

## Medical Policy Bulletin

Title:

Enzyme Replacement Therapy for Mucopolysaccharidosis (e.g., Aldurazyme<sup>®</sup>, Elaprase<sup>®</sup>, Vimizim<sup>®</sup>, Naglazyme<sup>®</sup>, Mepsevii<sup>™</sup>, etc.)

Policy #:

MA08.034d

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

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## Policy

**Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.**

Laronidase (Aldurazyme<sup>®</sup>) is considered medically necessary and, therefore, covered for use in individuals six months or older, when all of the following criteria are met, including dosing and frequency:

- Diagnoses of Hurler or Hurler-Scheie forms of mucopolysaccharidosis I (MPS I) or Scheie form of MPS I with moderate-to-severe symptoms, confirmed by one of the following:
  - Demonstrated deficiency of alpha-L-iduronidase (for example, in peripheral blood leukocytes, plasma, or cultured fibroblasts)
  - Confirmation of biallelic pathogenic variant(s) in the IDUA gene
- Dosing and frequency: 0.58 mg per kg of body weight administered once weekly as an intravenous infusion

Idursulfase (Elaprase<sup>®</sup>) is considered medically necessary and, therefore, covered for use in individuals at least 16 months of age when all of the following criteria are met, including dosing and frequency:

- Diagnosis of Hunter syndrome (Mucopolysaccharidosis II [MPS II]) confirmed by one of the following:
  - Deficiency of iduronidate 2-sulfatase in leukocytes, fibroblasts, or plasma and documentation of normal enzymatic activity of at least one other sulfatase in the same tissue type
  - Confirmation of a hemizygous pathogenic variant(s) in the IDS gene
- Dosing and frequency: 0.5 mg per kg of body weight administered once weekly as an intravenous infusion

Elosulfase alfa (Vimizim<sup>®</sup>) is considered medically necessary and, therefore, covered for use in individuals at least five years of age, when all of the following criteria are met, including dosing and frequency:

- Diagnosis of Mucopolysaccharidosis Type IVA (MPS IVA), also called Morquio A syndrome, has been confirmed by one of the following:
  - Deficiency of N-acetylgalactosamine-6-sulphatase (GALNS) in cultured fibroblasts or leukocytes
  - Confirmation of biallelic pathogenic variant(s) in the GALNS gene
- Dosing and frequency: 2 mg per kg given intravenously once every week

Galsulfase (Naglazyme®) is considered medically necessary and, therefore, covered for use in individuals at least five years of age when all of the following criteria are met, including dosing and frequency:

- Diagnosis of Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome) has been confirmed by one of the following:
  - Deficiency of N-acetylgalactosamine 4-sulfatase [ARSB] in leukocytes, fibroblasts, and dried blood spots
  - Confirmation of biallelic pathogenic variants in the ARSB gene
- Dosing and frequency: 1 mg/kg of body weight, administered once weekly as an intravenous infusion

Vestronidase alfa-vjbc (Mepsevii™) is considered medically necessary and, therefore, covered for use in infants at least five months of age, children, and adult individuals, when all of the following are met, including dosing and frequency:

- Diagnosis of mucopolysaccharidosis VII (MPS VII, Sly Syndrome) has been confirmed by one of the following:
  - Deficiency of beta-glucuronidase in peripheral blood leukocytes or cultured fibroblasts
  - Genetic testing confirming pathogenic variant(s) in the GUSB gene
- Dosing and frequency: 4 mg/kg administered by intravenous infusion every two weeks

## **EXPERIMENTAL/INVESTIGATIONAL**

All other uses of enzyme replacement therapy for mucopolysaccharidosis (e.g., Aldurazyme®, Elaprased®, Vimizim®, Naglazyme®, Mepsevii™, etc.) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

## **DOSING AND FREQUENCY REQUIREMENTS**

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of laronidase (Aldurazyme®), idursulfase (Elaprased®), elosulfase alfa (Vimizim®), galsulfase (Naglazyme®), vestronidase alfa-vjbc (Mepsevii™). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of laronidase (Aldurazyme®), idursulfase (Elaprased®), elosulfase alfa (Vimizim®), galsulfase (Naglazyme®), vestronidase alfa-vjbc (Mepsevii™) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for laronidase (Aldurazyme®), idursulfase (Elaprased®), elosulfase alfa (Vimizim®), galsulfase (Naglazyme®), vestronidase alfa-vjbc (Mepsevii™).

