**Subject:** Enzyme Replacement Therapy (ERT) for Lysosomal Storage Disorders (MPS I, VI)

- Aldurazyme (laronidase)
- Naglazyme (galsulfase)

**Original Effective Date:** 11/29/2016

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**DISCLAIMER**

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

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**SUMMARY OF EVIDENCE/POSITION**

This policy addresses the coverage of Enzyme Replacement Therapies (ERT) **Aldurazyme (laronidase)** for the treatment of **Mucopolysaccharidosis I; MPS I** and **Naglazyme (galsulfase)** for the treatment of **Maroteaux-Lamy Syndrome (Mucopolysaccharidosis VI; MPS VI)** when appropriate criteria are met.

The intent of the drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies.

- **Vimizim (elosulfase alfa)** is not included in this policy as it is an enzyme replacement therapy indicated for Mucopolysaccharidosis Type IV A (MPS IV A).

  REFER TO: **Vimizim (elosulfase alfa) MCP-247**

- The mucopolysaccharidoses (MPS) are inherited lysosomal storage disorders in which a deficiency of specific enzymes (depends on subtype) leads to the accumulation of mucopolysaccharides (a.k.a. glycosaminoglycans; GAGs). The accumulation of partially degraded GAG fragments in the lysosomes, results in permanent cellular dysfunction and clinical abnormalities which may manifest in various parts of the body. The symptoms and physical findings associated with MPS vary greatly depending on subtype and case. Common manifestations of MPS include central nervous system disease such as hydrocephalus or cervical spine myelopathy, cardiovascular and pulmonary disease, ophthalmologic disease, such as corneal clouding or retinal degeneration, hearing impairment, and musculoskeletal manifestations such as short stature, joint stiffness, or symptoms of peripheral nerve entrapment. There are seven types of MPS disorders which are differentiated by their clinical features and age of presentation and biochemically by their associated enzyme deficiency. MPS Type I has three subtypes, followed by MPS Types II, III, IV, VI, VII, and IX. MPS V (formerly Scheie syndrome) and MPS VIII are no longer acknowledged.

  - MPS I is caused by mutations in the alpha-L-iduronidase (IDUA) gene. This mutation results in an accumulation of the heparan sulfate and dermatan sulfate GAGs. There are three subtypes (i.e. attenuated...
phenotypes) of the disease which represent the spectrum of severity: Hurler (most severe), Hurler-Scheie (intermediate), and Scheie (least severe). The major difference between the three subtypes are the typical age at diagnosis and lifespan for each subtype. Patients with Hurler syndrome typically present during infancy and do not have a lifespan beyond five to ten years; while patients with Scheie syndrome typically present with symptoms during their late teen years and may have a normal life expectancy (however many of these patients die during their middle decades).

- MPS VI or Maroteaux-Lamy Syndrome is caused by mutations in the N-acetyl-galactosamine-4-sulfatase (ARSB) gene. This enzyme deficiency results in the accumulation of dermatan sulfate and chondroitin 4-sulfate GAGs.

- The goal of therapy is to reduce the accumulation of the toxic GAGs to prevent disease progression. The primary mechanism of action for therapy involves replacing the missing or defective GAG with a genetically engineered enzyme (ERT). The primary goals of therapy are to improve pulmonary symptoms and progression of symptoms and enhancement in the overall health and quality of life.

- Laronidase and galsulfase are the first pharmacotherapies available for their respective MPS syndrome and the first ERTs designed to target the underlying cause of each syndrome. Laronidase and galsulfase are hydrolytic lysosomal GAG-specific enzymes. Laronidase provides exogenous alpha-L-iduronidase (IDUA) in adults and pediatric patients 6 months and older with Hurler and Hurler-Scheie forms of MPS I and patients with Scheie form with moderate to severe symptoms. Galsulfase provides exogenous N-acetyl-galactosamine-4-sulfatase (ARSB) in adults and pediatric patients 5 years and older with MPS VI.

- Laronidase is a polymorphic variant of the human enzyme, alpha-L-iduronidase (IDUA) gene that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. IDUA is a lysosomal hydrolase that catalyzes the hydrolysis of terminal IDUA residues of dermatan sulfate and heparan sulfate.

- Galsulfase is a purified human enzyme that is produced by recombinant DNA technology in a Chinese hamster ovary line. Galsulfase (N-acetylgalactosamine 4-sulfatase; ARSB) is a lysosomal enzyme that catalyzes the cleavage of the sulfate ester from terminal-ARSB residues of GAG, chondroitin 4-sulfate and dermatan sulfate.

- The FDA approval of laronidase was based on two randomized trials of 45 patients, six years and older, with MPS I. Weekly laronidase treatment improved respiratory function and distance walked in a 26-week randomized, placebo-controlled trial. Patients who continued the study received weekly laronidase for an additional 182 weeks in an open-label, uncontrolled extension study. The patients’ respiratory function remained stable, while their distance walked continued to increase during the 182 week extension trial.

  - In this pivotal phase 3 study of laronidase patients treated with 0.58 mg/kg/week of laronidase had a statistically significant increase from baseline in percent predicted FVC and 6-MWT at 26 weeks compared with placebo. Percent predicted FVC remained stable, while 6-MWT continued to increase during the 182 week extension trial.

  - The results showed that laronidase improved performance on the percent predicted FVC and 6-MWT (primary outcomes). Laronidase was associated with a greater reduction in urinary dermatan sulfate and heparan sulfate levels compared with placebo; however, the clinical significance of this finding has not been established.

