Enzyme Replacement Therapy for Mucopolysaccharidosis I & VI  
[Aldurazyme (laronidase), Naglazyme (galsulfase)]  
Policy Number: C9997-A

CRITERIA EFFECTIVE DATES:

<table>
<thead>
<tr>
<th>ORIGINAL EFFECTIVE DATE</th>
<th>LAST REVIEWED DATE</th>
<th>NEXT REVIEW DATE</th>
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<tr>
<th>J CODE</th>
<th>TYPE OF CRITERIA</th>
<th>LAST P&amp;T APPROVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1458- galsulfase, 1 mg</td>
<td>RxPA</td>
<td>Q2 2019</td>
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<tr>
<td>J1931- laronidase, 0.1 mg</td>
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PRODUCTS AFFECTED:  
Aldurazyme (laronidase), Naglazyme (galsulfase)

DRUG CLASS:  
Mucopolysaccharidosis I (MPS I) - Agents

ROUTE OF ADMINISTRATION:  
Intravenous

PLACE OF SERVICE:  
Specialty Pharmacy or Buy and Bill

AVAILABLE DOSAGE FORMS:  
Aldurazyme SOLN 2.9MG/5ML, Naglazyme SOLN 1MG/ML

FDA-APPROVED USES:  
Naglazyme (galsulfase): indicated for Mucopolysaccharidosis VI (MPS VI); Maroteaux-Lamy syndrome. Naglazyme has been shown to improve walking and stair-climbing capacity.

Aldurazyme (laronidase): 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.

E76.01 Hurler’s syndrome
E76.02 Hurler-Scheie syndrome
E76.03 Scheie’s syndrome
E76.29 Other mucopolysaccharidoses

COMPENDIAL APPROVED OFF-LABEL USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: Mucopolysaccharidosis I (MPS I), Mucopolysaccharidosis VI (MPS VI)

REQUIRED MEDICAL INFORMATION:  
A. MUCOPOLYSACCHARIDOSIS:  

1. Diagnosis of Mucopolysaccharidosis I (MPS I) or Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy Syndrome) confirmed by: Documented reduced fibroblast or leukocyte IDUA or ARSB enzyme activity OR Molecular genetic testing of IDUA or ARSB
Prior Authorization Criteria

2. Member has 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 challenges AND

3. Prescribed as monotherapy: NOT to be used concurrently with other medications for Mucopolysaccharidosis AND

4. Documentation of the following: Member's weight dated within 1 month of the prior authorization request, Baseline 6-minute walk test (6-MWT) indicating the member walked at least 30 meters in six (6) minutes AND Percent predicted Forced Vital Capacity (% Predicted FVC) (Aldurazyme requests only)

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.

DURATION OF APPROVAL: Initial authorization: 12 months, Continuation of therapy: 12 months

QUANTITY:

*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
Only a 1-month supply may be dispensed at a time

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified geneticist, pediatric metabolic specialist, hematologist or physician experienced in the management of mucopolysaccharidoses (MPS).
Consultation notes must be submitted for initial request AND at least once annually for continuation of treatment requests.

AGE RESTRICTIONS:
*Aldurazyme (laronidase)*: 6 months of age to 65 years of age
*Naglazyme (galsulfase)*: 5 years of age to 29 years of age

GENDER:
Male and female

CONTINUATION OF THERAPY:

A. MUCOPOLYSACCHARIDOSIS:
1. Member currently meets ALL initial coverage criteria
   AND
2. Requested ERT remains for use as monotherapy: NOT to be used concurrently with other MPS drug therapy.
   AND
Prior Authorization Criteria

3. 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: Adherent to the prescribed medication regimen, Tolerance to therapy AND No severe adverse reactions or drug toxicity AND

4. 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 OR Percent predicted Forced Vital Capacity (% Predicted FVC) [Aldurazyme requests only]

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION: All other uses of laronidase (Aldurazyme); galsulfase (Naglazyme) are considered experimental/investigational and therefore, will follow Molina’s Off-Label policy. Exclusions include: MPS Types II, III, IV B, VII, and IX.

OTHER SPECIAL CONSIDERATIONS:

BACKGROUND:
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.

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.

APPENDIX:

<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>
</tr>
<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>
</tr>
<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>
<td>All types</td>
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Prior Authorization Criteria

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Types</th>
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<tbody>
<tr>
<td>Ocular manifestations: corneal clouding, refractive errors, glaucoma, papilledema</td>
<td>All types</td>
</tr>
<tr>
<td>Cognitive decline, loss of motor function, behavioral problems, epilepsy</td>
<td>I (mainly Hurler, Hurler-Scheie), severe II, III, VII</td>
</tr>
<tr>
<td>Abdominal manifestations: hepatomegaly, splenomegaly, umbilical/inguinal hernias, chronic diarrhea</td>
<td>All types</td>
</tr>
<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>
</tr>
<tr>
<td>Dental abnormalities: widely spaced and/or abnormal shaped teeth, weak enamel, gingival hyperplasia</td>
<td>I, II, IV, VI, VII</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Reduced quality of life, depressed feelings</td>
<td>All types</td>
</tr>
<tr>
<td>Coordination of care</td>
<td>All types</td>
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REFERENCES:


