CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761485Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AVLAYAH™ safely and effectively. See full prescribing information for AVLAYAH.

AVLAYAH (tividenofusp alfa-eknm) for injection, for intravenous use
Initial U.S. Approval: 2026

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

See full prescribing information for complete boxed warning.

- **Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. (5.1)**
- **Initiate AVLAYAH in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. (5.1)**
- **If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue AVLAYAH and immediately initiate appropriate medical treatment, including use of epinephrine. (5.1)**

----------INDICATIONS AND USAGE----------

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)

This indication is approved 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). (1)

Limitations of Use
AVLAYAH is not recommended for use in combination with other enzyme replacement therapies. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administration of AVLAYAH should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. (2.1)
- Obtain a baseline hemoglobin value in all patients. (2.1)
- Recommended AVLAYAH maintenance dosage for pediatric patients who weigh at least 5 kg is 15 mg/kg administered once weekly as an intravenous infusion over approximately 4 hours. (2.2, 2.6)
- Initiate AVLAYAH treatment with a dose escalation regimen. (2.2)
- See the full prescribing information for dosage and administration modifications and monitoring. (2.3)
- See the full prescribing information for preparation and administration instructions. (2.4, 2.6)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 150 mg of tividenofusp alfa-eknm as a lyophilized powder in a single-dose vial for reconstitution and further dilution. (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- *Infusion-Associated Reactions (IARs)*: If a severe IAR occurs, discontinue AVLAYAH and initiate appropriate medical treatment. (5.2)
- *Anemia*: Obtain baseline hemoglobin levels in all patients and monitor 3 months after initiation, and as clinically indicated. Administer appropriate supportive measures for anemia based on clinical judgment. (5.3)
- *Membranous Nephropathy:* Monitor serum creatinine and urinary protein to creatinine ratio. If membranous nephropathy is suspected, conduct diagnostic evaluation and initiate appropriate treatment. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥20%) were IAR, upper respiratory tract infection, ear infection, pyrexia, anemia, cough, vomiting, diarrhea, rash, COVID-19, rhinorrhea, nasal congestion, fall, headache, skin abrasion, and urticaria. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Denali Therapeutics toll-free at 1-833-ONE-DNLI (1-833-663-3654) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2026

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FULL PRESCRIBING INFORMATION

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

Patients treated with enzyme replacement therapies, including AVLAYAH, have experienced life-threatening hypersensitivity reactions, including anaphylaxis. Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy.

Initiate AVLAYAH in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue AVLAYAH and immediately initiate appropriate medical treatment, including use of epinephrine. Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and to seek immediate medical care should symptoms occur *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

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 is approved under accelerated approval based on the reduction of cerebrospinal fluid heparan sulfate *[see Clinical Studies (14)]*. 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 for the treatment of Hunter syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Important Recommendations Prior to AVLAYAH Treatment Initiation

Administer AVLAYAH under the supervision of a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis *[see Warnings and Precautions (5.1)]*.

Initiate AVLAYAH in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment *[see Warnings and Precautions (5.1)].*

Consider pretreatment with antihistamines, antipyretics, and/or corticosteroids *[see Warnings and Precautions (5.1, 5.2)]*.

Obtain a baseline hemoglobin value in all patients *[see Warnings and Precautions (5.3)]*.

2.2 Recommended Dosage

The recommended starting dosage of AVLAYAH 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), follow the dose escalation regimen in Table 1 *[see Warnings and Precautions (5.2)]*. Administer each dosage level for at least 4 weeks before escalating to the next dosage level.

The recommended maintenance dosage of AVLAYAH for pediatric patients who weigh at least 5 kg is 15 mg/kg administered once weekly via intravenous infusion.

Table 1: Recommended AVLAYAH Dosage for Pediatric Patients Weighing ≥5 kg [a]

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)

[a] Do not escalate the dosage level if the current dosage level is not tolerated *[see Dosage and Administration (2.3)]*.

2.3 Dosage and Administration Modifications and Monitoring

In the event of a *severe* hypersensitivity reaction (e.g., anaphylaxis) or a *severe* IAR, discontinue AVLAYAH and immediately initiate appropriate medical treatment. Consider the risks and benefits of re-administering AVLAYAH following a severe reaction. If the decision is made to re-administer AVLAYAH, re-evaluate pre-treatment medications, slow the infusion rate, and/or reduce the AVLAYAH dose. Monitor patients closely upon re-administration of AVLAYAH *[see Warnings and Precautions (5.1, 5.2)]*.

