▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
LAMZEDE® (velmanase alfa)

1. NAME OF THE MEDICINE

Velmanase alfa

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg of velmanase alfa.

After reconstitution, one mL of the solution contains 2 mg of velmanase alfa (10 mg/5 mL).

For the full list of excipients see section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Powder for injection.

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Enzyme replacement therapy for the treatment of non-central nervous system manifestations in patients with alpha-mannosidosis.

4.2 DOSE AND METHOD OF ADMINISTRATION

The treatment should be supervised by a physician experienced in the management of patients with alpha-mannosidosis or in the administration of other enzyme replacement therapies (ERT) for lysosomal storage disorders.

LAMZEDE should be administered by a healthcare professional with the ability to manage ERT. Healthcare professionals should be able to assess and manage medical emergencies, including anaphylaxis and other severe hypersensitivity reactions, and have access to appropriate treatments and equipment (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The treating physician should consider use of premedications, especially in those considered at higher risk such as paediatric patients or patients with previous reactions (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dosage

The recommended dose regimen is 1 mg/kg of body weight administered once every week by intravenous infusion at a controlled speed.

Method of administration

LAMZEDE requires reconstitution and is intended for intravenous infusion only.

LAMZEDE does not contain preservatives. Vials are for single use only.

Instructions for reconstitution

LAMZEDE should be reconstituted and administrated by a healthcare professional.

Aseptic technique is to be used during preparation. Filter needles must not be used during preparation.

a) The number of vials to be used should be calculated based on the individual patient's weight. The recommended dose of 1 mg/kg is determined using the following calculation:

- Patient's weight (kg) × dose (mg/kg) = Patient dose (in mg).
- Patient dose (in mg) divided by 10 mg/vial (content of one vial) = number of vials to reconstitute. If the number of calculated vials includes a fraction, it should be rounded up to the next whole number.
- Approximately 30 minutes prior to reconstitution, the required number of vials should be removed from the refrigerator. The vials should reach ambient temperature (between 15°C and 25°C) prior to reconstitution.
- Each vial is reconstituted by slowly injecting 5 mL of water for injections to the inside of the wall of each vial. Each mL of reconstituted solution contains 2 mg of velmanase alfa. Only the volume corresponding to the recommended dose should be administered.

Example:

- Patient's weight (44 kg) × dose (1 mg/kg) = Patient dose (44 mg).
- 44 mg divided by 10 mg/vial = 4.4 vials, therefore 5 vials should be reconstituted.
- From the total reconstituted volume, only 22 mL (corresponding to 44 mg) should be administered.

b) The powder should be reconstituted in the vial by a slow drop-wise addition of the water for injections down the inside of the vial and not directly onto the lyophilised powder. Forcefully ejecting the water for injections from the syringe onto the powder should be avoided to minimise foaming. The reconstituted vials should stand on the table for about 5-10 minutes. Thereafter each vial should be tilted and rolled gently for 15-20 seconds to enhance the dissolution process. The vial should not be inverted, swirled, or shaken.

c) An immediate visual inspection of the solution for particulate matter and discoloration should be performed after reconstitution. The solution should be clear and not used if opaque particles are observed or if the solution is discoloured. Due to the nature of the medicinal product, the reconstituted solution may occasionally contain some proteinaceous particles in form of thin white strands or translucent fibers which will be removed by the in-line filter during infusion (see point e).

d) The reconstituted solution is to be slowly withdrawn from each vial with caution to avoid foaming in the syringe. If the volume of the solution exceeds one syringe capacity, the required number of syringes should be prepared in order to replace the syringe quickly during the infusion.

Administration of intravenous infusion

e) The reconstituted solution should be administered using an infusion set equipped with a pump and an in-line low protein-binding 0.2 µm filter.

   The total volume of infusion is determined by the patient's weight and should be administrated over a minimum of 50 minutes for patients weighing up to 42 kg. Patients weighing 42 kg and greater should be infused at a maximum infusion rate of 25 mL/hour to control the protein load. It is recommended to always use the same dilution (2 mg/mL).