  - As with other ERT products, patients may develop neutralizing antibodies (NAbs) to laronidase. 93% of patients treated with laronidase 0.58 mg/kg/week tested positive for NAbs. The relationship between the presence of NAbs and long-term therapeutic response cannot be assessed. Although the presence of NAbs did not appear to have a significant effect on the efficacy or safety of laronidase, the long-term effect of immunogenicity of the product is unknown.
FDA approval of laronidase is also based on an open-label study of 20 patients with MPS I that were less than five years old. Weekly laronidase treatment improved mean urinary GAG levels declined during this 52-week trial.

- In this study, 16 patients were treated with 0.58 mg/kg/week of laronidase for 52 weeks, while four patients were treated with laronidase 0.58 mg/kg/week for 26 weeks, followed by 26 weeks of laronidase 1.16 mg/kg/week for the remaining 26 weeks.
- The results showed that laronidase decreased mean urinary GAG levels in all patients.
- All patients participating in this study developed NAbs to laronidase.

FDA approval of galsulfase is based on a phase 3, double-blind, randomized, placebo-controlled trial with an open label extension. A total of 39 MPS VI patients between 5 and 29 years were included in these trials. An open-label extension study, evaluated the long-term efficacy of galsulfase was evaluated for endurance and safety.

- In this study, the 19 patients were treated with 1 mg/kg/week galsulfase experienced a statistically significant increase in the mean distance walked in a 12-MWT (primary outcome) and the number of stairs climbed in a 3-MSC (secondary outcome) compared to baseline mean values. Galsulfase was also associated with a greater reduction in urinary dermatan sulfate and chondroitin 4-sulfate levels compared with placebo; however, the clinical significance of this finding has not been established.
- In this study, all of the patients treated with galsulfase tested positive for NAbs. However, there was no consistent predictive relationship between the presence of NAbs and the long-term efficacy of the product.

Prior to the approval of ERT for the treatment of MPS I and VI, the only alternatives were palliative or supportive care, which does not treat the underlying cause of the disease so it continued to progress. In consideration of the unmet need for the treatment of MPS I and VI, the benefits of ERT for patients with MPS I and VI outweigh the known risks since there are no clinical alternatives to laronidase and galsulfase for ERT in patients with MPS I and VI, respectively.

- Laronidase and galsulfase are reasonably safe with consideration of the seriousness of the disorder though this therapy is associated with development of NAbs and infusions reactions.
- The studies reviewed support the efficacy of the recombinant enzyme; however, efficacy was established based primarily on subjective tests of endurance and effort (% predicted FVC and 6-MWT are subjective tests which depend on the effort and motivation of the individual patient, which may be difficult to control in younger children) and long-term outcomes have not been established.

The journal of Genetics and Molecular Biology and Orphanet Journal of Rare Diseases recommend initiating treatment as soon as the diagnosis has been confirmed by an enzyme activity test.\textsuperscript{A, B}

**CLASSIFICATION: Metabolic Agents; Metabolic Enzymes**
Aldurazyme (laronidase)\(^a\)
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.\(^a\)

- **Orphan drug designation:** Treatment of patients with mucopolysaccharidosis-F

Naglazyme (galsulfase)\(^b\)
A hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). Naglazyme has been shown to improve walking and stair-climbing capacity.\(^b\)

- **Orphan drug designation:** Treatment of mucopolysaccharidosis Type VI (Maroteaux-Lamy syndrome)\(^c\)

**Available as:**
- Aldurazyme (laronidase): 5 mL vial (2.9 mg per vial)
- Naglazyme (galsulfase): 5 mL vial (5 mg per vial)

**FDA Approved:**
- Aldurazyme (laronidase): April 30, 2003
- Naglazyme (galsulfase): May 31, 2005

**Black Box Warnings:**
- Aldurazyme (laronidase): 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.\(^a\)
- Naglazyme (galsulfase): *None at the time of this writing*

**REMS:** *None at the time of this writing*
Aldurazyme (laronidase), Naglazyme (galsulfase) may be authorized for members who meet ALL of the following criteria [ALL]

1. Prescriber specialty [ONE]
   - Prescribed by, or in consultation with, a board-certified geneticist, pediatric metabolic specialist, hematologist or physician experienced in the management of mucopolysaccharidoses (MPS). Submit consultation notes if applicable.A,B

   **NOTE:** Consultation notes must be submitted for initial request AND at least once annually for continuation of treatment requests.

2. Diagnosis/Indication [ALL]
   
   **Clinical documentation required for all criterion (i.e. clinical notes from the member’s medical records including any applicable labs and/or tests, supporting the diagnosis)**

   - Diagnosis of Mucopolysaccharidosis I (MPS I) or Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy Syndrome) confirmed by:[ONE]
     - Documented reduced fibroblast or leukocyte IDUA or ARSB enzyme activityA,B
     - Molecular genetic testing of IDUA or ARSB

   - At least ONE (1) of the following symptoms of the disease: gait disturbance, growth deficiency, short stature, spinal abnormalities, chest abnormalities, joint abnormalities, respiratory compromise, cardiac valve abnormalities, muscular weakness, visual impairment, hearing loss, or dental abnormalities and oral health challenges¹

3. Age/Gender/Restrictions [AS APPLICABLE]
   - Aldurazyme (laronidase): 6 months of age to 65 years of age
     - The safety and effectiveness in patients younger than 6 months of age and older than 65 years of age has not been established.a

   - Naglazyme (galsulfase): 5 years of age to 29 years of age
     - Galsulfase has been administered to patients younger than 5 years of age in an open-label study with four infants between 3 months to 12.7 months of age. Safety results in infants were consistent with results observed in patients 5 to 29 years of age.a
     - The safety and effectiveness in patients older than 29 years of age has not been established.a

