Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Orphan Drug Evaluation: Enzyme Replacement Therapy for Hunter Syndrome

Date of Review: August 2026
Generic Name: Tividenofusp alfa-eknm
Idursulfase

End Date of Literature Search: 05/29/2026
Brand Name (Manufacturer): Avlayah (Denali Therapeutics Inc.)
Elaprase (Takeda Pharmaceuticals)

Dossier Received: No

Purpose for Review:

- To establish medically appropriate prior authorization (PA) criteria for 2 enzyme replacement therapies, idursulfase and tividenofusp alfa-eknm, which are Food and Drug Administration (FDA)-approved for management of symptoms associated with Hunter syndrome, also known as mucopolysaccharidosis type II (MPS II).
- The wholesale acquisition cost per 6 mg vial of idursulfase is $3,310.65. Idursulfase is dosed at 0.5 mg/kg once a week. For a 36 kg child, the dose would be 18 mg or 3 vials or $9,932 per week or $516,461 per year.
- Tividenofusp alfa-eknm has a maintenance dose of 15 mg/kg once weekly after administering the loading dose protocol. The cost for each 150 mg vial is $5,200. For a 36 kg child, the maintenance dose would be 4 vials (rounded to the nearest whole vial) and cost $20,800 per week or $1,081,600 per year.

Plain Language Summary:

- The Food and Drug Administration (FDA) has approved 2 medicines, idursulfase and tividenofusp alfa-eknm, to treat Hunter syndrome.
- Hunter syndrome is a rare condition caused by a gene mutation that is inherited from the mother. This condition mostly affects boys.
- In people with Hunter syndrome, the body cannot make enough of the enzyme (a type of protein) that normally breaks down long chains of complex sugar molecules. This causes a buildup of complex sugar which leads to tissue and organ damage (spleen, liver) and affects physical and mental development.
- Symptoms of Hunter syndrome begin to appear around 2 to 4 years of age. Symptoms can be mild or severe and include an abnormally large head, hearing loss, stiff joints, heart disease, damaged spinal cord, and slowed development in walking and talking.
- Idursulfase is an enzyme replacement therapy that replaces the missing enzyme in Hunter syndrome and slows down tissue damage. This medicine is given via an infusion into the vein (intravenously) once a week.
- In a year-long study of 96 patients with Hunter syndrome, people treated with idursulfase were able to walk 37 meters farther over 6 minutes, compared to people who received placebo. Side effects include fever, rash, and headaches.
- Tividenofusp alfa-eknm is another enzyme replacement therapy that was designed to treat specific symptoms of Hunter syndrome related to the nervous system and brain. This medicine is also given via an intravenous infusion once a week.
- In clinical studies, chemical signs of the disease called biomarkers were used to assess how well tividenofusp alfa-eknm works. Over 24 weeks, a harmful complex sugar called heparan sulfate was decreased by 91% in the fluid surrounding the spinal cord and brain (cerebrospinal fluid).

Author: Deanna Moretz, PharmD, BCPS

- There are no published studies to determine whether tividenofusp alfa-eknm improves neurologic symptoms of Hunter syndrome such as seizures, trouble thinking or learning, and hyperactivity. The most common side effects were related to how the drug is given, known as infusion-related reactions, such as fever, hives, and vomiting.
- The Drug Use Research and Management group recommends that the Oregon Health Authority pay for idursulfase and tividenofusp alfa-eknm for patients with Hunter syndrome after their provider documents medical appropriateness through a process called prior authorization.

Research Questions:

1. What is the evidence for the safety and efficacy of idursulfase in treating MPS II (Hunter syndrome)?
2. What is the evidence for the safety and efficacy of tividenofusp alfa-eknm is treating neurologic manifestations of MPS II?
3. Are there specific subpopulations for which idursulfase or tividenofusp-alfa-eknm is better tolerated or more effective for management of symptoms associated with MPS II?

Conclusions:

- Two enzyme replacement therapies, idursulfase and tividenofusp alfa-eknm, are FDA-approved for management of symptoms associated with MPS II.

<u>Idursulfase</u>

- In patients 5 years and older with MPS II, there is moderate-quality evidence from a single phase 2/3 trial (n=96) that weekly infusions of idursulfase 0.5 mg/kg improves exercise capacity as assessed by the 6-meter walk test (6MWT) by an average of 37 meters compared to placebo (p=0.013; 95% confidence interval [CI], not reported) over the course of a year.[1] Idursulfase does not improve lung function as assessed by predicted percent of forced vital capacity (FVC) (low-quality evidence).[1]
- An established minimal clinically important difference (MCID) for the 6MWT in patients with MPS II has not been formally defined in the clinical literature; however, the idursulfase investigators determined that a walking distance improvement of 30 to 44 meters over 52 weeks represented meaningful clinical benefit.[2]
- The most commonly reported adverse events with idursulfase in the phase 2/3 randomized controlled trial (RCT) were: headache (28%), pruritus (25%), urticaria (16%), musculoskeletal pain (13%), diarrhea (9%) and cough (9%).[3] Idursulfase has a boxed warning for risk of anaphylaxis.[3] In postmarketing reports, patients experienced anaphylactic reactions for up to several years after initiating idursulfase treatment.[3] Some patients had repeated anaphylactic events over a 2 to 4 month time period.[3]
- The phase 2/3 RCT of idursulfase was conducted in patients who were ambulatory and could follow directions to complete the pulmonary function testing. The efficacy of idursulfase in MPS II patients who were non-ambulatory, or who had severe MPS II with neurocognitive impairment was not evaluated.
- In patients 16 months to 5 years of age, no data are available to demonstrate improvement in MPS II disease-related symptoms or long-term clinical outcome.[3] In 2 open-label studies enrolling 38 people, treatment with idursulfase reduced spleen volume in adults and children aged 5 years and older.[3-5] The safety and efficacy of idursulfase have not been established in pediatric patients less than 16 months of age with MPS II.[3]
- Idursulfase cannot cross the blood brain barrier and IV administration does not mitigate neurologic manifestations of MPS II.[6]

<u>Tividenofusp alfa-eknm</u>

- Tividenofusp alfa-eknm is indicated for the treatment of neurologic manifestations of MPS II when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.[7] FDA-approval was based on the surrogate endpoint of reduction in cerebrospinal fluid (CSF) heparan sulfate levels from baseline to Week 24.[6] Heparan sulfate is theorized to be the toxic substrate responsible for neurodegeneration in MPS

