Clinical Policy: Tividenofusp Alfa-eknm (Avlayah)

Reference Number: CP.PHAR.748
Effective Date: 03.24.26
Last Review Date: 11.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® 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:

Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Mucopolysaccharidosis II: Hunter Syndrome (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)*;
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:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

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

Indication	Dosing Regimen	Maximum Dose
MPS II	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: Week 1 to Week 4: 3 mg/kg once weekly Week 5 to Week 8: 7.5 mg/kg once weekly Week 9 and beyond: 15 mg/kg once weekly	15 mg/kg/week

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	P&T Approval Date
Policy created pre-emptively	08.19.25	11.25
Drug is now FDA approved – criteria updated per FDA labeling: revised age requirement from ≥ 3 months to < 18 years at initiation of Avlayah; added requirements for weight ≥ 5 kg, absence of	04.29.26	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
advanced neurological impairment, and maximum dose of 15 mg/kg per week; references reviewed and updated.		

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.