Original Effective Date: 09/06/2026
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Last P&T Approval/Version: 07/29/2026
Next Review Due By: 07/2027
Policy Number: C30849-A

Avlayah (tividenofusp alfa-eknm)

PRODUCTS AFFECTED

Avlayah (tividenofusp alfa-eknm)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Hunter Syndrome (mucopolysaccharidosis II, MPS II)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. This clinical policy will be reviewed along with state and federal requirements, the benefit being administered and formulary preferencing. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available. The Pharmacy and Therapeutics Committee has determined that biosimilars may be preferred.

A. HUNTER SYNDROME (MUCOPOLYSACCHARIDOSIS II):
   1. Documented diagnosis of Hunter Syndrome (mucopolysaccharidosis II, MPS II)
      AND

2. Documentation diagnosis was confirmed by deficiency in iduronate- 2- sulfatase (IDS) enzyme activity through enzyme or molecular (DNA-based) testing, such as IDS gene testing [DOCUMENTATION REQUIRED]
   AND
3. Documentation of baseline urinary glycosaminoglycan (uGAG) level
   AND
4. Documentation by prescriber of baseline disease activity to be used to evaluate efficacy of therapy at renewal (i.e., liver size, cognitive function test, growth delay, behavioral assessment, physical exam, auditory function evaluation, and organ system assessment)
   NOTE: The same assessment should be used in the follow-up evaluation for reauthorization for continuation of therapy.
   AND
5. Member has no evidence of advanced neurologic impairment
   AND
6. Documentation member weighs at least 5 kg
   AND
7. Avlayah (tividenofusp alfa-eknm) will not be used in combination with another enzyme-replacement therapy for MPS II [Elaprase (idursulfase)]

CONTINUATION OF THERAPY:

A. HUNTER SYNDROME (MUCOPOLYSACCHARIDOSIS II):
   1. Documentation of positive response or disease stability with therapy as demonstrated by decreased urinary glycosaminoglycan (uGAG) levels compared with baseline (prior to therapy) [DOCUMENTATION REQUIRED]
      AND
   2. Documentation of improvement in the condition's signs and symptoms (i.e., attainment of developmental milestones, stabilization or improvement in cognitive functioning, reduction in behavioral abnormalities, decreased joint stiffness, preserved or improved hearing, and stable or improved organ function)
      NOTE: The same assessment should be what was provided on initial review. If the initial assessment tool is not appropriate (i.e., due to change in member's status or age range of the assessment), submit the rationale for change in assessment tool.
      AND
   3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified geneticist, metabolic specialist, pediatric neurologist, pediatric developmentalist, endocrinologist, or a physician who specializes in the treatment of lysosomal storage disorders, or a physician experienced in the management of mucopolysaccharidoses (MPS). [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

Up to 16 years of age

QUANTITY:

Week 1 to Week 4: 3 mg/kg once weekly
Week 5 to Week 8: 7.5 mg/kg once weekly
Week 9 and thereafter: 15 mg/kg once weekly (maintenance dosage)

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

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous

DRUG CLASS:
Mucopolysaccharidosis II (MPS II) – Agents

FDA-APPROVED USES:
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).

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Mucopolysaccharidosis II, MPS II (Hunter Syndrome) is an X-linked multisystem disorder caused by a deficiency of iduronate-2-sulfatase (IDS), an enzyme responsible for breaking down the glycosaminoglycans (GAGs) heparan sulfate (HS) and dermatan sulfate (DS). When IDS is deficient or absent, these GAGs accumulate within lysosomes, leading to cellular dysfunction and progressive damage across multiple organs and tissues, including the central nervous system (CNS).

The disease occurs almost exclusively in young males, approximately 1 in 100,000 to 1 in 170,000 males, although cases of affected females have been reported due to the selective inactivation of the X chromosome inherited by the father. Age of onset, disease severity, and rate of progression vary significantly among affected males.

Treatment of MPS II has centered on enzyme replacement therapy (ERT) with Elaprase (idursulfase), which was approved by the FDA in 2006 and has been shown to improve walking ability in patients 5 years and older and spleen size in patients 16 months and older. ERT with Elaprase can improve or stabilize many somatic manifestations of the disease, but because Elaprase does not cross the blood–brain barrier (BBB), it does not treat the cognitive decline seen in neuronopathic MPS II. Management therefore remains multidisciplinary and may include respiratory, cardiac, orthopedic, neurologic, rehabilitative, and supportive care, with treatment goals shaped by the severity of disease.