In the event of a *mild* to *moderate* hypersensitivity reaction or a *mild* to *moderate* IAR, 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 (see Table 3) *[see Warnings and Precautions (5.1, 5.2)].*

If the dose has been decreased due to an adverse reaction, evaluate when it is appropriate to increase the dose and follow the recommended dose escalation regimen to achieve the maintenance dosage of 15 mg/kg once weekly *[see Dosage and Administration (2.2)].*

2.4 Preparation Instructions

Prepare AVLAYAH using polypropylene syringes and infusion bags composed of polyvinylchloride (PVC) or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP); infusion sets composed of PVC or PE; and filter membranes composed of polyethersulfone (PES).

Use aseptic technique during preparation. Reconstitute and dilute AVLAYAH in the following manner:

Reconstitution Instructions

1) Determine the number of AVLAYAH vials to be reconstituted based on the patient's weight in kg and the recommended dosage *[see Dosage and Administration (2.2)]*. Round the number of vials up to the next whole number.
2) Remove the required number of AVLAYAH vials from the refrigerator and set aside for 15 to 30 minutes to allow vials to reach room temperature 20ºC to 25ºC (68ºF to 77ºF). Do not use an external heat source.
3) Reconstitute each vial 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.
4) Gently swirl each vial to completely dissolve the lyophilized powder. Do not invert or shake the vial. Each reconstituted vial will yield a concentration of 30 mg/mL of tividenofusp alfa-eknm.
5) Visually inspect the reconstituted solution in the vial(s) for particulate matter and discoloration. The solution should be clear to slightly opalescent and colorless to slightly brown/yellow, and free of visible particles. Discard the reconstituted AVLAYAH solution if it is discolored, cloudy, or contains visible particulates.

Dilution Instructions

Dilute the reconstituted AVLAYAH solution with 0.9% Sodium Chloride Injection to a final concentration between 0.6 mg/mL and 15 mg/mL *[see Dosage and Administration (2.6)]* in an infusion bag as follows:

1) Determine the appropriate volume of the infusion bag based on patient weight (see Table 2) and determine the volume of reconstituted AVLAYAH solution required for the calculated dose.
2) Prepare the infusion bag:
   a. Remove any airspace within the infusion bag.
   b. Withdraw a volume of 0.9% Sodium Chloride Injection from the infusion bag equivalent to the volume of AVLAYAH to be added.
3) Slowly withdraw the required volume of reconstituted solution from the AVLAYAH vial(s). Discard unused portion after each use; do not administer more than one dose from the vial.
4) Slowly inject AVLAYAH into the infusion bag of 0.9% Sodium Chloride Injection. Avoid introducing air into the infusion bag.
5) Gently invert the infusion bag to mix the solution. Do not shake.

Table 2: Recommended Total Infusion Volumes for AVLAYAH Based on Patient Weight and Dose

Patient Weight Range	AVLAYAH Dose		
	3 mg/kg	7.5 mg/kg	15 mg/kg
	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.

2.5 Storage Instructions for the Reconstituted and Diluted Solutions

Reconstituted Solution

Do not shake. Do not freeze.

If the reconstituted AVLAYAH vials are not diluted immediately, store at controlled room temperature between 20ºC to 25ºC (68ºF to 77ºF) for up to 4 hours.

Diluted Solution

If the diluted AVLAYAH solution is not used immediately, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours.

After removal of the diluted solution from the refrigerator:

- Completely infuse within 10 hours.
- Do not store back into the refrigerator.

Discard the diluted solution if refrigerated more than 24 hours or if the diluted solution cannot be completely infused within 10 hours after removal from the refrigerator.

Do not shake. Do not freeze.

2.6 Administration Instructions

1) Administer AVLAYAH without delay as an intravenous infusion using only infusion sets composed of PVC or PE and filter membranes composed of PES.
2) If the diluted solution was refrigerated, allow solution to equilibrate to room temperature prior to infusion.
3) Use a dedicated infusion line equipped with a sterile, non-pyrogenic, low protein-binding, 0.2 micron, in-line filter to administer AVLAYAH.

4) Infuse AVLAYAH over approximately 4 hours per the recommended infusion rates in Table 3. Increase the initial infusion rate to the subsequent infusion rate every hour based on patient tolerance. Total infusion time should not exceed 8 hours.

5) In the absence of hypersensitivity reactions and IARs, AVLAYAH infusion rate can be gradually increased to complete the infusion in a minimum infusion duration of 3 hours based on patient tolerance.

