x 15 minutes (50 µg/kg/hr)</td>
<td>Obtain vital signs, if stable then increase the rate to…</td>
</tr>
<tr>
<td>16 mL/hr x 15 minutes (100 µg/kg/hr)</td>
<td>Obtain vital signs, if stable then increase the rate to…</td>
</tr>
<tr>
<td>32 mL/hr x ~3 hours (200 µg/kg/hr)</td>
<td>For the remainder of the infusion.</td>
</tr>
</tbody>
</table>

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>
<tbody>
<tr>
<td>5 mL/hr x 15 minutes (10 µg/kg/hr)</td>
<td>Obtain vital signs, if stable then increase the rate to…</td>
</tr>
<tr>
<td>10 mL/hr x 15 minutes (20 µg/kg/hr)</td>
<td>Obtain vital signs, if stable then increase the rate to…</td>
</tr>
<tr>
<td>20 mL/hr x 15 minutes (50 µg/kg/hr)</td>
<td>Obtain vital signs, if stable then increase the rate to…</td>
</tr>
<tr>
<td>40 mL/hr x 15 minutes (100 µg/kg/hr)</td>
<td>Obtain vital signs, if stable then increase the rate to…</td>
</tr>
<tr>
<td>80 mL/hr x ~3 hours (200 µg/kg/hr)</td>
<td>For the remainder of the infusion.</td>
</tr>
</tbody>
</table>

Table 2: Incremental Rates for 250 mL ALDURAZYME® Infusion

(For use with Patients Weighing Greater than 20 kg)

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° to 8°C (36° 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.

3 DOSAGE FORMS AND STRENGTHS

ALDURAZYME is supplied as a sterile solution in 5 mL vials (2.9 mg per 5 mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Allergic Reactions [see Boxed Warning]
Anaphylaxis and severe allergic 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 failure, respiratory distress, stridor, tachypnea, bronchospasm, obstructive airways disorder, hypoxia, hypotension, bradycardia, and urticaria. If anaphylactic or other severe allergic 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 tracheostomy, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and IV corticosteroids (see Adverse Reactions (6)).

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.

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.

5.2 Acute Respiratory Complications Associated with Administration

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 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.

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 antistamine 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)).

5.4 Infusion Reactions

Because of the potential for infusion reactions, patients should receive antipyretics and/or antihistamines prior to infusion. If an infusion reaction occurs, regardless of pretreatment, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms (see Adverse Reactions (6)).

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the 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 allergic 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, with or without administering additional treatments including antihistamines, antipyretics, 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 Hurler form, 37 Hurler-Scheie, and 7 Scheie. Patients were randomized to receive either 0.58 mg/kg IV of ALDURAZYME per week for 26 weeks or placebo. All patients were treated with antipyretics 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. 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 bronchospasm, 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.

### 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)</th>
<th>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>Thrombocytopenia</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Corneal opacity</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Chest pain</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Face edema</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Gravitational edema</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Injection site pain</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Injection site reaction</td>
<td>4 (18)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hyperbilirubinemia</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Abscess</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>7 (32)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Hypertrefluxia</td>
<td>3 (14)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
<td>3 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>8 (36)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Poor venous access</td>
<td>3 (14)</td>
<td>0</td>
</tr>
</tbody>
</table>

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 reactions reported in 49% (22 of 45) of patients treated with ALDURAZYME. The most commonly reported infusion reactions included rash (13%), flushing (11%), pyrexia (11%), headache (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.

Clinical Trials 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 central venous catheterization required for ALDURAZYME infusion (15%).

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 adverse reactions in Study 3 were infusion 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 commonly reported infusion reactions occurring in ≥ 5% of patients were pallor, tremor, respiratory distress, wheezing, crepitations (pulmonary), pruritus, and rash.

6.2 Immunogenicity
In clinical trials, 99 of 102 patients (97%) treated with ALDURAZYME were positive for IgG antibodies to ALDURAZYME. No correlation was demonstrated between the presence of IgG anti-ALDURAZYME antibodies and therapeutic response (6 MWT and FVC) or the occurrence of allergic reactions. Potential for antibody neutralization of cellular uptake has not been assessed. No consistent association was demonstrated between the presence of antibodies that neutralize enzymatic activity and therapeutic response.

The data reflect the percentage of patients whose test results were considered positive for antibodies to ALDURAZYME using a specific enzyme-linked immunosorbent assay (ELISA) and confirmed by radio-immunoprecipitation (RIP). ALDURAZYME IgG antibodies were reported as titers. Drug-specific antibody was detected in 42 of the 45 patients (93.3%) treated in Study 1 and Study 2. The mean time to seroconversion was 51 days in patients 6 years and older. In Study 3, all patients (100%) 5 years old or younger developed IgG antibodies against ALDURAZYME with a mean time to seroconversion of 26 days [see Clinical Studies (14) for the Study populations].

