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Policy Number: C2720-A

Elaprase (idursulfase)

PRODUCTS AFFECTED

Elaprase (idursulfase)

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:
Hunter Syndrome (mucopolysaccharidosis II, MPS II)

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. HUNTER SYNDROME (MUCOPOLYSACCHARIDOSIS II):
1. Documented diagnosis of Hunter Syndrome (mucopolysaccharidosis II, MPS II) confirmed by deficiency in iduronate- 2- sulfatase enzyme activity through enzyme or molecular (DNA-based) testing, such as IDS gene testing [DOCUMENTATION REQUIRED]
   AND

2. Documentation of baseline values for all of the following [DOCUMENTATION REQUIRED]:
   i. Urinary glycosaminoglycan (uGAG)
   AND
   ii. Members 6 years or older (one of the following): 6-minute walk test (6-MWT) and/or percent predicted forced vital capacity (FVC).
   OR
   Members younger than 6 years of age (one of the following): spleen volume, liver volume, upper airway obstruction during sleep, cardiac status, growth velocity, FVC, and/or 6-minute walk test

AND

3. Documentation that member has at least ONE of the following symptoms consistent with MPS II: Progressive coarsening of facial features, short stature, joint stiffness, hepatosplenomegaly, hernias, ivory colored papular skin lesions located on the upper back and/or lateral upper arms and thighs, mental retardation, deafness, cerebral ventricular dilation, mild dysostosis multiplex of bone, hypertrichosis, thickened skin or Mongolian spots.
   AND
4. Prescriber attestation of absence of cognitive impairment and no evidence of significant and/or progressive neurodevelopmental involvement AND member is not on chronic invasive mechanical ventilation AND Member does not have a concomitant life-threatening or severe disease(s) where the long-term prognosis is unlikely to be influenced by Enzyme Replacement Therapy (ERT) (e.g., neuroblastoma, leukemia etc.)
   NOTE: For members with evidence of significant and/or progressive neurodevelopmental involvement, this would indicate that the member has the severe form of Hunter syndrome (MPS IIA). Evidence is lacking to support the use of idursulfase (Elaprase) in Hunter syndrome Type A, the more severe variant of the disease. Patients in clinical studies were required to cooperate with pulmonary function tests and, therefore, only patients with the milder form of Hunter syndrome were enrolled.

CONTINUATION OF THERAPY:

A. HUNTER SYNDROME (MUCOPOLYSACCHARIDOSIS II):

1. Documentation of positive response or disease stability with therapy as compared to baseline (prior to therapy) as evidenced by:
   (a) Decreased urinary glycosaminoglycan (GAG) levels
   AND
   (b) Members 6 years or older (one of the following): 6-minute walk test (6-MWT) and/or percent predicted forced vital capacity (FVC)
   OR
   Members younger than 6 years of age (one of the following): decreased hepatosplenomegaly, improvement in upper airway obstruction during sleep, cardiac status, growth velocity, FVC, and/or 6-minute walk test

AND

2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 12 months; Continuation: 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 a 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:
16 months of age and older

QUANTITY:
0.5 mg/kg body weight infused once weekly as IV infusion

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 Elaprase (idursulfase). For information on site of care, see
Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous Infusion

DRUG CLASS:
Mucopolysaccharidosis II (MPS II) – Agents

FDA-APPROVED USES:
Indicated for enzyme replacement therapy for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ELAPRASE has been shown to improve walking capacity in patients 5 years and older. In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome; however, treatment with ELAPRASE has reduced spleen volume similarly to that of adults and children 5 years of age and older. The safety and efficacy of ELAPRASE have not been established in pediatric patients less than 16 months of age.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Mucopolysaccharidoses (MPS) are a rare group of inherited storage disorders that are caused by the deficiency of specific lysosomal enzymes required for catabolism of glycosaminoglycans, which are long chains of carbohydrates. Glycosaminoglycans are used to help build bone, cartilage, tendons, corneas, skin, and connective tissues. There are seven different types of MPS discovered and they include:

- **MPS I** has a wide spectrum of clinical severity and has been subdivided into three phenotypes: Hurler Syndrome (severe), Hurler-Scheie syndrome (intermediate), and Scheie syndrome (mild). This disease is caused by a deficiency of a-L-iduronidase enzyme. Laronidase (Aldurazyme) is FDA approved for this condition.
- **MPS II** (Hunter syndrome) is an X-linked recessive disease caused by insufficient levels of lysosomal enzyme iduronate-2-sulfatase. There are 2 clinical subtypes of Hunter syndrome: MPS IIA and MPSIIB. Idursulfase (Elaprase) is FDA approved for this condition.

