

tividenofusp alfa-eknm (Avlayah™)

Policy # 00973

Original Effective Date: 07/01/2026

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of tividenofusp alfa-eknm (Avlayah™)† 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 to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of tividenofusp alfa-eknm (Avlayah) for non-FDA approved indications to be **investigational**.*

Background/Overview

Avlayah is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme 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. MPS II is a rare, X-linked lysosomal storage disorder caused by pathogenic variants in the *iduronate-2-sulfatase* (IDS) gene, resulting in deficiency of IDS enzyme activity. This deficiency causes accumulation of GAGs, including heparan sulfate (HS) and dermatan sulfate, throughout the body leading to progressive damage in multiple organs and tissues, including the central nervous system (CNS). Manifestations typically begin between 2 years and 4 years of age. Avlayah is an exogenous source of IDS enzyme fused to a proprietary enzyme transport vehicle that binds to the transferrin receptor allowing delivery of IDS to peripheral tissues and the CNS through receptor-mediated transcytosis across the blood–brain barrier (BBB). Avlayah is the first FDA-approved transferrin receptor therapy designed to specifically cross the BBB. MPS II affects approximately 500 individuals in the US and is classified into neuronopathic and non-neuronopathic phenotypes with approximately two-thirds of patients experiencing neuronopathic disease. Cardiovascular and respiratory failures represent leading causes of death for this patient population.

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Avlayah is supplied as a preservative-free powder for reconstitution in a single dose vial, with each vial containing 150 mg of Avlayah. The recommended starting dosage for pediatric patients weighing at least 5 kg is 3 mg/kg, administered once weekly via intravenous infusion. To reduce the risk of infusion-associated reactions (IARs), the dose should be gradually increased in accordance with the dose-escalation regimen described in the package insert. Each dosage level should be administered for a minimum of 4 weeks before increasing to the next level. The recommended maintenance dosage for pediatric patients weighing at least 5 kg is 15 mg/kg, administered once weekly via intravenous infusion. Administration should occur under the supervision of a healthcare provider knowledgeable in the management of hypersensitivity reactions, including anaphylaxis. Avlayah should be administered in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. Prior to its administration, pre-treatment with antihistamines, antipyretics, and/or corticosteroids should be considered. Avlayah is not recommended for use in combination with other enzyme replacement therapies.

Management of MPS II has been multidisciplinary and has included enzyme replacement therapy (ERT), respiratory, cardiac, orthopedic, neurologic, rehabilitative, and supportive care based on disease severity. Prior to the approval of Avlayah, idursulfase (Elaprase®)[‡] was the only FDA-approved ERT for MPS II. Approved in 2006, Elaprase has been shown to improve walking ability in patients 5 years of age and older and spleen size in patients 16 months of age and older. While Elaprase may improve or stabilize somatic manifestations of the disease, it does not cross the BBB and does not treat the cognitive decline seen in neuronopathic MPS II.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 was FDA approved in March 2026 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).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Avlayah was evaluated in Trial 1, a pivotal phase 1/2 multi-center, international, multi-cohort, single arm, open-label trial in 47 pediatric patients with Hunter syndrome, including 44 patients with neuronopathic Hunter syndrome and 3 patients with non-neuronopathic Hunter syndrome. Of the 47 patients enrolled, 46 patients completed part 1 of the study (up to Week 24), and 1 patient discontinued the study due to an adverse reaction prior to Week 24. In part 1 of Trial 1, patients

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received a starting dosage of Avlayah ranging from 3 mg/kg to 15 mg/kg weekly and a maximum dosage ranging from 3 mg/kg to 30 mg/kg weekly. Patients who received 30 mg/kg weekly dosage (2 times the approved recommended maintenance dosage) did not show additional reductions from baseline in cerebrospinal fluid (CSF) or urine heparan sulfate (HS) concentration compared to patients who received 15 mg/kg weekly. Of the 47 patients studied, 15 patients were enzyme ERT-naïve, and 32 patients were ERT-experienced (2 of whom had a history of prior treatment for Hunter syndrome with hematopoietic stem cell transplantation, and 2 of whom had a history of prior treatment for Hunter syndrome with gene therapy). In Trial 1, treatment with Avlayah resulted in a significant reduction of CSF HS. For the 44 patients who had measurements at Week 24, the CSF HS mean percent reduction from baseline was 91% (95% Confidence interval: 89%, 92%); the minimum and maximum percent change in CSF HS from baseline were 72% and 98%, respectively. At baseline, 0% (0 of 47) of patients had CSF HS levels below the upper limit of normal (ULN). At Week 24, 93% (41 of 44) of Avlayah-treated patients had CSF HS levels below the ULN.

A phase III trial is underway to understand the safety and efficacy of Avlayah.

References

1. Avlayah [package insert]. Denali Therapeutics, Inc. South San Francisco, CA.
2. New Drug Review: Avlayah. IPD Analytics. April 2026.
3. Denali therapeutics announces US FDA approval of Avlayah (tividenofusp alfa-eknm) for treatment of hunter syndrome (MPS II). Available at: Denali Therapeutics Announces U.S. FDA Approval of Avlayah (tividenofusp alfa-eknm) for Treatment of Hunter Syndrome (MPS II). Denali Therapeutics. March 25, 2026.
4. Kaplan, S. & Sutton, R. (2026). Mucopolysaccharidoses: Treatment. J. Kremen (Ed.), *UpToDate*. Retrieved March 23, 2026 from <https://www.uptodate.com/contents/mucopolysaccharidoses-treatment>.
5. McBride K, Berry S, et al. 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*, Volume 22, Issue 11, 2020, 1735-1742.
6. Elaprase® [prescribing information]. Takeda. Cambridge, MA. February 2025.
7. Avlayah Drug Evaluation. Express Scripts. April 8, 2026.

Policy History

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06/04/2026 Medical Policy Committee review

06/10/2026 Medical Policy Implementation Committee approval. New policy.

10/01/2026 Coding update

Next Scheduled Review Date: 06/2027

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Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	C9399, J3490, J3590 Add code effective 10/01/2026: J1757
ICD-10 Diagnosis	All Related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

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3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.