Clinical Policy: Tividenofusp Alfa-eknm (Avlayah)

Reference Number: PA.CP.PHAR.748
Effective Date: 06/2026
Last Review Date: 05/2026

Description

Tividenofusp alfa-eknm (Avlayah™) is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme.

FDA Approved Indication(s)

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 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).

Limitation(s) of use: Avlayah is not recommended for use in combination with other enzyme replacement therapies for the treatment of Hunter syndrome.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Avlayah is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Mucopolysaccharidosis II: Hunter Syndrome (must meet all)**:**

1. Diagnosis of MPS II (Hunter syndrome) confirmed by one of the following (a or b):
   a. Enzyme assay demonstrating a deficiency of iduronate 2-sulfatase (*IDS*) activity;
   b. Genetic confirmation of pathogenic or likely pathogenic mutation(s) in the *IDS* gene;
2. Age < 18 years at initiation of Avlayah;
3. Member's weight meets both of the following (a and b):
   a. Documentation of current weight in kg;
   b. Current weight ≥ 5 kg;
4. Member does not have advanced neurological impairment (e.g., severe cognitive decline, profound functional dependence);
5. Avlayah is not prescribed concurrently with Elaprase®;
6. Dose does not exceed 15 mg/kg per week.

Approval duration: 12 months

B. Other diagnoses/indications
1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Mucopolysaccharidosis II: Hunter Syndrome (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy as evidenced by improvement or stabilization in the individual member's MPS II manifestation profile *(see Appendix D for examples)*;
3. Member does not have advanced neurological impairment (e.g., severe cognitive decline, profound functional dependence);
4. Avlayah is not prescribed concurrently with Elaprase;
5. Documentation of member's current weight in kg;
6. If request is for a dose increase, new dose does not exceed 15 mg/kg per week.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
IDS: iduronate 2-sulfatase
MPS II: mucopolysaccharidosis II

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): none
- Boxed warning(s): hypersensitivity reaction including anaphylaxis

Appendix D: General Information

- The presenting symptoms and clinical course of MPS II can vary from one individual to another. Positive response to MPS II therapy may include, but is not limited to, improvement or stabilization in any of the following:
  - Percent predicted forced vital capacity (FVC)
  - 6-minute walk test
  - Splenomegaly
  - Diarrhea
  - Joint stiffness
  - Growth deficiencies
  - Adaptive behavior and cognition (e.g., Vineland-3 Adaptive Behavior score, Bayley Scales of Infant and Toddler Development-Third Edition [BSID-III] score)
  - Hepatomegaly
  - Hearing

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>MPS II</td><td>Recommended starting dose for patients weighing ≥ 5 kg is 3 mg/kg IV once weekly. Dose is titrated to a maintenance dose of 15 mg/kg once weekly per the following dose escalation regimen:

<table><tr><th>Dosing Week</th><th>Dosage Level</th></tr><tr><td>Week 1 to Week 4</td><td>3 mg/kg once weekly</td></tr><tr><td>Week 5 to Week 8</td><td>7.5 mg/kg once weekly</td></tr><tr><td>Week 9 and beyond</td><td>15 mg/kg once weekly</td></tr></table></td><td>15 mg/kg/week</td></tr>
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VI. Product Availability

Single-dose vial for injection: 150 mg as a lyophilized powder

VII. References

1. Avlayah Prescribing Information. South San Francisco, CA: Denali Therapeutics, Inc.; March 2026. Available at: https://www.denalitherapeutics.com/wp-content/uploads/2026/03/USPI-AVLAYAH-Mar2026.pdf. Accessed April 8, 2026.
2. 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.
3. 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). Genetics in Medicine. 2020;22:1735-42.
4. Scarpa M, Lampe C. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1274/. Accessed April 8, 2026.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-

date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3590	Unclassified biologics

Reviews, Revisions, and Approvals	Date
Policy created	05/2026