## **REQUIRED DOCUMENTATION**

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

When coverage of laronidase (Aldurazyme®), idursulfase (Elaprased®), elosulfase alfa (Vimizim®), galsulfase (Naglazyme®), vestronidase alfa-vjbc (Mepsevii™) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed

literature) to the Company that supports this request.

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## Guidelines

There is no Medicare coverage determination addressing this drug; therefore, the Company policy is applicable.

### **BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable Evidence of Coverage, enzyme replacement therapy for mucopolysaccharidosis (e.g., Aldurazyme®, Elaprase®, Vimizim®, Naglazyme®, Mepsevii™, etc.) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria and dosing and frequency requirements listed in this medical policy are met.

Certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when enzyme replacement therapy for mucopolysaccharidosis (e.g., Aldurazyme®, Elaprase®, Vimizim®, Naglazyme®, Mepsevii™, etc.) is covered under a member's medical benefit (Part B benefit). It does not address instances when enzyme replacement therapy for mucopolysaccharidosis (e.g., Aldurazyme®, Elaprase®, Vimizim®, Naglazyme®, Mepsevii™, etc.) is covered under a member's pharmacy benefit (Part D benefit).

### **BLACK BOX WARNINGS**

Refer to the specific manufacturer's prescribing information for any applicable Black Box Warnings.

### **US FOOD AND DRUG ADMINISTRATION (FDA) STATUS**

Laronidase (Aldurazyme®) received initial US Food and Drug Administration (FDA) approval on April 30, 2003.

Idursulfase (Elaprase®) was approved by the FDA on July 2006 for individuals with Hunter syndrome (Mucopolysaccharidosis II).

Elosulfase alfa (Vimizim®) was approved by the FDA on February 2014 for individuals with Mucopolysaccharidosis type IVA (Morquio A syndrome).

Galsulfase (Naglazyme®) was approved by the FDA on May 2005 for individuals with Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome).

Vestronidase alfa-vjvk (Mepsevii™) was approved by the FDA on November 11, 2017 for individuals with mucopolysaccharidosis VII (Sly syndrome).

### **PEDIATRIC USE**

The safety and effectiveness of idursulfase (Elaprase®) in individuals below 16 months of age have not been established. In individuals 16 months to five years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome; however, treatment with idursulfase (Elaprase®) has reduced spleen volume similarly to that of adults and children five years of age and older.

The safety and effectiveness of elosulfase alfa (Vimizim®) and Galsulfase (Naglazyme®) in individuals below five years of age have not been established.

The safety and effectiveness of laronidase (Aldurazyme®) have not been established in individuals below 6 months of age.

The safety and effectiveness of vestronidase alfa-vjvk (Mepsevii™) have not been established in pediatric individuals below five months of age.

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## Description

Mucopolysaccharidosis (MPS) is a group of rare, inherited lysosomal storage disorders that affect glycosaminoglycan (GAG) degradation by the mutation in a lysosomal enzyme essential to GAG breakdown. The mutation can lead to the absence of the enzyme or a mutated inactive enzyme. Glycosaminoglycans are polysaccharides that play important roles in many tissues such as lubricant in joint fluid and the ground substance or bone and cartilage. MPS is clinically characterized by abnormalities in multiple organ systems and reduced life expectancy. There are several types of MPS.

