Drug Coverage Policy

Effective Date 6/1/2025
Coverage Policy Number.....IP0563
Policy Title.....Lamzede

Enzyme Replacement Therapy – Lamzede

- Lamzede® (velmanase alfa-tycv intravenous infusion – Chiesi)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Lamzede, a recombinant human lysosomal alpha-mannosidase, is indicated for the treatment of **non-central nervous system manifestations of alpha-mannosidosis** in adult and pediatric patients.[1]

Disease Overview
Alpha-mannosidosis is an ultra-rare autosomal recessive lysosomal storage disease. It is estimated to occur in 1 to 2:1,000,000 live births.[2] Alpha-mannosidosis results from reduced activity of the lysosomal enzyme, alpha-mannosidase, which is caused by gene variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1*). This results in accumulation of mannose-rich oligosaccharides in various tissues, which leads to significant and diverse multi-systemic manifestations. This can include progressive motor function disturbances and physical disability, hearing and speech

impairment, intellectual disability, and immune deficiency. Lamzede is the first and only enzyme replacement therapy approved for alpha-mannosidosis in the United States. There are no other FDA approved therapies for alpha-mannosidosis. Treatment is generally targeted towards management of the various clinical manifestations of the disease. Hematopoietic stem cell transplantation (HSCT) has been used to prevent cognitive decline, preserve neurocognitive function, and prevent early death.[2-4] However, not all patients are eligible for HSCT and it is associated with the risk of mortality and complications. Lamzede has been approved by the European Medicines Agency (EMA) in 2018. Diagnosis of alpha-mannosidosis is confirmed by molecular genetic testing and identification of biallelic pathogenic variants in *MAN2B1*.[5] Alpha-mannosidase enzyme activity in peripheral blood leukocytes is 5% to 10% of normal activity in affected individuals.

Clinical Efficacy
The efficacy of Lamzede in adult and pediatric patients with alpha-mannosidosis was established in two pivotal studies (rhLAMAN-05 and rhLAMAN-08) and one non-pivotal trial (rhLAMAN-10).[2-4] Patients with a confirmed diagnosis of alpha-mannosidosis, defined as alpha-mannosidase activity less than 10% of normal activity in blood leukocytes were enrolled. Lamzede demonstrated a statistically significant clearance of serum oligosaccharides vs. placebo in the pivotal trials. Lamzede also demonstrated improvement in endurance, pulmonary function, motor proficiency testing, and a decrease in serum immunoglobulins.

Dosing Information
The recommended dosage of Lamzede is 1 mg/kg (actual body weight) administered once every week as an intravenous infusion.[1] The total volume of infusion is determined by the patient's actual body weight and should be administered over a minimum of 60 minutes for patients weighing up to 49 kg. Patients weighing ≥ 50 kg should be infused at a maximum infusion rate of 25 mL/hour to control the protein load.

Safety
Lamzede has a Boxed Warning for hypersensitivity reactions, including anaphylaxis.[1] Other Warnings/Precautions for Lamzede include infusion-associated reactions and embryofetal toxicity. Pretreatment with antihistamines, antipyretics, and/or corticosteroids should be considered to reduce the risk of hypersensitivity and infusion-related reactions.

Coverage Policy

Lamzede is considered medically necessary when the following are met:

POLICY STATEMENT
Prior Authorization is required for medical benefit coverage of Lamzede. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lamzede as well as the monitoring required for adverse events and long-term efficacy, approval requires Lamzede to be prescribed by or in consultation with a physician who specializes in the condition being treated.

FDA-Approved Indication

1. **Alpha-mannosidosis.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient has a confirmed diagnosis of alpha-mannosidosis, defined as alpha-mannosidase activity less than 10% of normal activity in blood leukocytes; AND
   - **B)** Patient has biallelic pathogenic variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1)* as confirmed by genetic testing; AND
   - **C)** Patient has non-central nervous system manifestations; AND
     Note: Examples of non-central nervous system manifestations include progressive motor function disturbances, physical disability, hearing and speech impairment, skeletal abnormalities, and immune deficiency.
   - **D)** The medication is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

     Dosing. Up to 1 mg/kg (actual body weight) administered by intravenous infusion no more frequently than every week.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Lamzede for any other use is considered not medically necessary. Criteria will be updated as new published data are available.

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0217	Injection, velmanase alfa-tycv, 1 mg

References

1. Lamzede® intravenous infusion [prescribing information]. Cary, NC: Chiesi USA; 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;41(6):1215-1223.
3. Guffon N, Konstantopoulou V, Hennermann JB, et al. Long-term safety and efficacy of velmanase alpha (VA) treatment in children under 6 years of age with alpha-mannosidosis (AM). Presented at: 14th International Congress of Inborn Errors of Metabolism (ICIEM 2021); Sydney, Australia; November 21-23, 2021.

4. Lund A, Borgwardt L, Cattaneo F, et al. Comprehensive long-term efficacy and safety of recombinant human alpha-mannosidase (velmanase alfa) treatment in patients with alpha-mannosidosis. *J Inherit Metab Dis*. 2018;41:1225-1233.
5. Guffon N, Tylki-Szymanska A, Borgwardt L, et al. Recognition of alpha-mannosidosis in paediatric and adult patients: Presentation of a diagnostic algorithm from an international working group. *Mol Genet Metab*. 2019;126(4):470-474.

Type of Revision	Summary of Changes	Date
Annual Review	No criteria changes	7/1/2024
Annual Review	**Alpha-mannosidosis.** **Updated from** "Patient has biallelic pathogenic variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1)* as confirmed by mutation testing" **to** "Patient has biallelic pathogenic variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1)* as confirmed by genetic testing"	6/1/2025