09-J4000-50

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Subject: Velmanase alfa-tycv (Lamzede) intravenous infusion

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DESCRIPTION:

Alpha-mannosidosis (AM) is a rare lysosomal storage disorder caused by a MAN2B1 gene mutation, which results in a deficiency of the alpha-mannosidase enzyme. This enzyme deficiency causes intracellular accumulation of mannose-rich oligosaccharides in various tissues of the body. The prevalence of AM is approximately 1 in 500,000 to 1 in 1 million individuals, and there are no known gender or ethnicity predispositions. Symptoms of AM vary and may include, but are not limited to, infections due to immunodeficiency, hepatosplenomegaly, hearing impairment, mental function and speech impairment, muscular weakness, joint abnormalities, ataxia, and characteristic facial features such as a large head, low hairline, prominent forehead, gingival hyperplasia, and enlarged tongue. Unfortunately, the wide variety of clinical symptoms often delays diagnosis.

AM patients are typically diagnosed based on genetic testing or through assessment of alpha-mannosidase activity in peripheral blood leukocytes (i.e., enzyme activity is usually 5%−10% of normal). Once diagnosed, AM is classified as mild, moderate, or severe. Mild AM presents after 10 years of age and is characterized by slow disease progression, muscle weakness, and absence of skeletal abnormalities. Moderate AM presents before 10 years of age and is characterized by slow disease progression that includes skeletal abnormalities and ataxia. Severe AM presents in infancy and is characterized by rapid disease progression and early death from central nervous system (CNS) involvement. Life expectancy for untreated AM patients varies depending on disease severity and onset of clinical manifestations, as some patients with less severe forms have lived into the sixth decade of life.

Until recently, treatment for AM was predominately symptomatic management. Allogeneic hematopoietic stem cell transplantation (HSCT) has been used in some cases for younger patients

before significant complications develop. On February 16, 2023, the FDA approved velmanase alfa-tycv (Lamzede), a recombinant human lysosomal alpha-mannosidase, for the treatment of non-central nervous system manifestations of AM in adult and pediatric patients. Velmanase alfa-tycv (Lamzede) provides an exogenous source of alpha-mannosidase. Velmanase alfa-tycv is internalized via binding to the mannose-6-phosphate receptor on the cell surface and transported into lysosomes where it is thought to exert its enzyme activity.

The efficacy and safety of velmanase alfa-tycv (Lamzede) for AM has been evaluated in a phase III study as well as a smaller single-arm pediatric study. The phase III multicenter, randomized, double-blinded, placebo-controlled, parallel group study evaluated velmanase alfa-tycv (Lamzede) in 25 patients (13 adult and 12 pediatric). Enrolled patients had alpha-mannosidase activity below 11% of normal and in the range of 8 to 29 µmol/h/mg at baseline. Additionally, all patients but one were naïve to velmanase alfa-tycv (Lamzede). Fifteen patients (8 adult and 7 pediatric) received velmanase alfa-tycv (Lamzede) at a dose of 1 mg/kg given weekly as an intravenous infusion and 10 patients (5 adult and 5 pediatric) received placebo. The clinical endpoints evaluated included a change from baseline for the 3-minute stair climbing test (3MSCT; in steps/min), 6-minute walking test (6MWT; in meters), forced vital capacity (FVC; % predicted), and serum oligosaccharide concentration (µmol/L). All patients completed the 52-week study. Table 1 lists the study results.