- **MPS III** (Sanfilippo syndrome) is caused by deficient enzyme heparin N-sulfatase (Sanfilippo A), alpha-N-acetylglucosaminidase (Sanfilippo B), acetyl-CoAlpha-glucosaminide acetyltransferase (Sanfilippo C), or N-acetylglucosamine 6-sulfatase (Sanfilippo D).
- **MPS IV** (Morquio syndrome) has two subtypes as a result of deficient enzymes N- acetyl galactosamine 6-sulfatase (Type A) or beta-galactosidase (Type B). Elosulfase alfa (Vimizim) is FDA approved to for patients with MPS IVA or Morquio A syndrome.
- **MPS VI** (Maroteaux Lamy) is characterized by the absence or marked reduction in N-acetylgalactosamine 4-sulfatase. Galsulfase (Naglazyme) is FDA approved for this condition.
- **MPS VII** (Sly syndrome) is deficiency in enzyme beta-glucuronidase. Vestronidase alfa (Mepsevii) is FDA approved for this condition.

Mucopolysaccharidosis II, MPS II (Hunter's Syndrome) is an X-linked multisystem disorder characterized by glycosaminoglycan (GAG) accumulation due to the deficiency of the enzyme iduronate-2-sulfatase (which breaks down the GAG heparin sulfate and dermatan sulfate inside cells). GAG accumulation in various tissues and organs leads to a wide spectrum of clinical manifestations affecting multiple organs and physiologic systems and causes a variety of physical and neurological problems including skeletal deformities, cardiomyopathy respiratory problems, learning disabilities, and hearing loss. Idursulfase serves as a replacement for the deficient enzyme in people with MPS II. The disease occurs almost exclusively in young males, approximately 1 in 100,000 to 1 in 170,000 males, although cases of affected females have been reported due to the selective inactivation of the X chromosome inherited by the father. Age of onset, disease severity, and rate of progression vary significantly among affected males. Most therapies for MPS are directed toward treatment of complications and are not specific for the underlying abnormality. Supportive or symptomatic management can improve the quality of life for patients and their families but cannot prevent the inevitable decline in function. The main aim of therapy is to improve the quality of life and survival in MPSII patients who do not have neurological involvement.

Elaprase (idursulfase), a purified form of human iduronate-2-sulfatase, is for the treatment of Hunter syndrome, (MPS II). The deficiency of iduronate-2-sulfatase production causes an accumulation of glycosaminoglycans (GAG) in cells throughout the body. The buildup of these carbohydrates produces a variety of physical and neurological problems including abnormal bone and joint growth, respiratory problems, learning disabilities, and hearing loss. Many people with severe MPS II die during early adolescence, but people with milder forms of the disorder can live well into adulthood. Idursulfase serves as a replacement for the deficient enzyme in people with MPS II. Idursulfase is produced by recombinant DNA technology in a human cell line and is the first treatment for Hunter syndrome.

Pivotal Trial

FDA approval of Elaprase was based on the results of one clinical trial. In a randomized, double-blind trial of patients aged 5 to 31 years with Hunter syndrome (n=96), idursulfase IV infusion significantly improved walking capacity compared with placebo. Patients were randomized to receive idursulfase 0.5 mg/kg once weekly, idursulfase 0.5 mg/kg once every other week, or placebo for the duration of the study (53 weeks). The treatment duration was 53 weeks. The primary efficacy endpoint was a score based on the change from baseline to week 53 in distance walked during a 6-minute walk test (6-MWT) and the change in forced vital capacity (FVC) percentages. The primary endpoints showed the greatest statistically significant difference between the weekly Elaprase treated group and the placebo group (p=0.0049). 94 of the 96 patients completed the study (Muenzer et al. 2006). The authors concluded that weekly infusions of idursulfase produced a clinical benefit based on the significant improvements in the two-component composite endpoint, 6MWT distance and %FVC compared to placebo.

