

SUMMARY OF PRODUCT CHARACTERISTICS

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 offwhite powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alphanmannosidosis. 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 alphanmannosidosis 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. For infusion rate see section "Method of administration".

Special populations

Renal or hepatic impairment

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

Elderly

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

Paediatric population

No dose adjustment is necessary for the paediatric population.

Method of administration

For intravenous infusion use only.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

The reconstituted solution of Lamzede should be administered using an infusion set equipped with a pump and an inline low proteinbinding 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 infusionrelated 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.

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

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.

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 anaphylactictype reactions occur, immediate discontinuation of velmanase alfa is recommended and current medical standards for emergency treatment are to be followed.

Infusionrelated 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. Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Patients were not routinely premedicated 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 treatmentrelated 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 antivelmanase 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 clinical studies at any time under treatment, 8 patients out of 33 (24%) developed IgGclass antibodies to velmanase alfa. 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 'sodiumfree'.

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 alphanmannosidase in alphanmannosidosis patients, Lamzede should be used during pregnancy only when strictly needed.

Breastfeeding

It is unknown whether velmanase alfa or its metabolites are excreted in human milk. Nevertheless, the absorption of any ingested milkcontaining 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 (18%), IRRs (9%), diarrhoea (12%), headache (9%), arthralgia (9%), increased appetite (6%) and pain in extremity (6%).

All of these adverse reactions were nonserious. IRRs include hypersensitivity in 3 patients and anaphylactoid reaction in 1 patient. These reactions were nonserious and mild to moderate in intensity.

A total of 2 serious adverse reactions (loss of consciousness in 1 patient and acute renal failure in 1 patient) were observed. In both cases the patients recovered without sequelae.

Tabulated list of adverse reactions

The adverse reactions reflecting exposure of 33 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. 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 in clinical studies in patients with alphanmannosidosis treated with velmanase alfa

System organ class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity(1)	Common
	Anaphylactoid reaction(1)	Common
Metabolism and nutrition disorders	Increased appetite	Common

System organ class	Adverse reaction	Frequency
Psychiatric disorders	Psychotic behaviour	Common
	Initial insomnia	Common
Nervous system disorders	Confusional state	Common
	Loss of consciousness(2)	Common
	Syncope	Common
	Tremor	Common
	Dizziness	Common
	Headache	Common
Eye disorders	Eye irritation	Common
	Eyelid oedema	Common
	Ocular hyperaemia	Common
Cardiac disorders	Bradycardia	Common
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Abdominal pain	Common
	Abdominal pain upper	Common
	Nausea(1)	Common
	Vomiting(1)	Common
	Reflux gastritis	Common
Skin and subcutaneous tissue disorders	Urticaria(1)	Common
	Hyperhidrosis(1)	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
	Back pain	Common
	Joint stiffness	Common
	Myalgia	Common
Renal and urinary disorders	Pain in extremity	Common
	Renal failure acute(2)	Common
General disorder and administration site conditions	Pyrexia(1)	Very common
	Catheter site pain	Common
	Chills(1)	Common
	Feeling hot(1)	Common
	Fatigue	Common
Investigations	Malaise(1)	Common
	Weight increase	Very common
Injury, poisoning and procedural complications	Procedural headache	Common

⁽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, nausea, vomiting, pyrexia, chills, feeling hot, malaise, urticaria, anaphylactoid reaction and hyperhidrosis) were reported in 9% of the patients (3 out of 33 patients) in clinical studies. All were mild or moderate in severity and none were reported as a serious adverse event. 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 as a potentially causative contributor to the occurrence of the event.

Loss of consciousness

In one patient, loss of consciousness considered related to the study treatment with recovery after a few seconds was reported. The patient received saline infusion in a hospital setting and was then discharged after 6-hour observation.

The patient later experienced epileptic seizures that were considered not related.

Paediatric population

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 alphanmannosidosis 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 the national reporting system listed in Appendix V.

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. PHARMACOLOGICAL PROPERTIES

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 alphanmannosidase. The amino acid sequence of the monomeric protein is identical to the naturally occurring human enzyme, alphanmannosidase. Velmanase alfa is intended to supplement or replace natural alphanmannosidase, an enzyme that catalyses the sequential degradation of hybrid and complex highmannose oligosaccharides in the lysosome, reducing the amount of accumulated mannose-rich oligosaccharides.

Clinical efficacy and safety

A total of 33 patients (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 CHAQVAS pain (visual analogue scale)).

In the phase 3 pivotal multicentre, double-blind, randomised, placebo-controlled, parallel group study rhLAMANO5, 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 rhLAMANO5 (source data: rhLAMANO5)

Patients	Treatment with velmanase alfa for 12 months (n=15)		Treatment with placebo for 12 months (n=10)		Velmanase alfa vs. placebo
	Baseline actual value Mean (SD)	Absolute change from baseline Mean	Baseline actual value Mean (SD)	Absolute change from baseline Mean	
Serum oligosaccharide concentration (µmol/l)					
Overall⁽¹⁾	6.8 (1.2)	-5.11	6.6 (1.9)	-1.61	-3.50
[95% CI]		[-5.66; -4.56]		[-2.28; -0.94]	[-4.37; -2.62]
p-value					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⁾	52.9 (11.2)	0.46	55.5 (16.0)	-2.16	2.62
[95% CI]		[-3.58; 4.50]		[-7.12; 2.80]	[-3.81; 9.05]
p-value					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)					