Table 1: Change in Endpoints from Baseline at 52 weeks

Endpoint	Velmanase alfa-tycv (n = 15)	Placebo (n = 10)	Treatment Difference (95% confidence interval)
3MSCT (steps/min)			
Baseline mean (SD)	52.9 (11.2)	55.5 (16.0)	--
Mean absolute change from baseline (SD)	0.6 (8.6)	-2.4 (5.5)	2.6 (-3.8, 9.1)
Mean relative change (%) from baseline (SD)	0.5 (16.1)	-3.6 (13.1)	3.4 (-9.5, 16.3)
FVC (% predicted)			
Baseline mean (SD)	81.7 (20.7)	90.4 (10.4)	--
Mean absolute change from baseline (SD)	8.2 (9.9)	2.0 (12.6)	5.5 (-5.0, 16.1)
Mean relative change (%) from baseline (SD)	11.4 (13.1)	1.9 (15.4)	7.4 (-5.7, 20.5)
6MWT (meters)			
Baseline mean (SD)	459.6 (72.3)	465.7 (140.5)	--
Mean absolute change from baseline (SD)	4.4 (46.1)	-4.6 (40.8)	7.4 (-30.7, 45.5)
Mean relative change (%) from baseline (SD)	1.2 (9.8)	-0.8 (10.8)	1.6 (-7.2, 10.4)
Serum oligosaccharides (µmol/L)			
Baseline mean (SD)	6.8 (1.2)	6.6 (1.9)	

Mean absolute change from baseline (SD)	-5.1 (1.2)	-1.6 (1.7)	-3.5 (-4.4, -2.6)
Mean relative change (%) from baseline (SD)	-75.8 (11.2)	-20.3 (24.0)	-55.6 (-69.3, -41.9)

Velmanase alfa-tycv (Lamzede) was also evaluated in a single-arm, open-label study in pediatric AM patients less than 6 years of age. All patients had alpha-mannosidase activity below 10% of normal at baseline. The study enrolled five patients (3 males and 2 females) ranging from 3.7 to 5.9 years of age (mean age = 4.5 years). Patients received velmanase alfa-tycv (Lamzede) 1 mg/kg as an intravenous infusion once weekly (4 patients for 24 months, 1 patient for 40 months). The mean (SD) absolute and percentage changes from baseline for serum oligosaccharides at 24 months were -7.7 (4.27) µmol/L and -65.8% (23.1%), respectively.

The most common adverse drug reactions (incidence > 20%) reported with velmanase alfa-tycv (Lamzede) in clinical studies are nasopharyngitis, pyrexia, headache, arthralgia, and hypersensitivity reactions including anaphylaxis.

POSITION STATEMENT:

Site of Care: If velmanase alfa-tycv (Lamzede) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46: Site of Care Policy for Select Specialty Medications.

The administration of velmanase alfa-tycv (Lamzede) intravenous infusion **meets the definition of medical necessity** when **ALL** of the following are met:

1. Member has a diagnosis of alpha-mannosidosis.
2. Documentation of one of the following (a or b): – Laboratory documentation must be submitted
    a. Deficiency in alpha-mannosidase enzyme activity as measured in fibroblasts or leukocytes.
    b. Genetic test demonstrating biallelic pathogenic variants in MAN2B1.
3. Documentation of elevated serum oligosaccharide concentration. – Laboratory or medical record documentation must be submitted.
4. Treatment is for non-central nervous system disease manifestations (e.g., skeletal abnormalities, myopathy, motor function disturbances, immunodeficiency).
5. Prescribed by a specialist who treats patients with alpha-mannosidosis such as a neurologist, neuromuscular specialist, endocrinologist, or geneticist.
6. The dose does not exceed 1 mg/kg/dose via intravenous infusion once weekly.

Approval duration: 6 months

Velmanase alfa-tycv (Lamzede) intravenous infusion is considered **experimental or investigational** for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

Continuation of velmanase alfa-tycv (Lamzede) intravenous infusion **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), OR the member has previously met all indication-specific initiation criteria.
2. Documentation of stability or improvement in serum oligosaccharide concentration. – Laboratory or medical record documentation must be submitted.
3. Member has a clinical meaningful response (e.g., improvement in motor function, improvement in pulmonary function, reduction in infections) with no significant adverse drug reactions (e.g., severe hypersensitivity reactions) necessitating discontinuation of therapy.
4. Prescribed by a specialist who treats patients with alpha-mannosidosis such as a neurologist, neuromuscular specialist, endocrinologist, or geneticist.
5. The dose does not exceed 1 mg/kg/dose via intravenous infusion once weekly.