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]
   
   **Clinical documentation required for all criterion (i.e. clinical notes from the member’s medical records including any applicable labs and/or tests, supporting the diagnosis)**

   - Prescribed as monotherapy: NOT to be used concurrently with other medications for Mucopolysaccharidosis (MPS) [i.e. Aldurazyme, Naglazyme]
5. Contraindications*/Exclusions/Discontinuations

There are no contraindications listed in the manufacturer's labeling.\(^{a,b}\)

There are no known significant interactions

Authorization will not be granted if ANY of the following conditions apply [ANY]

- Non-FDA approved indications
- Known hypersensitivity to laronidase (Aldurazyme); galsulfase (Naglazyme) or other enzyme replacement therapies

Exclusions [ANY]

- MPS Types II, III, IV B, VII, and IX
- Concurrent use of laronidase (Aldurazyme); galsulfase (Naglazyme) or other enzyme replacement therapies in conjunction with each other
- Member does not meet ALL of the above coverage criteria

Special Populations (*not absolute contraindications or exclusions but for case-by-case consideration as applicable)

Aldurazyme

- Pregnancy: Category B
  - There is a MPS I Registry that collects data on pregnant women with MPS I who are treated with Aldurazyme.

- Lactation: It is not known if Aldurazyme is present in human milk.
  - There is a MPS I Registry that collects data on breastfeeding women with MPS I who are treated with Aldurazyme.

Naglazyme

- Pregnancy: Category B
  - There is a MPS VI Registry that collects data on pregnant women with MPS VI who are treated with Naglazyme.

- Lactation: It is not known if Naglazyme is present in human milk.
  - There is a MPS VI Registry that collects data on breastfeeding women with MPS VI who are treated with Naglazyme.

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member’s medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

- Member’s weight dated within 1 month of the prior authorization request
  - NOTE: Member’s weight must be provided at time of prior authorization request and for any subsequent dose increases. Requests for amounts above initially authorized limits will require documentation of an updated patient weight for review and authorization.

- Baseline 6-minute walk test (6-MWT) indicating the member walked at least 30 meters in six (6) minutes\(^{a,b,E}\)
  - At baseline, all enrolled patients could walk more than 5 meters (m) but less than 270 m in six minutes\(^{a,b,E}\).
  - The 6-MWT is a validated measure of endurance which evaluates the global and integrated responses of the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism\(^E\)

- Percent predicted Forced Vital Capacity (% Predicted FVC) [Aldurazyme requests only]
  - At baseline, all enrolled patients had a baseline FVC value that was less than or equal to 80% of the patient’s predicted normal FVC value based on polgar predicted values for standing height for children 5 through 7 years of age and Hankinson predicted values for ages 8 and above\(^b\)
Aldurazyme (laronidase), Naglazyme (galsulfase) may be authorized for continuation of therapy if all of the following criteria are met: [ALL]

1. Initial Coverage Criteria [ALL]
   - Member currently meets ALL initial coverage criteria
   - If Prescriber is not a board-certified geneticist, metabolic specialist, or physician experienced in the management of patients with mucopolysaccharidoses, recent consultation notes must be submitted for continuation of treatment requests.
   - Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.
   - Requested ERT remains for use as monotherapy: NOT to be used concurrently with other MPS drug therapy.

2. Compliance [ALL]
   - Adherence to therapy at least 85% of the time as verified by Prescriber and member’s medication fill history (review Rx history for compliance), including: [ALL]
     - Adherent to the prescribed medication regimen
     - Tolerance to therapy
     - No severe adverse reactions or drug toxicity
   
   NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy
   - History of non-compliance or non-adherence as verified by member’s medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

3. Labs/Reports/Documentation required [ALL APPLICABLE]
   - Documentation of positive response or disease stability to therapy (as compared to baseline; prior to therapy), including but not limited to, improvement in the following conditions: [AT LEAST ONE]
     - Baseline 6-minute walk test (6-MWT) indicating the member walked at least 30 meters in six (6) minutes
       - At baseline, all enrolled patients could walk more than 5 meters (m) but less than 270 m in six minutes.
       - The 6-MWT is a validated measure of endurance which evaluates the global and integrated responses of the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism.
     - Percent predicted Forced Vital Capacity (% Predicted FVC) [Aldurazyme requests only]
       - At baseline, all enrolled patients had a baseline FVC value that was less than or equal to 80% of the patient’s predicted normal FVC value based on polgar predicted values for standing height for children 5 through 7 years of age and Hankinson predicted values for ages 8 and above.
Note: For Aldurazyme, the primary endpoint was the change from baseline in the 6-MWT distance and percent predicted FVC vs placebo at week 26. The secondary endpoints were the overall change in Apnea/Hypopnea Index, liver volume, Child Health Assessment Questionnaire/Health Assessment Questionnaire (CHAQ/HAQ) Disability Index Score, active joint Range of Motion (ROM), and urinary glycosaminoglycans (GAGs). Though statistical significance was only observed in the 6-MWT and % Predicted FVC results, favorable improvement was seen in the majority of exploratory efficacy endpoints used in the phase 3 clinical trials for Aldurazyme. The favorable improvement over placebo were seen in most of the secondary endpoints, though none reached statistical signifies an overall treatment effect from Aldurazyme across the patient population.\(^a\)

Note: For Naglazyme, the primary endpoint was the change from baseline in the 12-MWT distance. The secondary endpoint was the overall change in 3-MSCT and urinary GAGs. Active joint ROM was a tertiary endpoint in the trial. Statistical significance was achieved with the primary endpoint, only clinical significance was achieved with the secondary endpoint. Joint pain and stiffness did not significantly differ between the placebo and galsulfase treatment groups.\(^b\)

4. Discontinuation of Treatment [ANY]
Discontinue treatment if ANY of the following conditions applies: [ANY]
- Intolerable adverse effects or drug toxicity
- Persistent and uncorrectable problems with adherence to treatment
- Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- Contraindications to therapy
  - Non-FDA approved indications
  - Known hypersensitivity to laronidase (Aldurazyme); galsulfase (Naglazyme) or other enzyme replacement therapies

*There are no contraindications listed in the manufacturer's labeling.\(^a,b\)*
*There are no known significant interactions.\(^a,b\)*

NOTE: Discontinuation of ERT should be considered if treatment goals are not reached, if individual does not comply with infusions or clinical monitoring of treatment goals.