   The treating physician should consider using a slower rate of infusion (than that given above) in patients new to treatment in order to reduce the risk of infusion-related reactions (IRRs). Also consider using a slower rate in patients with previous IRRs who are continuing treatment.

f) When the last syringe is empty, the dose syringe is replaced with a 20 mL syringe filled with sodium chloride 9 mg/mL (0.9%) solution for injection. A volume of 10 mL sodium chloride solution should be administered through the infusion system to infuse the remaining fraction of LAMZEDE in the line to the patient.

The patient should be observed for IRRs for at least one hour after the infusion according to clinical conditions and the physician's judgment (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Home infusion

Infusion of LAMZEDE at home may be considered for patients who are tolerating their infusions well. The decision to have a patient move to home infusion should be made after evaluation and recommendation by the treating physician, taking into consideration patient history. IRRs can occur even in patients previously tolerating treatment well. The risks and benefits of home infusion should be discussed with the patient and/or carers.

Home infusions should be administered by a healthcare professional able to assess and manage infusion reactions, including serious reactions and anaphylaxis, and who has access to appropriate treatments and equipment. Dose and infusion rate in home setting should remain the same used in the hospital setting and should be changed only under the supervision of a healthcare professional and treating physician.

In the event of an IRR, including hypersensitivity reactions or anaphylactic reactions, the infusion rate should be decreased or stopped based on the severity of the reaction, and other appropriate treatments should be instituted (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Special populations

Women of childbearing potential

Verify that the patient is not pregnant prior to initiating treatment with LAMZEDE (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Elderly

No data are available and no relevant use in elderly patients.

Renal or hepatic impairment

No dose adjustment is necessary for patients with renal or hepatic impairment.

Paediatric population

No dose adjustment is necessary for the paediatric population.

4.3 CONTRAINDICATIONS

Severe allergic reaction to the active substance or to any of the excipients listed in section 6.1 LIST OF EXCIPIENTS.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General consideration on the treatment

As the accumulation of end organ damage progresses over time, it is more difficult for the treatment to reverse the damage or to show improvements. As with other enzyme replacement therapies, velmanase alfa does not cross the blood-brain-barrier. It should be considered by the treating physician that the administration of velmanase alfa does not affect the irreversible complications (i.e. skeletal deformities, disostosis multiplex, central nervous system manifestations and impaired cognitive function).

Hypersensitivity/anaphylaxis

Hypersensitivity reactions have been reported in patients in clinical studies and anaphylaxis is considered as a potential risk with LAMZEDE (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Appropriate medical support should be readily available when velmanase alfa is administered.

If severe allergic or anaphylactic-type reactions occur, immediate discontinuation of velmanase alfa is recommended and current medical standards for emergency treatment are to be followed.

Infusion-related reaction

Administration of velmanase alfa may result in an IRR, including anaphylactic-type reactions (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The symptoms reported included hypersensitivity, cyanosis, nausea, vomiting, pyrexia, chills, feeling hot, malaise, urticaria, anaphylactoid reaction and hyperhidrosis. The IRRs observed in clinical studies of velmanase alfa were characterised by a rapid onset of symptoms and were of mild to moderate severity.

Prior to velmanase alfa administration, consider pre-treating with antihistamines, antipyretics and/or corticosteroids to reduce the risk of infusion-related reactions (IRRs). IRRs may still occur in patients after receiving pre-treatment.

- If a severe IRR occurs, discontinue velmanase alfa immediately and initiate appropriate medical treatment. Consider the risks and benefits of re-administering velmanase alfa following a severe IRR. 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 IRR occurs, consider slowing the infusion rate or temporarily with-holding the dose.

The patient should be kept under observation for IRRs for one hour or longer after the infusion, according to the treating physician's judgement.

Immunogenicity

There is a potential for immunogenicity.

Anti-drug antibodies may play a role in treatment-related reactions observed with the use of velmanase alfa. To further evaluate the relationship, in instances of development of severe IRRs or lack or loss of treatment effect, physicians with access to testing should consider testing patients for the presence of anti-velmanase alfa antibodies.

In the exploratory and pivotal clinical studies, a treatment-emergent (boosted/induced) ADA response was detected in 4 out of 33 (12.1%) velmanase alfa treated patients; 2 out of these 4 patients experienced IRRs that were successfully managed by reducing the rate of infusion of velmanase alfa and/or pre-medication with corticosteroids and antihistamines.