II.[6] A key review issue for the FDA was whether reduction in CSF levels of heparan sulfate could reasonably predict clinical benefit in patients with severe MPS II.[6] Continued FDA-approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.[7]

- There is insufficient evidence that tividenofusp alfa prevents or delays neurocognitive decline in people with MPS II.[6] Efficacy in people with advanced neurologic impairment is unknown. It is hypothesized that once irreversible central nervous system (CNS) damage has occurred, initiating an intervention to replace the deficient enzyme may not benefit patients.[6]
- There is low-quality evidence from a phase 1/2 single-arm, open-label trial (n=47) that CSF heparan sulfate levels were reduced with tividenofusp alfa treatment from 837.5 ng/mL at baseline to 69 ng/mL at Week 24, reflecting a mean percent reduction of 91.4%.[6,8] Levels of CSF heparan sulfate observed at 24 weeks are levels observed in healthy individuals, which range from 50 to 70 ng/mL, and are almost always below 200 ng/mL.[6,9]
- In the phase 1/2 study, 41 participants (87%) had at least one infusion-related reaction; symptom severity was moderate in 55% of participants and severe in 6% of participants (low-quality evidence).[8] Tividenofusp alfa has a boxed warning for risk of hypersensitivity reactions including anaphylaxis.[7] Other common adverse events reported with tividenofusp alfa include upper respiratory tract infection (60%), pyrexia (55%), cough (47%), vomiting (43%), diarrhea (40%), rash (40%), anemia (38%), coronavirus disease 2019 (38%), and rhinorrhea (38%).[8]
- Administration of tividenofusp may cause anemia and/or membranous nephropathy.[7] The manufacturer recommends obtaining baseline hemoglobin levels before starting therapy and monitoring serum creatinine levels and urine-to-protein creatinine ratio during therapy.[7] Tividenofusp alfa-eknm is not recommended for use in combination with other enzyme replacement therapies, as combination therapy has not been studied and could increase the risk of severe hypersensitivity reactions.[7]
- It is not clear if tividenofusp alfa will improve motor function in patients with MPS II, as those outcomes have not been studied to date.
- An ongoing phase 2/3, multicenter, double-blind, randomized trial of tividenofusp alfa compared with idursulfase will evaluate the relative effects on safety, cognitive, and behavioral outcomes in patients with MPS II.[8]

Recommendations:

- Create a Preferred Drug List (PDL) class of drugs for MPS II (Hunter syndrome).
- Implement prior authorization (PA) criteria for the use of idursulfase and tividenofusp alfa-eknm, based on the indications that are FDA-approved in patients with MPS II.

Background:

- Mucopolysaccharidosis type II is a rare, X-linked genetic disorder of lysosomal storage. An enzyme replacement therapy, idursulfase, was approved in 2006 by the FDA as a treatment for patients with MPS II.[3] A second enzyme replacement therapy, tividenofusp alfa-eknm, received FDA approval in March 2026 for the treatment of neurologic manifestations of MPS II.[7] Both medications are administered via IV infusion once a week, using a weight based dosing regimen.[3,7]
- There are currently 12 known enzyme deficiencies that cause MPS comprising 8 different clinical types. Other enzyme replacement therapies (i.e., laronidase, galsulfase) have been approved to treat MPS type I and MPS type IV, respectively.[1] These therapies are subject to the Oregon Health Plan (OHP) orphan drug policy and PA criteria.
- A genetic mutation in the *IDS* gene causes MPS II.[1] The *IDS* gene regulates production of the iduronate 2-sulfatase enzyme which is responsible for breaking down complex sugar molecules called glycosaminoglycans (previously known as mucopolysaccharides).[1] The 2 glycosaminoglycan substrates that have been identified in MPS II are heparan sulfate and dermatan sulfate.[6] When these glycosaminoglycans accumulate inside lysosomes, cellular damage and tissue

destruction occurs in the respiratory, cardiovascular, skeletal, and neurologic systems.[1] Iduronate 2-sulfastase enzyme deficiency may be due to total lack of enzyme, but is more often from decreased enzyme production, decreased catalytic activity, or protein misfolding.[10]

- Prenatal diagnosis is available if the mother is a carrier of the genetic *IDS* mutation.[1] Newborn screening for MPS II was added to the Recommended Uniform Screening Panel (RUSP) in 2022. A definitive diagnosis of MPS II is established by demonstrating reduced or absent iduronate 2-sulfatase enzyme activity in leukocytes, fibroblasts, serum, or plasma; or molecular genetic testing for mutations in the *IDS* gene.[1] A determination of urinary glycosaminoglycan levels assists in screening potential positive patients; however, this assay is not very sensitive with many false-negative results.[1]
- Mucopolysaccharidosis type II almost always occurs in males but has been reported in a few symptomatic females, through skewing of X-chromosome inactivation.[10,11] The reported global prevalence of MPS II is 1 in 170,000 live births.[11] Signs and symptoms begin to appear in children between the ages of 2 years and 4 years.[2]
- In the Oregon Health Plan (OHP) population, 10 patients had a diagnosis of MPS II from 1/1/25 to 1/1/26. Nine of those patients are enrolled in a Coordinated Care Organization (CCO) and the tenth was enrolled was Fee-for-Service (FFS) but is no longer eligible for OHP.
- Common presenting features of MPS II include facial dysmorphism, enlarged tongue, hoarse voice, organomegaly, joint stiffness and contractures, pulmonary dysfunction secondary to skeletal deformities, myocardial enlargement and valvular dysfunction, hearing loss, and short stature.[11] Complications of MPS II can include congestive heart failure, chronic otitis media, joint and bone abnormalities, declining brain function, obstructive apnea, carpal tunnel syndrome, hernias, seizures, and behavioral problems.[11]
- MPS II has a variable age of onset and variable rate of progression, depending upon the phenotype.[11] Two MPS II phenotypes have been identified: a severe, neuronopathic phenotype (nMPS II) and a mild/attenuated, non-neuronopathic phenotype (nnMPS II).[6]
- Approximately 60% of patients with MPS II have the severe, neuronopathic form (nMPS II) and are likely to experience neuronopathic symptoms at about 3–4 years of age, including behavioral changes, attention difficulties, speech delay, cognitive decline, and poor performance at school.[12] Neurodegeneration is theorized to be related to excess heparan sulfate.[6] In patients with neuronopathic involvement, death usually occurs in the second decade of life due to progressive neurocognitive deterioration and cardiorespiratory failure.[6]
- Patients with minimal or no neuronopathic involvement (nnMPS II) may survive into the fifth or sixth decade of life with normal intellectual development.[11] Symptoms of MPS II may not present until adolescence or adulthood in people with this attenuated MPS II phenotype.[6] Death in patients with nnMPS II is usually due complications associated with obstructive airway disease and/or cardiac failure.[6]
- Goals of treatment include slowing progression of the disease, minimizing complications related to MPS II, and improving quality of life.[10] Surgery to replace defective cardiac valves, repair inguinal hernias, and remove tonsils and/or adenoids is often needed.[10] Hematopoietic stem cell transplantation has not demonstrated clear neurological benefit to date and is not recommended for patients with MPS II due to the high rate of morbidity and mortality associated with this therapy.[10]
- A clinical practice resource was published by the American College of Medical Genetics and Genomics (ACMGG) in 2020.[10] Most rare diseases, even those with approved therapies, lack enough high-quality data to be able to create an evidence-based guideline to assist clinicians in the care of people with these conditions.[10] A previous systematic review[13] of treatment for MPS II demonstrated insufficient strength in all data analyzed to create a definitive practice guideline based solely on published evidence.[10] Due to insufficient high-quality evidence, this practice resource was developed by the ACMGG based on consensus of the 10 committee members with experience in managing MPS II.[10] Only one enzyme replacement therapy, idursulfase, was available in 2020, when this resource was published. No guidance has been issued that includes recommendations for prescribing tividenofusp alfa-eknm. The ACMGG practice resource suggests the following criteria for the use of the enzyme replacement therapy, idursulfase:
    - All individuals with severe MPS II or predicted to have severe MPS II based on genotype warrant starting enzyme replacement therapy, prior to showing signs or symptoms.[10]