Type	Disorder Name(s)	GAG Storage Material	Deficient Enzyme	Replacement Drug
MPS I	Hurler, Hurler-Scheie, Scheie	Dermatan sulfate, Heparan sulfate	Alpha - L-iduronidase	Laronidase (Aldurazyme®)
MPS II	Hunter	Dermatan sulfate, Heparan sulfate	Iduronate-2-sulfatase	Idursulfase (Elaprase®)
MPS III A-D	Sanfilippo	Heparan sulfate	Heparan N-sulfatase alpha-N-acetylglucosaminidase acetyl-CoA; alpha-glucosaminide acetyltransferase N-acetylglucosamine 6-sulfatase	
MPS IV A,B	Morquio	Keratan sulfate, chondroitin sulfate, Keratan sulfate	Galactose 6-sulfatase Beta-galactosidase	A- Elosulfase alfa (Vimizim®)
MPS V	This is now known as Scheie Syndrome, a subtype of MPS I.			
MPS VI	Maroteaux-Lamy	Dermatan sulfate, Chondroitin sulfate	Arylsulfatase B	Galsulfase (Naglazyme®)
MPS VII	Sly syndrome	Dermatan sulfate, Heparan sulfate, Chondroitin sulfate	Beta- glucuronidase	Vestronidase alfa-vjvk (Mepsevii™)
MPS IX		Hyaluronan	Hyaluronidase	

The failure of GAG degradation causes an accumulation of partially degraded GAG inside lysosomes, which leads to an elevation of GAG fragments in urine, blood, and cerebral spinal fluid and cell, tissue, and organ dysfunction. Replacement of the deficient enzyme with an exogenous enzyme is one option to treat individuals with MPS.

MPS I can be classified into three subtypes, Hurler (severe), Hurler-Scheie, or Scheie (mild) syndrome. Some common symptoms are joint stiffness, corneal clouding, and ear, nose, and throat infections. MPS I is an autosomal recessive disorder caused by a deficiency of alpha-L-iduronidase. This leads to an accumulation of dermatan sulfate and heparan sulfate. Laronidase (Aldurazyme®), a polymorphic variant of the human enzyme alpha-L-iduronidase, was approved by the US Food and Drug Administration (FDA), as an orphan drug (a drug used to treat, prevent, or diagnose a rare disease), for individuals with Hurler and Hurler-Scheie forms of MPS I and for those with the Scheie form who have moderate-to-severe symptoms. The risk and benefits of treating mildly affected patients with the Scheie form have not been established.

MPS II, also known as Hunter Syndrome, is an X-linked disorder caused by a deficiency of iduronate-2-sulfatase leading to the accumulation of heparan sulfate and dermatan sulfate. Some common symptoms are skeletal abnormalities, hepatosplenomegaly, and mental retardation. Early onset (one to two years) is associated with the severe form of MPS II. Idursulfase (Elaprase®) was approved by the FDA as an orphan drug for individuals with MPS II or Hunter Syndrome. Idursulfase (Elaprase®) is a purified form of human iduronate-2-sulfatase.

MPS III, also known as Sanfilippo syndrome, has subtypes A to D. Some common symptoms are progressive intellectual disability and loss of previously acquired skills. This type leads to an accumulation of heparan sulfate. It is primarily a brain disease making enzyme replacement therapy not an option for treatment because the exogenous enzyme is unable to cross the blood-brain barrier.

MPS IV, also known as Morquio syndrome, is a progressive disease with predominant skeletal manifestations, like skeletal abnormalities, loose joints, and underdevelopment of odontoid process. MPS IV has two forms, A and B. MPS IV A is due to galactosamine-6-sulfatase deficiency causing a buildup of keratan sulfate and chondroitin sulfate. MPS IV B is due to beta galactosidase deficiency causing a buildup of keratan sulfate. Of MPS IV, only MPS IV A can be treated with exogenous enzymes. The FDA approved elosulfase alfa (Vimizim®), a purified human enzyme N-acetyl-galactosamine-6-sulfatase, as an orphan drug for MPS IVA.

MPS V is now known as Scheie syndrome, a subtype of MPS I.

MPS VI, also known as Maroteaux-Lamy syndrome, is an autosomal recessive disorder caused by a mutation in arylsulfatase B leading to an accumulation of dermatan sulfate and chondroitin 4-sulfate. Galsulfase (Naglazyme®), purified human enzyme galsulfase, was approved by the FDA in May 2005 to improve walking and stair-climbing capacity in individuals with MPS VI.

MPS VII, also known as Sly syndrome, is an autosomal recessive disorder caused by a mutation in beta-glucuronidase leading to an accumulation of heparan sulfate, dermatan sulfate, chondroitin-4-sulfate, and chondroitin-6-sulfate. Vestronidase alfa-vjvk (Mepsevii™) is a recombinant human lysosomal beta glucuronidase that was approved by the FDA for the treatment of MPS VII or Sly Syndrome. The effect of vestronidase alfa-vjvk (Mepsevii™) has not been determined in central nervous system manifestations of MPS VII.

