Reference number(s)
7459-A

Standard Medicare Part B 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 will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

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The following documentation must be available, upon request, for all submissions:

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 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)].

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 less than 18 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 does not have advanced neurologic impairment.
- Hemoglobin, serum creatinine, and urinary protein to creatinine ratio have been assessed at baseline and will be monitored as outlined in the manufacturer's prescribing information.
- The requested medication will not be used in combination with other enzyme replacement therapies for the treatment of Hunter syndrome (e.g., Elaprase).

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- Initial and subsequent doses of the requested medication will not exceed 15 mg/kg once weekly.

Continuation of Therapy[4]

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- Member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the Coverage Criteria section.
- 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.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Avlayah.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Recognition and diagnosis of mucopolysaccharidosis II (Hunter Syndrome).
- Multidisciplinary management of Hunter syndrome.
- An Intravenous Brain-Penetrant Enzyme Therapy for Mucopolysaccharidosis II.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Avlayah are covered.

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Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using enzyme assays or genetic testing to confirm the diagnosis prior to using Avlayah to treat MPS II can be found in a guideline published by Martin et al. Diagnosis can be confirmed by assessing the enzyme activity on cultured fibroblasts, leukocytes, plasma, or serum. Absent or low I2S activity in males is diagnostic of Hunter syndrome. Mutation analysis may be used to confirm Hunter syndrome in males. Mutations that result in complete absence of the enzyme or its activity are commonly associated with Hunter syndrome with neurologic involvement.

The prescribing information for Avlayah recommends against its use in combination with other enzyme replacement therapies for the treatment of Hunter syndrome.

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. Martin R, Beck M, Eng C, et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). Pediatrics. 2008;121(2). Available at: www.pediatrics.org/cgi/content/full/121/2/e377.
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.

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