Table 3: AVLAYAH Infusion Rate Based on Total Infusion Volume

Total Infusion Volume	Infusion Duration		
	First hour	Second hour	Third hour to completion
	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

6) At the end of the infusion, flush the infusion line with 0.9% Sodium Chloride Injection using the final infusion rate that was used to administer AVLAYAH.

7) Do not infuse AVLAYAH in the same intravenous infusion line with other products.

Home Infusion

If a patient reaches and tolerates the maintenance AVLAYAH dosage, the patient may receive home infusion under the supervision of a healthcare provider *[see Dosage and Administration (2.1, 2.7)]*. The decision to have patients move to home infusion should be made after evaluation and recommendation by a healthcare provider.

In case of a missed dose or an IAR, contact a healthcare provider.

2.7 Missed Dose

If an AVLAYAH dose is missed, skip the missed dose. Do not double a dose to compensate for a missed dose. Restart AVLAYAH treatment as soon as possible, maintaining the one-week interval between infusions thereafter. Resume dosing at the last administered dosage following the recommended infusion rate *[see Dosage and Administration (2.6)]*.

3 DOSAGE FORMS AND STRENGTHS

For injection: 150 mg of tividenofusp alfa-eknm as a white to off-white lyophilized powder with a cake-like appearance in a single-dose vial for reconstitution and further dilution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

Life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients treated with enzyme replacement therapies (ERTs), including AVLAYAH *[see Adverse Reactions (6)]*. Symptoms of anaphylaxis that have occurred with AVLAYAH have included tachycardia, hypotension, wheezing, vomiting, hives, and lip and tongue swelling. Anaphylaxis has occurred during the early course of ERT and after extended duration of therapy.

Administer AVLAYAH under the supervision of a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. Initiate AVLAYAH in a healthcare setting with appropriate medical monitoring and support measures including access to cardiopulmonary resuscitation equipment.

Prior to AVLAYAH administration, consider pre-treatment with antihistamines, antipyretics, and/or corticosteroids.

- If a *severe* hypersensitivity reaction (including anaphylaxis) occurs, discontinue AVLAYAH and immediately initiate appropriate medical treatment, including use of epinephrine. Consider the risks and benefits of re-administering AVLAYAH following a severe hypersensitivity reaction (including anaphylaxis). If the decision is made to re-administer AVLAYAH, re-evaluate pre-treatment medications (e.g., antihistamines, antipyretics, and/or corticosteroids), slow the infusion rate, and/or reduce the AVLAYAH dose. Monitor patients closely upon re-administration of AVLAYAH.
- Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis, and to seek immediate medical care should symptoms occur.
- 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 (see Table 3). Re-evaluate the pre-treatment medication regimen *[see Dosage and Administration (2.3)]*.

If the dose has been decreased due to an adverse reaction, evaluate when it is appropriate to increase the dose and follow the recommended dose escalation regimen to achieve the maintenance dosage of 15 mg/kg once weekly *[see Dosage and Administration (2.2)].*

5.2 Infusion-Associated Reactions

Infusion-associated reactions (IARs) have been reported in patients treated with AVLAYAH *[see Adverse Reactions (6.1)]*. IARs are defined as adverse reactions occurring during or within 24 hours of the infusion. Symptoms of IARs observed with AVLAYAH can include (but are not limited to) chills, angioedema, hypotension, tachycardia, urticaria, vomiting, wheezing, pyrexia, flushing, erythema, rash, cough, diarrhea, abdominal pain, retching, headache, irritability, and papules. IARs have been reported more frequently in ERT-naïve patients compared to ERT-experienced patients. Cases of infusion-associated reactions occurring 2 hours or more after completion of the infusion have occurred with AVLAYAH.

Prior to AVLAYAH administration, consider pre-treatment with antihistamines, antipyretics, and/or corticosteroids to reduce the risk of IARs. IARs may still occur in patients after receiving pre-treatment. Onset of IARs was most common during the first 8 weeks of treatment with a median time to onset of approximately 2 weeks for the first IAR; IARs declined in frequency with continued use of AVLAYAH. IARs may still occur despite extended duration of AVLAYAH treatment. Appropriate medical monitoring and support measures, including cardiopulmonary resuscitation equipment, should be readily available during AVLAYAH administration.

- If a *severe* IAR occurs, discontinue AVLAYAH and immediately initiate appropriate medical treatment. Consider the risks and benefits of re-administering AVLAYAH following a severe IAR. If the decision is made to re-administer AVLAYAH, re-evaluate pre-treatment medications, slow the infusion rate, and/or reduce the AVLAYAH dose. Monitor patients closely upon re-administration of AVLAYAH.
- If a *mild or moderate* IAR 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.

