New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Lamzede® (velmanase alfa-tycv)) [Chiesi Farmaceutici S.p.A.]** (VEL-man-ase AL-fa)
Dosage Formulations:	10 mg single-dose vials of white to off-white powder for reconstitution with 5 mL of sterile water. Each reconstituted vial yields a concentration of 2mg/mL. Can be supplied as one, five, or ten vials per carton.
FDA Approval Date: **FDB File Date:**	FDA: February 16, 2023 FDB: February 26, 2023
Indication:	Treatment of non-central nervous system manifestations of alpha-mannosidosis (AM).
Mechanism of Action:	Lamzede is a recombinant form of human alpha-mannosidase intended to provide or supplement natural alpha-mannosidase, an enzyme that is involved in the degradation of mannose–rich oligosaccharides to prevent their accumulation in various tissues in the body.
Dose/ Administration:	• Lamzede is dosed at 1 mg/kg of actual body weight once weekly as an intravenous infusion <u>Directions for reconstitution</u> • Calculate dose and determine number of vials needed. Round up to next whole number. Example: *78 kg x 1 mg/kg = 78 mg ÷ 10 mg/vial = 7.8 vials, round up to 8 vials* • Reconstitute each vial by slowly injecting 5 mL of Sterile Water for Injection, down the inside wall of each vial • Allow the reconstituted vials to stand on the table for 5 to 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 • 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. <u>Directions for administration</u> • Use an infusion set equipped with a pump and a low protein binding, 0.2-micron, in-line filter • The total infusion volume is determined by the patient's actual body weight ○ Patients weighing up to 49 kg – Administer over 60 minutes ○ Patients weighing 50 kg and greater - Maximum infusion rate of 25 mL/hr (50 mg/hr) • When the last syringe is empty, replace the dosage syringe with a 20 mL syringe filled with 0.9% sodium chloride for injection • Infuse an additional 10 mL of 0.9% Sodium Chloride Injection through the infusion system to flush any remaining Lamzede through the line
Disease State Clinical Highlights:	• AM is a rare genetic lysosomal storage disorder characterized by a deficiency in alpha-mannosidase. Pathogenic variants in the *MAN2B1* gene cause alpha-mannosidosis as this gene provides instructions for making the enzyme alpha-mannosidase. This enzyme works within liposomal cells to break down complex sugars, including oligosaccharides, which are important in the building of bones, cartilage, skin, and tendons • Without this enzyme-assisted breakdown, oligosaccharides will accumulate in the lysosomes causing cell malfunction and eventual death. Tissues and organs are damaged by the abnormal accumulation of oligosaccharides, leading to the characteristic features of AM • The deficiency can manifest with varying degrees of physical and intellectual disability

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- Because of wide-ranging symptoms, it is frequently misdiagnosed
  - The presence of oligosaccharides in urine is suggestive of the disease
  - Besides genetic testing, the measurement of alpha-mannosidase activity in nucleated cells via a fluorometric assay is the most reliable diagnostic method
- There are three main forms of alpha-mannosidosis, characterized by severity and rate of progression:

Form	Common Symptoms
Type 1	Muscle weakness, mild-to-moderate intellectual disability
Type 2	Skeletal abnormalities, weakness, ataxia
Type 3	All Type 2 features, plus severe intellectual disability, hydrocephalus, hepatosplenomegaly

- Type 1 is slowly progressive and is often not diagnosed until teenage years, while Type 3 is rapid, life-threatening, and usually diagnosed at birth. Type 2 is the most common form and is usually diagnosed before the age of 10. Depending on severity and rate of progression, it is possible for patients to live into middle age with AM
- The estimated prevalence of AM is approximately 1 in 500,000 to 1,000,000 people in the general population.

Drug Clinical Highlights:

- Lamzede is the first enzyme replacement therapy approved in the United States for treatment of the non-central nervous system manifestations of AM. Lamzede does not cross the blood brain barrier.

Warnings and Precautions

- Hypersensitivity Reactions, Including Anaphylaxis
  - 50% of clinical trial participants experienced hypersensitivity reactions
    - 5% experienced anaphylaxis
  - The manufacturer recommends considering pretreating participants with antihistamines, antipyretics, and/or corticosteroids
- Infusion-Associated Reactions
  - 50% of clinical trial participants experienced infusion-associated reactions (IARs)
    - One patient discontinued treatment dure to frequent IARs
  - Most common (>10%) reactions manifested as chills, pyrexia, vomiting, erythema, urticaria, rash, and conjunctivitis
  - As with hypersensitivity reactions, recommended to consider pretreating participants with antihistamines, antipyretics, and/or corticosteroids to avoid serious IARs
- Embryo-Fetal Toxicity
  - Lamzede may cause embryo-fetal harm if administer to a pregnant female (based on animal reproduction studies)
  - Verify pregnancy status prior to initiating Lamzede
  - If a participant becomes pregnant during treatment, it is recommended to consider the need for Lamzede, potential fetal risk, and potential adverse outcomes from untreated AM

Clinical Trials

NCT01681953

- Phase 3 multicenter, randomized, double-blinded, placebo-controlled, parallel group trial of adult and pediatric patients with AM
- Evaluated the efficacy of Lamzede over 52 weeks at a dose of 1 mg/kg given weekly as an intravenous infusion
- Total of 25 patients enrolled (13 adult, 12 pediatric)
- Primary Outcome Measures
  - Reduction of oligosaccharides in serum
  - Number of steps climbed in 3 minutes (3MSCT)
- Prioritized Secondary Outcome Measures
  - Forced vital capacity (FVC)