- Individuals with signs or symptoms with either attenuated or severe MPS II warrant enzyme replacement therapy.[10]
- Individuals with attenuated MPS II who are not showing signs or symptoms of disease do not warrant enzyme replacement therapy.[10]
- Individuals receiving enzyme replacement therapy who have developed allergic reactions that cannot be controlled by standard therapies or immunomodulation should have enzyme replacement therapy discontinued.[10]
- Clinical evaluation of liver and spleen size are recommended for judging clinical effectiveness of treatment (idursulfase), with optional use of imaging modalities (ultrasound or MRI of the abdomen) to follow organ size. Pulmonary function tests are recommended if the individual can reliably perform them, but there are concerns on the utility of the 6MWT. Lab studies of glycosaminoglycans are recommended, as well as antibodies to enzyme replacement therapy to assess infusion reactions. Finally, neuropsychology testing is recommended for following disease progress.[10]

Drug Information

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

I. ELAPRASE (idursulfase) for Intravenous infusion:

FDA-approved indication:

- Idursulfase has been shown to improve walking capacity in patients 5 years and older.[3]
- 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.[3] In 2 open-label studies (n=38 total enrollment) treatment with idursulfase reduced spleen volume in adults and children aged 5 years and older with MPS II.[3-5]
- The safety and efficacy of idursulfase have not been established in pediatric patients less than 16 months of age.[3]
- Of note: Idursulfase cannot cross the blood brain barrier and intravenous (IV) administration does not mitigate neurologic manifestations of MPS II.[6] An implantable CSF reservoir containing idursulfase is approved in Japan to mitigate CNS symptoms of MPS II.[6]

The phase 2/3 RCT used to support FDA approval of idursulfase is described in **Table 1.** Noteworthy trial design and patient characteristics include:

- Trial duration: 53 weeks
- Number of participants: 96 males with MPS II
- Study arms: idursulfase 0.5 mg/kg IV once a week, idursulfase 0.5 mg/kg IV every other week, or placebo
- Key inclusion criteria:
  - Aged 5-31 years
  - At least one clinical sign of MPS II: hepatosplenomegaly, valvular heart disease, evidence of obstructive pulmonary disease, or radiographic evidence of skeletal abnormalities (dysostosis multiplex)
  - Documented iduronate 2-sulfatase enzyme deficiency $\leq$ 10% of the lower limit of normal in plasma, fibroblasts, or leukocytes
  - Baseline FVC < 80% of predicted normal value
  - Ambulatory: able to stand 6 minutes and walk at least 5 meters
- Key exclusion criteria:
  - Unable to follow directions to complete pulmonary function testing or 6MWT
  - History of tracheostomy, cord blood transplant or bone marrow transplant

- Baseline disease severity and population characteristics:
  - Mean age: 14.2 years
  - 82% were White
  - Male gender: 100%
  - Mean baseline walking distance on the 6MWT: 395 meters (range: 49 to 565 meters)
  - Mean Predicted FVC: 55% (range 16% to 79%)
  - Mean Weight: 36 kg
- Setting: Weekly visits to an infusion center for IV administration of placebo or idursulfase over 3 hours. Patients assigned to the idursulfase arm every other week received placebo infusions in the off week.
- Magnitude of benefit and clinical relevance of results:
  - Change in 6MWT: For idursulfase weekly versus placebo, the idursulfase group averaged 37 meters greater gain in the 6MWT over the course of the year (95% CI, not reported; p=0.013).[1] The minimal clinically MCID for the 6MWT depends on the condition being evaluated.[14] One study determined that a change of 14 to 30.5 meters may be clinically important across a variety of disease states.[14] An established MCID for the 6MWT in patients with MPS II has not been formally defined in the clinical literature; however, the idursulfase investigators determined that a walking distance improvement of 30 to 44 meters represented meaningful clinical benefit.[2] There was no statistical difference between placebo and idursulfase every other week (difference 23 meters, 95% CI -2.31 to 49.91; p=0.73).[1]
  - Change in predicted percent of FVC: not statistically significant for any of the comparisons.[1] A 10% relative improvement over baseline in the percent FVC is considered by the American Thoracic Society to be a clinically significant change.[1] According to the FDA review, It is difficult to connect changes in FVC with changes in organomegaly in patients with MPS II, as predicted percent of FVC is expressed as a percentage of normal value an individual of comparable age and height.[1] However, measuring height is difficult in patients with MPS II as not all patients can stand erect due to joint contractures and joint disease for an accurate measurement.[1] Therefore, predicted lung function values based on height is of unclear reliability in this patient population.[1] In MPS II, the primary potential pulmonary effects of the disease process are on structures external to the lung, most notably the upper airway, skeleton, and possibly liver and spleen; the FVC and other pulmonary function tests are measures that combine potential effects on the lung itself and structures external to it, not just on the lung alone.[1]
- Safety signals:
  - Idursulfase prescribing information contains a boxed warning for life-threatening anaphylaxis.[3] In 2 clinical trials with idursulfase, 16 of 108 (15%) patients experienced hypersensitivity reactions involving 3 body systems: cutaneous, respiratory or cardiovascular.[3] Of these 16 patients, 11 (69%) experienced anaphylactic reactions with symptoms of bronchospasm, cyanosis, dyspnea, erythema, edema (facial and peripheral), flushing, rash, respiratory distress, urticaria, vomiting, and wheezing.[3] In postmarketing reports, patients receiving idursulfase experienced anaphylactic reactions up to several years after initiating treatment.[3] Some patients had repeated anaphylactic events over 2 to 4 months.[3]
  - Most commonly reported adverse events with idursulfase in the phase 2/3 RCT of 96 patients were: headache (28%), pruritus (25%), urticaria (16%), musculoskeletal pain (13%), diarrhea (9%) and cough (9%).[3] If infusion reactions occurred, management included use of antihistamines and/or corticosteroids prior or during infusions, a slower rate of infusion, and/or early discontinuation of infusion if serious symptoms developed.[2]