Of note, 6 out of 33 (18.2%) patients had a positive ADA test at baseline, before the administration of velmanase alfa. Furthermore, only 3 out of 33 (9.1%) patients experienced IRRs (2 out of these 3 patients with positive ADA tests within 6 months from IRR occurrence), while 10 out of 33 (30.3%) patients had a positive ADA test at some point during the clinical trials, indicating that ADA positivity is a poor predictor of IRRs. High ADA levels might be a stronger predictor of IRRs, however no clear correlation has been established.

In a paediatric clinical study in patients below 6 years, 4 out of 5 patients (80%) developed IgG-class antibodies to velmanase alfa. In this study, the immunogenicity test was performed with a different and more sensitive method and therefore the incidence of patients developing IgG-class antibodies to velmanase alfa was higher but not comparable to data of the previous studies. Only one of the 5 treated patients experiencing mild-to-moderate infusion reactions that were coincident with relatively high levels of ADA. This single patient was able to continue treatment with routine clinical management measures.

In the exploratory and pivotal clinical studies, there were only two patients with persistent, treatment-emergent high ADA levels. One of these two patients (maximal level 440 U/mL) was classified as a responder in terms of >70% reduction of serum oligosaccharide concentration. The other patient was an initial responder with reductions in serum oligosaccharide concentration, but a later increase of ADA to exceptionally high level (1,012 U/ml) was associated with an increase in serum oligosaccharides relative to the levels detected during earlier treatment.

In a paediatric clinical study in patients below 6 years, the single patient with relatively high levels of ADA (maximal level 174 U/mL) and mild-to-moderate infusion reactions had a complete response as demonstrated by sustained reduction in serum oligosaccharide concentrations. In summary, 2 out of these 3 patients with high ADA levels sustained a good response to velmanase alfa treatment in terms of reductions in serum oligosaccharide concentration.

Embryofetal toxicity

Based on findings in animal reproduction studies, LAMZEDE may cause fetal harm when administered to a pregnant woman.

LAMZEDE is not recommended during pregnancy and in women of childbearing potential not using effective contraception, unless the potential benefits to the mother outweigh the potential risks, including those to the fetus (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per vial and is essentially ‘sodium-free’.

Use in the elderly

See section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

See section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed. As velmanase alfa is a recombinant human protein, no cytochrome P450 mediated drug-drug interactions are expected.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no clinical data on the effects of velmanase alfa on fertility. Animal studies did not show evidence of impaired fertility in male and female rats when velmanase alfa was administered intravenously twice weekly at doses up to 30 mg/kg (AUC ~21-fold higher than the clinical AUC at maximum recommended human dose).

Use in pregnancy - Pregnancy Category D

There are no data from the use of velmanase alfa in pregnant women.

Intravenous (IV) administration of velmanase alfa to pregnant rats during the period of organogenesis caused skeletal malformations (duplicate of the 1st to the 6th sternebrae, cleft palate and palantine, and severely bent scapulae) at 20 mg/kg/day with exposure (AUC) ~49-fold the clinical exposure at maximum recommended human dose (MRHD). The no observed adverse effect level (NOAEL) was at 10 mg/kg/day, with exposure (AUC) 11-fold the clinical exposure at MRHD. In rabbits, lower fetal and placental weights (7 and 11%, respectively) and increased incidence of incomplete ossification of various bones were observed at 30 mg/kg/day, with exposures (AUC) 33-fold higher than observed at MRHD, occurring in the context of lower maternal body weight gain. The NOAEL was at 10 mg/kg/day with exposure (AUC) 0.2-fold the clinical exposure at MRHD.

LAMZEDE is not recommended during pregnancy and in women of childbearing potential not using effective contraception, unless the potential benefits to the mother outweigh the potential risks, including those to the fetus.

Perform a pregnancy test prior to treatment initiation with LAMZEDE. Women of childbearing potential are advised to use effective contraception during treatment and for 14 days after the last dose if LAMZEDE is discontinued.

Use in lactation

It is unknown whether velmanase alfa or its metabolites are excreted in human milk.

In a pre- and postnatal development study, velmanase alfa was administered intravenously to pregnant rats from gestational day 6 to lactation day 20 every third day. No adverse effects were observed in the offspring up to the highest dose tested of 30 mg/kg (estimated to yield exposure to velmanase alfa (AUC) 21-fold higher than that in patients at the MRHD).