If the dose has been decreased due to an adverse reaction, evaluate when it is appropriate to increase the dose and follow the recommended dose escalation regimen to achieve the maintenance dosage of 15 mg/kg once weekly *[see Dosage and Administration (2.2)]*.

Patients with Hunter syndrome may have compromised cardiac and respiratory function which may predispose them to a higher risk of severe complications from IARs. Closely monitor patients with compromised cardiac and respiratory function following AVLAYAH administration.

5.3 Anemia

Anemia has been reported in patients treated with AVLAYAH *[see Adverse Reactions (6.1)]*.

The incidence of anemia after initiation of AVLAYAH was higher in patients with pre-existing anemia compared to those without pre-existing anemia. Reductions in hemoglobin levels were generally observed by Week 13, though the 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; management may include supplementation with iron.

Obtain hemoglobin levels prior to initiating AVLAYAH, at 3 months after initiation, and periodically thereafter as clinically indicated. Administer appropriate supportive measures for anemia based on clinical judgment.

5.4 Membranous Nephropathy

A case of steroid-refractory membranous nephropathy with immune complex deposits in the kidney was reported in an AVLAYAH-treated patient *[see Adverse Reactions (6.1)]*. Monitor serum creatinine and urinary protein to creatinine ratio. If membranous nephropathy is suspected, conduct diagnostic evaluation and initiate appropriate treatment. Consider risks and benefits of continuing AVLAYAH in patients who develop membranous nephropathy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions Including Anaphylaxis *[see Warnings and Precautions (5.1)]*
- Infusion-Associated Reactions *[see Warnings and Precautions (5.2)]*
- Anemia *[see Warnings and Precautions (5.3)]*
- Membranous Nephropathy *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of AVLAYAH was evaluated in male pediatric patients with Hunter syndrome in Trial 1 *[see Clinical Studies (14)]*. A total of 47 male patients (age range: 3 months to 13 years) received intravenous AVLAYAH at 3 mg/kg to 30 mg/kg (0.2 to 2 times the approved recommended maintenance dose) weekly, and the majority of patients received 15 mg/kg intravenously weekly after Week 24. The median (minimum, maximum) duration of exposure was 117 (19, 219) weeks.

In Trial 1, the most common adverse reactions (≥20%) reported in AVLAYAH-treated patients were infusion-associated reaction (IAR), upper respiratory tract infection, ear infection, pyrexia, anemia, cough, vomiting, diarrhea, rash, COVID-19, rhinorrhea, nasal congestion, fall, headache, skin abrasion, and urticaria.

Dose interruptions of AVLAYAH due to an adverse reaction occurred in 91% of patients. The most frequently reported adverse reaction leading to dose interruption was IAR (31 [66%] patients). Other frequently reported adverse reactions leading to dose interruption were COVID-19 (18 [38%] patients), pyrexia (16 [34%]), upper respiratory tract infection (16 [34%]), nasal congestion (6 [13%]), and vomiting (6 [13%]). Dose interruption included skipped infusions due to an adverse reaction as well as temporary infusion pauses with subsequent completion during the same visit.

Dose reductions of AVLAYAH due to adverse reactions occurred in 57% of patients; the majority of these reactions were IARs.

In Trial 1, one (2%) AVLAYAH-treated patient experienced anaphylaxis, which occurred in the first month of treatment.

Table 4 summarizes adverse reactions that occurred in >15% of AVLAYAH-treated pediatric patients with Hunter syndrome.

Table 4: Adverse Reactions That Occurred in >15% in AVLAYAH-treated Pediatric Patients With Hunter Syndrome (Trial 1)

Adverse Reaction	Any Severity N (%) (N = 47)
Infusion-associated reaction [a]	41 (87%)
Upper respiratory tract infection	28 (60%)
Ear infection [b]	26 (55%)
Pyrexia	26 (55%)
Anemia [c]	24 (51%)
Cough	22 (47%)
Vomiting	20 (43%)
Diarrhea	19 (40%)
Rash	19 (40%)
COVID-19	18 (38%)
Rhinorrhea	18 (38%)
Nasal congestion	17 (36%)
Fall	11 (23%)
Headache	11 (23%)
Skin abrasion	11 (23%)
Urticaria	10 (21%)
Constipation	8 (17%)
Contusion	8 (17%)
Gastroenteritis	8 (17%)
Infusion site extravasation	8 (17%)
Insomnia	8 (17%)
Neutropenia	8 (17%)

[a] Infusion-associated reaction includes infusion-related reaction.
[b] Ear infection includes ear infection, otitis media, otitis media acute, otitis externa.
[c] Anemia includes anemia, iron deficiency anemia, and decreased hemoglobin.