See **Table 1** for major evidence limitations including:

- Risk of selection bias.
- Applicability concerns related to appropriate populations for treatment with idursulfase. Patients who were non-ambulatory, who had severe MPS II with neurocognitive impairment, or who were under 5 years of age were excluded from the study.

Table 1. Comparative Evidence Table for Idursulfase

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints (change from baseline to Week 53)	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Muenzer, J., et al.[1,2] Phase 2/3, DB, PC, MC, RCT	1. Idursulfase 0.5 mg/kg IV once a week 2. Idursulfase 0.5 mg/kg IV once every other week 3. Placebo IV once a week Duration: 52 weeks	Demographics: -Mean age: 14.2 yo -Race White: 82% Asian: 3% Black: 4% Other: 11% -Mean baseline 6MWT walk distance: 395 meters (range: 49 to 565 meters) -Mean Predicted FVC: 55% (range 16% to 79%) -Mean Weight: 36 kg -Gender: 100% male -Mean age at symptom onset: 28 months -Mean disease duration: 9.4 years Key Inclusion Criteria: - aged 5-31 yo - MPS II based on clinical signs and biochemical criteria* -Abnormal FVC < 80% predicted -Able to stand 6 minutes and walk 5 meters Key Exclusion Criteria: -Prior bone marrow or cord blood transplant -Tracheostomy -Unable to complete 6MWT or pulmonary function testing	ITT: 1. 32 2. 32 3. 32 PP: 1. 31 2. 32 3. 31 Attrition: 1. 1 (3%) 2. 0 3. 1 (3%)	Co-Primary Endpoints: ***Adjusted LSM change in 6MWT*** Weekly IDS vs. Placebo 1. 44.3 ± 12.3 meters (SEM) 3. 7.3 ± 9.5 meters (SEM) Difference: 37 meters 95% CI, NR; P=0.0131 EOW IDS vs. Placebo 2. 30.3 ± 10.3 (SEM) 3. 7.3 ± 9.5 (SEM) Difference: 23 meters 95% CI: NR; P=0.0732 ***Adjusted LSM change in predicted FVC%*** Weekly IDS vs. Placebo 1. 3.45 ± 1.77 (SEM) 3. 0.75 ± 1.71 (SEM) Difference: 2.7 95% CI, NR; P=0.0650 EOW IDS vs. Placebo 2. 0.004 ± 1.32 (SEM) 3. 0.75 ± 1.71 (SEM) Difference: -0.746 95% CI, NR; P=0.9531 Secondary Endpoint: ***Mean percent change in urinary GAG levels*** 1. -52.5 ± 5.3 (SEM) 2. -44.7 ± 4.0 (SEM) 3. 21.4 ± 11.6 (SEM) p<0.0001 vs. placebo; 95% CI NR ***Mean percent change in liver volume*** 1. -25.3 ± 1.6 (SEM) 2. -24.0 ± 1.7 (SEM) 3. -0.8 ± 1.6 (SEM) p<0.0001 vs. placebo; 95% CI NR	NA NS NS NS	Headache: 1. 19 (59%) 2. 21 (66%) 3. 14 (44% Nasopharyngitis 1. 17 (53%) 2. 19 (59%) 3. 15 (47%) Abdominal Pain 1. 13 (41%) 2. 19 (59%) 3. 16 (50%) Infusion Site Swelling 1. 1 (3%) 2. 4 (13%) 3. 4 (13%) Infusion-related adverse effect 1. 22 (69%) 2. 22 (69%) 3. 21 (66%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization not reported. Patients were stratified by age (5-11 yo, 12-18 yo, 19-31 yo) and baseline disease score (combined 6MWT and % FVC scores). Baseline demographics were balanced across the 3 treatment groups, although placebo-treated patients were younger and smaller than the active comparator, there was overlap between groups for age at onset of MPS II and baseline disease score. Performance Bias: Low. Investigators and participants blinded to treatment assignment. Detection Bias: Low. Primary outcome assessment was conducted by a clinician not involved with the study. Infusion reactions may have resulted in unblinding of investigators, patients or caregivers. Attrition Bias: Low. 2 patients died during the study, otherwise all patients completed the 52-week trial. Reporting Bias: Low. All outcomes reported as prespecified in the protocol. Other Bias: Unclear. Study conducted by the manufacturer. Three investigators report payments from the manufacturer for consulting, speaking, travel, and research. **Applicability**: Patient: Children less than 5 years of age were not included in the RCT. Enrollment does not fully depict the full disease severity spectrum as those who could not complete testing due to being bed-bound, severely debilitated or with an intellectual disability were excluded. Intervention: An initial phase 1/2 RCT in 12 patients with MPS II showed that idursulfase decreased urinary GAG excretion and decreased liver/spleen sizes. The phase 2/3 study had a phase 2 component to determine if weekly or every other weekly infusions were effective. Weekly infusions showed the most significant benefit for an improved ability to walk longer distances over 6 minutes. Comparator: Placebo is an appropriate comparator to evaluate efficacy.