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- Distance walked in 6 minutes (6MWT)

- Key Inclusion Criteria
  - A confirmed diagnosis of AM as defined by alpha-mannosidase activity < 10% of normal activity
  - Age at the time of screening ≥ 5 years and ≤ 35 years
  - The ability to physically and mentally cooperate in the tests
- Key Exclusion Criteria
  - Diagnosis cannot be confirmed by alpha-mannosidase activity < 10% of normal activity
  - Participant cannot walk without support
  - Presence of known chromosomal abnormality and syndromes affecting psychomotor development, other than AM
  - Known clinically significant cardiovascular, hepatic, pulmonary, or renal disease or other medical conditions that, in the opinion of the Investigator, would preclude participation in the trial
  - Pregnancy
- Methods and Results
  - Measured after 12 months:

	Lamzede (n=15)	Placebo (n=10)	Treatment Difference (95% CI)
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)

- Post-hoc analysis showed improved results of the 3MSCT in pediatric patients compared to adults, perhaps indicating earlier treatment produces more clinical benefit

Treatment-Emergent Adverse Events (TEAEs)

	Lamzede (n=15)		Placebo (n=10)	
	n (%)	Events	n (%)	Events
Any TEAE	15 (100)	157	9 (90.0)	113

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Treatment-related TEAEs*	7 (46.7)	30	5 (50.0)	9
Serious TEAEs**	5 (33.3)	5	0 (0.0)	0

*Events that occurred in a reasonable timeframe from the time of drug administration and stopped when drug was discontinued
**Defined as death, life-threatening experience, a requirement for or prolonging hospitalization, a significant disability or incapacity, a congenital abnormality, or any medical event that required medical or surgical intervention to prevent an outcome listed above

- Four of the serious TEAEs were deemed unrelated to treatment
  - Fifth was acute renal failure after 12 months of Lamzede therapy

NCT02998879

- Single-arm, Phase II open label trial
- Total of 5 pediatric patients enrolled (aged 3.7 to 5.9 years)
- Primary Outcome Measures
  - Safety and tolerability of Lamzede (by measurement of adverse events)
  - Detection of anti-Lamzede antibodies
- Secondary Outcome Measures
  - Reduction of oligosaccharides in serum
- Key Inclusion Criteria
  - A confirmed diagnosis of AM as defined by alpha-mannosidase activity < 10% of normal activity (historical data)
  - Age at the time of screening < 6 years
  - The ability to physically and mentally cooperate in the tests
- Key Exclusion Criteria
  - Diagnosis cannot be confirmed by alpha-mannosidase activity < 10% of normal activity
  - Presence of known chromosomal abnormality and/or syndromes affecting psychomotor development, other than AM
  - Known clinically significant cardiovascular, hepatic, pulmonary, or renal disease or other medical conditions that, in the opinion of the Investigator, would preclude participation in the trial
- Methods and Results
  - Mean (SD) absolute changes from baseline for serum oligosaccharides at 24 months: -7.7 (4.27) µmol/L

Price Per Unit (WAC):

$4,000.00 per vial
$1,456,000 per year based on 1mg/kg weekly dosing of a 70 kg patient ($ 28,000 per week)

Therapeutic Alternatives:

- Lamzede is the first and only FDA-approved medication for AM. It received orphan drug designation by the FDA for this indication
- Allogeneic hematopoietic stem cell transplantation (HSCT) is another AM treatment option, but not all patients are eligible, results are highly variable, and treatment carries a risk of mortality
- Traditional treatment of AM is supportive and mainly aimed at mitigating disease complications:
  - Physical therapy for weakness and gait disturbances
  - Hearing aids and neurofeedback for hearing loss
  - Antiepileptic medications for seizure prophylaxis
  - Placement of CSF shunts to combat hydrocephalus

Prior Authorization Approval Criteria:

Must meet the following criteria:

<u>Initial Therapy:</u>

- Participant must have documented baseline 3MSCT, 6MWT, FVC, Serum oligosaccharides **AND**

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	• Participant is currently not pregnant **AND** • Prescribed by or in consultation with a specialist in the treated disease state **AND** • Documented diagnosis of AM (ICD10 E77.1) confirmed by: ○ Molecular genetic testing revealing pathogenic variants of the *MAN2B1* gene **OR** ○ Documentation of deficient acid alpha-mannosidase activity in leukocytes or other nucleated cells • Initial approval for one year Continuation of Therapy: • Documentation of compliance with Lamzede • Documentation of benefit of therapy defined by one of the following: ○ Improvement in 3MSCT (steps/min) from baseline ○ Improvement in 6MWT (meters) from baseline ○ Improvement in FVC (% predicted) from baseline ○ Reduction of serum oligosaccharides from baseline • Continued approval is for one year Denial Criteria: • Therapy will be denied if all approval criteria are not met • Participant is currently pregnant Default Approval Period: • One year **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Documentation of the following clinical and laboratory criteria at intervals of at least 12 months: ○ 3MSCT (steps/min) ○ 6MWT (meters) ○ FVC (% predicted) ○ Serum oligosaccharides
Implication to State Medicaid Program:	**LOE:** TBD

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