Date: 14 November 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lamzede

International non-proprietary name: velmanasum alfa

Pharmaceutical form: powder for solution for infusion

Dosage strength(s): 10 mg

Route(s) of administration: intravenous use

Marketing Authorisation Holder: Chiesi SA

Marketing Authorisation No.: 68591

Decision and Decision date: temporary authorisation in accordance with Art. 9a TPA approved on 26 August 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document which provides information relating to a submission at a particular point in time and will not be updated after publication.

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Table of contents

1 Terms, Definitions, Abbreviations 3
2 Background Information on the Procedure 4
2.1 Applicant's Request(s) 4
2.2 Indication and Dosage 4
2.2.1 Requested Indication 4
2.2.2 Approved Indication 4
2.2.3 Requested Dosage 4
2.2.4 Approved Dosage 4
2.3 Regulatory History (Milestones) 4
3 Medical Context 5
4 Quality Aspects 6
4.1 Drug Substance 6
4.2 Drug Product 6
4.3 Quality Conclusions 7
5 Nonclinical Aspects 8
5.1 Pharmacology 8
5.2 Pharmacokinetics 8
5.3 Toxicology 9
5.4 Nonclinical Conclusions 10
6 Clinical and Clinical Pharmacology Aspects 11
7 Risk Management Plan Summary 12
8 Appendix 13

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of new active entity for the active substance velmanasum alfa in the medicinal product mentioned above.

Orphan Drug status
The applicant requested Orphan Drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan Drug status was granted on 15 October 2021.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Enzyme replacement therapy for non-neurological manifestations in patients with mild to moderate alpha-mannosidosis.

2.2.2 Approved Indication

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

2.2.3 Requested Dosage

Summary of the applied standard dosage:
The recommended dose is 1 mg/kg body weight, administered once weekly as a controlled-rate intravenous infusion.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	8 December 2021
Formal control completed	10 December 2021
List of Questions (LoQ)	11 February 2022
Answers to LoQ	16 May 2022
Predecision	4 July 2022
Answers to Predecision	8 August 2022
Final Decision	26 August 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Alpha-mannosidosis is a rare inherited enzyme deficiency that disrupts the degradation of glycoproteins. This disorder harms the cells as a result of accumulation of mannose-rich oligosaccharides in all tissues of the body. Patients with the disease may have skeletal abnormalities, muscle weakness, liver or spleen enlargement, intellectual disability and distinctive facial features. Severity of symptoms differs between patients. Alpha-mannosidosis is estimated to occur in approximately 1 in 500,000 to 1 in 1,000,000 people worldwide.

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4 Quality Aspects

4.1 Drug Substance

Velmanase alfa is an active form of the human lysosomal enzyme alpha-mannosidase. Lysosomal alpha-mannosidases are members of the glycoside hydrolase family 38 (GH38 Class II). They are involved in the catabolism of Asn-linked glycans of glycoproteins and play a vital role in maintaining cellular homeostasis. Once in the lysosome, the active enzyme alpha-mannosidase starts to degrade stored oligomannoses, releasing mannose units which can then be reused by the body.
Velmanase alfa is expressed in a genetically modified Chinese hamster ovary (CHO) cell line.
Velmanase alfa is manufactured using a fed-batch production process in a production bioreactor. The cell broth is harvested and velmanase alfa is subsequently purified in several chromatographic steps. The purification process also contains dedicated viral clearance steps. The drug substance velmanase alfa is stored frozen in its final form.
The fermentation and purification processes were validated and demonstrated a consistent manufacturing process that effectively reduces process-related impurities. The characterisation of the physicochemical and biological properties of the drug substance and its impurities was performed using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity/ impurity tests (e.g. SEC, RP-HPLC, SDS-PAGE, cIEF), protein concentration and biological activity. Batch analysis data of development, clinical and process validation batches were provided. All batch release data comply with the drug substance specifications valid at the time of batch release. All the analytical methods are described and non-compendial methods were validated in accordance with ICH guidelines.
The drug substance is stored under appropriate storage conditions. No significant changes have been observed within the proposed shelf life.

4.2 Drug Product

The finished product is a sterile lyophilised dosage form of 10 mg velmanase alfa intended for intravenous infusion after reconstitution with sterilised water for injections.
Prior to lyophilisation the product is formulated in an aqueous buffered solution at pH 7.5, containing disodium phosphate, sodium dihydrogen phosphate, glycine and mannitol. All excipients comply with the European Pharmacopoeia.
The finished-product manufacturing process consists of thawing, pooling and mixing, sterile filtration, filling, lyophilisation/stoppering and inspection steps, and is conducted at Patheon Italia S.p.A., Ferentino FR, Italy. Process validation studies were executed at commercial scale using several validation batches.
The specifications include relevant tests and limits, e.g. for appearance, colour, clarity, identity, potency, pH, moisture content, osmolality, purity and impurities tests (SEC, SDS-PAGE, RP-HPLC), protein concentration by UV, particles, sterility and bacterial endotoxins. All non-compendial methods have been validated in accordance with ICH guidelines.
Batch analysis data of several batches from the commercial site are provided. The container closure system of the finished product consists of a glass vial with a bromobutyl rubber stopper and an aluminium crimping cap. All components coming into contact with the finished product comply with Ph. Eur. requirements.
The drug product is stored at 2-8°C; no meaningful changes have been observed under the proposed storage conditions. A shelf life of 36 months has been accepted.