MPS VIII is no longer recognized.

MPS IX is a rare disorder resulting from a deficiency of hyaluronidase leading to an accumulation of hyaluronan. Currently there is no FDA-approved enzyme replacement therapy for hyaluronidase deficiency.

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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## Coding

**Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.**

**The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.**

**In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.**

**The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.**

### CPT Procedure Code Number(s)

N/A

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### ICD - 10 Procedure Code Number(s)

N/A

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### ICD - 10 Diagnosis Code Number(s)

E76.01 Hurler's syndrome  
E76.02 Hurler-Scheie syndrome  
E76.03 Scheie's syndrome  
E76.1 Mucopolysaccharidosis, type II  
E76.210 Morquio A mucopolysaccharidoses  
E76.29 Other mucopolysaccharidoses

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### HCPCS Level II Code Number(s)

J1322 Injection, elosulfase alfa, 1 mg  
J1458 Injection, galsulfase, 1 mg  
J1743 Injection, idursulfase, 1 mg  
J1931 Injection, laronidase, 0.1 mg  
J3397 Injection, vestronidase alfa-vjvk, 1 mg

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### Revenue Code Number(s)

N/A

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## Policy History

### Revisions From MA08.034d:

03/28/2025	This policy has been reissued in accordance with the Company's annual review process.
05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
03/22/2023	This policy has been reissued in accordance with the Company's annual review process.
05/04/2022	This policy has been reissued in accordance with the Company's annual review process.
08/11/2021	This policy has been reissued in accordance with the Company's annual review process.

03/25/2020	This policy has been reissued in accordance with the Company's annual review process.
<b>06/03/2019</b>	This version of the policy will become effective 06/03/2019. This policy has been updated to be consistent with the US Food and Drug Administration (FDA) labeling, including age requirements. Dosing and frequency requirements were added for all the agents. Laboratory and/or genetic testing requirements were added to all diagnoses.

**Revisions From MA08.034c:**

01/01/2019	This policy has been identified for the HCPCS code update, effective 01/01/2019.  The following HCPCS code has been <b>added</b> to this policy: J3397 Injection, vestronidase alfa-vjvk, 1 mg  The following HCPCS codes have been <b>termed</b> from this policy: C9399 Unclassified drugs or biologicals J3590 Unclassified biologics
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**Revisions From MA08.034b:**

03/16/2018	This policy has undergone a routine review and the medical necessity criteria have been revised to reflect the United States Food and Drug Administration (FDA) labeling and drug compendia (i.e., Micromedex, AHFS-DI, Lexicomp).
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**Revisions From MA08.034a:**

06/07/2017	This policy has been reissued in accordance with the Company's annual review process.
02/03/2016	The policy has been reviewed and reissued to communicate the Company's continuing position on enzyme replacement therapy for mucopolysaccharidosis (e.g., Aldurazyme®, Elaprased®, Vimizim®, Naglazyme®, etc.).
02/11/2015	This policy was updated to be consistent with US Food and Drug Administration (FDA) Labeling and Drug Compendia. The name of this policy was changed from Laronidase (Aldurazyme®) to Enzyme Replacement Therapy for Mucopolysaccharidosis (e.g., Aldurazyme®, Elaprased®, Vimizim®, Naglazyme®, etc.). Idursulfase (Elaprased®), elosulfase alfa (Vimizim®), and galsulfase (Naglazyme®) was added to the policy and the individual policies will be removed. Criteria for Idursulfase (Elaprased®), elosulfase alfa (Vimizim®), and galsulfase (Naglazyme®) was added to the policy section based on US Food and Drug Administration (FDA) Labeling and Drug compendium.  The following ICD-10 diagnosis codes have been added to this policy: E76.1, E76.210, E76.29  The following HCPCS codes have been added to this policy: J1322, J1458, J1743

**Revisions From MA08.034:**

01/01/2015	This is a new policy.
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Version Effective Date:

06/03/2019

Version Issued Date:

06/03/2019

Version Reissued Date:

03/28/2025