Nevertheless, the absorption of any ingested milk-containing velmanase alfa in the breastfed child is considered to be minimal. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for velmanase alfa.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

LAMZEDE has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

rhLAMAN-05 Study

The safety of LAMZEDE was evaluated in the double-blind, randomised, placebo-controlled, parallel group rhLAMAN-05 study which included a total of 15 LAMZEDE-treated patients (8 adult patients aged 18-35 years old and 7 paediatric patients aged 6-17 years old). All patients received LAMZEDE 1 mg/kg weekly via intravenous infusion for 52 weeks.

A serious adverse reaction of acute renal failure was reported in 1 (7%) LAMZEDE-treated patient (see Description of selected adverse reactions). Table 1 lists adverse events that occurred in at least 2 LAMZEDE-treated patients in rhLAMAN-05. '

Table 1. Adverse events (≥2 patients) in adult and paediatric patients with alpha- mannosidosis treated with LAMZEDE in rhLAMAN-05

Adverse event	**LAMZEDE N=15 n (%)**	**Placebo N=10 n (%)**
Nasopharyngitis	10 (66)	7 (70)
Pyrexia	6 (40)	5 (50)
Headache	5 (33)	3 (30)
Arthralgia	3 (20)	1 (10)
Acute tonsillitis	2 (13)	0
Urinary tract infection[(1)]	2 (13)	1 (10)
Eye pruritus	2 (13)	0
Gastroenteritis	2 (13)	0
Hypersensitivity	2 (13)	0
Influenza	2 (13)	0
Syncope	2 (13)	0
Toothache	2 (13)	0
Back pain	2 (13)	1 (10)
Ear infection	2 (13)	1 (10)

[(1)] "Urinary tract infection" is composed of similar terms

rhLAMAN-08 study

In an open-label study (rhLAMAN-08), 5 paediatric patients aged 3 to 5 years old received LAMZEDE weekly for a mean exposure of 121 weeks. One patient treated with LAMZEDE (20%) experienced serious reactions (chills and hyperthermia on the same occasion). The adverse reactions that occurred in at least 2 of 5 patients (in addition to Table 1) included cough, otitis media, rhinitis, conjunctivitis, fall, ligament sprain, oropharyngeal pain, swelling face and upper respiratory tract infection.

rhLAMAN-10 study

rhLAMAN-10 was an integrated analysis that pooled the cumulative databases from LAMZEDE Phase 1, 2 and 3 trials. A total of 33 patients aged 6 to 35 years old (14 adults, 19 paediatric) received LAMZEDE weekly for a mean exposure of 89 weeks in adult patients and 155 weeks in paediatric patients.

One patient was withdrawn from the study due to repeated IRRs and was successfully reintroduced after a 89 week treatment pause.

The adverse reactions that occurred in at least 10% of patients (in addition to Table 1 and rhLAMAN-08) included abdominal pain upper, contusion, excoriation, post-lumbar puncture syndrome, wound, weight increased, erythema, rash and tooth extraction.

Tabulated list of adverse reactions

The adverse reactions reported from clinical studies, post-authorisation safety studies and spontaneous reporting are listed in Table 2.

Adverse reactions are classified by system organ class and preferred term according to the MedDRA frequency convention. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequency is defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data).

Table 2. Adverse reactions reported from clinical studies, post-authorisation safety studies and spontaneous reporting

System organ class	Frequency	Adverse reaction
Infections and infestations	Not known	Bacterial disease carrier, endocarditis, furuncle, staphylococcal infection
Immune system disorders	Common	Hypersensitivity[(1)], anaphylactoid reaction[(1)]
Metabolism and nutrition disorders	Common	Increased appetite
	Not known	Decreased appetite
Psychiatric disorders	Common	Psychotic behaviour, initial insomnia
	Not known	Agitation, encopresis, psychotic disorder, nervousness
Nervous system disorders	Common	Loss of consciousness[(2)], tremor, confusional state, syncope, headache, dizziness, ataxia, nervous system disorder, somnolence
Eye disorders	Common	Eyelid oedema, eye irritation, ocular hyperaemia
	Not known	Lacrimation increased
Ear and labyrinth disorders	Not known	Deafness
Cardiac disorders	Common	Cyanosis[(1)], bradycardia
	Not known	Aortic valve incompetence, palpitations, tachycardia
Vascular disorders	Not known	Hypotension, vascular fragility
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis
	Not known	Oropharyngeal pain, pharyngeal oedema, wheezing
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Vomiting[(1)], abdominal pain upper, nausea[(1)], abdominal pain, reflux gastritis
	Not known	Odynophagia
Skin and subcutaneous tissue disorders	Common	Urticaria[(1)], hyperhidrosis[(1)]
	Not known	Angioedema, erythema, rash
Musculoskeletal and connective tissue disorders	Common	Arthralgia, pain in extremity, joint stiffness, myalgia, back pain
	Not known	Joint swelling, joint warmth
Renal and urinary disorders	Common	Renal failure acute[(2)]
General disorder and administration site conditions	Very common	Pyrexia[(1)]
	Common	Chills, catheter site pain, feeling hot[(1)], fatigue, malaise[(1)]
	Not known	Asthenia
Investigations	Very common	Weight increase
Injury, poisoning and procedural complications	Common	Procedural headache
	Not known	Infusion related reaction

[(1)] Preferred terms considered as IRR (see Infusion-related reaction)

[(2)] Selected adverse reaction (see Description of selected adverse reactions)

Description of selected adverse reactions

Infusion-related reaction (IRR)

An IRR was an adverse reaction which occurred during or up to 2 hours after the infusion of LAMZEDE. IRRs (including hypersensitivity, cyanosis, nausea, vomiting, pyrexia, chills, feeling hot, malaise, urticaria, anaphylactoid reaction and hyperhidrosis) were reported in 13% of the patients (5 out of 38 patients) in clinical studies. All were mild or moderate in severity and 2 were reported as a serious adverse reaction (see section 5.1 PHARMACODYNAMIC PROPERTIES). All patients who experienced IRRs recovered.

See also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Acute renal failure

In the clinical studies, one patient experienced acute renal failure considered possibly related to the study treatment. Acute renal failure was of moderate severity leading to temporary discontinuation of the study treatment and fully resolved within 3 months. Concomitant long-term treatment with high doses of ibuprofen was noted during the occurrence of the event.

Loss of consciousness

In one patient, one event of loss of consciousness was reported during the treatment in the clinical trials. The event occurred 8 days after last infusion and after 14 months of treatment. A connection to the test drug could not be ruled out despite the long period from last infusion and until the event occurred. The patient recovered within few seconds and was taken to the hospital, where she/he received sodium chloride 9 mg/mL (0.9%) solution for infusion and was then discharged after 6-hour observation. The patient continued in the study with no change in dose level.

No other related event of loss of consciousness has been reported either in the clinical either in the commercial setting.

Paediatric population

Children age below 6 years old

A total of 5 patients with alpha-mannosidosis below 6 years received velmanase alfa in a clinical study. The safety profile was similar to that observed in the previous studies, with similar frequency, type and severity of adverse events.

Children age group 6 to 17 years old

The safety profile of velmanase alfa in clinical studies involving children and adolescents was similar to that observed in adult patients. Overall, 58% of patients (19 out of 33 patients) with alpha-mannosidosis receiving velmanase alfa in clinical studies were aged 6 to 17 years at the start of the study.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no experience with overdose of velmanase alfa. The maximum dose of velmanase alfa in clinical studies was a single administration of 100 units/kg (approximately corresponding to 3.2 mg/kg). During the infusion with this higher dose, fever of mild intensity and short duration (5 hours) was observed in one patient. No treatment was administered.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes.
ATC code: A16AB15.

Mechanism of action

Velmanase alfa is a recombinant form of human alpha-mannosidase. The amino acid sequence of the monomeric protein is identical to the naturally occurring human enzyme, alpha-mannosidase.

Velmanase alfa is intended to supplement or replace natural alpha-mannosidase, an enzyme that catalyses the sequential degradation of hybrid and complex high-mannose oligosaccharides in the lysosome, reducing the amount of accumulated mannose-rich oligosaccharides.