Exclusions
- MPS Types II, III, IV B, VII, and IX *Reference ‘Coverage Exclusions’ section for further information
- Concurrent use of laronidase (Aldurazyme); galsulfase (Naglazyme) or other enzyme replacement therapies in conjunction with each other
- Member does not meet ALL of the above coverage criteria
1. Recommended Dosage [ALL APPLICABLE]

   - **Aldurazyme (laronidase)**
     MPS, Type I (Hurler and Hurler-Scheie forms) and Scheie form with moderate to severe symptoms
     - Usual dosage: 0.58 mg/kg of body weight as an IV infusion once a week

   - **Naglazyme (galsulfase)**
     MPS, Type VI (Maroteaux-Lamy syndrome)
     - Usual dosage: 1 mg/kg IV once weekly infused over a period of at least 4 hours; initial infusion rate (250 mL infusion) 6 mL/hr for first hour; may increase rate to 80 mL/hr for remaining 3 hours

2. Authorization Limit [ALL]

   - Quantity limit
     - Aldurazyme: 0.58 mg/kg IV once every week (dose is limited to 0.58 mg/kg given intravenously once every week); up to 52 infusions per year
     - Naglazyme: 1 mg/kg IV once every week (dose is limited to 1 mg/kg given intravenously once every week); up to 52 infusions per year
     NOTE: Member’s weight must be provided at time of prior authorization request and for any subsequent dose increases. Requests for amounts above initially authorized limits will require documentation of an updated patient weight for review and authorization.

   - Dispensing limit: Only a 1-month supply may be dispensed at a time

   - Duration of initial authorization: **Six (6) months**

   - Continuation of treatment: Re-authorization for continuation of treatment is required every **six (6) months** to determine continued need based on documented positive clinical response

   - Duration of continuation of treatment: May be authorized up to **6 months** at a time.

3. Route of Administration [ALL]

   - Aldurazyme (laronidase) and Naglazyme (galsulfase) are considered **provider-administered** medications.
     ERT should be supervised by a physician or health professional experienced in the management of patients with MPS. Administration of ERT should be carried out by an appropriately trained health professional with the ability to manage medical emergencies. Home administration by a health professional trained in recognizing and managing serious infusion reactions may be considered only for patients who are tolerating their infusions well under the direction of the prescribing physician.

   - If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.
This policy addresses Aldurazyme (laronidase) and Naglazyme (galsulfase) for the treatment of MPS I and VI, respectively. All other uses of Aldurazyme (laronidase), Naglazyme (galsulfase) that are not an FDA-approved indication or included in ‘Coverage Criteria’ section of this policy are considered experimental/investigational and is not a covered benefit of this policy. The following list may not be all-inclusive and is subject to change based on research and medical literature, or at the discretion of Molina Healthcare:

- MPS Types II, III, IV A/B, VII, and IX
- Concurrent use of laronidase (Aldurazyme); galsulfase (Naglazyme) or other enzyme replacement therapies in conjunction with each other

### SUMMARY OF EVIDENCE

- The mucopolysaccharidoses (MPS) are inherited lysosomal storage disorders that are characterized by an abnormal build-up of mucopolysaccharides (a.k.a. glycosaminoglycans; GAGs). GAGs build-up due to a deficiency of the enzymes necessary to break down GAGs within the lysosome. The accumulation of partially degraded GAG fragments in the lysosomes, results in permanent cellular dysfunction and clinical abnormalities which may manifest in various parts of the body. There are seven types of mucopolysaccharidoses (MPS) disorders which are differentiated by their clinical features and age of presentation and biochemically by their associated enzyme deficiency. MPS Type I has three subtypes, followed by MPS Types II, III, IV, VI, VII, and IX. MPS V (formerly Scheie syndrome) and MPS VIII are no longer acknowledged.
  - MPS I is an autosomal recessive disorder which is caused by mutations in the alpha-L-iduronidase (IDUA) gene. These mutations leads to a deficiency of IDUA, which is required for the degradation of heparan sulfate and dermatan sulfate and thus the storage of these GAGs in the lysosome. There are three subtypes (i.e. attenuated phenotypes) of the disease which represent the spectrum of severity: Hurler (most severe), Hurler-Scheie (intermediate), and Scheie (least severe). Each subtype includes varying degrees of spinal abnormalities, joint stiffness, cardiac and respiratory abnormalities and characteristic facial features. The major difference between the three subtypes are the typical age at diagnosis and lifespan for each subtype. Patients with Hurler syndrome typically present during infancy and do not have a lifespan beyond five to ten years; while patients with Scheie syndrome typically present with symptoms during their late teen years and may have a normal life expectancy (however many of these patients die during their middle decades).
  - MPS VI or Maroteaux-Lamy Syndrome is an autosomal recessive disorder caused by mutations in the N-acetyl-galactosamine-4-sulfatase (ARSB) gene. This enzyme deficiency results in the accumulation of dermatan sulfate and chondroitin 4-sulfate GAGs. Severity of symptoms depends on the degree of the enzyme deficiency, however, symptoms include coarse facial features, corneal clouding, joint abnormalities, skeletal malformations, hepatosplenomegaly, and hearing loss.