				Mean percent change in spleen volume 1. -25.1 ± 2.4 (SEM) 2. -19.8 ± 3.2 (SEM) 3. 7.2 ± 4.2 (SEM) p<0.0001 vs. placebo; 95% CI NR				Outcomes: Changes in 6MWT and FVC were used for FDA approval of other enzyme replacement therapies, although their clinical meaningfulness in MPS II is uncertain. Secondary endpoints for urinary GAG excretion and liver and spleen volumes have uncertain clinical meaningfulness. Setting: 9 study sites: 4 in the United States, 3 in the United Kingdom, 1 site each in Brazil and Germany

Abbreviations: 6MWT = 6 minute walk test; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; EOW = every other week; FDA = Food and Drug Administration; FVC = forced vital capacity; GAGs = glycosaminoglycans; I2S = iduraonate-2-sulfatase; IDS = idursulfase; IV = intravenous; kg = kilograms; ITT = intention to treat; LSM = least squares mean; mITT = modified intention to treat; MPS II = Mucopolysaccharidosis type II; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SEM = standard error of the mean; yo = years old

* Clinical signs of MPS II included at least one of the following: hepatosplenomegaly, obstructive airway disease, or radiographic evidence of skeletal abnormalities; Biochemical evidence included documented plasma, fibroblast, or leukocyte I2S enzyme deficiency ≤ 10% normal range

II. AVLAYAH (tividenofusp alfa-eknm) for IV infusion

Mechanism of action and FDA-approved indication:

- Tividenofusp alfa-eknm provides an exogenous source of iduronate 2-sulfatase enzyme fused to an enzyme transport vehicle to enhance delivery into the CNS.[7]
- Tividenofusp alfa-eknm is indicated for neurologic manifestations of MPS II in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.[7]
- Tividenofusp alfa-eknm is not recommended for use in combination with other enzyme replacement therapies as combination therapy has not been studied and could increase the risk of severe hypersensitivity reactions.[7]

The clinical trial used to support FDA approval is described and evaluated below in **Table 2.** Noteworthy trial design and patient characteristics include:

- Trial design and duration: Phase 1/2, single-arm, open-label trial over 24 weeks with an 80-week safety extension, and 157-week open-label extension
- Number of participants: 47 males
- Study Arms: 5 dosing regimens of tividenofusp alfa - weekly IV infusions of 3, 7.5, or 15 mg per kilogram of body weight, with or without dose escalation (up to 30 mg per kilogram for cohort A), followed by a weekly infusion of 15 mg per kilogram for all 5 dosing cohorts.[8]
- Participants subdivided by age and phenotype into 5 cohorts:
    - Cohort A: Participants aged ≥5 to ≤10 years with nMPS II (n=5)
    - Cohort B: Participants aged ≥1 to ≤18 years with nnMPS II, nMPS II, or unknown phenotype (n=18)
    - Cohort C: Participants aged <4 years with nMPS II (this cohort could include participants ≥4 to ≤18 years of age if participant is a blood relative of a participant <4 years of age) (n=8)
    - Cohort D: Participants aged ≤18 years with nnMPS II or nMPS II with preexisting hepatomegaly who have never taken standard-of-care enzyme replacement therapy (n=5)
    - Cohort E: nMPS II participants aged ≥6 years at screening, nnMPS II participants <6 or ≥17 years at screening, and nMPS II participants ≥1 to ≤18 years at screening with a history of prior hematopoietic stem cell transplant (n=10)
- Key inclusion criteria:

- Confirmed MPS II based upon reduced iduronate 2-sulfatase enzyme activity in plasma, fibroblasts, or leukocytes and documented mutation in *IDS* gene
- For participants with nMPS II: Cognitive standard score or development quotient of 85 or less at screening or a documented decline of at least 7.5 points in the standard score in the previous 6 to 18 months. The developmental quotient was calculated as developmental age divided by chronologic age multiplied by 100; a score of 100 indicates age-expected development.[8]
- If receiving idursulfase, must have tolerated a minimum of 4 months of treatment prior to study enrollment. (If patients had received idursulfase, no mandated washout period was initiated before starting tividenofusp alfa).[8]

- Key exclusion criteria:
  - Use of any CNS-targeted enzyme replacement therapy within 3 months of screening for participants aged 5 years and older or within 6 months for those less than 5 years of age.
  - Use of gene therapy or stem cell therapy at any time (except for participants in Cohort E)
  - Clinically significant thrombocytopenia or other coagulation abnormality. Note: anemia is a risk factor due to the ability of the fragment crystallizable component of tividenofusp alfa to bind to human transferrin receptor, which plays a role in iron homeostatis.[6]
  - Contraindication for lumbar punctures
  - Clinically significant history of stroke, epilepsy, head trauma with loss consciousness, or any CNS disease not MPS II-related within 1 year of screening
  - Placement of a ventriculoperitoneal (VP) shunt or any other brain surgery within 30 days of screening
- Baseline disease severity and population characteristics:
  - Median age: 5 years (range: 3 months to 13 years); 30% were less than 4 years old
  - Phenotype: nMPS II: 44 (94%); nnMPS II phenotype: 3 (6%)
  - Previously received enzyme replacement therapy: 32 (68%)
  - Type of genetic variant:
    - Missense or synonymous: 22 (47%)
    - Large deletion, rearrangement, stop, frameshift or splice: 25 (53%)
- Magnitude of benefit and clinical relevance of results:
  - The primary objective was safety in the dose-finding Phase 1/2 study. Safety endpoints included adverse events, infusion-related reactions, and anemia.[8] All 47 participants had at least one adverse event; the maximum severity was moderate in 68% and severe in 28%.[8] A total of 18 participants (38%) had at least one serious adverse event.[8] Of these, 3 had at least one serious adverse event that was considered by the investigator to be related to treatment (2 had infusion-related reactions and 1 had anemia); all continued to receive tividenofusp alfa in the study.[8] One participant (2%) discontinued the study owing to a treatment-related adverse event (infusion-related reaction).[8]
  - Another primary objective was change in total urinary glycosaminoglycan levels over 24 weeks, as accumulation of glycosaminoglycans leads to lysosomal dysfunction in multiple organs and tissues.[6,8] Mean baseline urine glycosaminoglycan level was 44.1 mg/mmol creatinine (n=47) and at Week 24 the mean level was 13 mg/mmol creatinine (n=38) for a 57% mean reduction at week 24 (95% CI, 49 to 65).[6] While data from this phase 1/2 study appears to suggest that tividenofusp alfa has favorable effects on biomarkers of somatic disease (e.g., urine glycosaminoglycan and liver volume) in selected subjects with MPS II, there are significant limitations including small number of treatment-naïve subjects, confounding effects of idursulfase use at baseline, limited number of subjects with hepatomegaly/splenomegaly at baseline, changes in imaging modalities during the study and novel methods of interpretation that leads to uncertainty in the effect of tividenofusp alfa on these outcomes.[6]