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Velmanase alfa-tycv (Lamzede) is recombinant human lysosomal alpha-mannosidase indicated for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients.
- Velmanase alfa-tycv (Lamzede) is dosed at 1 mg/kg (actual body weight) administered via an intravenous infusion once every week. Administration of the infusion is over a minimum of 60 minutes for patients weighing up to 49 kg. Patients weighing 50 kg and greater should be infused at a maximum infusion rate of 25 mL/hour to control the protein load. Use an infusion set equipped with a pump and a low protein binding, 0.2-micron, in-line filter to administer.
- If one or more doses are missed, restart the treatment as soon as possible, as long as it is at least 3 days from the next scheduled dose. If it is within 3 days from the next scheduled dose, give only the next dose per schedule.
- Aseptic technique should be followed during the preparation of velmanase alfa-tycv (Lamzede). Prior to reconstitution remove the number of needed vials from the refrigerator and set aside for approximately 30 minutes to allow the vials to come to room temperature. Reconstitute each vial by slowly injecting 5 mL of Sterile Water for Injection, down the inside wall of each vial. Avoid adding the Sterile Water for Injection to the vial forcefully or directly onto the lyophilized powder to minimize foaming. Allow the reconstituted vials to stand on the table for 5 – 15 minutes. Then gently tilt and roll each vial for 15 – 20 seconds to enhance the dissolution process. Each vial will yield a concentration of 2 mg/mL. Do not invert, swirl, or shake the vials.

- Visually inspect the reconstituted solution in the vials for particulate matter and discoloration. The solution should be clear to slightly opalescent. Due to the nature of velmanase alfa-tycv (Lamzede), the solution may occasionally contain some proteinaceous particles in the form of thin white strands or translucent fibers which will be removed by the in line filter during infusion. Discard if opaque particles are present or the solution is discolored. Slowly withdraw the required volume from the vials with caution to avoid foaming in the syringe. If the volume of the solution exceeds one syringe capacity, prepare the required number of syringes in order to replace the syringe quickly during the infusion. Discard unused portion remaining in the vials.
- If the reconstituted velmanase alfa-tycv (Lamzede) vial is not used immediately, store the vial refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours inclusive of infusion time. Protect from light during refrigeration. Do not freeze. Reconstituted velmanase alfa-tycv (Lamzede) vial must be infused within 10 hours after removal from the refrigerator, inclusive of total infusion time. Discard if not used within 10 hours. Infuse reconstituted solution within 24 hours from the time of preparation, which includes the storage time in the refrigerator, the time at room temperature, and the duration of the infusion.

Dose Adjustments

- In the event of a mild to moderate hypersensitivity reaction or a mild to moderate infusion-associated rection, consider temporarily holding the infusion for 15 to 30 minutes, slowing the infusion rate to 25% to 50% of the recommended rate, and initiating appropriate medical treatment.

  If symptoms:

  - Persist despite temporarily holding or slowing the infusion, stop the infusion and monitor the patient. If symptoms continue to persist, discontinue the infusion, and consider re-initiating the infusion within 7 to 14 days at 25% to 50% of the recommended rate with appropriate pretreatment.
  - Subside following holding or slowing the infusion, resume infusion at 25% to 50% the recommended rate. If tolerated, increase the infusion rate by increments of 25% of the recommended rate until the recommended infusion rate is reached. Closely monitor the patient.

Drug Availability

- Injection: 10 mg of velmanase alfa-tycv as a lyophilized powder in a single-dose vial for reconstitution. Each vial will yield a concentration of 2 mg/mL.
  - One 10 mg single-dose vial in a carton: NDC 10122-180-02
  - Five 10 mg single-dose vials in a carton: NDC 10122-180-05
  - Ten 10 mg single-dose vials in a carton: NDC 10122-180-10
- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.