Description of Selected Adverse Reactions

Infusion-Associated Reaction

Three (6%) AVLAYAH-treated patients experienced severe IARs. One patient permanently discontinued treatment due to an IAR.

Anemia

Two (4%) AVLAYAH-treated patients experienced severe anemia (defined as hemoglobin <8 g/dL) prior to Week 24. One (2%) AVLAYAH-treated patient, aged 0.5 years, experienced moderate anemia (hemoglobin 9.2 g/dL), which was considered serious due to the patient's age.

Membranous Nephropathy

A case of biopsy-confirmed, steroid-refractory membranous nephropathy with immune complex deposits in the kidney was reported in an AVLAYAH-treated patient.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of AVLAYAH during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Animal studies to evaluate the potential for embryofetal developmental toxicity and pre- and postnatal developmental toxicity of tividenofusp alfa-eknm have not been conducted.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of tividenofusp alfa-eknm in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AVLAYAH and any potential adverse effects on the breastfed infant from AVLAYAH or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of AVLAYAH have been established under accelerated approval 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 and the information on this use is discussed throughout the labeling *[see Indications and Usage (1)]*. The safety and effectiveness of AVLAYAH have not been established in pediatric patients weighing less than 5 kg.

8.5 Geriatric Use

Clinical trials of AVLAYAH in patients with Hunter syndrome did not include patients 65 years of age or older.

11 DESCRIPTION

Tividenofusp alfa-eknm is a fusion protein consisting of the hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme iduronate-2-sulfatase (IDS) fused to the N-terminus of an immunoglobulin G1 (IgG1) fragment, crystallizable (Fc). It is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. The approximate molecular weight of tividenofusp alfa-eknm is 110 kDa.

AVLAYAH (tividenofusp alfa-eknm) for injection is a sterile, preservative-free, white to off-white lyophilized powder with a cake-like appearance for intravenous infusion after reconstitution and dilution. Each single-dose vial contains 150 mg tividenofusp alfa-eknm, and the inactive ingredients dibasic sodium phosphate (5 mg), methionine (7.5 mg), monobasic sodium phosphate (7.7 mg),

polysorbate 20 (3 mg), sodium chloride (14.6 mg), and sucrose (300 mg). The pH is 6.5 after reconstitution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 glycosominoglycans (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).

Tividenofusp alfa-eknm provides an exogenous source of IDS. The fragment, crystallizable (Fc) component of tividenofusp alfa-eknm 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. Tividenofusp alfa-eknm 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 tividenofusp alfa-eknm and TfR will contribute to its uptake into cells in the brain and peripheral tissues.

12.2 Pharmacodynamics

In clinical studies with AVLAYAH, the relative concentrations of HS or DS in human cerebrospinal fluid (CSF) and urine were estimated based on an assessment of selected disaccharides following enzymatic digestion of HS or DS. It is not possible to directly quantify intact HS or DS concentrations in human CSF or urine using currently available bioanalytical methods. Differences in bioanalytical methods preclude meaningful comparison of the pharmacodynamic results based on HS or DS concentrations in clinical studies with AVLAYAH with the results in other clinical studies.

In Trial 1, reductions in CSF HS from baseline were observed in AVLAYAH-treated pediatric patients with Hunter syndrome *[see Clinical Studies (14)].* Reductions in urine HS (86%), urine DS (91%), and total urine GAGs (57%) from baseline were observed at Week 24 in AVLAYAH-treated pediatric patients with Hunter syndrome. At baseline, 2 of 47 (4%) patients had total urine GAG levels below the upper limit of normal (ULN). At Week 24, 26 of 38 (68%) patients had total urine GAG levels below the ULN. The relationship between changes in CSF HS, urine HS, urine DS, and total urine GAG levels to clinical response in patients with Hunter syndrome has not been established.

In Trial 1, higher serum tividenofusp alfa-eknm concentrations appeared to be associated with greater reductions of CSF HS and urine HS concentrations from baseline, with maximum effect achieved at 15 mg/kg of AVLAYAH once weekly (the recommended maintenance dosage).

The time to maximum effect on pharmacodynamic response and the exposure-response relationship for the safety and effectiveness of tividenofusp alfa-eknm have not been fully characterized.

12.3 Pharmacokinetics

The pharmacokinetics of tividenofusp alfa-eknm were evaluated in pediatric patients with Hunter syndrome aged 3 months to 13 years (age at baseline).

