SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lamzede 10 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 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.

*Velmanase alfa is produced in mammalian Chinese Hamster Ovary (CHO) cells using recombinant DNA technology.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis. See sections 4.4 and 5.1.

4.2 Posology 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 disorder. Administration of Lamzede should be carried out by a healthcare professional with the ability to manage ERT and medical emergencies.

Posology

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

The effects of treatment with velmanase alfa should be periodically evaluated and discontinuation of treatment considered in cases where no clear benefits could be observed.

Special populations

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

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.

Method of administration

For intravenous infusion use only.

Instructions on reconstitution of the medicinal product before administration

The reconstituted solution should be clear. Do not use if opaque particles are observed or if the solution is discoloured (see section 6.6).

The reconstituted solution of Lamzede should be administered using an infusion set equipped with a pump and an in-line low protein-binding 0.22 µm filter. The infusion duration should be calculated individually considering a maximum infusion rate of 25 mL/hour to control the protein load. The infusion duration should be a minimum of 50 minutes. A slower infusion rate may be prescribed when clinically appropriate according to the physician's judgment, for example at the beginning of the treatment or in case of previous infusion-related reactions (IRRs).
For the calculation of the infusion rate and the infusion time based on body weight see the table in section 6.6.

The patient should be observed for IRRs for at least one hour after the infusion according to clinical conditions and the physician's judgment. For further instructions, see section 4.4.

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. Patients experiencing

infusion-related reactions, including hypersensitivity reactions or anaphylactic reactions, during the home infusion need to immediately reduce the infusion rate or to stop the infusion process considering the severity of the reaction and seek the attention of a healthcare professional. Dose and infusion rate in home setting should remain the same used in the hospital setting; they could be changed only under the supervision of a healthcare professional and treating physician.

Appropriate training should be given by the treating physician and/or nurse to the patient and/or caregiver prior to initiation of home infusion.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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, neurological manifestations and impaired cognitive function).

Hypersensitivity

Hypersensitivity reactions have been reported in patients in clinical studies. 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 anaphylactoid reaction (see section 4.8). The IRRs observed in clinical studies of velmanase alfa were characterised by a rapid onset of symptoms and were of mild to moderate severity.

The management of IRRs should be based on the severity of the reaction and includes slowing the infusion rate, treatment with medicinal products such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with increased infusion time. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Most of the patients were not routinely pre-medicated prior to infusion of velmanase alfa during clinical studies.

In case symptoms such as angioedema (tongue or throat swelling), upper airway obstruction or hypotension occur during or immediately after infusion, anaphylaxis or an anaphylactoid reaction should be suspected. In such a case, treatment with an antihistamine and corticosteroids should be considered as being appropriate. In the most severe cases, the current medical standards for emergency treatment are to be observed.

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

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, patients should be tested for the presence of anti-velmanase alfa antibodies. In case the patient's condition deteriorates during ERT, cessation of treatment should be considered.

There is a potential for immunogenicity.
In the exploratory and pivotal clinical studies at any time under treatment, 8 patients out of 33 (24%) developed IgG-class antibodies to velmanase alfa.
In a paediatric clinical study in patients below 6 years, 4 patients out of 5 (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.
No clear correlation was found between antibody titres (velmanase alfa IgG antibody level) and reduction in efficacy or occurrence of anaphylaxis or other hypersensitivity reactions.
The development of antibodies has not been shown to affect clinical efficacy or safety.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of velmanase alfa in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As velmanase alfa aims at normalizing alpha-mannosidase in alpha-mannosidosis patients, Lamzede is not recommended to be used during pregnancy unless the clinical condition of the woman requires treatment with velmanase alfa.

Breast-feeding

It is unknown whether velmanase alfa or its metabolites are excreted in human milk. Nevertheless, the absorption of any ingested milk-containing velmanase alfa in the breastfed child is considered to be minimal and no untoward effects are therefore anticipated. Lamzede can be used during breastfeeding.

Fertility

There are no clinical data on the effects of velmanase alfa on fertility. Animal studies do not show evidence of impaired fertility.

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 Undesirable effects

Summary of the safety profile

The most common adverse reactions observed were weight increase (15%), IRRs (13%), diarrhoea (10%), headache (7%), arthralgia (7%), increased appetite (5%) and pain in extremity (5%).
The majority of these adverse reactions were non-serious. IRRs include hypersensitivity in 3 patients and anaphylactoid reaction in 1 patient. These reactions were mild to moderate in intensity.
A total of 4 serious adverse reactions (loss of consciousness in 1 patient, acute renal failure in 1 patient, chills and hyperthermia in 1 patient) were observed. In all cases the patients recovered without sequelae.

Tabulated list of adverse reactions

The adverse reactions reflecting exposure of 38 patients treated with velmanase alfa in clinical studies are listed in the table 1 below. 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 1: Adverse reactions reported from clinical studies, post-authorization safety studies and spontaneous reporting in patients with alpha-mannosidosis treated with velmanase alfa

System organ class	Adverse reaction	Frequency
Infections and infestations	Bacterial disease carrier	Not known
	Endocarditis	Not known
	Furuncle	Not known
	Staphylococcal infection	Not known
Immune system disorders	Hypersensitivity(1)	Common
	Anaphylactoid reaction(1)	Common
Metabolism and nutrition disorders	Increased appetite	Common
	Decreased appetite	Not known
Psychiatric disorders	Psychotic behaviour	Common
	Initial insomnia	Common
	Agitation	Not known
	Encopresis	Not known
	Psychotic disorder	Not known
	Nervousness	Not known
Nervous system disorders	Loss of consciousness(2)	Common
	Tremor	Common
	Confusional state	Common
	Syncope	Common
	Headache	Common
	Dizziness	Common
	Ataxia	Not known
	Nervous system disorder	Not known
	Somnolence	Not known
Eye disorders	Eyelid oedema	Common
	Eye irritation	Common
	Ocular hyperaemia	Common
	Lacrimation increased	Not known
Ear and labyrinth disorders	Deafness	Not known
Cardiac disorders	Cyanosis(1)	Common
	Bradycardia	Common
	Aortic valve incompetence	Not known
	Palpitations	Not known
	Tachycardia	Not known

System organ class	Adverse reaction	Frequency
Vascular disorders	Hypotension	Not known
	Vascular fragility	Not known
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common
	Oropharyngeal pain	Not known
	Pharyngeal oedema	Not known
	Wheezing	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting[(1)]	Common
	Abdominal pain upper	Common
	Nausea[(1)]	Common
	Abdominal pain	Common
	Reflux gastritis	Common
	Odynophagia	Not known
Skin and subcutaneous tissue disorders	Urticaria[(1)]	Common
	Hyperhidrosis[(1)]	Common
	Angioedema	Not known
	Erythema	Not known
	Rash	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Common
	Pain in extremity	Common
	Joint stiffness	Common
	Myalgia	Common
	Back pain	Common
	Joint swelling	Not known
	Joint warmth	Not known
Renal and urinary disorders	Renal failure acute[(2)]	Common
General disorder and administration site conditions	Pyrexia[(1)]	Very common
	Chills[(1)]	Common
	Catheter site pain	Common
	Feeling hot[(1)]	Common
	Fatigue	Common
	Malaise[(1)]	Common
	Asthenia	Not known
Investigations	Weight increase	Very common
Injury, poisoning and procedural complications	Procedural headache	Common
	Infusion related reaction	Not known

[(1)] Preferred terms considered as IRR as described in the section below
[(2)] Selected adverse reaction as described in the section below

Description of selected adverse reactions

Infusion-related reaction
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). All patients who experienced IRRs recovered.

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) with alpha-mannosidosis receiving velmanase alfa in clinical studies were aged 6 to 17 years at the start of the study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via:
Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 the management of adverse reactions, see sections 4.4 and 4.8.

5.1 Pharmacodynamic properties

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

Mechanism of action

Velmanase alfa, the active substance of Lamzede, 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 efficacy and safety

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. A total of 25 patients were enrolled, including 12 paediatric subjects (age range: 6 to 17 years; mean: 10.9 years) and 13 adult subjects (age range: 18 to 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 2. A pharmacodynamic effect with statistically significant decrease of serum oligosaccharides in comparison to placebo was demonstrated. The results observed in patients below 18 years of age showed an improvement. In patients over 18 years old a stabilisation has been demonstrated. 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 2: Results from placebo-controlled clinical study rhLAMAN-05 (source data: rhLAMAN-05)

	Treatment with velmanase alfa for 12 months (n=15)		**Treatment with placebo for 12 months (n=10)**		**Velmanase alfa vs. 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**
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)	
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 3). The effects of velmanase alfa were more evident in patients younger than 18 years.

Table 3: Change of clinical endpoints from baseline to the last observation in rhLAMAN-10 study (source data: 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 4).

Table 4: Multiparametric responder analysis: MCID[(1)] Responders Rates by Endpoints and Domains (source data: 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

Use of velmanase alfa in the children below 6 years is supported by the evidence of the clinical study rhLAMAN08.

Overall, there were no safety issues from use of velmanase alfa in paediatric patients below 6 years of age with alpha-mannosidosis. Four of 5 patients developed anti-velmanase alfa antibodies during the study, and 3 patients developed neutralising/inhibitory antibodies. Two Patients (both anti-velmanase alfa antibodies positive) experienced a total of 12 IRRs, all manageable, with no event leading to discontinuation of study treatment. Two IRRs were assessed as serious and resolved on the same day of occurrence. Premedication before infusion was used, when necessary, as a measure to further reduce risks related to IRRs. Efficacy analysis demonstrated reduction in concentrations of serum oligosaccharides, increase in IgG levels, and suggested improved endurance and hearing. Lack of accumulation of velmanase alfa at steady state and the safety/efficacy results confirm that the dose of 1 mg/kg is appropriate in paediatric patients (aged below 6 years). The study suggests benefits of early treatment with velmanase alfa in children aged below 6 years.