- The main secondary endpoint was the change in CSF levels of heparan sulfate over 24 weeks.[8] With tividenofusp alfa treatment, levels were reduced from 837.5 ng/mL at baseline to 69 ng/mL at Week 24, reflecting a mean percent reduction of 91.4% (95% CI: 90 to 92).[6] Levels of CSF heparan sulfate observed at 24 weeks are levels observed in healthy individuals, which range from 50 to 70 ng/mL, and are almost always below 200 ng/mL.[6,9] The treatment effect appears sustained beyond Week 24, although there was incomplete follow-up of subjects beyond that time point.[6]
- Heparan sulfate is theorized to be the toxic substrate responsible for neurodegeneration in MPS II.[6] A key review issue for the FDA was whether reduction in CSF levels of heparan sulfate could reasonably predict clinical benefit in patients with severe MPS II.[6] Nonclinical, clinical and literature data were submitted to the FDA to support reduction in CSF levels of heparan sulfate can predict clinical benefit in the neurologic manifestations of Hunter syndrome.[6] The nature of the benefit (e.g., preventing neurocognitive decline vs. delaying the rate of decline in neurocognition) is not yet known.[6] It is hypothesized that once irreversible CNS damage has occurred, initiating an intervention to replace the deficient enzyme may not benefit patients.[6] It also remains uncertain whether (or how to define) a cognitive function threshold and/or age threshold beyond which initiating treatment with tividenofusp alfa will or will not result in benefit.[6] At the present time, there are key residual uncertainties including the MPS II population (e.g., patients who initiate treatment with minimal/no neurodegeneration vs advanced neurodegenerative disease, younger MPS II patients vs older MPS II patients, etc.) in whom reductions in CSF heparan sulfate are reasonably likely to predict clinical benefit on the neuronopathic manifestations of the disease.[6] Another uncertainty is what is the nature of the benefit (e.g., preventing neurocognitive decline versus slowing the rate of decline in neurocognition) of treatment with tividenofusp alfa.[6]
- An ongoing phase 2/3, multicenter, double-blind, randomized trial of tividenofusp alfa as compared with standard-of-care enzyme replacement therapy (idursulfase)(ClinicalTrials.gov number, NCT05371613) will evaluate the relative effects on safety, cognitive, and behavioral outcomes in patients with MPS II.[8]

- Safety signals:
  - Tividenofusp alfa has a boxed warning for risk of hypersensitivity reactions including anaphylaxis.[7]
  - In the phase 1/2 trial, a total of 41 participants (87%) had at least one infusion-related reaction, with moderate symptoms in 55% of participants and severe symptoms in 6% of participants.[8] Infusion-related reactions were generally clinically manageable with premedication, by slowing the infusion rate, reducing the dose, or both. A small number of participants required a slower dose-escalation phase.[8] The incidence of infusion-related reactions declined over time and the use of premedication, including glucocorticoids, also appeared to decrease as the study progressed.[8] One participant with previous idursulfase exposure had severe infusion-related reactions in weeks 3 and 4 that met the Sampson criteria for anaphylaxis.[8] The dose in this participant was escalated slowly to the target of 15 mg per kilogram at week 30, and he continued treatment.[8]
  - Other common adverse events included upper respiratory tract infection (60%), pyrexia (55%), cough (47%), vomiting (43%), diarrhea (40%), rash (40%), anemia (38%), coronavirus disease 2019 (38%), and rhinorrhea (38%).[8]
  - Administration of tividenofusp may cause anemia and/or membranous nephropathy.[7] The manufacturer recommends obtaining hemoglobin levels before treatment and monitoring serum creatinine levels and urine-to-protein creatinine ratio during therapy.[7]

See **Table 2** for major evidence limitations including:

- Risk of selection, performance, and detection bias.
- Applicability concerns related to appropriate populations for treatment (i.e. primarily children with severe MPS II).