The maximum serum concentration (C_{max}) increased proportionally with dose, while the area under the serum concentration-time curve (AUC_{tau}) increased in a greater-than-dose-proportional manner across the dose range of 3 mg/kg to 30 mg/kg (0.2 to 2 times the approved recommended maintenance dosage). Table 5 shows the C_{max} and AUC_{tau} of tividenofusp alfa-eknm following the recommended starting dosage and recommended maintenance dosage *[see Dosage and Administration (2.2)]*.

Table 5: C_{max} and AUC_{tau} of Tividenofusp Alfa-eknm in Pediatric Patients With Hunter Syndrome

Pharmacokinetic Parameter	Week 1 (3 mg/kg weekly)	Week 24 (15 mg/kg weekly)
	Geometric Mean (Range)	Geometric Mean (Range)
C_{max} (mcg/mL)	33.1 (19.9 – 50.3)	204 (19.5 – 615)
AUC_{tau} (h·mcg/mL)	277 (82.4 – 446)	3,000 (839 – 12,100)

Abbreviations: AUC_{tau} = area under the serum concentration-time curve from 0 to 168 hours after the start of infusion; C_{max} = maximum serum concentration.

Distribution

The geometric mean (range) volume of distribution of tividenofusp alfa-eknm was 2.7 (1.4 to 9.6) L.

Elimination

Tividenofusp alfa-eknm is cleared via linear and nonlinear mechanisms and the total clearance was increased in the presence of anti-tividenofusp alfa-eknm antibodies *[see Clinical Pharmacology (12.6)].* The geometric mean (range) total clearance of tividenofusp alfa-eknm was 0.14 (0.05 to 0.45) L/h following 15 mg/kg weekly dosing of AVLAYAH at Week 24.

Patients are predicted to have a 97% reduction from C_{max} in tividenofusp alfa-eknm concentrations at a median time of 40 hours (5th to 95th percentile: 18.6 to 74.1 hours) after the end of the first 3 mg/kg AVLAYAH infusion at Week 1 and 41 hours (5th to 95th percentile: 23.3 to 100 hours) after the end of the first 15 mg/kg AVLAYAH infusion at Week 9.

Metabolism

Tividenofusp alfa-eknm is expected to be metabolized into small peptides via catabolic pathways.

Specific Populations

Following the approved recommended weight-based dosage, no clinically significant differences in tividenofusp alfa-eknm serum C_{max} or AUC_{tau} were observed based on age (3 months to 16 years) or body weight (7 kg to 80 kg).

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADAs in the studies described below with the incidence of ADAs in other studies, including those of AVLAYAH or of other tividenofusp alfa products.

In Trial 1 *[see Clinical Studies (14)]*, anti-tividenofusp alfa-eknm antibodies (referred to as ADAs) were detected in 100% (47/47) of AVLAYAH-treated patients with Hunter syndrome following 19 to 219 weeks of treatment. In Trial 1, neutralizing antibodies (NAbs) that inhibit enzyme activity of tividenofusp alfa-eknm were detected in 87% (41/47) of AVLAYAH-treated patients with Hunter syndrome. NAbs that inhibit cellular uptake of tividenofusp alfa-eknm were not characterized in this trial.

Among the 10 enzyme replacement therapy (ERT)-experienced and 13 ERT-naïve patients with Hunter syndrome who were ADA negative at baseline, all of the patients became ADA positive following AVLAYAH treatment.

ADA responses in both ERT-experienced and ERT-naïve patients with Hunter syndrome were more frequently directed against the IDS component of tividenofusp alfa-eknm than the Fc component. ADA titers peaked at approximately Week 13, remained elevated through Week 24, and declined thereafter in the majority of patients.

Antibodies against other IDS ERTs are expected to be cross-reactive to tividenofusp alfa-eknm.

Prevalence for ADAs and NAbs that inhibited enzyme activity in AVLAYAH-treated pediatric patients with Hunter syndrome are summarized in Table 6.

Table 6: ADA and NAb Prevalence at Baseline and Post-AVLAYAH Treatment in Pediatric Patients With Hunter Syndrome

	ERT-Experienced [a] (N = 32)	**ERT-Naïve [b] (N = 15)**
ADA		
Baseline	22/32 (69%)	2/15 (13%)
Following AVLAYAH Treatment	32/32 (100%)	15/15 (100%)
NAb		
Baseline	10/32 (31%)	0/15 (0%)
Following AVLAYAH Treatment	26/32 (81%)	15/15 (100%)

Abbreviations: ADA = anti-drug antibody (anti-tividenofusp alfa-eknm antibody); ERT = enzyme replacement therapy; NAb = neutralizing antibody.

