APPENDIX Q: AVLAYAH (tividenofusp alfa-eknm) Clinical Guideline for Home Intravenous Therapy

I. PHARMACOLOGY OVERVIEW

Refer to manufacturer's full Prescribing Information for the most up to date information.

A. Background and Indication:
AVLAYAH (tividenofusp alfa-eknm) 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.

Hunter syndrome is an X-linked recessive lysosomal storage disorder caused by deficiency of iduronate-2-sulfatase (IDS), leading to accumulation of heparan sulfate and dermatan sulfate in tissues and organs including the central nervous system. Tividenofusp provides an exogenous source of IDS and utilizes transferrin receptor-mediated transport to cross the blood-brain barrier and deliver enzyme replacement to peripheral tissues and the CNS.

Limitations of Use:
Tividenofusp is not recommended for use in combination with other enzyme replacement therapies. Additionally, initial doses should be administered in a controlled healthcare setting. Due to the risk of anaphylaxis and the high incidence of infusion-related reactions, patients should complete dose escalation and demonstrate tolerance to the maintenance dose prior to transition to home infusion.

B. Dosing:

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 (maintenance dosage)

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

*Dosing is based off actual body weight. Tividenofusp has not been studied in extremes of body weight

C. Dose Adjustments: Do not escalate dosing if current dosage is not tolerated. Infusion interruptions, rate reductions, or dose reductions may be required for hypersensitivity reactions or infusion-associated reactions.

1. If a severe hypersensitivity reaction occurs and the decision is made to re-administer tividenofusp, re-evaluate pre-medications, slow the infusion rate, and/or reduce dose.

2. If a mild or moderate hypersensitivity reaction occurs, temporarily hold the infusion and/or reduce the infusion rate by at least 50% from the current rate, then titrate up to the recommended infusion rate as tolerated.

D. Duration: Duration of therapy is dependent upon patient response, tolerability, and provider discretion.

E. Contraindications: None.

F. Warnings and Precautions:

1. **Hypersensitivity Reactions and Anaphylaxis:** Life-threatening hypersensitivity reactions, including anaphylaxis, can occur during or after tividenofusp infusion and have been observed both early in therapy and after extended duration of treatment. Symptoms may include tachycardia, hypotension, wheezing, vomiting, hives, and lip or tongue swelling. Prior to administration, consider pretreatment with antihistamines, antipyretics, and/or corticosteroids. If a severe hypersensitivity reaction occurs, discontinue infusion immediately and initiate appropriate medical treatment including epinephrine.
2. **Infusion-Associated Reactions (IARs):** Infusion-associated reactions may occur during infusion or within 24 hours following tividenofusp administration. Symptoms may include chills, hypotension, tachycardia, urticaria, wheezing, flushing, rash, cough, vomiting, diarrhea, headache, pyrexia, and angioedema. IARs have been reported more frequently in enzyme replacement therapy (ERT)-naïve patients compared to ERT-experienced patients. Reactions are most common during the first 8 weeks of therapy with a median time to onset of 2 weeks of therapy, although delayed reactions and reactions after extended treatment duration may still occur. IARs declined in frequency with continued use of tividenofusp. Consider pretreatment with antihistamines, antipyretics, and/or corticosteroids prior to infusion, although IARs may still occur. Appropriate medical monitoring and access to cardiopulmonary resuscitation equipment should be readily available during administration, particularly in patients with compromised cardiac or respiratory function who may be at increased risk for severe complications.
3. **Anemia:** Anemia has been reported during tividenofusp therapy, particularly in patients with pre-existing anemia. Reductions in hemoglobin were most commonly observed within the first 13 weeks of therapy, although occurrence was observed up to one year in some patients. Overall, the incidence and severity of anemia decreased over time, with the majority of patients recovering by Week 24. Anemia did not result in treatment discontinuation, and management may include iron supplementation. Obtain baseline hemoglobin levels prior to initiation, repeat monitoring approximately 3 months after initiation, and continue periodic monitoring as clinically indicated.

4. **Membranous Nephropathy:** Membranous nephropathy with immune complex deposition has been reported during tividenofusp therapy. Monitor serum creatinine and urine protein-to-creatinine ratio periodically during treatment. If membranous nephropathy is suspected, initiate appropriate diagnostic evaluation and treatment and assess risks versus benefits of continuing therapy.
5. **Pregnancy and Lactation:** There are no available human data regarding tividenofusp use during pregnancy or lactation. Animal reproductive studies have not been conducted. The developmental and health benefits of breastfeeding should be weighed against the mother's clinical need for therapy and any potential adverse effects on the infant.

G. Pharmacokinetics:

1. Volume of distribution: approximately 2.7 L
2. Clearance: approximately 0.14 L/hour following maintenance dosing
3. Metabolism: expected catabolism into small peptides

H. Adverse Drug Reactions:

1. >10%:
    a. Dermatologic: excoriation of skin, skin rash, urticaria
    b. Gastrointestinal: constipation, diarrhea, gastroenteritis, vomiting
    c. Hematologic & oncologic: anemia, bruise, neutropenia
    d. Hypersensitivity: infusion-related reaction
    e. Immunologic: antibody development (including neutralizing antibodies)
    f. Infection: coronavirus infection
    g. Nervous system: falling, headache, insomnia
    h. Respiratory: cough, nasal congestion, rhinorrhea, upper respiratory tract infection
    i. Miscellaneous: fever
2. 1% to 10%:
    a. Hypersensitivity: anaphylaxis
    b. Renal: membranous glomerulonephritis
3. Frequency Not Defined:
    a. Hypersensitivity: hypersensitivity reaction

I. Drug Interactions: None known. Consult interaction database for patient-specific assessment.

II. NURSING PROCEDURES

A. Supplies may include but are not limited to:

1. Alcohol wipes
2. Gloves
3. Tape
4. IV access supplies as applicable
    a. Peripheral IV access supplies for patients requiring peripheral IV access
        1) IV start Kit
        2) Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾")
        3) Extension set 8" with needless connector
    b. Port access supplies for patients with a port
        1) Port needle (ex. 22 Gauge x ¾ to 1" safe step)
        2) Needless connector
        3) Central line dressing change kit
5. IV pole
6. Syringes (10-50 mL depending on patient's weight and dose) with needles (20 G x 1")
7. Ambulatory pump tubing with 0.2-micron filter
8. Pole mounted ambulatory pump
9. Battery change procedure teaching sheet
10. Continuous delivery mode teaching sheet
11. Pump return box
12. Sharps container

B. Prescription Items:

1. Vials of tividenofusp
2. Sterile Water for Injection
3. 0.9% NaCl diluent bag (25 mL/ 50 mL/ 100 mL/ 250 mL)
4. 0.9% sodium chloride stock bag for flushing (25 mL)
5. Standard flushes per protocol
6. Anaphylaxis kit

C. How Supplied: Tividenofusp is supplied as a sterile, preservative-free, white to off-white lyophilized powder in a single-dose vial containing 150 mg tividenofusp alfa-eknm.

D. Storage and Handling: Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake

E. Compatibility: Compatible with polypropylene syringes, PVC or polyolefin infusion bags, PVC or PE infusion sets, and polyethersulfone (PES) filter membranes.

F. Procedures:

1. Explain reasoning for visit and use of enzyme replacement therapy.
2. Don gloves.
3. Counsel patient on warnings, precautions, and potential side effects including but not limited to: hypersensitivity reactions, infusion-associated reactions, and anemia.
4. Obtain IV access.
5. Prepare product. Preferred preparation for each ERT medication is a home mix unless case-by-case scenarios warrant preparation by the dispensing pharmacy.

