Neighborhood Health Plan OF RHODE ISLAND™
910 Douglas Pike, Smithfield, RI 02917 : 1-800-963-1001 : nhpri.org

Avlaya (tividenofusp alfa-eknm) (Intravenous)

Effective Date: 11/1/2026
Review Date: 8/17/2026
Scope: Medicaid, Commercial, Medicare

I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

Max Units (per dose and over time) [HCPCS Unit]:

- 1,800 mg every 7 days

III. Summary of Evidence:

Avlayah (tividenofusp alfa-eknm) is a lysosomal enzyme replacement therapy indicated for the treatment of the neurologic manifestations of Hunter syndrome (mucopolysaccharidosis type II, MPS II) in presymptomatic or symptomatic pediatric patients weighing at least 5 kg, initiated prior to advanced neurologic impairment. Approval was supported by a phase 1/2 multicenter, multi-cohort, enrolling 47 pediatric patients aged 3 months to 13 years with MPS II, including severe/neuronopathic and attenuated/non-neuronopathic phenotypes, with approximately two-thirds previously treated with enzyme replacement therapy. The primary endpoint demonstrated a mean 91% reduction in cerebrospinal fluid heparan sulfate (CSF HS) at 24 weeks, with 93% of patients achieving levels below the upper limit of normal, a surrogate endpoint reasonably likely to predict disease modification. The most common adverse reactions (incidence ≥20%) were infusion-associated reactions, upper respiratory tract infection, ear infection, pyrexia, anemia, cough, vomiting, diarrhea, rash, COVID-19, rhinorrhea, nasal congestion, fall, headache, skin abrasion, and urticaria. Avlayah is the first therapy designed to cross the blood–brain barrier to address the neurologic complications in MPS II.

IV. Initial Criteria

Coverage is provided in the following conditions:

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Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements.

- Member is pediatric and weighs at least 5 kg; **AND**
- Avlayah is prescribed by or in consultation with a physician who specializes in the treatment of metabolic disease and/or lysosomal storage disorders; **AND**
- Documented baseline age-appropriate values for one or more of the following have been obtained:
    - Members 5 years of age or greater: 6-minute walk test (6MWT), percent predicted forced vital capacity (FVC), joint range of motion, left ventricular hypertrophy, growth, quality of life measure (CHAQ/HAQ/MPS HAQ), and/or urinary glycosaminoglycan (uGAG)/urinary heparan sulfate (uHS); **OR**
    - Members less than 5 years of age: spleen volume, liver volume, FVC, 6-MWT, and/or urinary glycosaminoglycan (uGAG)/urinary heparan sulfate (uHS); **AND**

NOTE: For very young members in which FVC or 6-MWT are not suitable for measuring, requests will be reviewed on a case-by-case basis.

Universal Criteria [1-5]

- Will not be used in combination with other enzyme replacement therapies indicated for the treatment of Hunter Syndrome (e.g., Elaprase (idursulfase), etc.); **AND**
- Member hemoglobin levels will be obtained prior to initiation of therapy, at 3 months after initiation, and periodically thereafter, as clinically indicated; **AND**
- Member serum creatinine and urinary protein to creatinine ratio will be assessed and member will be monitored for the development of membranous nephropathy throughout therapy; **AND**

Hunter Syndrome (Mucopolysaccharidosis II; MPS II) † Φ [1,5]

- Member has documentation of a definitive diagnosis of MPS II as confirmed by one of the following:
    - Deficient or absent iduronate 2-sulfatase (I2S) enzyme activity in white cells, fibroblasts, or plasma in the presence of normal activity of at least one other sulfatase; **OR**
    - Detection of pathogenic (or likely pathogenic) variants in the *IDS* gene by molecular genetic testing; **AND**
- Member has clinical documentation of neurologic manifestations associated with MPS II, or the patient is presymptomatic and at risk for neurologic manifestations; **AND**

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- The member does not have advanced neurologic impairment, as determined by the treating specialist

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

V. Renewal Criteria

Authorizations can be renewed based on the following criteria:

- Member continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section IV; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe hypersensitivity reactions including anaphylaxis, severe infusion associated reactions (chills, angioedema, hypotension, tachycardia, urticaria, vomiting, wheezing, pyrexia, flushing, erythema, rash, cough, diarrhea, abdominal pain, retching, headache, irritability, papules, etc.), severe anemia, membranous nephropathy, etc.; **AND**
- Member has demonstrated a beneficial response to therapy compared to pretreatment age-appropriate baseline values in one or more of the following:
    - Members 5 years of age or greater: stabilization or improvement in percent predicted FVC and/or 6-MWT, increased joint range of motion, decreased left ventricular hypertrophy, improved growth, improved quality of life (clinically meaningful change in the CHAQ/HAQ/MPS HAQ disability index), and/or reduction in uGAG/uHS levels; **OR**
    - Members less than 5 years of age: reductions in spleen and/or liver volume, stabilization/improvement in FVC and/or 6-MWT, and/or reduction in uGAG/uHS levels

VI. Dosage/Administration

Indication	Dose
Hunter Syndrome;	**Starting Dose for pediatric members weighing at least 5 kg:** 3 mg/kg administered once weekly via intravenous infusion.

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<table>
<tr>
<td>MPS II</td>
<td><u>Maintenance Dose for pediatric members weighing at least 5 kg</u>: 15 mg/kg administered once weekly via intravenous infusion.

<u>NOTE</u>:

• Refer to the dosing table below for the appropriate dose escalation regimen and administer each dosage level for at least 4 weeks before escalating to the next dosage level.

• Do not escalate the dosage level if the current dosage level is not tolerated.

<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>
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VII. Billing Code/Availability Information

<u>HCPCS Code:</u>

- J1757 – Injection, tividenofusp alfa-eknm, 1 mg

<u>NDC:</u>

- Avlayah 150 mg lyophilized powder for injection in a single-dose vial: 84976-0001-xx

VIII. References

1. Avlayah [package insert]. San Francisco, CA; Denali Therapeutics, Inc.; March 2026. Accessed April 2026.
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11. Muenzer J, Wraith J, Beck M, *et al.* A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). *Genet Med* 8, 465–473 (2006) doi:10.1097/01.gim.0000232477.37660.fb
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13. Muenzer J, Giugliani R, Scarpa M, Tylki-Szymańska A, Jego V, Beck M. Clinical outcomes in idursulfase-treated patients with mucopolysaccharidosis type II: 3-year data from the hunter outcome survey (HOS). Orphanet J Rare Dis. 2017 Oct 3;12(1):161. doi: 10.1186/s13023-017-0712-3. PMID: 28974237; PMCID: PMC5627440.
14. Muenzer J, Burton Bk, Harmatz P, et al. An Intravenous Brain-Penetrant Enzyme Therapy for Mucopolysaccharidosis II. N Engl J Med 2026;394:39-50. DOI: 10.1056/NEJMoa2508681

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15. McBride, K.L., Berry, S.A., Braverman, N. *et al.* Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi derived practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 22, 1735–1742 (2020). https://doi.org/10.1038/s41436-020-0909-z

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
E76.1	Mucopolysaccharidosis, type II

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)

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Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Policy Rationale:

Avlayah was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use of Avlayah according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For Medicare members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.

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