Reference number(s)
7458-A

Specialty Guideline Management
Avlayah

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Avlayah	tividenofusp alfa-eknm

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Avlayah is 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.

This indication is approved under accelerated approval based on the reduction of cerebrospinal fluid heparan sulfate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitations of Use

Avlayah is not recommended for use in combination with other enzyme replacement therapies for the treatment of Hunter syndrome.

All other indications are considered experimental/investigational and not medically necessary.

Documentation

Submission of the following information is necessary to initiate the prior authorization review:

Initial Requests:

- Chart notes, medical records, or lab results documenting all of the following:
  - Enzyme assay demonstrating a deficiency of iduronate-2-sulfatase enzyme activity (i.e., less than or equal to 10% of the lower limit of the normal range, per laboratory preforming the test).
  - Pathogenic (or likely pathogenic) variant in the IDS gene.
  - Baseline cerebrospinal fluid, blood, or urine heparan sulfate; hemoglobin, serum creatinine, and urinary protein to creatinine ratio assessments.

Continuation Requests:

- Chart notes, medical records, or lab results documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression [e.g., improvement, stabilization, or slowing of disease progression for cerebrospinal fluid, blood, or urine heparan sulfate levels; Vineland Adaptive Behavior Scale Adaptive Score Composite, liver volume, 6-minute walk test (6MWT), cognitive and language-and-motor domain age-equivalent score (AES), Bayley scales of infant and toddler development, third edition (BSID-III); or nonverbal index (NVI) of the Kaufman assessment battery for children, second edition (KABC-II)].

Prescriber Specialties

This medication must be prescribed by or in consultation with a physician who specializes in the treatment of metabolic disease and/or lysosomal storage disorders.

Coverage Criteria

Mucopolysaccharidosis II (MPS II, Hunter syndrome)[1-4]

Authorization of 12 months may be granted for treatment of MPS II (Hunter syndrome) when all of the following criteria are met:

- Member is 3 months to 13 years of age.
- Member weighs 5 kg or greater.
- Diagnosis of MPS II is confirmed by both of the following:

  - Enzyme assay demonstrating a deficiency of iduronate-2-sulfatase (I2S) enzyme activity (i.e., less than or equal to 10% of the lower limit of the normal range, per laboratory preforming the test) in plasma, white blood cells, and/or skin fibroblasts, and
  - Pathogenic (or likely pathogenic) variant in the IDS gene.
- Member has neuronopathic MPS II (e.g., developmental delay, cognitive impairment, behavioral issues, seizures, ataxia, gait disturbances).
- Member does not have advanced neurologic impairment.
- Cerebrospinal fluid, blood, or urinary heparan sulfate; hemoglobin, serum creatinine, and urinary protein to creatinine ratio have been assessed at baseline and will be monitored as clinically appropriate.
- Member does not have documented loss of activity of sulfatases other than iduronate-2-sulfatase (I2S), indicating multiple sulfatase deficiency.
- Member does not have documented mutation of other genes, including loci adjacent to the IDS gene (e.g., fragile X mental retardation 1 [FMR1] or AF4/FMR2 family member 2 [i.e., AFF2 or FMR2]) that are known to be associated with developmental delay, seizures, or other significant central nervous system (CNS) disorders.
- Member does not have clinically significant thrombocytopenia (i.e., platelet count less than 100,000 mm^3), other clinically significant coagulation abnormality, or significant active bleeding.
- Member does not have clinically significant anemia, defined as a hemoglobin level less than 10.0 g/dL.
- Member does not have contraindication(s) to lumbar puncture procedure.
- Member does not have any clinically significant CNS trauma or disorder, including severe untreated intracranial hypertension, that, in the opinion of the provider, may make treatment with the requested medication unsafe for the member.
- Member does not have history of serious adverse reaction to the I2S enzyme or any component of the requested medication (e.g., hypersensitivity or anaphylaxis requiring hospitalization).
- The requested medication will not be used in combination with other enzyme replacement therapies for the treatment of Hunter syndrome (e.g., Elaprase).
- Initial and subsequent doses of the requested medication will not exceed 15 mg/kg once weekly.

Continuation of Therapy[1,4]

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in the coverage criteria section who meet all of the following criteria:

- Member demonstrates a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression [e.g., improvement, stabilization, or slowing of disease progression for cerebrospinal fluid, blood, or urine heparan sulfate levels; Vineland Adaptive Behavior Scale Adaptive Score Composite, liver volume, 6-minute walk test (6MWT), cognitive and language-and-motor domain age-equivalent score (AES), Bayley scales

of infant and toddler development, third edition (BSID-III); or nonverbal index (NVI) of the Kaufman assessment battery for children, second edition (KABC-II)].
- The requested medication will not be used in combination with other enzyme replacement therapies for the treatment of Hunter syndrome (e.g., Elaprase).
- The requested dose does not exceed 15 mg/kg once weekly.

References

1. Avlayah [package insert]. San Francisco, CA: Denali Therapeutics, Inc.; March 2026.
2. Muenzer J, Beck M, Eng CM, et al. Multidisciplinary management of Hunter syndrome. Pediatrics. 2009;124(6):e1228-e1239.
3. Scarpa M, Lampe C. Mucopolysaccharidosis Type II. 2007 Nov 6 [Updated 2025 Jan 16]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1274/
4. Muenzer J, Burton BK, Harmatz P, et al. An Intravenous Brain-Penetrant Enzyme Therapy for Mucopolysaccharidosis II. N Engl J Med. 2026;394(1):39-50. doi:10.1056/NEJMoa2508681