- Diagnosis of MPS is based on clinical suspicion constituting grounds for performing an evaluation of urinary GAG concentration. Excess concentrations of specific GAGs (e.g. heparan sulfate, dermatan, chondroitin 4-sulfate), helps define which enzymes (e.g. IDUA, ARSB) should be tested initially. A diagnosis of MPS is confirmed via enzyme assay, documenting the deficient enzyme activity that is specific to each type of MPS.

- To date, there is no known cure for MPS I and VI. The current standard of care is medical and surgical management of the involved systems with the goal of palliation, prevention, and slowing of the progression of complications. At the time of this writing, laronidase and galsulfase, are the only biologically-directed therapies available to treat the primary metabolic block of each respective MPS. Other than symptom management there are no alternatives for this disorder.
Treatment and monitoring goals for an individual patient should be established by a multidisciplinary team and should be dependent on where in the natural history of disease the patient is determined to best fit. Specific treatment goals should be based on disease/functional stabilization and/or prevention of symptom onset.

Hurler Syndrome (MPS I) occurs in approximately 1 in 100,000 newborns. Scheie Syndrome (MPS I) is less common and occurs in about 1 in 500,000 newborns.\(^8\)

The exact incidence of MPS VI is unknown, although it is estimated to occur in 1 in 250,000 to 600,000 newborns.\(^9\)

**Pharmacologic Agents/Conventional Therapy**

Treatment of MPS consists of a primary mechanism of action for therapy involving the replacement of the missing or defective GAG with a genetically engineered enzyme (ERT). The primary goals of therapy are to improve pulmonary symptoms and progression of symptoms and enhancement in the overall health and quality of life.

**Enzyme Replacement Therapy (ERT):** ERTs act by supplementing the enzyme deficiency depending on the MPS subtype, in order to assist the breakdown of the GAGs within the lysosome.

- The two ERT therapies currently available are **Aldurazyme (laronidase)** and **Naglazyme (galsulfase)**. ERT is currently the standard of care for treatment and is used in symptomatic patients.
  - Infants with MPS I: Hematopoietic stem cell transplantation (HSCT) is considered the standard of care in infants with severe MPS I – Hurler subtype. ERT is recommended for either severe patients prior to transplantation or for attenuated MPS I patients.
  - The goal of ERT is to provide the appropriate amount of enzyme to allow excess material to be degraded. Thus, enzyme replacement therapy works by supplementing or replacing the MPS patient’s missing or deficient enzyme. Because ERT does not cross the blood brain barrier, it does not address conditions or symptoms related to the central nervous system.

**Enzyme Replacement Therapy (ERT): Aldurazyme (laronidase), Naglazyme (galsulfase)**

**Aldurazyme (laronidase)**\(^{a,1,2,3}\) was FDA-approved in April 2003 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. It is a polymorphic variant of the human enzyme, alpha-L-iduronidase (IDUA) gene that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. IDUA is a lysosomal hydrolase that catalyzes the hydrolysis of terminal IDUA residues of dermatan sulfate and heparan sulfate.

*Studies 1 and 2: Clinical Studies in Patients 6 Years and Older*

In a randomized, double-blind, placebo-controlled trial, the safety and efficacy of Aldurazyme was evaluated for use in 45 patients with MPS I, including 1 patient with Hurler subtype, 37 patients with Hurler-Scheie subtype, and 7 patients with Scheie subtype of MPS I. Patients were randomly selected to receive Aldurazyme 0.58 mg/kg of body weight (n=22) once weekly or placebo (n=23) once weekly for 26 weeks. The primary efficacy end points compared the median change from baseline to week 26 between groups in % predicted FVC and in 6-minute walk test (6-MWT) distance. All patients baseline percent predicted forced vital capacity (% predicted FVC) was less than or equal to 77%.

Inclusion criteria comprised of patients that had a documented diagnosis of MPS I confirmed by measurable clinical signs and symptoms of MPS I and a fibroblast or leukocyte IDUA enzyme activity level of less than 10% of the lower limit of the normal range of the measuring laboratory. Female patients of childbearing potential with a negative pregnancy test at baseline (all female patients of child bearing age and sexually mature male patients were advised to use a medically accepted method of contraception throughout the study). Patients were required to be able to stand independently for 6 minutes and walk a minimum of 5 meters within 6 minutes. Patients were also required to be capable of performing the FVC spirometry. The patients had a baseline FVC value that was less than or equal to 80% of the patient’s predicted normal FVC value (Polgar predicted values for children 5 to 7 years old and Hankinson predicted values for ages 8 and up).
Patients that had undergone tracheostomy, previously undergone a bone marrow transplant, were pregnant or lactating, used an investigational drug with 30 days prior to study enrollment, had a medical condition, serious intercurrent illness, or other extenuating circumstance that could have significantly interfered with study compliance including all prescribing evaluations and follow-up activities, or a known hypersensitivity to recombinant human-Alpha-L-Iduronidase (rhIDU) or to components of the active or placebo test solutions were excluded from the study.

Results: Both groups had similar baseline characteristics. After 26 weeks, patients receiving Aldurazyme compared with placebo showed mean improvements of 5.6% predicted FVC (median 3.0; p=0.009) and 38.1 meters in 6-MWT distance (median 38.5; p=0.066; p=0.039, ANCOVA). The use of Aldurazyme also significantly reduced hepatomegaly and urinary GAG excretion. In the more severely affected patients there was improvement in apnea/hypopnea and shoulder flexion.