Nine patients in Study 1 and Study 2, collectively, who experienced severe infusion reactions were tested for ALDURAZYME-specific IgG antibodies and complement activation. IgG 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. 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 allergic reactions and tested positive for IgE. 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
The following adverse reactions have been identified during post approval use of ALDURAZYME. 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.

In postmarketing experience with ALDURAZYME, severe and serious infusion reactions have been reported, some of which were life-threatening, including anaphylactic shock [see Boxed Warning and Warnings and Precautions (5) and laryngeal edema.

Adverse reactions resulting in death reported in the postmarketing setting with ALDURAZYME treatment included cardio-respiratory arrest, respiratory failure, cardiac failure, and pneumonia. These events have been reported in MPS I patients with significant underlying disease. Additional adverse reactions included fatigue, edema peripheral, erythema and cyanosis.

There have been a small number of reports of extravasation in patients treated with ALDURAZYME. There have been no reports of tissue necrosis associated with extravasation.

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 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)].

8.3 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 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 events 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-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 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. 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
catalyzes 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 (Cmax) 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 (Vd) 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 (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 laronidase by Week 12. Between Weeks 1 and 12, increases in the plasma
concentrations of antibodies 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 titer of antibodies.

The pharmacokinetics of laronidase were evaluated in 6 year old or younger patients (N=7 to
9) with MPS I who received 0.58 mg/kg of body weight once weekly of ALDURAZYME as a 4-hour infusion in the open label clinical study (Study 3). After the 26th infusion, the
95% confidence interval of the geometric mean values of PK parameters ranged from 0.6 to
1.6 µg/mL for the maximum plasma concentrations (Cmax), from 1.3 to 4.4 µg • hour/mL for
area under the plasma concentration-time curve (AUC∞), from 0.12 to 0.56 L/kg for volume of
distribution (Vd), from 2.2 to 7.7 mL/min/kg for plasma clearance (CL), and from 0.3 to 1.9
hours for elimination half-life (t1/2).

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,
age 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 anti-infectives 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 4).

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

<table>
<thead>
<tr>
<th></th>
<th>ALDURAZYME* (N=22)</th>
<th>Placebo (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced Vital Capacity (percent of predicted normal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment Baseline</td>
<td>Mean ± s.d.</td>
<td>48 ± 15</td>
</tr>
<tr>
<td>Week 26</td>
<td>Mean ± s.d.</td>
<td>50 ± 17</td>
</tr>
<tr>
<td>Change from Baseline to Week 26</td>
<td>Mean ± s.d.</td>
<td>1 ± 7</td>
</tr>
<tr>
<td>Difference in Change from Baseline to Week 26 Between Groups</td>
<td>Median</td>
<td>1</td>
</tr>
<tr>
<td>6-Minute Walk Distance (meters)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment Baseline</td>
<td>Mean ± s.d.</td>
<td>319 ± 131</td>
</tr>
<tr>
<td>Week 26</td>
<td>Mean ± s.d.</td>
<td>339 ± 127</td>
</tr>
<tr>
<td>Change from Baseline to Week 26</td>
<td>Mean ± s.d.</td>
<td>20 ± 69</td>
</tr>
<tr>
<td>Difference in Change from Baseline to Week 26 Between Groups</td>
<td>Median</td>
<td>28</td>
</tr>
<tr>
<td>Difference in Change from Baseline to Week 26 Between Groups</td>
<td>Mean (95% CI)</td>
<td>39 (-2.79)</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 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.

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 0.16 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 solution in single-use, clear Type I glass 5 mL vials,
containing 2.9 mg laronidase per 5 mL solution. 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. Protect from light. Do not use ALDURAZYME after the expiration date on the vial. This product contains no preservatives.

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.MPSregistry.com or by calling (800) 745-4447.

ALDURAZYME is manufactured by:
BioMarin Pharmaceutical Inc.
Novato, CA 94949
US License Number 1649

ALDURAZYME is distributed by:
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Important Safety Information can be found on the inside cover of this billing guide. Please see enclosed Full Prescribing Information, including Boxed Warning.
An Ongoing Commitment

For more than 25 years, Sanofi Genzyme has been committed to researching and developing products for people living with lysosomal storage disorders such as MPS I disease.

Providing comprehensive and confidential care coordination that addresses the unique needs of those living with MPS I disease is part of this ongoing commitment.

To learn more about Sanofi Genzyme Support Services, call 1-800-745-4447 (option 3).