MEDICAL POLICY

Avlayah® (tividenofusp alfa-eknm)

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available.

DESCRIPTION

Avlayah (tividenofusp alfa-eknm) is an enzyme replacement therapy indicated for the treatment of neurologic manifestations of mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.

This indication was approved by the Food and Drug Administration (FDA) in March 2026 under accelerated approval based on the reduction of cerebrospinal fluid heparan sulfate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

POLICY

Avlayah (tividenofusp alfa-eknm) is considered **not medically necessary** for all indications, including the treatment of MPS II due to insufficient evidence to demonstrate clinical efficacy.

CLINICAL RATIONALE

Avlayah (tividenofusp alfa-eknm) is the first enzyme replacement therapy approved for the treatment of neurologic manifestations of MPS II, also known as Hunter syndrome, when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment and is

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administered as a weekly weight-based intravenous (IV) infusion. Avlayah is a fusion protein comprising iduronate-2-sulfatase (IDS) enzyme linked to an engineered transferrin receptor (TfR)-binding Fc domain, designed to cross the blood-brain barrier to deliver IDS to the central nervous system (CNS) and treat both neurologic and peripheral manifestations of Hunter syndrome.

Clinical Studies

The accelerated FDA approval of Avlayah (tividenofusp alfa-eknm) was based on a 24-week Phase 1/2, multicenter, open-label, single-arm, international, multicohort trial followed by an 80-week safety extension and 157-week open-label extension. A total of 47 male pediatric participants (median age 5 years; range 3 months – 13 years) were enrolled including 44 with neuronopathic MPS II. Participants were treated with Avlayah 15mg/kg IV weekly.

The primary objective was to evaluate the safety and tolerability of Avlayah. All 47 patients (100%) reported at least one treatment-emergent adverse event, most commonly infusion-related reactions. Three participants had serious treatment-emergent adverse events; all continued treatment. Anemia was a prespecified adverse event of special interest given the transferrin receptor-mediated mechanism. A total of 24 participants (51%) had at least one anemia-composite adverse event (anemia, iron-deficiency anemia, or decreased hemoglobin level). No participants discontinued the study owing to anemia.

Secondary objectives assessed central nervous system and peripheral effects through cerebrospinal fluid (CSF) and urinary heparan sulfate (HS) levels, urinary glycosaminoglycans (GAGs), adaptive behavior (assessed with the Vineland Adaptive Behavior Scales), and liver volume. The mean reduction from baseline in CSF HS was 91% (95% CI, 90-92%), urinary HS 88% (95% CI, 85-90%), and urinary GAGs 62% (95% CI, 58-66%). Among participants who were still in the study at week 49 and had Vineland assessments, 49% (17 of 35) had stabilization or improvement in the rate of adaptive-behavior skill gain. At baseline, 24% of participants (5 of 21) who were evaluated with abdominal magnetic resonance imaging had abnormal liver volumes. After treatment, liver volumes were normal in all the participants at week 24 (18 of 18) and week 49 (14 of 14).

The most common adverse reactions were infusion-related reactions (87%) despite routine premedication. Other common adverse events included upper respiratory tract infection (60%), pyrexia (55%), cough (47%), vomiting (43%), diarrhea (40%), rash (40%), anemia (38%), coronavirus disease 2019 (38%), and rhinorrhea (38%). Severe adverse events included infusion related reactions (6%), anemia (4%), and constipation (4%).

In summary, the clinical benefit of treatment of Hunter syndrome with Avlayah (tividenofusp alfa-eknm) has not been sufficiently demonstrated based on the currently available evidence. An ongoing Phase 2/3 study is anticipated and may provide additional clinically meaningful endpoints to more clearly demonstrate clinical benefit that correlates with the surrogate biomarker results from the initial study.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J1757 - Injection, tividenofusp alfa-eknm, 1 mg (10/1/2026)
- C9399 – Unclassified drugs or biologicals
- J3490 – Unclassified drugs
- J3590 – Unclassified biologics

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- 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. doi:10.1056/NEJMoa2508681

POLICY HISTORY

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