Patients	Treatment with velmanase alfa for 12 months (n=15)		Treatment with placebo for 12 months (n=10)		Velmanase alfa vs. placebo Adjusted mean difference
	Baseline actual value Mean (SD)	Absolute change from baseline Mean	Baseline actual value Mean (SD)	Absolute change from baseline Mean	
Overall⁽¹⁾	459.6 (72.26)	3.74	465.7 (140.5)	-3.61	7.35
[95% CI]		[-20.32; 27.80]		[-33.10; 25.87]	[-30.76; 45.46]
p-value					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⁾	81.67 (20.66)	8.20	90.44 (10.39)	2.30	5.91
[95% CI]		[1.79; 14.63]		[-6.19; 10.79]	[-4.78; 16.60]
p-value					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 longterm efficacy and safety of velmanase alfa was investigated in the uncontrolled, open label, phase 3 clinical study rhLAMAN10 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 EQ5D5L (euro quality of life5 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 rhLAMAN10 study (source data: rhLAMAN10)

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 posthoc 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: rhLAMAN05; rhLAMAN10)

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%

Domain	Criterion	Responders Rates		
		rhLAMAN-05 study n=25		rhLAMAN-10 study n=33
		Placebo 12 months	Lamzede 12 months	Lamzede Last Observation
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

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) and adult patients. No clinical data are available in children below the age of 6 years.

The European Medicines Agency has deferred the obligation to submit the results of studies with Lamzede in one or more subsets of the paediatric population in the treatment of alpha-mannosidosis disease (see section 4.2 for information on paediatric use).

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 alphanosidosis disease.

Absorption

Lamzede is administered through intravenous infusion. At steadystate 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 steadystate 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. firstorder) 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

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

5.3 Preclinical safety data

Nonclinical 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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Mannitol
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).

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

Lamzedez requires reconstitution and is intended for intravenous infusion only.

Each vial is for single use only.

Instructions for reconstitution and administration

Lamzedez should be reconstituted and administered 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 dropwise 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 inline 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 inline low proteinbinding 0.22 µm filter.

The total volume of infusion is determined by the patient's weight and should be administered over a minimum of 50 minutes. 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)	Patient weight (kg)	Dose (mL)	Maximum infusion rate (mL/h)	Minimum infusion time (min)
5	2.5	3	50	53	26.5	25	64
6	3	3.6	50	54	27	25	65
7	3.5	4.2	50	55	27.5	25	67
8	4	4.8	50	56	28	25	67
9	4.5	5.4	50	57	28.5	25	68
10	5	6	50	58	29	25	70
11	5.5	6.6	50	59	29.5	25	71
12	6	7.2	50	60	30	25	72
13	6.5	7.8	50	61	30.5	25	73
14	7	8.4	50	62	31	25	74
15	7.5	9	50	63	31.5	25	76
16	8	9.6	50	64	32	25	77
17	8.5	10.2	50	65	32.5	25	78
18	9	10.8	50	66	33	25	79
19	9.5	11.4	50	67	33.5	25	80
20	10	12	50	68	34	25	82

Patient weight (kg)	Dose (mL)	Maximum infusion rate (mL/h)	Minimum infusion time (min)	Patient weight (kg)	Dose (mL)	Maximum infusion rate (mL/h)	Minimum infusion time (min)
21	10.5	12.6	50	69	34.5	25	83
22	11	13.2	50	70	35	25	84
23	11.5	13.8	50	71	35.5	25	85
24	12	14.4	50	72	36	25	86
25	12.5	15	50	73	36.5	25	88
26	13	15.6	50	74	37	25	89
27	13.5	16.2	50	75	37.5	25	90
28	14	16.8	50	76	38	25	91
29	14.5	17.4	50	77	38.5	25	92
30	15	18	50	78	39	25	94
31	15.5	18.6	50	79	39.5	25	95
32	16	19.2	50	80	40	25	96
33	16.5	19.8	50	81	40.5	25	97
34	17	20.4	50	82	41	25	98
35	17.5	21	50	83	41.5	25	100
36	18	21.6	50	84	42	25	101
37	18.5	22.2	50	85	42.5	25	102
38	19	22.8	50	86	43	25	103
39	19.5	23.4	50	87	43.5	25	104
40	20	24	50	88	44	25	106
41	20.5	24.6	50	89	44.5	25	107
42	21	25	50	90	45	25	108
43	21.5	25	52	91	45.5	25	109
44	22	25	53	92	46	25	110
45	22.5	25	54	93	46.5	25	112
46	23	25	55	94	47	25	113
47	23.5	25	56	95	47.5	25	114
48	24	25	58	96	48	25	115
49	24.5	25	59	97	48.5	25	116
50	25	25	60	98	49	25	118
51	25.5	25	61	99	49.5	25	119
52	26	25	62				

f) When the last syringe is empty, the dosage 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 Lamzedez 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 Farmaceutici S.p.A. - Via Palermo 26/A - 43122 Parma - Italy

8. MARKETING AUTHORISATION NUMBER

EU/1/17/1258/001 - EU/1/17/1258/002 - EU/1/17/1258/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23/03/2018

10. DATE OF REVISION OF THE TEXT

07/2020

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

APPLICABLE TO ITALY ONLY:

Classe di Rimborsabilità: H

Regime di dispensazione: Medicinale soggetto a prescrizione medica limitativa, da rinnovare volta per volta, vendibile al pubblico su prescrizione di centri ospedalieri o di specialisti - su prescrizione dei centri per le malattie rare identificati dalle regioni (RNRL).

Prezzo la pubblico riportati sotto per confezione:

MEDICINALE (confezione) PREZZO PUBBLICO (€)

Lamzedez 10 mg polvere per soluzione per infusione - confezione da 1 flaconcino € 1.609,14

Lamzedez 10 mg polvere per soluzione per infusione - confezione da 5 flaconcini € 8.045,70

Lamzedez 10 mg polvere per soluzione per infusione - confezione da 10 flaconcini € 16.091,40

Lamzedez is not yet reimbursed in all European countries. Please contact your local Chiesi office for more information on reimbursement in your country.

