CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Avlayah Utilization Management Medical Policy
- Avlayah™ (tividenofusp alfa-eknm intravenous infusion – Denali)

REVIEW DATE: 04/01/2026; selected revision 04/22/2026

OVERVIEW

Avlayah, a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme, 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 ≥ 5 kg prior to advanced neurologic impairment.[1]

This indication is approved under accelerated approval based on the reduction of cerebrospinal fluid heparan sulfate.[1] Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitations of Use: Avlayah is not recommended for use in combination with other enzyme replacement therapies.[1]

Disease Overview

MPS II, or Hunter syndrome, is a rare, X-linked lysosomal storage disorder characterized by a deficiency of iduronate-2-sulfatase, leading to the accumulation of the glycosaminoglycans dermatan sulfate and heparan sulfate.[2-5] Males are almost exclusively affected, although a small number of case reports describe females with Hunter syndrome.[4,5] The onset, progression, and severity of MPS II are variable.[2,3,5] Most patients with MPS II have a severe form of the disease with neurologic involvement, resulting in cognitive impairment and progressive neurologic decline.[2,4,5] This phenotype is referred to as neuronopathic. Alternatively, in the non-neuronopathic phenotype, cognitive function is generally preserved and manifestations are predominantly somatic.[2] These manifestations include coarse facial features, hepatosplenomegaly, cardiac and respiratory disease, short stature, and joint stiffness with contractures.[3,4]

A definitive diagnosis of MPS II is established by demonstrating deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma, or by identification of pathogenic mutations in the iduronate-2-sulfatase gene.[3,6] Treatment of MPS II consists of enzyme replacement therapy with Elaprase® (idursulfase intravenous infusion).[2-5,7] Hematopoietic stem cell transplantation has not demonstrated clear neurologic benefit to date and is not recommended for MPS II due to the high rates of morbidity and mortality associated with this therapy.[3,5]

Clinical Efficacy

The efficacy of Avlayah was demonstrated in a Phase I/II multicenter, international, multi-cohort, single-arm, open-label trial that enrolled 47 pediatric patients with Hunter syndrome; 44 patients had neuronopathic disease and 3 patients had non-neuronopathic disease.[1,8] All of the patients were male; the median baseline age was 5 years (range 3 months to 13 years of age). Of the 47 patients, 32 had previously been treated with enzyme replacement therapy (i.e., Elaprase), with a median duration of prior treatment of 26 months (range 1 month to 134 months). Avlayah demonstrated a significant reduction of heparan sulfate in cerebrospinal fluid. For the 44 patients who had measurements at Week 24, the mean reduction from baseline was 91% (95% confidence interval [CI]: 89%, 92%), with individual reductions ranging from 72% to 98%. At baseline, none of the patients had cerebrospinal fluid heparan sulfate levels below the

upper limit of normal; at Week 24, 93% of patients treated with Avlayah achieved levels below the upper limit of normal.

Dosing Information

The recommended starting dose of Avlayah is 3 mg/kg administered once weekly via intravenous (IV) infusion.[1] To reduce the risk of infusion-associated reactions, patients should follow the dose escalation regimen in Table 1; doses should not be escalated if the current dose was not tolerated. Administer each dose level for at least 4 weeks before escalating to the next dose level. The recommended maintenance dose is 15 mg/kg administered weekly.

Table 1. Recommended Avlayah Dose for Pediatric Patients.[1]

Dosing Week	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

Guidelines

An expert consensus practice resource from the American College of Medical Genetics and Genomics was published in 2020; a recommendation was made to initiate treatment with Elaprase at the time of diagnosis and prior to symptom onset for individuals predicted to have severe MPS II, as well as for individuals with symptoms regardless of the predicted severity.[7] The expert panel also recommended against presymptomatic treatment for individuals expected to have non-neuronopathic Hunter's syndrome; however, this recommendation is complicated by genetic variability and uncertainty in predicting clinical phenotype.

Safety

Avlayah carries a Boxed Warning for hypersensitivity reactions, including anaphylaxis.[1] Avlayah should be initiated in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Avlayah. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Avlayah as well as the monitoring required for adverse events and long-term efficacy, approval requires Aalayah to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Avlayah is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Mucopolysaccharidosis Type II (Hunter Syndrome).** Approve for 1 year if the patient ALL of the following (A, B, C, and D):
   - **A)** Patient weighs ≥ 5 kg; AND
   - **B)** The diagnosis is established by ONE of the following (i or ii):
     - **i.** Patient has a laboratory test demonstrating deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma; OR
     - **ii.** Patient has a molecular genetic test demonstrating an iduronate-2-sulfatase gene variant; AND
   - **C)** According to the prescriber, the patient does not have advanced neurologic impairment; AND
   - **D)** Avlayah is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Approve the following dosing regimens (A, B, and/or C):
   Note: A dosing escalation schedule is recommended as below. Patients are recommended to be maintained at the same dose for 4 weeks prior to escalation. However, if a current dose is not tolerated, patients may remain on this dose for longer than 4 weeks.
   - **A)** For Week 1 to Week 4, the dose must not exceed 3 mg/kg administered intravenously no more frequently than once a week; AND/OR
   - **B)** For Week 5 to Week 8, the dose must not exceed 7.5 mg/kg administered intravenously no more frequently than once a week; AND/OR
   - **C)** For Week 9 and all dosing thereafter, the dose must not exceed 15 mg/kg administered intravenously no more frequently than once a week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Avlayah is not recommended in the following situations:

1. **Concomitant Use of Avlayah with Elaprase® (idursulfase intravenous infusion)**. Elaprase is indicated for Hunter syndrome (Mucopolysaccharidosis type II [MPS II].[9] Use of Avlayah in combination with other enzyme replacement therapies for the treatment of Hunter syndrome (MPS II) is not recommended.[1]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Avlayah™ intravenous infusion [prescribing information]. South San Francisco, CA: Denali; March 2026.
2. Ream MA, Lam WKK, Grosse SD, et al. Evidence and recommendation for mucopolysaccharidosis type II newborn screening in the United States. *Genet Med*. 2023;25(2):100330.
3. Scarpa M, Almassy 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.
4. Muenzer J, Beck M, Eng CM, et al. Multidisciplinary management of Hunter syndrome. *Pediatrics*. 2009;124:e1228-e1239.
5. Giugliani R, Federhen A, Munoz Rojas MV, et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. *Genet Mol Biol*. 2010;33:589-604.
6. D'Avanzo F, Rigon L, Zanetti A, Tomanin R. Mucopolysaccharidosis type II: One hundred years of research, diagnosis, and treatment. *Int J Mol Sci*. 2020;21:E1258.
7. McBride KL, Berry SA, Braverman N; ACMG Therapeutics Committee. Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi derived practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2020 Nov;22(11):1735-1742.

8. 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.
9. Elaprase® intravenous infusion [prescribing information]. Cambridge, MA: Takeda; February 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	04/01/2026
Selected Revision	**Mucopolysaccharidosis Type II (Hunter Syndrome).** The requirement for a patient to be < 18 years of age was removed. The dosing requirements were clarified to state "and/or" to allow for more than one dosing regimen to be approved. A corresponding Note was added to clarify the recommended dosing escalation schedule and to note that patients may be maintained on a dose for longer than 4 weeks depending on tolerability. **Conditions Not Recommended for Approval.** Concomittant use of Avlayah with other enzyme replacement therapies was clarified to specify concomitant use of Avlayah with Elaprase (idursulfase intravenous infusion).	04/22/2026