Avlayah (tividenofusp alfa-eknm) is an IDS enzyme that delivers IDS to peripheral tissues and to the CNS via receptor-mediated transcytosis across the BBB. The approval of Avlayah is based on the reduction of a key disease biomarker, cerebrospinal fluid heparan sulfate (CSF HS), as a surrogate endpoint reasonably

likely to predict clinical benefit in the treatment of neurologic manifestations of Hunter syndrome when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.

Trial 1 (NCT04251026) was a Phase 1/2, multicenter, international, multicohort, single-arm, open-label trial of Avlayah in 47 pediatric patients with MPS II, including 44 patients with the neuronopathic form and 3 patients with the non-neuronopathic form.

In Trial 1, reductions in CSF HS from baseline were observed in Avlayah-treated pediatric patients with Hunter syndrome. Reductions in urine HS (86%), urine DS (91%), and total urine GAGs (57%) from baseline were observed at Week 24 in Avlayah-treated pediatric patients with Hunter syndrome. Higher serum tividenofusp alfa-eknm concentrations appeared to be associated with greater reductions of CSF HS and urine HS concentrations from baseline, with maximum effect achieved at 15 mg/kg of Avlayah once weekly (the recommended maintenance dosage).

Decreases in CSF HS, the biomarker supporting the accelerated approval of Avlayah, demonstrate that the drug is reaching the brain and potentially affecting the underlying disease biology. However, CSF HS is a surrogate endpoint rather than a direct measure of clinical outcomes, such as cognition or functional status. This is an important consideration, particularly because CSF HS is a relatively new surrogate endpoint in this disease and its ability to reliably predict long-term clinical benefit is still being established. Notably, early clinical data provide supportive signals beyond the biomarker, with treatment associated with stabilization or modest improvements in adaptive behavior, cognition, hearing, and liver volume in the Phase 1/2 trial.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Avlayah (tividenofusp alfa-eknm) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Avlayah include: no labeled contraindications.

Exclusions/Discontinuation:
Patients treated with enzyme replacement therapies, including Avlayah (tividenofusp alfa-eknm), have experienced life-threatening hypersensitivity reactions, including anaphylaxis. If a severe hypersensitivity reaction (e.g., anaphylaxis) or a severe infusion-associated reaction occurs, discontinue Avlayah and immediately initiate appropriate medical treatment, including use of epinephrine.

OTHER SPECIAL CONSIDERATIONS:
Avlayah (tividenofusp alfa-eknm) has a Black Box Warning for risk of anaphylaxis. Initiate Avlayah (tividenofusp alfa-eknm) in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and to seek immediate medical care should symptoms occur.

Initiate Avlayah in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. If a patient reaches and tolerates the maintenance Avlayah dosage, the patient may receive home infusion under the supervision of a healthcare provider. If an Avlayah dose is missed, skip the missed dose. Do not double a dose to compensate for a missed dose. Restart Avlayah treatment as soon as possible, maintaining the one-week interval between infusions thereafter.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association*

(AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.

HCPCS CODE	DESCRIPTION
J3590	Unclassified biologics

AVAILABLE DOSAGE FORMS:
Avlayah SOLR 150MG single-dose vial

REFERENCES

1. Avlayah (tividenofusp alfa-eknm) for injection, for intravenous use [prescribing information]. South San Francisco, CA: Denali Therapeutics Inc.; March 2026.
2. McBride, K. L., Berry, S. A., Braverman, N., et al. (2020). 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, 22(11), 1735–1742. https://doi.org/10.1038/s41436-020-0909-z
3. Denali Therapeutics Inc. (2025). A study of tividenofusp alfa (DNL310) in pediatric participants with Hunter syndrome (ClinicalTrials.gov Identifier: NCT04251026). ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04251026
4. Muenzer, J., Burton, B. K., Harmatz, P., Rajan, D. S., Jones, S. A., van den Hout, J. M. P., & Mitchell, J. J. (2026). An intravenous brain-penetrant enzyme therapy for mucopolysaccharidosis II. New England Journal of Medicine, 394(1), 39–50. https://doi.org/10.1056/NEJMoa2508681
5. Denali Therapeutics Inc. (2025). A study to determine the efficacy and safety of tividenofusp alfa (DNL310) vs idursulfase in pediatric and young adult participants with neuronopathic (nMPS II) or non-neuronopathic mucopolysaccharidosis type II (nnMPS II) (COMPASS) (ClinicalTrials.gov Identifier: NCT05371613). ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05371613
6. National Institutes of Health, Genetic and Rare Diseases Information Center. (2026, February). Mucopolysaccharidosis type 2. Retrieved June 11, 2026, from https://rarediseases.info.nih.gov/diseases/6675/mps-ii

SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q3 2026