Oscar Clinical Guideline: Lamzede (velmanase alfa-tycv) (PG146, Ver. 1)

Lamzede (velmanase alfa-tycv)

Summary

Alpha-mannosidosis (AM) is an extremely rare and serious autosomal recessive disorder caused by pathogenic variants in the MAN2B1 gene. This results in a deficiency of alpha-mannosidase, a lysosomal enzyme, leading to the progressive accumulation of mannose-rich oligosaccharides in various organs and tissues. AM has a prevalence of 1:500,000 and affects men and women equally, and it can potentially impact individuals of any ethnic group.

AM presents with varying symptoms, progression, and severity among patients, even those who share the same genetic variant. It is categorized into three subtypes: the severe form (type 3), moderate form (type 2), and mild form (type 1).

1. Type 3 (severe form) manifests in early life (prenatal or first year) with progressive intellectual disability; deafness, cataract, corneal clouding, hydrocephalus, progressive ataxia, dysostosis multiplex, hernia, hepatomegaly; immune deficiency (frequent bacterial infections) rapidly progressive, fatal within first decade. Type 2 (moderate form) is typically manifest before 10 years of age and includes skeletal abnormalities, myopathy, and progression with ataxia

appearing by the 2nd or 3rd decade, often leading to death in early adulthood, most commonly from pneumonia.

2. Type 1 (mild form) typically manifests after the first decade with absence of skeletal abnormalities, progressive myopathy and ataxia, usually resulting in loss of ability to independently ambulate and wheelchair dependence. Death often occurs within the fourth to fifth decade, most commonly from pneumonia.

Across the subtypes, manifestations may include intellectual disability, psychiatric symptoms, hearing loss, and ophthalmologic issues. Patients with milder forms can survive into later adulthood, but myopathy and ataxia are progressive over time, leading to most adult patients becoming non-ambulatory.

Until recently, the standard of care for AM was symptomatic treatment addressing the medical complications of the disease. Hematopoietic stem cell transplant (HSCT) has been explored as a possible treatment to preserve neurocognitive function and prevent early death in younger AM patients, but results have been variable, and HSCT is not considered a standard of care at this time. However, a new breakthrough was achieved with the approval of Lamzede (velmanase alfa-tycv), the first and only enzyme replacement therapy approved for the treatment of non-central nervous system manifestations of AM in both adult and pediatric patients in the U.S.

- A Phase III clinical trial involving 25 patients (both adult and pediatric sub-groups) with AM found Lamzede to be more effective than placebo at treating non-neurological effects of AM.
- Effectiveness was measured by a change in the level of oligosaccharides in patients' blood after a year of treatment, and physical endurance was measured as a change in the number of steps the patient could climb on a staircase.
    - After one year of treatment, patients receiving Lamzede showed a threefold average decrease in oligosaccharide levels compared to those receiving placebo, and could climb about half a step more in one minute than they could previously, while patients receiving placebo could climb two steps less.
    - The specific clinical data that led to the approval of Lamzede remains uncertain.

Definitions

"**3-Minute Stair Climbing Test (3-MSCT)**" is a physical test used to measure functional capacity and endurance. Patients are asked to climb as many stairs as possible in three minutes, and the result is often used to track disease progression or improvement in response to treatment.

"**6-Minute Walking Test (6-MWT)**" is a submaximal exercise test that measures aerobic capacity and endurance. The distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes is measured.

"**Biallelic Pathogenic Variants**" refers to the presence of mutations in both copies of a gene (one inherited from each parent) that contribute to disease development. In the context of alpha-mannosidosis, it refers to mutations in both copies of the MAN2B1 gene.

"**Fibroblasts**" are a type of cell found in connective tissue, which produces collagen and other fibers. They play a crucial role in wound healing and maintaining the structural integrity of most tissues and organs.

"**Forced Vital Capacity (FVC)**" is a measure of the amount of air a person can exhale forcefully and quickly after taking a deep breath.

"**Non-Central Nervous System Manifestations**" refer to the symptoms or signs of a disease that do not involve the brain and spinal cord, which constitute the central nervous system. In the context of alpha-mannosidosis, these could include skeletal abnormalities, myopathy, motor function disturbances, immunodeficiency, and other issues that do not directly involve the brain and spinal cord.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Lamzede (velmanase alfa-tycv)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a neurologist, metabolic specialist , geneticist or physician experienced in managing this disorder; ***AND***
2. Prescribed for the treatment of non-central nervous system manifestations (i.e., skeletal abnormalities, myopathy, motor function disturbances, immunodeficiency, etc.) of alpha-mannosidosis; ***AND***
3. Supporting documentation is provided that shows either:
    a. Identification of biallelic pathogenic variants in the *MAN2B1* gene through molecular genetic testing; ***or***
    b. **BOTH** of the following:
        i. Identification of deficiency of lysosomal enzyme acid alpha-mannosidase (MAN2B1) in leukocytes or other nucleated cells; ***and***

ii. alpha-mannosidase enzyme activity in peripheral blood leukocytes is 5%-10% of normal activity; ***AND***

4. The prescribed dose of Lamzede (velmanase alfa-tycv) is 1 mg/kg (actual body weight), administered once a week.

If the above prior authorization criteria is met, the requested medication will be approved for 6 months.

Medical Necessity Criteria for Reauthorization

Reauthorization of Lamzede (velmanase alfa-tycv) for another 12 months will be granted if the member has the following :

1. Clinical chart documentation (within the last 6 months) showing a beneficial response to therapy or stabilization of the disease, compared to pretreatment age-appropriate baseline values in at least one of the following:
    a. Stability or improvement in serum oligosaccharide concentration; ***and/or***
    b. Stability or improvement in the 6-minute walking test (6-MWT); ***and/or***
    c. Stability or improvement in the 3-minute stair climbing test (3-MSCT); ***and/or***
    d. Stability or improvement in forced vital capacity (FVC) (% predicted); ***and/or***
    e. Slowing in the rate of disease progression or clinical decline; ***AND***
2. Documentation indicating monitoring the presence of antibodies; ***AND***
3. Documentation reporting the safety of the medication; no report of anaphylaxis reaction characterized by symptoms such as difficulty breathing, swelling of the throat and tongue, a drop-in blood pressure and cardiorespiratory failure.

Experimental or Investigational / Not Medically Necessary

Lamzede (velmanase alfa-tycv) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name
CPT/HCPCS Codes considered medically necessary if criteria are met:

Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
C9399	Unclassified drugs or biologicals
J3590	Unclassified biologics
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
E77.1	Defects in glycoprotein degradation

References

1. Lamzede (velmanase alfa) [prescribing information]. Parma, Italy: Chiesi Farmaceutici S.p.A.; February 2023.
2. 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, randomised, placebo-controlled trial. J Inherit Metab Dis. 2018 Nov;41(6):1215-1223. doi: 10.1007/s10545-018-0185-0. Epub 2018 May 30.
3. Santoro L, Zampini L, Padella L, et al. Early biochemical effects of velmanase alfa in a 7-month-old infant with alpha-mannosidosis. JIMD Rep. 2020;55(1):15-21. doi:10.1002/jmd2.12144

Clinical Guideline Revision / History Information

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