Conclusions: Aldurazyme improves respiratory function and physical capacity, reduces GAG storage, and has a favorable safety profile in patients with MPS I. Some of the limitations of the study are the limited sample size which can be attributed to the rarity of the disease and the FVC calculations are less reliable for patients whose height is below the third percentile for the general population.

The second study was an open-label, uncontrolled extension study, the safety and efficacy of Aldurazyme was studied for use in the same 45 patients with MPI I. The primary outcome measures were an increase in % predicted FVC and a longer distance walked during the 6-MWT. All patients (previous placebo and treatment arms) received Aldurazyme 0.58 mg/kg weekly for an additional 182 weeks.

Exclusion criteria included patients who are pregnant or lactating, received an investigational drug within 30 days prior to study enrollment, and patients with a medical condition, serious concurrent illness, or other extenuating circumstances that may significantly interfere with study compliance including all prescribed evaluations and follow-up activities.

Results: Both groups had similar baseline characteristics as reported in the double-blind study. After 208 weeks, 40 patients (89% enrolled) completed the trial and were considered adherent by receiving at least 80% of their scheduled infusions. The % predicted FVC remained stable. The 6-MWT distance increased 31.7±10.2 meters in the first 2 years, with a final gain of 17.1±16.8 meters. Aldurazyme infusions were generally well tolerated except in 1 patient who experienced anaphylaxis. Infusion-associated reactions occurred in 53% of patients, were mostly mild, easily managed, and decreased markedly after 6 months. One patient died as a result of an upper respiratory infection unrelated to treatment. Laronidase-antibodies developed in 93% of patients, while 29% of patients were seronegative at their last assessment.

Conclusions: This study exhibits the long-term safety and clinical efficacy of Aldurazyme in attenuated MPS I patients. The study also highlights the magnitude and chronology of treatment effects and supports the idea that prompt diagnosis and early intervention maximizes treatment outcomes. Some of the limitations of the study are the limited sample size which can be attributed to the rarity of the disease and the FVC calculations are less reliable for patients whose height is below the third percentile for the general population.

Study 3: Clinical Studies in Patients 6 Years and Younger
In this prospective, open-label study, 20 patients with MPS I that were less than 5 years old (16 with Hurler subtype, and 4 with Hurler-Scheie subtype) received 0.58 mg/kg weekly for 52 weeks. Four patients underwent a dosage increase to 1.16 mg/kg weekly after completing the first 25 weeks at 0.58 mg/kg weekly because the patient’s urinary GAG levels were > 200 µg/mg creatinine at week 22.

Patients with a diagnosis of MPS I based on genotyping that were less than 5 years of age at the time of enrollment and had confirmed IDUA deficiency with a fibroblast or leukocyte IDUA enzyme activity of less than 10% of the lower limit of the normal range or below the detection range of the measuring laboratory were included in the study.
Patients under consideration or had undergone HSCT, had acute hydrocephalus at the time of enrollment, had clinically significant organic disease (with the exception of symptoms relating to MPS I) including: cardiovascular, hepatic, pulmonary, neurologic, or renal disease, other serious concurrent illness, received any investigational product within 30 days prior to trial enrollment or had a severe hypersensitivity to Aldurazyme were excluded from the study.

Results: Overall, Aldurazyme was well tolerated at both dosages; however, two patients did not complete the study at the lower dosage. One patient died and one patient discontinued due to adverse effects. The median age of the patients was 2.9 years. There were 12 male patients and only 8 female patients enrolled. 94% of patients experienced improved clinical status at week 52. Mean urinary GAG levels declined by 50% at week 13 and was sustained thereafter. A more robust decrease in urinary GAGs was observed in patients with low antibody levels and those who were receiving 1.16 mg/kg weekly. The liver edge decreased by 69.5% on palpation in those patients with a palpable liver at the time the study started. The proportion of patients with left ventricular hypertrophy decreased from 53% to 17% at week 52. A global assessment of the sleep studies revealed improvement or stabilization in 67% of the patients. The apnea/hypopnea index decreased by 5.8 events per hour. The younger patients with Hurler syndrome (< 2.5 years) and all 4 patients with Hurler-Scheie subtype exhibited normal mental development trajectories during the treatment period.

Conclusions: Aldurazyme provides clinical benefit in patients who have severe MPS I and are less than 5 years old. ERT is not curative and may not improve all affected organs and systems in individuals when irreversible damage has developed. Limitations of the study were the lack of control group and the limited sample size which can be attributed to the rarity of the disease.

Naglazyme (galsulfase)\(^{6,7}\) was FDA-approved in May 2005 for MPS VI (Maroteaux-Lamy syndrome). It has been shown to improve walking and stair-climbing capacity. It is a formulation of galsulfase, which is a purified human enzyme that is produced by recombinant DNA technology in a Chinese hamster ovary line. Galsulfase (N-acetylgalactosamine 4-sulfatase; ARSB) is a lysosomal enzyme that catalyzes the cleavage of the sulfate ester from terminal-ARSB residues of GAG, chondroitin 4-sulfate and dermatan sulfate.

A total of 56 patients with MPS VI, ages 5 years to 29 years, were enrolled in four clinical studies. The majority of patients had severe manifestations of the disease as evidenced by poor performance on a test of physical endurance.