Table 2. Comparative Evidence Table for Tividenofusp alfa-eknm

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Muenzer, J., et al[6,8] Phase 1/2, OL, MC single-arm study	4 different dosing regimens in 5 cohorts: Cohort A: Tividenofusp alfa 3 mg/kg/wk x 2 wks, 7.5 mg/kg/wk x 2 wks, 15 mg/kg/wk x 4 weeks, then 30 mg/kg via IV infusion once a week for 18 wks Cohort B1: Tividenofusp alfa 3 mg/kg/wk x 12 weeks then 3, 7.5, or 15 mg/kg/wk x 12 weeks via IV infusion Cohort B2: Tividenofusp alfa 7.5 mg/kg via IV infusion once a week x 24 wks Cohorts B3, C, D and E: Tividenofusp alfa 15 mg/kg via IV infusion once a week x 24 wks Trial Duration: 24 weeks followed by 80-week safety extension (30 mg/kg and 15 mg/kg dosing regimens) and 157-week OL extension (15 mg/kg for all participants)	Demographics: -Median age: 5 yo (range: 3 months to 13 yo) - nMPS II: 44 (94%) - nnMPS II: 3 (6%) - Previous ERT: 32 (68%) - Male: 100% - Race White: 27 (57%) Asian: 4 (9%) Black: 4 (9%) Not Reported: 8 (17%) Other: 1 (2%) More than 1 race: 3 (6%) Key Inclusion Criteria: -Males with MPS II -aged ≤ 18 yo Key Exclusion Criteria: -Use of any CNS-targeted enzyme replacement therapy within 3 months of screening for participants aged 5 years and older or within 6 months for those less than 5 years of age. -Use of gene therapy or stem cell therapy at any time (except for participants in Cohort E) -Clinically significant thrombocytopenia or other coagulation abnormality -Contraindication for lumbar punctures -Clinically significant history of stroke, epilepsy, head trauma with loss consciousness, or any CNS disease not MPS II-related within 1 year of screening -Placement of a VP shunt or any other brain surgery within 30 days of screening	ITT: Total = 47 Dose-finding cohorts (A, B1, B2): n=20 Standard 15 mg/kg dosing cohorts (B3, C, D,E): n=27 PP: 1. 46 Attrition: 1. 1 (2%)	Primary Endpoints: Change from baseline in urinary GAG concentrations Baseline: 44.1 mg/mmol creatinine Week 24: 13 mg/mmol creatinine 57% reduction 95% CI: 49 to 65 Secondary Endpoints Mean change in CSF heparan sulfate level from baseline to Week 24 Baseline: 837.5 ng/mL Week 24: 69 ng/mL 91% reduction 95% CI: 90 to 92 Mean change in urinary heparan sulfate level from baseline to Week 24 Baseline: 97.2 ng/mL Week 24: 8.1 ng/mL 86% reduction 95% CI 83 to 89	NA for all	TEAEs: Mild: 8 (17%) Moderate: 35 (74%) Severe: 4 (9%) Infusion-related reactions: 27 (57%) Anemia: 11 (23%) AE leading to dose interruption: 34 (72%) Upper respiratory tract infection 11 (23%) Pyrexia 11 (235) Cough 8 (17%) Vomiting 14 (30%) Diarrhea 9 (19%) Rash 10 (21%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Not randomized; no comparator group. Performance Bias: High. Single-arm; OL study. Detection Bias: High. Single-arm; OL design. Attrition Bias: Low. 1 patient discontinued the study due to an adverse event. Reporting Bias: Low. All outcomes reported as prespecified in the protocol. Other Bias: Unclear. Trial design, execution, and data analysis completed by the manufacturer. **Applicability**: Patient: Children less than 18 yo with MPS II were included in this study. 94% had nMPS II. Intervention: Primarily a dose finding safety study. Dosing started at 3 mg/kg once a week and titrated up to 15 mg/kg once a week. Comparator: No comparator, OL study design. Outcomes: Safety was the primary outcome. Impact on biomarkers of substrate accumulation in CNS and urine were surrogate, secondary endpoints. Clinical impact of reducing GAG and heparan sulfate levels has not been determined in MPS II population. Setting: 7 sites in North America and Europe 4 sites in the United States; 1 site each in Canada, United Kingdom, and Netherlands

Abbreviations: AE = adverse event; RR = absolute risk reduction; CI = confidence interval; CSF = cerebrospinal fluid; DB = double-blind; ERT = enzyme replacement therapy; GAGs = glycosaminoglycans; ITT = intention to treat; kg = kilograms; IV= intravenous; MPS II = Type II mucopolysaccharidosis; MC = multi-center; mg = milligrams; N = number of subjects; NA = not applicable; nMPS II = Neuronopathic MPS II; nnMPS II = non-neuronopathic MPS II; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open-label; PP = per protocol; RCT = randomized controlled trial; TEAEs = treatment-emergent adverse events; VP = ventriculoperitoneal; wks = weeks; yo = years old

References:

1. Center for Drug Evaluation and Research. Application Number 1251510/0. Medical Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125151s0000_Elaprase_MedR.pdf Accessed June 2, 2026.
2. Muenzer J, Wraith JE, Beck M, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). *Genet Med*. Aug 2006;8(8):465-73. doi:10.1097/01.gim.0000232477.37660.fb
3. ELAPRASE (idursulfase) injection for intravenous infusion. Prescribing Information. Lexington, MA; Shire Human Genetic Therapies, Inc. 11/2018.
4. Okuyama T, Tanaka A, Suzuki Y, et al. Japan Elaprase Treatment (JET) study: idursulfase enzyme replacement therapy in adult patients with attenuated Hunter syndrome (Mucopolysaccharidosis II, MPS II). *Mol Genet Metab*. Jan 2010;99(1):18-25. doi:10.1016/j.ymgme.2009.08.006
5. Giugliani R, Hwu W-L, Tylki-Szymanska A, Whiteman DAH, Pano A. A multicenter, open-label study evaluating safety and clinical outcomes in children (1.4–7.5 years) with Hunter syndrome receiving idursulfase enzyme replacement therapy. *Genet Med*. 2014/06/01/ 2014;16(6):435-441. doi:https://doi.org/10.1038/gim.2013.162
6. Center for Drug Evaluation and Research. Application Number 761485Orig1s000. Integrated Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2026/761485Orig1s000IntegratedR.pdf Accessed June 2, 2026.
7. AVLAYAH (tividenofusp alfa-eknm) for intravenous infusion. Prescribing Information. South San Francisco, CA; Denali Therapeutics, Inc. 3/2026.
8. Muenzer J, Burton BK, Harmatz P, et al. An Intravenous Brain-Penetrant Enzyme Therapy for Mucopolysaccharidosis II. *The New England journal of medicine*. Jan 1 2026;394(1):39-50. doi:10.1056/NEJMoa2508681
9. Hendriksz CJ, Muenzer J, Vanderver A, et al. Levels of glycosaminoglycans in the cerebrospinal fluid of healthy young adults, surrogate-normal children, and Hunter syndrome patients with and without cognitive impairment. *Mol Genet Metab Rep*. Dec 2015;5:103-106. doi:10.1016/j.ymgmr.2015.11.001
10. McBride KL, Berry SA, Braverman N. Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi derived practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. Nov 2020;22(11):1735-1742. doi:10.1038/s41436-020-0909-z
11. Martin R, Beck M, Eng C, et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). *Pediatrics*. Feb 2008;121(2):e377-86. doi:10.1542/peds.2007-1350
12. Al-Hertani W, Pathak RR, Evuarherhe O, et al. Intravenous Idursulfase for the Treatment of Mucopolysaccharidosis Type II: A Systematic Literature Review. *Int*. Aug 6 2024;25(16)doi:10.3390/ijms25168573
13. da Silva EM, Strufaldi MW, Andriolo RB, Silva LA. Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome). *Cochrane Database Syst Rev*. Feb 5 2016;2(2):Cd008185. doi:10.1002/14651858.CD008185.pub4
14. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract*. Apr 2017;23(2):377-381. doi:10.1111/jep.12629

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVLAYAH™ safely and effectively. See full prescribing information for AVLAYAH.

AVLAYAH (tividenofusp alfa-eknm) for injection, for intravenous use
Initial U.S. Approval: 2026

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

See full prescribing information for complete boxed warning.

