Original Effective Date: 11/01/2016
Current Effective Date: 09/20/2023
Last P&T Approval/Version: 07/26/2023
Next Review Due By: 7/2024
Policy Number: C9997-A

Enzyme Replacement Therapy for Lysosomal Storage Disorders (MPS I, VI) [Aldurazyme, Naglazyme]

PRODUCTS AFFECTED

Aldurazyme (laronidase), Naglazyme (galsulfase)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Mucopolysaccharidosis (MPS)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. MUCOPOLYSACCHARIDOSIS (MPS):
   1. (a) Documented diagnosis of Mucopolysaccharidosis I (MPS I) or Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy Syndrome) confirmed by reduced fibroblast or leukocyte IDUA or

ARSB enzyme activity OR Molecular genetic testing of IDUA or ARSB [DOCUMENTATION REQUIRED]
AND

2. Documented baseline values for all of the following [DOCUMENTATION REQUIRED]:
   i. Urinary glycosaminoglycan (GAG) levels
   AND
   ii. Members 6 years of age or older (one of the following): 6-minute walk test (6-MWT) and/or percent predicted Forced Vital Capacity (% Predicted FVC)
   OR
   Members less than 6 years (one of the following): upper airway obstruction during sleep, cardiac status, growth velocity, mental development, FVC, hepatosplenomegaly, and/or 6-minute walk test

AND

3. Documentation that member has at least ONE 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
4. Prescriber attests that the requested ERT will be used as monotherapy: NOT to be used concurrently with other medications for Mucopolysaccharidosis

CONTINUATION OF THERAPY:

A. MUCOPOLYSACCHARIDOSIS (MPS):

1. Prescriber attests to or clinical reviewer has found that requested ERT remains for use as monotherapy: NOT to be used concurrently with other MPS drug therapy
AND
2. Documentation of positive response or disease stability to therapy as compared to baseline (prior to therapy) as evidenced by:
   a) Decreased urinary glycosaminoglycan (GAG) levels
   AND
   b) Members 6 years of age or older (one of the following): 6-minute walk test (6- MWT) and/or Percent predicted Forced Vital Capacity (% Predicted FVC)
   OR
   Members less than 6 years (one of the following): decreased hepatosplenomegaly, improvement in upper airway obstruction during sleep, cardiac status, growth velocity, mental development, FVC, and/or 6-minute walk test

AND

3. Prescriber attests to or clinical reviewer has found no evidence of severe adverse events or unacceptable toxicity from the drug [e.g., hypersensitivity reactions, anaphylaxis, severe type III immune-mediated reactions (e.g., membranous glomerulonephritis) have occurred]

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified geneticist, metabolic specialist, pediatric neurologist, pediatric developmentalist, endocrinologist, or a physician who specializes in the treatment of lysosomal storage disorders or physician experienced in the management of mucopolysaccharidoses (MPS). [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

Aldurazyme (laronidase): 6 months of age to 65 years of age
Naglazyme (galsulfase): 3 months of age to 29 years of age

QUANTITY:
Aldurazyme (laronidase): 0.58 mg/kg of body weight as an IV infusion once weekly
Naglazyme (galsulfase): 1 mg/kg of body weight as an IV infusion once weekly

Maximum Quantity Limits – Only a 1-month supply may be dispensed at a time.

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Aldurazyme and Naglazyme. For information on site of care, see:
Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous

DRUG CLASS:
Mucopolysaccharidosis I (MPS I) – Agents, Mucopolysaccharidosis VI (MPS VI) - Agents

FDA-APPROVED USES:
Aldurazyme (laronidase) is indicated for adult and pediatric patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms.
Limitations of Use: The risks and benefits of treating mildly affected patients with the Scheie form have not been established. Aldurazyme has not been evaluated for effects on the central nervous system manifestations of the disorder.

Naglazyme (galsulfase) is indicated for patients with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). Naglazyme has been shown to improve walking and stair-climbing capacity.

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

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
- Forced vital capacity (FVC): In the clinical trials of Aldurazyme in patients ≥ 6 years of age, the mean increase in percent of predicted forced vital capacity (FVC) observed corresponded to a 10% relative improvement over the baseline FVC, which is considered by the American Thoracic Society to be a clinically significant change and not due to week-to-week variability.
- 6-minute walk test (6MWT): In the clinical trials of Aldurazyme in patients ≥ 6 years of age, patients treated with Aldurazyme demonstrated a 19.7- meter mean increase in the 6-minute walk test (6MWT) after 26 weeks.

BACKGROUND AND OTHER 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 (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.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of laronidase (Aldurazyme) and galsulfase (Naglazyme) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Aldurazyme (laronidase) and Naglazyme (galsulfase) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:
Boxed Warning **(**Aldurazyme): Risk of anaphylaxis-- Life-threatening anaphylactic reactions have been observed in some patients during laronidase infusions. Therefore, ensure that appropriate medical support is readily available when laronidase is administered. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise because of infusion reactions and may require additional monitoring.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J1458	Injection, Galsulfase, 1mg
J1931	Injection, Laronidase, 0.1mg

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

REFERENCES

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15. Harmatz, P. R., Garcia, P., Guffon, N., Randolph, L. M., Shediac, R., Braunlin, E., Lachman, R. S., & Decker, C. (2014). Galsulfase (Naglazyme®) therapy in infants with mucopolysaccharidosis VI. Journal of inherited metabolic disease, 37(2), 277–287. https://doi.org/10.1007/s10545-013-9654-7

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Prescriber Requirements Quantity FDA-Approved Uses	Q3 2023
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Prescriber Requirements Contraindications/Exclusions/Discontinuation References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file