In the randomized, double-blind, multicenter, placebo-controlled clinical trial, 38 patients with MPS VI received 1 mg/kg Naglazyme or placebo, once-weekly for 24 weeks. The patients’ ages ranged from 5 to 29 years. Enrollment was restricted to patients with a 12-minute walk distance of 5 to 400 meters. All patients were treated with antihistamines prior to each infusion.

The Naglazyme-treated group showed greater mean increases in the distance walked in 12 minutes (12-minute walk test, 12-MWT) and in the rate of stair climbing in a 3-minute stair climb test, compared with the placebo group. (p=0.025 and p=0.053, respectively)\(^6\)

Following the 24-week placebo-controlled study period, 38 patients received open-label Naglazyme for 72 weeks. Among the 19 patients who were initially randomized to Naglazyme and who continued to receive treatment for 72 weeks (total of 96 weeks), increases in the 12-MWT distance and in the rate of stair climbing were observed compared to the start of the open-label period (mean ± SD change): 72±116 meters and 5.6±10.6 stairs/minute, respectively. Among the 19 patients who were randomized initially to placebo for 24 weeks, and then crossed over to treatment with Naglazyme, the increases after 72 weeks of Naglazyme treatment compared to the start of the open-label period, (mean ± SD change): were 118±127 meters and 11.1±10.0 stairs/minute, for the 12-MWT and the rate of stair climbing, respectively.

Bioactivity was evaluated with urinary GAG concentration. Overall, 95% of patients showed at least a 50% reduction in urinary GAG levels after 72 weeks of treatment with Naglazyme. No patient receiving Naglazyme reached the normal range for urinary GAG levels.
In an additional open-label extension study, patients receiving Naglazyme showed maintenance of initial improvement in endurance for approximately 240 weeks.

Summary of Evidence

- **Primary/Secondary Objectives:**
  - **Aldurazyme:** The primary objective of the studies was to evaluate the impact of Aldurazyme treatment upon endurance in patients with MPS I, as measured by the change from baseline in the number of meters walked in six minutes [6-Minute Walk Test; 6-MWT] at week 26 as compared with placebo. The other primary endpoint was percent predicted Forced Vital Capacity (% predicted FVC) which is a measurement obtained via a pulmonary function test. It measures the volume of air that can be maximally forcefully exhaled and therefore contains the Forced Expiratory Volume-1 (FEV1) within it. Secondary efficacy endpoints were the overall change in Apnea/Hypopnea Index (number of absent and shallow breaths per hour of sleep), liver volume (as measured by MRI), Child Health Assessment Questionnaire/Health Assessment Questionnaire (CHAQ/HAQ) Disability Index Score (patient questionnaire that measures the degree of disability), active joint Range of Motion (ROM) (measures shoulder flexion ability to maximally raise one’s arm overhead without assistance), and urinary glycosaminoglycans (GAGs) (measures concentration of GAG relative to creatinine in urine).
  - **Naglazyme:** The primary objective of the studies was to evaluate the impact of Naglazyme treatment upon endurance in patients with MPS VI, as measured by the change from baseline in the number of meters walked in 12 minutes [12-Minute Walk Test; 12-MWT] at week 24 as compared with placebo. Secondary efficacy endpoints were the rate of stair climbing in three minutes [3-minute stair climb test; 3-MSCT] and urinary glycosaminoglycans (GAGs).

- **Results:**
  - **Aldurazyme:** Both groups had similar baseline characteristics. After 26 weeks, patients receiving Aldurazyme compared with placebo showed mean improvements of 5.6% predicted FVC (median 3.0; p=0.009) and 38.1 meters in 6-MWT distance (median 38.5; p=0.066; p=0.039, ANCOVA). The use of Aldurazyme also significantly reduced hepatomegaly and urinary GAG excretion. In the more severely affected patients there was improvement in apnea/hypopnea and shoulder flexion. During the extension study, both groups had similar baseline characteristics as reported in the double-blind study. After 208 weeks, 40 patients (89% enrolled) completed the trial and were considered adherent by receiving at least 80% of their scheduled infusions. The % predicted FVC remained stable. The 6-MWT distance increased 31.7±10.2 meters in the first 2 years, with a final gain of 17.1±16.8 meters. Aldurazyme infusions were generally well tolerated except in 1 patient who experienced anaphylaxis. Infusion-associated reactions occurred in 53% of patients, were mostly mild, easily managed, and decreased markedly after 6 months. One patient died as a result of an upper respiratory infection unrelated to treatment. Laronidase-antibodies developed in 93% of patients, while 29% of patients were seronegative at their last assessment.
  - **Naglazyme:** The mean distance walked in the 12-MWT and the mean number of stairs climbed per minute were higher in patients treated with galsulfase than in the placebo group after 24 weeks. Sustained improvements were seen for the entire study period. Endurance improved in all patients after starting ERT and was sustained for at least 2 to 5 years in most patients as supported by the open-label extension trial. Urinary GAG levels decreased significantly more in patients treated with galsulfase than in those treated only with placebo. In the open-label phase 3 extension study, urinary GAG levels remained on average 71% lower than baseline for patients who were switched from placebo at 24 weeks and treated with galsulfase up to week 96, compared to 72% lower than baseline for patients on galsulfase throughout the study to the same end-point. Joint pain and stiffness did not significantly differ between the placebo and galsulfase treatment groups.
Position:

- In consideration of the unmet need for treatment, the benefits of ERT for patients with MPS I and VI outweigh the known risks. Prior to the approval of this ERT for the treatment for MPS I and VI, the only alternatives were palliative or supportive care, which does not treat the underlying cause of the disease so it continues to progress.

Guidelines for Treatment (2010, 2011)<sup>A,B</sup>

These guidelines were developed by a multidisciplinary specialists for the diagnosis, treatment, and monitoring of patients with MPS. MPS requires lifelong, multidisciplinary, disease-specific care by a dedicated team of specialists. The guidelines recommend that a metabolic specialists coordinate that care to identify the early signs of organ damage and ensure optimal patient outcomes. Due to the progressive nature of MPS, the Guidelines urge early initiation of treatment with ERT.

Some recommendations from the Guideline includes:<sup>A,B</sup>

- Multidisciplinary management coordinated by a metabolic specialist.
- Ongoing evaluations by specialists to determine disease progression, surgical risks, and interventions.
- Initiating ERT to address the underlying enzyme deficiency.

**DEFINITIONS**

**Mucopolysaccharidosis I (MPS I):** A progressive, multisystemic, autosomal recessive disorder in which a lysosomal enzyme, alpha-L-iduronidase (IDUA), is not functioning properly. Has three subtypes Hurler, Hurler-Scheie, and Scheie which indicate the degree of enzyme deficiency.

**Hurler Syndrome:** A subtype of MPS I, the most severe form of MPS I.

**Hurler-Scheie Syndrome:** A subtype of MPS I, the intermediate form of MPS I.

**Scheie Syndrome:** A subtype of MPS I, the least severe form of MPS I.

**Maroteaux-Lamy Syndrome:** A progressive, multisystemic, autosomal recessive disorder in which a lysosomal enzyme, N-acetyl-galactosamine-4-sulfatase (ARSB), is not functioning properly.

**Mucopolysaccharidosis (MPS) disorders:** A group of disorders in which a lysosomal enzyme needed for the breakdown of GAGs is deficient or absent. Morquio A can be classified as an MPS disorder.

**Mucopolysaccharidosis VI (MPS VI):** See Maroteaux-Lamy syndrome.

**Six-minute walk test (6-MWT):** Six-minute walk test (6-MWT) measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway.

The 6-MWT is validated as a measure of endurance in the clinical setting, assessing the functional reserves of the cardiovascular, pulmonary, or musculoskeletal systems. The 6-MWT was the primary efficacy endpoint in the Aldurazyme pivotal phase 3 trial.

**Twelve-minute walk test (12-MWT):** Twelve-minute walk test (12-MWT) measures the distance an individual is able to walk over a total of twelve minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in twelve minutes. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway.
The 12-MWT is validated as a measure of endurance in the clinical setting, assessing the functional reserves of the cardiovascular, pulmonary, or musculoskeletal systems. The 12-MWT was the primary efficacy endpoint in the Nagalzyme pivotal phase 3 trial.

**Three-minute stair climb test (3-MSCT):** The number of stairs that can be climbed by a test subject in 3 minutes. Like the 6MWT, this test assesses the functional capacity/status of patients. The 3-MSCT was a secondary efficacy endpoint in the Naglazyme pivotal phase 3 trial.

**Urinary Glycosaminoglycans (GAGs):** A clinical measure of GAGs in the urine. Urinary GAGs level was a secondary efficacy endpoint in the Aldurazyme and Naglazyme pivotal phase 3 trials.

### APPENDIX

#### Appendix A: Clinical Manifestations and Medical Issues of MPS

<table>
<thead>
<tr>
<th>Common Clinical Manifestations and Medical Issues</th>
<th>MPS Types</th>
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<tbody>
<tr>
<td>Musculoskeletal manifestations: deformities of the spine, thoracic cage, hips, knees, skull, and/or hands, short stature, joint abnormalities, joint pain, joint restriction/hypermobility</td>
<td>All types</td>
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<tr>
<td>Spinal cord issues: spinal instability, cord compression, myelopathy</td>
<td>I, II, IV, VI</td>
</tr>
<tr>
<td>Ear, nose, throat manifestations, speech problems</td>
<td>All types</td>
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<tr>
<td>Respiratory manifestations: upper and/or lower airway obstruction, restrictive disease, sleep-disordered breathing</td>
<td>All types</td>
</tr>
<tr>
<td>Cardiac manifestations: aortic and mitral valve insufficiency / stenosis, left ventricular hypertrophy, abnormal diastolic function, pulmonary hypertension</td>
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<tr>
<td>Ocular manifestations: corneal clouding, refractive errors, glaucoma, papilledema</td>
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<tr>
<td>Cognitive decline, loss of motor function, behavioral problems, epilepsy</td>
<td>I (mainly Hurler, Hurler-Scheie), severe II, III, VII</td>
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<tr>
<td>Abdominal manifestations: hepatomegaly, splenomegaly, umbilical/inguinal hernias, chronic diarrhea</td>
<td>All types</td>
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<tr>
<td>Papular pearly rash across the scapulae, dermal melanocytosis, hirsutism</td>
<td>II, III, VI</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>I, II, VI</td>
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<tr>
<td>Dental abnormalities: widely spaced and/or abnormal shaped teeth, weak enamel, gingival hyperplasia</td>
<td>I, II, IV, VI, VII</td>
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<td>Frequent surgery, diagnostic procedures requiring anesthesia</td>
<td>All types</td>
</tr>
<tr>
<td>Follow-up of late effects/complications related to hematopoietic stem cell transplantation</td>
<td>Mainly MPS I-Hurler</td>
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<tr>
<td>Reduced quality of life, depressed feelings</td>
<td>All types</td>
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<td>Coordination of care</td>
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#### CODING INFORMATION:

THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

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**REFERENCES**

**Package Insert, FDA, Drug Compendia**


**Clinical Trials, Definitions, Peer-Reviewed Publications**


**Government Agencies, Professional Societies, and Other Authoritative Publications**