Instructions below are refelctive of home mix guidelines:

a. Remove tividenofusp vials from refrigerator and allow to reach room temperature for approximately 15-30 minutes.
b. Reconstitute each vial aseptic technique with 5.2 mL of Sterile Water for Injection by slowly injecting the diluent onto the inside wall of each vial to avoid foaming. Do not inject forcefully or directly onto the lyophilized powder.
c. Gently swirl to dissolve. Do not shake or invert. Each reconstituted vial will yield a concentration of 30 mg/mL of tividenofusp.
d. Visually inspect solution for particulate matter or discoloration. The solution should be clear to slightly opalescent and colorless to slightly brown/yellow, and free of visible particles.
e. Withdraw and discard a volume from the dilution bag equivalent to the calculated tividenofusp dose volume prior to dilution. Withdraw the calculated dose from the vial(s) and inject into appropriately sized 0.9% Sodium Chloride dilution bag to a final concentration between 0.6 mg/mL and 15 mg/mL. See chart below. Mix gently.

	AVLAYAH Dose		
	3 mg/kg	**7.5 mg/kg**	**15 mg/kg**
Patient Weight Range	**Recommended Total Infusion Volumes [a]**		
5 kg to less than 10 kg	25 mL	25 mL or 50 mL	25 mL or 50 mL
10 kg to less than 20 kg	25 mL or 50 mL	25 mL, 50 mL, or 100 mL	25 mL, 50 mL, or 100 mL
20 kg to less than 25 kg	25 mL, 50 mL, or 100 mL	25 mL, 50 mL, or 100 mL	25 mL, 50 mL, or 100 mL
25 kg to less than 50 kg	25 mL, 50 mL, or 100 mL	25 mL, 50 mL, or 100 mL	50 mL or 100 mL
50 kg to less than 60 kg	50 mL or 100 mL	50 mL or 100 mL	100 mL
60 kg to less than 100 kg	50 mL, 100 mL, or 250 mL	50 mL, 100 mL, or 250 mL	100 mL or 250 mL
100 kg or greater	100 mL or 250 mL	100 mL or 250 mL	250 mL

[a] Ensure the final concentration of the diluted AVLAYAH solution is between 0.6 mg/mL and 15 mg/mL.

f. Infusion should be titrated using an electronic pump. Administer using a dedicated infusion line with a sterile, non-pyrogenic, low protein-binding 0.2 micron inline filter. Infuse over approximately 4 hours using recommended infusion rate titrations below. In the absence of hypersensitivity reactions and IARs, infusion rate can be gradually increased to complete the infusion in a minimum duration of 3 hours based on patient tolerance. Infusions should not exceed 8 hours:

	Infusion Duration		
	First hour	**Second hour**	**Third hour to completion**
Total Infusion Volume	**Infusion Rate (mL/hour)**		
25 mL	2.5 mL/hour	5 mL/hour	10 mL/hour
50 mL	5 mL/hour	10 mL/hour	20 mL/hour
100 mL	10 mL/hour	20 mL/hour	40 mL/hour
250 mL	25 mL/hour	50 mL/hour	100 mL/hour

g. Upon completion of infusion: Flush the infusion set with the provided 25 mL bag of 0.9% sodium chloride at the same infusion rate set at the final infusion rate used to administer tividenofusp.

h. Monitor patient and vital signs periodically during the infusion (including after each titration) and 30 minutes after completion of infusion.

REFERENCES

Avlayah [package insert]. Denali Therapeutics; 3/2026.

Hunter Syndrome (Mucopolysaccharidosis Type II). UpToDate. Accessed 2026.

Tividenofusp: Drug Information. *UpToDate.* Accessed May 14, 2026. https://www.uptodate.com/contents/ tividenofusp-drug-information

REVIEW HISTORY:

Review Date:	Approved By:	Approved Date:	Description of Changes:
8/7/2026	David Benedict	8/7/2026	Appendix created