Data are presented as n/N (%). Prevalence reflects ADA detected at baseline or post-baseline.

[a] ERT-experienced was defined as patients who had ≥4 months of ERT treatment at any time prior to AVLAYAH treatment initiation.

[b] ERT-naïve was defined as patients who had <4 months of continuous ERT treatment at any time prior to AVLAYAH treatment initiation.

Anti-Drug Antibody Effects on Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy

Development of ADAs was associated with reduced serum tividenofusp alfa-eknm concentrations. AVLAYAH-treated patients who developed higher ADA titers had greater reductions in serum tividenofusp alfa-eknm concentrations. The observed ADA-associated pharmacokinetic changes did not result in significant effects on the reduction in CSF HS or urine HS at the recommended dosage *[see Dosage and Administration (2.2)]*.

The effect of ADAs on the safety of AVLAYAH in patients with Hunter syndrome has not been fully characterized.

The effect of ADAs on the effectiveness of AVLAYAH in the treatment of Hunter syndrome is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Animal studies to evaluate the carcinogenic potential of tividenofusp alfa-eknm have not been conducted.

Mutagenesis

Studies to evaluate the mutagenic potential of tividenofusp alfa-eknm have not been conducted.

Impairment of Fertility

In a fertility and embryonic development study in transgenic mice, twice weekly intravenous tividenofusp alfa-eknm doses were administered to females for two weeks prior to mating and through day 4 of gestation, and to males two weeks prior to mating. No adverse effects on fertility parameters were observed in either female or male transgenic mice at exposures approximately 12-fold greater than those observed in patients at the maintenance dosage level of 15 mg/kg (based on AUC).

14 CLINICAL STUDIES

Trial 1 (NCT04251026) was a Phase 1/2 multi-center, international, multi-cohort, single-arm, open-label trial of AVLAYAH 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 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 (0.2 to 2 times the approved recommended maintenance dosage) *[see Dosage and Administration (2.2)].* 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 *[see Clinical Pharmacology (12.2)].* The most common AVLAYAH dosage (57% of the patients) in Trial 1 was 15 mg/kg administered once weekly.

All 47 patients in Trial 1 were male, with a baseline median age of 5 years (range: 3 months to 13 years of age). The patient population consisted of 27 White (57%), 4 Black or African American (9%), 4 Asian (9%), 3 who were more than one race (6%), 1 of another race (2%), and 8 of an unknown race (17%). Ethnicity consisted of 7 patients who were Hispanic or Latino (15%), 38 who were Not Hispanic or Latino (81%), and 2 of an unknown ethnicity (4%). Of the 47 patients, 15 patients were enzyme replacement therapy (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 (HSCT), and 2 of whom had a history of prior treatment for Hunter syndrome with gene therapy. The median duration of previous ERT treatment was 26 months (range: 1 to 134 months).

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% CI: 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

AVLAYAH (tividenofusp alfa-eknm) for injection is supplied as a sterile, preservative-free, white to off-white lyophilized powder with a cake-like appearance in a single-dose vial. Each vial contains 150 mg of tividenofusp alfa-eknm. AVLAYAH is available as one carton containing a 150 mg single-dose vial (NDC 84976-001-01).

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.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions Including Anaphylaxis, and Infusion-Associated Reactions

Advise the patient and/or caregiver that life-threatening hypersensitivity reactions, including anaphylaxis, and infusion-associated reactions (IARs) may occur with AVLAYAH treatment.

Advise the patient and/or caregiver that anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy.

Inform the patient and/or caregiver of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis, and IARs and to seek immediate medical care should symptoms occur *[see Warnings and Precautions (5.1, 5.2)]*.

Anemia

Inform the patient and caregiver that anemia may occur during AVLAYAH treatment. Advise the patient and/or caregiver of the symptoms of anemia (e.g., fatigue, pallor). Instruct the patient and/or caregiver to contact their healthcare provider if those symptoms occur *[see Warnings and Precautions (5.3)]*.