Children age group 6 to 17 years old

Use 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.

Exceptional circumstances authorisation

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease, it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

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

Absorption

Lamzede is administered through 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.

Biotransformation

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

Elimination

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/(Non)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).
Special populations

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.

Elderly (≥65 years old)

As no patients older than 41 years have been identified across Europe, no relevant use in elderly patients is expected.

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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, juvenile toxicity and toxicity to reproduction and development.

6.1 List of excipients

Disodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Mannitol (E 421)
Glycine

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

Reconstituted solution for infusion

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C.
From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C.

6.4 Special precautions for storage

Store and transport refrigerated (2°C - 8°C). Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL vial (Type I glass) with a bromobutyl rubber stopper, an aluminium seal and a polypropylene flip off cap.
Each vial contains 10 mg of velmanase alfa.

Pack sizes of 1, 5 or 10 vials per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Lamzede requires reconstitution and is intended for intravenous infusion only.
Each vial is for single use only.

Instructions for reconstitution and administration

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.

e) The reconstituted solution should be administered using an infusion set equipped with a pump and an in-line low protein-binding 0.22 μm filter.
The total volume of infusion is determined by the patient's weight and should be administrated over a minimum of 50 minutes. It is recommended to use always the same dilution (2 mg/ml). For patients weighing less than 18 kg, and receiving less than 9 mL reconstituted solution, the infusion rate should be calculated so that the infusion time is ≥50 minutes. The maximum infusion rate is 25 mL/hour (see section 4.2). The infusion time can be calculated from the following table:

Patient weight (kg)	**Dose (mL)**	**Maximum infusion rate (mL/h)**	**Minimum infusion time (min)**
5	2.5	3	50
6	3	3.6	50
7	3.5	4.2	50
8	4	4.8	50
9	4.5	5.4	50
10	5	6	50
11	5.5	6.6	50
12	6	7.2	50
13	6.5	7.8	50
14	7	8.4	50

Patient weight (kg)	**Dose (mL)**	**Maximum infusion rate (mL/h)**	**Minimum infusion time (min)**
53	26.5	25	64
54	27	25	65
55	27.5	25	67
56	28	25	67
57	28.5	25	68
58	29	25	70
59	29.5	25	71
60	30	25	72
61	30.5	25	73
62	31	25	74

Patient weight (kg)	Dose (mL)	Maximum infusion rate (mL/h)	Minimum infusion time (min)
15	7.5	9	50
16	8	9.6	50
17	8.5	10.2	50
18	9	10.8	50
19	9.5	11.4	50
20	10	12	50
21	10.5	12.6	50
22	11	13.2	50
23	11.5	13.8	50
24	12	14.4	50
25	12.5	15	50
26	13	15.6	50
27	13.5	16.2	50
28	14	16.8	50
29	14.5	17.4	50
30	15	18	50
31	15.5	18.6	50
32	16	19.2	50
33	16.5	19.8	50
34	17	20.4	50
35	17.5	21	50
36	18	21.6	50
37	18.5	22.2	50
38	19	22.8	50
39	19.5	23.4	50
40	20	24	50
41	20.5	24.6	50
42	21	25	50
43	21.5	25	52
44	22	25	53
45	22.5	25	54
46	23	25	55
47	23.5	25	56
48	24	25	58
49	24.5	25	59
50	25	25	60
51	25.5	25	61
52	26	25	62

Patient weight (kg)	Dose (mL)	Maximum infusion rate (mL/h)	Minimum infusion time (min)
63	31.5	25	76
64	32	25	77
65	32.5	25	78
66	33	25	79
67	33.5	25	80
68	34	25	82
69	34.5	25	83
70	35	25	84
71	35.5	25	85
72	36	25	86
73	36.5	25	88
74	37	25	89
75	37.5	25	90
76	38	25	91
77	38.5	25	92
78	39	25	94
79	39.5	25	95
80	40	25	96
81	40.5	25	97
82	41	25	98
83	41.5	25	100
84	42	25	101
85	42.5	25	102
86	43	25	103
87	43.5	25	104
88	44	25	106
89	44.5	25	107
90	45	25	108
91	45.5	25	109
92	46	25	110
93	46.5	25	112
94	47	25	113
95	47.5	25	114
96	48	25	115
97	48.5	25	116
98	49	25	118
99	49.5	25	119

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.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Chiesi Limited
333 Styal Road
Manchester
M22 5LG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 08829/0188

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/01/2023

10 DATE OF REVISION OF THE TEXT

13/01/2023