- **Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. (5.1)**
- **Initiate AVLAYAH in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. (5.1)**
- **If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue AVLAYAH and immediately initiate appropriate medical treatment, including use of epinephrine. (5.1)**

----------INDICATIONS AND USAGE----------

AVLAYAH is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment. (1)

This indication is approved under accelerated approval based on reduction of cerebrospinal fluid heparan sulfate observed in patients treated with AVLAYAH. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s). (1)

Limitations of Use
AVLAYAH is not recommended for use in combination with other enzyme replacement therapies. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administration of AVLAYAH should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. (2.1)
- Obtain a baseline hemoglobin value in all patients. (2.1)
- Recommended AVLAYAH maintenance dosage for pediatric patients who weigh at least 5 kg is 15 mg/kg administered once weekly as an intravenous infusion over approximately 4 hours. (2.2, 2.6)
- Initiate AVLAYAH treatment with a dose escalation regimen. (2.2)
- See the full prescribing information for dosage and administration modifications and monitoring. (2.3)
- See the full prescribing information for preparation and administration instructions. (2.4, 2.6)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 150 mg of tividenofusp alfa-eknm as a lyophilized powder in a single-dose vial for reconstitution and further dilution. (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- *Infusion-Associated Reactions (IARs)*: If a severe IAR occurs, discontinue AVLAYAH and initiate appropriate medical treatment. (5.2)
- *Anemia*: Obtain baseline hemoglobin levels in all patients and monitor 3 months after initiation, and as clinically indicated. Administer appropriate supportive measures for anemia based on clinical judgment. (5.3)
- *Membranous Nephropathy:* Monitor serum creatinine and urinary protein to creatinine ratio. If membranous nephropathy is suspected, conduct diagnostic evaluation and initiate appropriate treatment. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥20%) were IAR, upper respiratory tract infection, ear infection, pyrexia, anemia, cough, vomiting, diarrhea, rash, COVID-19, rhinorrhea, nasal congestion, fall, headache, skin abrasion, and urticaria. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Denali Therapeutics toll-free at 1-833-ONE-DNLI (1-833-663-3654) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2026

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ELAPRASE safely and effectively. See full prescribing information for ELAPRASE.

ELAPRASE® (idursulfase) injection, for intravenous use
Initial U.S. Approval: 2006

WARNING: RISK OF ANAPHYLAXIS

See full prescribing information for complete boxed 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. (5.1, 5.3, 6)

----------INDICATIONS AND USAGE----------

ELAPRASE is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated 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 (1).

----------DOSAGE AND ADMINISTRATION----------

The recommended dosage is 0.5 mg per kg of body weight administered once every week as an intravenous infusion (2).

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 6 mg/3 mL (2 mg/mL) in single-use vial (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions Including Anaphylaxis: Ensure that personnel administering product are adequately trained in cardio-pulmonary resuscitative measures and have ready access to emergency medical services (EMS) (5.1).
- Risk of Hypersensitivity, Serious Adverse Reactions, and Antibody Development in Hunter Syndrome Patients with Severe Genetic Mutations: Hunter syndrome patients aged 7 years and younger with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations experienced a higher incidence of hypersensitivity reactions, serious adverse reactions, and anti-idursulfase antibody development (5.2).
- Risk of Acute Respiratory Complications: Patients with compromised respiratory function or acute febrile or respiratory illness may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient's clinical status prior to administration of ELAPRASE and consider delaying the ELAPRASE infusion (5.3).

----------ADVERSE REACTIONS----------

The most common adverse reactions occurring in at least three patients (≥9%) aged five years and older were headache, pruritus, musculoskeletal pain, urticaria, diarrhea, and cough. The most common adverse reactions occurring in at least three patients (≥10%) aged seven years and younger were pyrexia, rash, vomiting, and urticaria. In all clinical trials, the most common adverse reactions requiring medical intervention were hypersensitivity reactions, and included rash, urticaria, pruritus, flushing, pyrexia, and headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2025

Appendix 2: Proposed Prior Authorization Criteria

Enzyme Replacement Therapy for Hunter syndrome

Goal(s):

- Ensure medically appropriate use of enzyme replacement therapies that are FDA-approved for management of Hunter syndrome (also known as mucopolysaccharidosis [MPS] type II).

Length of Authorization:

- Up to 12 months

Requires PA:

- Elaprase® (idursulfase) and Avlayah™ (tividenofusp alfa-eknm) for provider administered claims.

Covered Populations: FFS and CCO patients beginning 1/1/26 for idursulfase and 5/1/2026 for tividenofusp alfa

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved age and indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the drug prescribed by or in consultation with a provider with expertise in managing lysosomal storage disorders (i.e. metabolic disorder specialist, endocrinologist, geneticist).	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient prescribed any other enzyme replacement therapies for Hunter syndrome? Note: Use of dual enzyme replacement therapy in Hunter syndrome has not been evaluated.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5

Approval Criteria		
5. Has the diagnosis of Hunter syndrome (or MPS type II) been confirmed by either: • genetic testing OR • an enzyme assay showing deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma?	**Yes:** Go to #6 Document date and test results_____	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for idursulfase?	**Yes:** Go to #7	**No:** Go to #10
7. Is the patient aged 16 months or older? Note: The safety and efficacy of idursulfase in patients aged less than 16 months has not been established.	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there documentation of one of the following symptoms of MPS type II: • Hepatosplenomegaly or • Skeletal deformities or • Neurocognitive decline or • Cardiovascular disorders or • Impaired respiratory function ?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Have one of the following tests to document baseline disease severity been documented: • Spleen volume or • Liver volume or • Forced vital capacity (FVC) or • 6-minute walk test (6MWT)?	**Yes**: Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for tividenofusp alfa-eknm?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Is there documentation of neurologic manifestations consistent with Hunter syndrome (e.g., cognitive impairment, developmental delay, seizures, or structural brain abnormalities on MRI)?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Have baseline hemoglobin, serum creatinine and urinary protein to creatinine levels been obtained? Note: Due to risk of anemia, baseline hemoglobin should be obtained before starting therapy and reassessed 3 months afterwards. Because of the risk of membranous nephropathy, creatinine and urinary protein to creatinine ration should be monitored if membranous nephropathy is suspected.	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 8/2026 (DM)
Implementation: TBD