Clinical trials

A total of 33 patients enrolled in the exploratory and pivotal studies (20 males and 13 females, ranging in age from 6 to 35 years) were exposed to velmanase alfa in five clinical studies. Patients were diagnosed based on alpha-mannosidase activity <10% of normal activity in blood leukocytes. Patients with the most severe rapidly progressing phenotype (with a deterioration within one year and central nervous system involvement) were excluded. Based on this criteria mild to moderate patients, presenting heterogeneous severity with ability to perform endurance tests, large variability of clinical manifestations and age of onset were enrolled.

Overall effects of treatment were evaluated in the domains of pharmacodynamics (reduction of serum oligosaccharides), functional (three-minute stair climbing test (3MSCT), six-minute walking test (6MWT), and forced vital capacity (FVC) % predicted) and quality of life (childhood health assessment questionnaire (CHAQ) disability index (DI) and CHAQ VAS pain (visual analogue scale)).

In the phase 3 pivotal multi-centre, double-blind, randomised, placebo-controlled, parallel group study (rhLAMAN-05), the efficacy and safety of repeated administrations of velmanase alfa over 52 weeks at a dose of 1 mg/kg given weekly as intravenous infusion were investigated. The primary endpoints for the study were change from baseline to week 52 in serum oligosaccharides and 3MSCT. The secondary endpoints were change from baseline to week 52 in 6MWT and FVC%.

A total of 25 patients were enrolled, including 12 paediatric subjects (age range: 6-17 years; mean: 10.9 years) and 13 adult subjects (age range: 18-35 years; mean: 24.6). All but one patient were naïve to the treatment with velmanase alfa. In total 15 patients (7 paediatrics and 8 adults) received active treatment and 10 patients received placebo (5 paediatrics and 5 adults). The results (serum oligosaccharide concentration, 3MSCT, 6MWT and FVC%) are presented in Table 3.

A pharmacodynamic effect with statistically significant decrease of serum oligosaccharides in comparison to placebo was demonstrated (mean difference: -3.50 µmol/L; 95% CI: -4.37; -2.62; p<0.001). The results observed in patients below 18 years of age showed statistically non-significant trends towards improvement in 3MSCT (mean change (SD) from baseline: 3.5 (10.0) vs. -2.3 (5.4) steps/min), 6MWT (mean change (SD) from baseline: 12.3 (43.2) vs. 3.6 (43.0) metres) and FVC% (mean change (SD) from baseline: 14.2 (8.7) vs. 8.0 (4.2) % of predicted) relative to placebo. In patients over 18 years old a stabilisation was observed in clinical endpoints / functional domains compared to a worsening of these endpoints in the placebo group coherent with the slowly progressive nature of alpha-mannosidosis. The numerical improvement of most clinical endpoints over placebo (2 to 8%) observed in the year of observation could be suggestive of the ability of velmanase alfa to slow down the existing disease progression.

Table 3. Results from placebo-controlled clinical study (rhLAMAN-05)

	Treatment with velmanase alfa for 12 months (n=15)		**Treatment with placebo for 12 months (n=10)**		**Velmanase alfa versus placebo**
Patients	**Baseline actual value Mean (SD)**	**Absolute change from baseline Mean**	**Baseline actual value Mean (SD)**	**Absolute change from baseline Mean**	**Adjusted mean difference**
Primary endpoints					
Serum oligosaccharide concentration (µmol/L)					
Overall[(1)] [95% CI] p-value	6.8 (1.2)	-5.11 [-5.66; -4.56]	6.6 (1.9)	-1.61 [-2.28; -0.94]	-3.50 [-4.37; -2.62] p<0.001
<18 years[(2)]	7.3 (1.1)	-5.2 (1.5)	6.0 (2.4)	-0.8 (1.7)	-
≥18 years[(2)]	6.3 (1.1)	-5.1 (1.0)	7.2 (1.0)	-2.4 (1.4)	
3MSCT (steps/min)					
Overall[(1)] [95% CI] p-value	52.9 (11.2)	0.46 [-3.58; 4.50]	55.5 (16.0)	-2.16 [-7.12; 2.80]	2.62 [-3.81; 9.05] p=0.406
<18 years[(2)]	56.2 (12.5)	3.5 (10.0)	57.8 (12.6)	-2.3 (5.4)	-
≥18 years[(2)]	50.0 (9.8)	-1.9 (6.7)	53.2 (20.1)	-2.5 (6.2)	
Secondary endpoints					
6MWT (metres)					
Overall[(1)] [95% CI] p-value	459.6 (72.26)	3.74 [-20.32; 27.80]	465.7 (140.5)	-3.61 [-33.10; 25.87]	7.35 [-30.76; 45.46] p=0.692
<18 years[(2)]	452.4 (63.9)	12.3 (43.2)	468.8 (79.5)	3.6 (43.0)	-
≥18 years[(2)]	465.9 (82.7)	-2.5 (50.4)	462.6 (195.1)	-12.8 (41.6)	
FVC (% of predicted)					
Overall[(1)] [95% CI] p-value	81.67 (20.66)	8.20 [1.79; 14.63]	90.44 (10.39)	2.30 [-6.19; 10.79]	5.91 [-4.78; 16.60] p=0.278
<18 years[(2)]	69.7 (16.8)	14.2 (8.7)	88.0 (10.9)	8.0 (4.2)	-
≥18 years[(2)]	93.7 (17.7)	2.2 (7.2)	92.4 (10.8)	-2.8 (15.5)	

