Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
tividenofusp alfa-eknm (Avlayah™)	MP-RX-FP-189-26	☒ MMM MA ☒ MMM MultiHealth	7/22/2026	7/22/2026
			Last Review Date: 7/22/2026	Frequently Revision: Annual

Service Category:

- ☐ Anesthesia
- ☐ Surgery
- ☐ Radiology Procedures
- ☐ Pathology and Laboratory Procedures
- ☐ Medicine Services and Procedures
- ☐ Evaluation and Management Services
- ☐ DME/Prosthetics or Supplies
- ☒ Other: Part B Drugs

Service Description:

This document addresses Avlayah™ (tividenofusp alfa-eknm), an enzyme replacement therapy approved by the Food and Drug Administration (FDA) to treat neurologic manifestations of Mucopolysaccharidosis II (Hunter syndrome) when initiated in presymptomatic or symptomatic pediatric individuals 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 individuals treated with Avlayah. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Background Information:

The mucopolysaccharidoses are a group of inherited metabolic diseases caused by the deficiency of lysosomal enzymes needed to break down mucopolysaccharides or glycosaminoglycan (GAGs). The progressive accumulation of GAGs in lysosomes leads to respiratory, cardiac, skeletal and connectivity, neurologic and ophthalmologic complications. There are seven distinct types of mucopolysaccharidosis (I, II, III, IV, VI, VII, and IX). Accurate diagnosis is important to provide disease-specific enzyme replacement therapy. Diagnosis is confirmed through urinary GAG concentration measurement, enzymatic activity measurement or genetic testing.

Avlayah is indicated for the treatment of neurologic manifestations of Hunter syndrome (MPS II) in presymptomatic or symptomatic pediatric patients weighing at least 5 kg, prior to advanced neurologic impairment. Avlayah is manufactured using Denali Therapeutics' proprietary TransportVehicle™ (TV) platform. The molecule consists of the enzyme iduronate-2-sulfatase (IDS) fused to an engineered Fc domain designed to bind the transferrin receptor. This fusion construct enables receptor-mediated transcytosis across the blood-brain barrier (BBB), facilitating enzyme delivery to the central nervous system to address neurologic manifestations of the disease that are not accessible via conventional enzyme replacement therapies.

Avlayah has a boxed warning for hypersensitivity reactions including life-threatening anaphylaxis. Reactions have occurred during the early course of enzyme replacement therapy and after extended duration of therapy. Appropriate medical support should be available during Avlayah administration. If a severe hypersensitivity reaction occurs, Avlayah should be discontinued immediately, and appropriate medical treatment should be initiated. Patients should be monitored closely following such reactions, and the risks and benefits of readministering Avlayah should be carefully weighed.

Approved Indications

A. 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.

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Limitations of Use: AVLAYAH is not recommended for use in combination with other enzyme replacement therapies.

Other Uses

A. None.

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Medical Necessity Guidelines:

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Tividenofusp-alfa-eknm (Avlayah™)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

Initial requests for Avlayah (tividenofusp alfa-eknm) may be approved if the following criteria are met:

i. Individual is less than 18 years of age AND weighs at least 5 kg; **AND**

ii. Individual has a diagnosis of Mucopolysaccharidosis II (MPS II, Hunter syndrome) demonstrated by (Scarpa 2011, Wraith 2008):

A. Deficiency in iduronate 2-sulfatase enzyme activity as measured in fibroblasts or leukocytes combined with normal enzyme activity level of another sulfatase, and documentation is provided;

OR

B. Pathologic iduronate 2-sulfatase gene mutation, and documentation is provided; **AND**

iii. Individual is requesting Avlayah for the treatment of neurologic manifestations of MPS II (Hunter syndrome); **AND**

iv. Individual does not have advanced neurologic impairment.

B. Criteria For Continuation of Therapy

Continuation requests for Avlayah (tividenofusp alfa-eknm) may be approved if the following criteria are met:

i. Documentation is provided that there is clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to reduction in cerebrospinal fluid heparan sulfate (HS), improvement in neurologic function) compared to the predicted natural history trajectory of disease; **AND**

ii. Documentation is provided that the individual is being monitored in accordance with the Prescribing Information, including monitoring of hemoglobin levels prior to initiation, at 3 months after initiation, and periodically thereafter as clinically indicated; and serum creatinine and urinary protein-to-creatinine ratio for membranous nephropathy; **AND**

iii. Documentation is provided that the individual has not experienced unacceptable toxicity from Avlayah therapy, including but not limited to severe hypersensitivity reactions, including

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anaphylaxis, severe infusion-associated reactions, clinically significant anemia, or membranous nephropathy.

C. Authorization Duration

i. Initial Approval Duration: Up to 12 months
ii. Reauthorization Approval Duration: Up to 12 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

Avlayah (tividenofusp alfa-eknm) may not be approved for the following:

i. Individual using in combination with Elaprase or with other enzyme replacement therapies for the treatment of Hunter syndrome ; **OR**
ii. When the above criteria are not met and for all other indications.

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Limits or Restrictions:

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosing/Limits

tividenofusp alfa-eknm (Avlayah) injection 150 mg single-dose vial	• Starting dosage:
	  ○ Patients weighing at least 5 kg: 3 mg/kg IV once weekly
	• Maintenance dosage:
	  ○ Patients weighing at least 5 kg: 15 mg/kg IV once weekly

Exceptions	

• To reduce the risk of infusion-associated reactions (IARs), Avlayah should be initiated using the recommended dose-escalation regimen. Each dosage level should be administered for at least 4 weeks before escalating to the next dosage level.
  ○ 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 as maintenance dose	

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Codes Information:

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

ICD-10 Diagnostic Codes:

Codes	Description
E76.1	Mucopolysaccharidosis, type II [Hunter's syndrome]

HCPCS Codes:

Codes	Description
C9399	Unclassified drugs or biologicals [when specified as Avlayah (tividenofusp alfa-eknm)]
J3590	Unclassified biologics [when specified as Avlayah (tividenofusp alfa-eknm)]
S9357	Home infusion therapy, enzyme replacement intravenous therapy, (e.g., Imiglucerase); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

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Reference Information:

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: April 16, 2026.
2. Denali Therapeutics Inc. AVLAYAH™ (tividenofusp alfa-eknm) for injection, for intravenous use: Prescribing Information. Denali Therapeutics Inc.; revised March 2026. Accessed July 1, 2026.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lehman TJ, Miller N, Norquist B, Underhill L, Keutzer J. Diagnosis of the mucopolysaccharidoses. Rheumatology (Oxford). 2011;50 Suppl 5:v41-v48. doi:10.1093/rheumatology/ker390.
5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
6. 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.
7. Scarpa M, Almássy Z, Beck M, et al. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. Orphanet J Rare Dis. 2011; 6:72.
8. Wang RY, Bodamer OA, Watson MS, Wilcox WR. American College of Medical Genetics (ACMG) Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genet Med. 2011; 13(5):457-484.
9. Wraith JE, Scarpa M, Beck M, et al. Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. Eur J Pediatr. 2008; 167(3):267-277.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History:

Type of Review	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Policy Inception	Elevance Health's Medical Policy adoption.	7/13/2026	7/22/2026