Manufactured by:
Denali Therapeutics Inc.
161 Oyster Point Boulevard
South San Francisco, CA 94080
U.S. License Number: 2385

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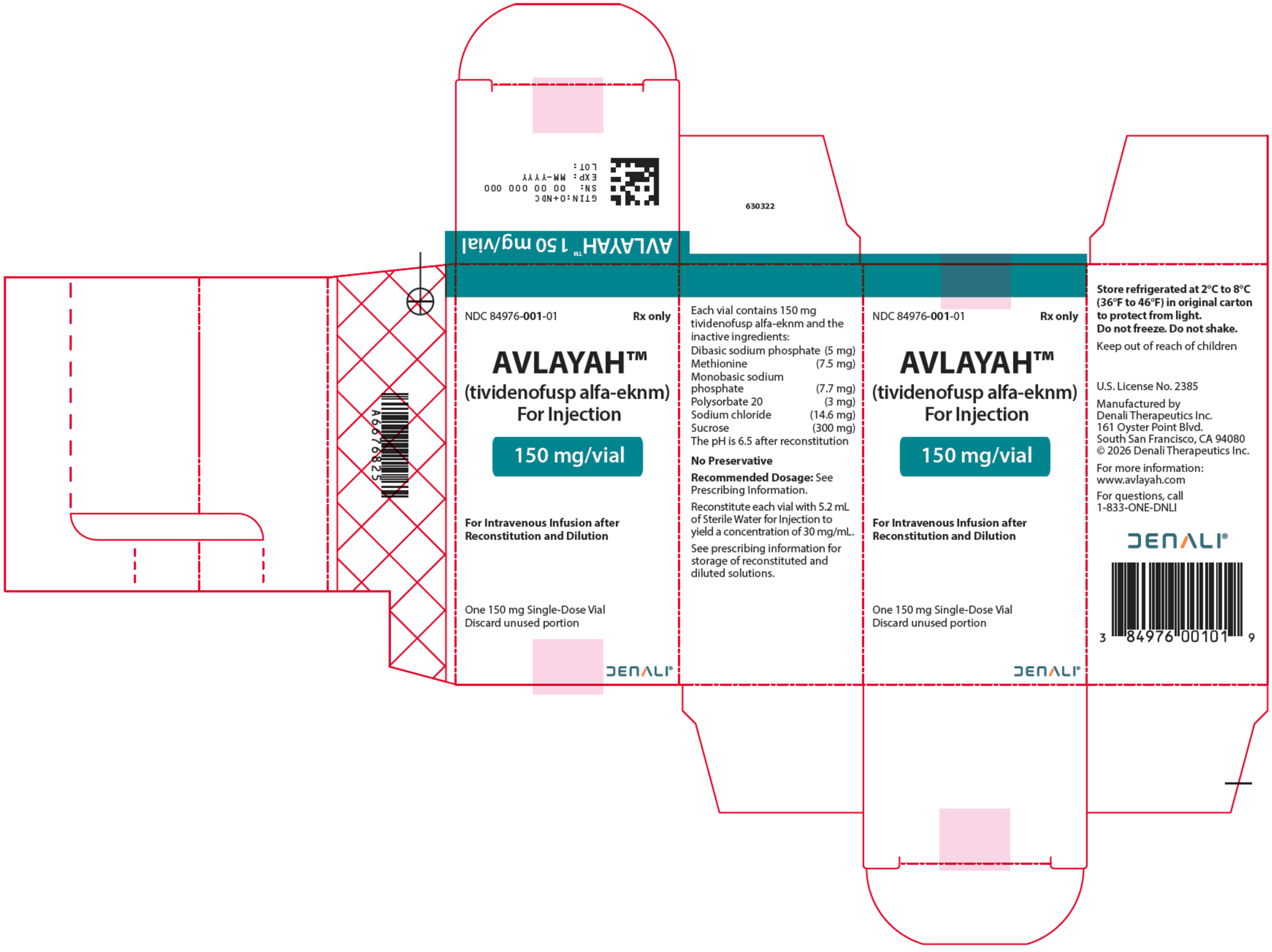

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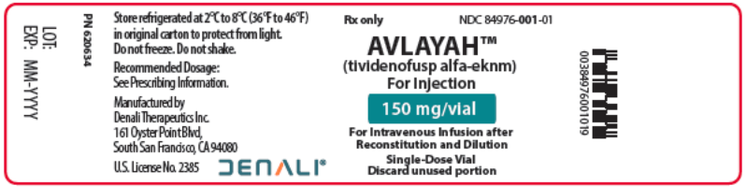
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EXP: MM-YYYY
PN 626934
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Recommended Dosage: See Prescribing Information.
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DENALI
Rx only
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AVLAYAH™
(tividenofusp alfa-eknm)
For Injection
150 mg/vial
For Intravenous Infusion after Reconstitution and Dilution
Single-Dose Vial
Discard unused portion
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