PRECAUTIONS:

Boxed Warning

Hypersensitivity Reactions Including Anaphylaxis: Patients treated with velmanase alfa-tycv (Lamzede) have experienced hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during velmanase alfa-tycv (Lamzede) administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue velmanase alfa-tycv (Lamzede) immediately and initiate appropriate medical treatment. In patients with severe hypersensitivity reaction, a desensitization procedure to velmanase alfa-tycv (Lamzede) may be considered.

Contraindications

None

Precautions/Warnings

Infusion-Associated Reactions (IARs): Infusion-associated reactions (IARs) have been reported in velmanase alfa-tycv (Lamzede) treated patients. The most frequent symptoms of IARs that occurred in >10% of the population were pyrexia, chills, erythema, vomiting, cough, urticaria, rash and conjunctivitis. Similar symptoms were observed in adult and pediatric populations. Prior to velmanase alfa-tycv (Lamzede) administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids to reduce the risk of infusion-associated reactions (IARs). However, IARs may still occur in patients after receiving pretreatment. If a severe IAR occurs, discontinue velmanase alfa-tycv (Lamzede) immediately and initiate appropriate medical treatment. Consider the risks and benefits of readministering velmanase alfa-tycv (Lamzede) following a severe IAR. Patients may be rechallenged using slower infusion rates. Once a patient tolerates the infusion, the infusion rate may be increased to reach the recommended infusion rate. If a mild or moderate IAR occurs, consider slowing the infusion rate or temporarily withholding the dose as outlined in the Dose Adjustments section.

Embryo-Fetal Toxicity: Based on findings from animal reproduction studies, velmanase alfa-tycv (Lamzede) may cause embryo-fetal harm (e.g., skeletal and visceral malformations during the organogenesis period) when administered to a pregnant female. It is important to note that these malformations occurred at exposures approximately 7- (rats) and 2.5-fold (rabbits) those observed in patients. The decision to continue or discontinue velmanase alfa-tycv (Lamzede) treatment during pregnancy should consider the female's need for velmanase alfa-tycv (Lamzede), the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal disease. For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with velmanase alfa-tycv (Lamzede). Advise females of reproductive potential to use effective contraception during treatment with velmanase alfa-tycv (Lamzede) and for 14 days after the last dose is discontinued.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0217	Injection, velmanase alfa-tycv, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

E77.1	Defects in glycoprotein degradation

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None applicable.

RELATED GUIDELINES:

Site of Care Guideline for Select Specialty Medications, 09-J3000-46

OTHER:

None applicable.

REFERENCES:

1. Borgwardt L, Guffon N, Amraoui Y, et al. Efficacy and safety of velmanase alfa in the treatment of patients with alpha-mannosidosis: results from the core and extension phase analysis of a phase III multicentre, double-blind, randomized, placebo-controlled trial. J Inherit Metab Dis. 2018;41(6):1215-1223. doi:10.1007/s10545-018-0185-0.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2024. URL www.clinicalpharmacilogy-ip.com Accessed 10/28/24.
3. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2023. URL http://www.dynamed.com. Accessed 10/25/23.
4. Lamzede (velmanase alfa-tycv) intravenous infusion [package insert]. Chiesi USA, Inc., Cary (NC): February 2023.

5. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 10/28/24.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/24.

GUIDELINE UPDATE INFORMATION:

06/15/23	New Medical Coverage Guideline. Velmanase alfa-tycv (Lamzede) intravenous infusion for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients.
07/15/23	Revision of guideline to include Site of Care to the position statement and to update the billing codes
12/15/23	Review and revision of the guideline, consisting of updating the references.
01/01/24	Revision: Added HCPCS code J0217 and deleted code J3490.
12/15/24	Review and revision of the guideline, consisting of revising the position statement to require only laboratory documentation for genetic testing and updating the references.