[(1)] For overall: adjusted mean change and adjusted mean difference estimated by ANCOVA model are presented

[(2)] By age: unadjusted mean and SD are presented.

The long-term efficacy and safety of velmanase alfa was investigated in the uncontrolled, open-label, phase 3 clinical study (rhLAMAN-10) in 33 subjects (19 paediatrics and 14 adults, from 6 to 35 years at treatment initiation) who previously participated in velmanase alfa studies. An integrated database was created by pooling cumulative databases from all studies with velmanase

alfa. Statistically significant improvements were detected in serum oligosaccharide levels, 3MSCT, pulmonary function, serum IgG and EQ-5D-5L (euro quality of life-5 dimensions) over time, up to the last observation (Table 4). The effects of velmanase alfa were more evident in patients younger than 18 years.

Table 4. Change of clinical endpoints from baseline to the last observation study (rhLAMAN-10)

Parameter	Patients n=33	Baseline actual value Mean (SD)	Last observation % change from baseline (SD)	p-value [95% CI]
Serum oligosaccharide concentration (µmol/L)	Overall	6.90 (2.30)	-62.8 (33.61)	<0.001 [-74.7; -50.8]
3MSCT (steps/min)	Overall	53.60 (12.53)	13.77 (25.83)	0.004 [4.609; 22.92]
6MWT (metres)	Overall	466.6 (90.1)	7.1 (22.0)	0.071 [-0.7; 14.9]
FVC (% of predicted)	Overall	84.9 (18.6)	10.5 (20.9)	0.011 [2.6; 18.5]

Data suggest that the beneficial effects of the treatment with velmanase alfa diminish with the increase of disease burden and disease-related respiratory infections.

A post-hoc multiparametric responders analysis supports the benefit of longer treatment with velmanase alfa in 87.9% of responders in at least 2 domains at last observation (Table 5).

Table 5. Multiparametric responder analysis: MCID[(1)] Responders rates by endpoints and domains (rhLAMAN-05; rhLAMAN-10)

Domain	Criterion	Responders rates		
		rhLAMAN-05 study n=25		rhLAMAN-10 study n=33
		Placebo 12 months	Lamzede 12 months	Lamzede Last observation
Pharmacodynamic	Oligosaccharides	20.0%	100%	91.0%
Pharmacodynamic domain response	**Oligosaccharides**	**20.0%**	**100%**	**91.0%**
Functional	3MSCT	10.0%	20.0%	48.5%
	6MWT	10.0%	20.0%	48.5%
	FVC (%)	20.0%	33.3%	39.4%
Functional domain response	**Combined**	**30.0%**	**60.0%**	**72.7%**
Quality of Life	CHAQ-DI	20.0%	20.0%	42.2%
	CHAQ-VAS	33.3%	40.0%	45.5%
QoL Domain	**Combined**	**40.0%**	**40.0%**	**66.7%**
Overall response	**Three domains**	**0**	**13.3%**	**45.5%**
	Two domains	**30.0%**	**73.3%**	**42.4%**
	One domain	**30.0%**	**13.3%**	**9.1%**
	No domains	**40.0%**	**0**	**3.0%**

[(1)] MCID: minimal clinically important difference

Paediatric population

Children below 6 years old

Velamanse alfa was investigated in a single-arm trial in paediatric alpha-mannosidosis patients less

than 6 years of age (rhLAMAN-08). All patients had alpha-mannosidase activity below 10% of normal at baseline. The trial enrolled five patients ranging from 3.7 to 5.9 years of age (mean 4.5 years). Patients received velamanase alfa 1 mg/kg as 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.