Results: Patients treated with weekly infusions of idursulfase for 53 weeks had a mean increase in the six- minute walk test and percent predicted FVC. Treatment also decreased mean urinary GAG levels and liver and spleen volume. Growth, sleep apnea, cardiac function, quality of life, and mortality were not examined.

- Following 53 weeks of treatment, patients receiving idursulfase had a significantly greater improvement over baseline in the two-component composite score (consisting of the results of a 6-MWT and percent-predicted FVC) than those receiving placebo, with the greatest difference occurring

in patients receiving idursulfase once weekly.

- When the outcome parameters were evaluated individually, a greater improvement in the 6-MWT (a 35 m greater mean increase), but not in percent-predicted FVC was observed in patients receiving idursulfase once weekly compared with those receiving placebo.
- Urinary GAG concentrations were markedly reduced (but still remained above the upper limit of normal in about 50% of patients) in patients receiving idursulfase once weekly and were essentially unchanged in those receiving placebo.
- Sustained reductions in liver and spleen volumes were observed in patients receiving idursulfase once weekly, while such volumes were essentially unchanged in those receiving placebo.

Anaphylactoid reactions were observed in some patients during infusion. The most common infusion-related reactions included headache, fever, cutaneous reaction, and hypertension. The frequency of infusion-related reactions decreased with time.

Patients with certain types of genetic mutations, such as complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice-site mutations were more likely to develop neutralizing antibodies and to experience hypersensitivity reactions compared with those with other mutations, such as missense mutation.

Extension Trial

During the 24-month, extension trial (n=94 of 96), walking capacity improved for an additional 8 months of treatment; however, improvement in walking capacity and other endpoints at 24 months was not observed, and the long-term efficacy of idursulfase on pulmonary function in patients with Hunter syndrome remains unclear. Although improvement in disease-related symptoms and long-term clinical outcomes have not been demonstrated in patients aged 16 months to 5 years, spleen volume reduced similarly to that observed in adults and children 5 years or older during a 53-week, open-label, uncontrolled study (n=28) of patients aged 16 months to 7.5 years with Hunter syndrome.

- Limited experience in children younger than 5 years of age suggests that early initiation of ERT may delay or prevent the development of irreversible manifestations of the disease (Muenzer J, 2011; Tylki-Szymanska A, et al. 2012). Therefore, the effects of ERT with idursulfase in children under 5 years of age need to be further investigated considering the early introduction of therapy with consequent limitation of the formation of lysosomal storage may potentially lead to better outcomes in the evolution of the disease.
- **Current evidence is limited given there was only one randomized clinical trial found in the medical literature.** The pivotal study leading to approval of phase II/III study was of only 53 weeks duration. A systematic review considers the pivotal trial good quality; however, notes that 'it failed to describe important outcomes. It has been demonstrated that enzyme replacement therapy (ERT) with idursulfase is effective in relation to functional capacity (6MWT and per cent predicted FVC), liver and spleen volumes and urine GAG excretion in people with MPS II compared with placebo. However, no available evidence in the included study or in the wider literature on outcomes such as sleep apnea, cardiac function, quality of life and mortality.' Further trials are required to determine the long-term effects of ERT. Clinically relevant outcomes should be assessed, such as improvements in cardiac function, respiratory function, including sleep apnea, stabilization of skeletal abnormality, quality of life, need of hospitalizations and mortality. (Cochrane Database of Systematic Reviews 2016)

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Elaprase (idursulfase) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Elaprase (idursulfase) include: no labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:

BLACK BOX WARNING:

Life-threatening anaphylactic reactions, presenting as respiratory distress, hypoxia, hypotension, urticaria and/or angioedema of throat or tongue have occurred in some patients during and up to 24 hours after

ELAPRASE infusions. Closely observe patients during and after ELAPRASE administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions and 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
J1743	Injection, idursulfase, 1mg

AVAILABLE DOSAGE FORMS:
Elaprase (idursulfase) Soln for IV Infusion 6 MG/3ML (2 MG/ML)

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