

5.30.105

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Subsection:	Endocrine and Metabolic Drugs	Original Policy Date:	April 10, 2026
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Last Review Date: September 17, 2026

Avlayah

Description

Avlayah (tvidenofusp alfa-eknm)

Background

Hunter Syndrome is an inherited X-linked recessive lysosomal storage disease caused by a deficiency of iduronate-2-sulfatase (IDS), a lysosomal enzyme, that degrades heparan sulfate (HS) and dermatan sulfate (DS), the two primary glycosaminoglycans (GAGs) in the lysosome. Insufficiency or absence of IDS leads to accumulation of GAGs, including HS and DS, and subsequent lysosome dysfunction in multiple organs and tissues, including the central nervous system (CNS). Avlayah (tvidenofusp alfa-eknm) provides an exogenous source of IDS. The fragment, crystallizable (Fc) component of Avlayah binds to the apical domain of the transferrin receptor (TfR) and delivers IDS to peripheral tissues and to the CNS through receptor-mediated transcytosis across the blood-brain barrier. Avlayah is internalized via binding to the mannose-6-phosphate receptor on the cell surface and transported into lysosomes where it is thought to exert enzymatic activity and reduce accumulated GAGs. In addition, since TfR is ubiquitously expressed, it is expected that the interaction of Avlayah and TfR will contribute to its uptake into cells in the brain and peripheral tissues (1).

Regulatory Status

FDA-approved indication: 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 (1).

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Limitations of use: (1)

Avlayah is not recommended for use in combination with other enzyme replacement therapies.

Avlayah carries a boxed warning regarding hypersensitivity reactions including anaphylaxis. Initiate Avlayah in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. If severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue Avlayah and immediately initiate appropriate medical treatment, including use of epinephrine (1).

Avlayah has been associated with infusion-associated reactions (IARs), anemia, and membranous nephropathy. To reduce the risk of IARs, consider pre-treatment with antihistamines, antipyretics, and/or corticosteroids. Obtain hemoglobin levels prior to initiating Avlayah, at 3 months after initiation, and periodically thereafter as clinically indicated. If membranous nephropathy is suspected, conduct diagnostic evaluation and initiate appropriate treatment (1).

The safety and effectiveness of Avlayah in pediatric patients weighing less than 5 kg have not been established (1).

Related policies

Elaprase

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Avlayah may be considered **medically necessary** if the conditions indicated below are met.

Avlayah may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnosis

Patient must have the following:

Hunter Syndrome (mucopolysaccharidosis type II)

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AND ALL of the following:

- a. Used for the treatment of neurological manifestations of Hunter syndrome
- b. Weight $\geq$ 5 kg
- c. **NO** concurrent use with another enzyme replacement therapy for Hunter Syndrome (i.e., Elaprase)

Prior – Approval *Renewal* Requirements

Same as above

Policy Guidelines**Pre - PA Allowance**

None

Prior - Approval Limits

Duration 2 years

Prior – Approval *Renewal* Limits

Same as above

Rationale**Summary**

Avlayah (tvidenofusp alfa-eknm) is indicated for patients with Hunter syndrome (Mucopolysaccharidosis type II, MPS II). Avlayah carries a boxed warning regarding hypersensitivity reactions including anaphylaxis. Avlayah has been associated with infusion-associated reactions (IARs), anemia, and membranous nephropathy. The safety and effectiveness of Avlayah in pediatric patients weighing less than 5 kg have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Avlayah while maintaining optimal therapeutic outcomes.

References

1. Avlayah [package insert]. South San Francisco, CA: Denali Therapeutics Inc.; March 2026.

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Policy History

Date	Action
April 2026	Addition to PA
September 2026	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 17, 2026 and is effective on October 1, 2026.