Children age group 6 to 17 years old

Safety and efficacy of velmanase alfa in the age group 6 to 17 years is supported by evidence from clinical studies in paediatric (19 out of 33 patients enrolled in the exploratory and pivotal studies) and adult patients.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

LAMZEDE is administered by intravenous infusion. At steady-state after weekly infusion administration of 1 mg/kg of velmanase alfa, the mean maximum plasma concentration was about 8 µg/mL and was reached at 1.8 hours after the start of administration corresponding to the mean infusion duration time.

Distribution

As expected for a protein of this size, the steady-state volume of distribution was low (0.27 L/kg), indicating distribution confined to plasma. The clearance of velmanase alfa from plasma (mean 6.7 mL/h/kg) is consistent with a rapid cellular uptake of velmanase alfa via mannose receptors.

Metabolism

The metabolic pathway of velmanase alfa is predicted to be similar to other natural occurring proteins that degrade into small peptides and amino acids.

Excretion

After the end of the infusion, velmanase alfa plasma concentrations fell in a biphasic fashion with a mean terminal elimination half-life of about 30 hours.

Linearity

Velmanase alfa exhibited a linear (i.e. first-order) pharmacokinetic profile, and C_{max} and AUC increased proportionally to the dose with doses ranging from 0.8 to 3.2 mg/kg (corresponding to 25 and 100 units/kg).

Anti-drug Antibodies (ADA)

At the population level, ADA positive subjects (n=8) in the rhLAMAN-10 integrated analysis had a lower geometric mean velmanase alfa plasma concentration at steady-state compared to the ADA negative subjects (N=23) at all post-infusion time points. At the steady-state 10-minute post-infusion time point, corresponding the highest velmanase alfa plasma concentrations, the geometric mean velmanase alfa plasma concentration was 2365.3 µg/L for ADA positive subjects compared to 7880.8 µg/L for ADA negative subjects. Overall, an ADA level higher than 30 U/mL appears to be associated with a clear reduction in velmanase alfa plasma concentration, although a possible negative impact cannot be excluded for ADA levels greater than 10 U/mL.

Special populations

Gender

There were no apparent pharmacokinetic gender differences in patients with alpha-mannosidosis disease.

Renal or hepatic impairment

Velmanase alfa is a protein and is predicted to be metabolically degraded into amino acids. Proteins larger than 50,000 Da, such as velmanase alfa, are not eliminated renally. Consequently, hepatic and renal impairment are not expected to affect the pharmacokinetic of velmanase alfa.

Paediatric population

Pharmacokinetic data from paediatric patients recapitulate the data from the adult population. In particular, lack of accumulation of velmanase alfa at steady state, as well as the safety/efficacy data, confirm that the dose of 1 mg/kg is appropriate also in patients younger than 6 years.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies were conducted to evaluate genotoxicity.

Carcinogenicity

No studies were conducted to evaluate carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Dibasic sodium phosphate dihydrate
Monobasic sodium phosphate dihydrate
Mannitol
Glycine

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Unopened vial

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Reconstituted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, use reconstituted solution immediately or may be stored at 2°C to 8°C for up to 24 hours.

Single use in one patient only. Contains no antimicrobial preservative. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vial

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Supplied in a sterile, single-use Type 1 glass 10 mL vial with a bromobutyl rubber stopper, an aluminium seal and a polypropylene flip off cap.

Pack sizes: 1, 5 or 10 vials per carton.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Velmanase alfa is a recombinant human lysosomal alpha-mannosidase and is produced in a Chinese Hamster Ovary (CHO) cell line.

CAS number

1492823-75-2I

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8. SPONSOR

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Melbourne, VIC 3000.

Email: medinfo.au@chiesi.com

9. DATE OF FIRST APPROVAL

TBC

10. DATE OF REVISION

TBC

Summary table of changes

Section changed	Summary of new information
All	New Product Information