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4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well-described and demonstrate a consistent quality of drug substance and drug product. The shelf life of the drug substance and drug product is supported by data from recommended storage conditions and by accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

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5 Nonclinical Aspects

5.1 Pharmacology

Pharmacodynamic data showed that velmanase alfa exerts biological activity comparable to that of the natural enzyme. Fibroblasts from alpha-mannosidosis patients, human normal healthy fibroblasts, HeLa (human cervical cancer cells) and J774 cells (mouse monocytic/macrophage cell line) internalised a small fraction (0.5-2%) of velmanase alfa in a similar manner. Mannose-6-phosphate (M6P) receptor deficient mouse fibroblasts showed that the internalisation of velmanase alfa is M6P receptor dependent, although at very high velmanase alfa concentrations (>0.1 mg/mL) other uptake routes are not excluded. After internalisation, velmanase alfa is processed in lysosomes. The highest intracellular activity was measured in mouse fibroblasts (70 mU/mg), followed by human (50 mU/mg), rabbit (26 mU/mg), rat (24 mU/mg) and cynomolgus monkey (23 mU/mg) fibroblasts after incubation with ≥200 mU/mL velmanase alfa.
Proof of concept was confirmed in *in vivo* studies in mannosidosis knockout (α-mKO) mice and in immune tolerant Tg+/α-mKO mice, permitting the assessment of long-term efficacy. The selected animal models are considered suitable for the assessment of the clinical utility of velmanase alfa as they phenotypically resemble the mild form of the human disease in terms of sugar accumulation in tissues.
Studies in α-mKO mice showed that velmanase alfa reduced the levels of oligosaccharides in liver, kidney and heart (80-90%) after two injections of 250 mU velmanase alfa/g body weight, 3.5 days apart. High doses (500 U/kg; 19 mg/kg) were needed for the reduction of mannosyl-linked oligosaccharides in central nervous tissues (cortex) and lower dose (250 U/kg; 9.7 mg/kg) for the same effect in the peripheral nervous tissues (neurones, trigeminal ganglion).
Concerning long-term efficacy, treatment of Tg+/α-mKO mice for 12 weeks (up to 500 U/kg; bi-weekly) showed a dose-dependent increase in brain lysate velmanase alfa activity (5-14% of wild-type activity) as well as reduction of oligosaccharides in the brain and decreased microglia activation. When weekly dosing was used for the same period, a higher dose was needed (750 U/kg; 28 mg/kg) to achieve similar effects, pointing to the importance of continuous exposure.
An improvement in neuromotor function and in short-term memory was observed in a study with 4-month-old mice (15.6 mg/kg). Treatment for 30 weeks or longer improved the spatial-cognitive abilities of α-mKO mice to a significant degree, whereas a shorter treatment period (10 weeks) resulted in a modest effect. Long-term treatment was, however, unable to restore higher cognitive abilities (measured in the Morris-type water maze with hidden escape platform) to the level observed in healthy mice.

5.2 Pharmacokinetics

Validated assays were used for the measurement of velmanase alfa and anti-velmanase alfa antibodies in animal matrices. The pharmacokinetic behaviour of velmanase alfa intravenous (IV) infusion was similar across animal species used for the safety assessment. Across all repeated-dose studies, the increase in exposure was dose-dependent on Day 1. However, the exposure measured at later time points dropped due to the appearance of ADA. $T_{1/2}$ was 9 h in mice, 13-16 h in rats, and 13 h in monkeys, which is lower than in humans ($T_{1/2}$ 30 h). No sex-related differences in pharmacokinetics were observed in rats and monkeys. Male mice had higher exposure in the 26-week study in the two higher dose groups compared to females. The volume of distribution was similar to the blood volume, suggesting limited tissue uptake of velmanase alfa. According to the results from distribution studies in mice (single IV dose of 1000 U/kg), the highest velmanase alfa activity was measured 1 h post dose in the liver, followed by heart, lung, spleen, thymus, kidney and brain (measured in cerebrospinal fluid (CSF)), suggesting that it crosses the blood-brain barrier (BBB). However, velmanase alfa activity was not detected in CSF in humans, indicating that it does not cross the BBB in humans. As velmanase alfa is a protein, it is expected to undergo proteolytic degradation; therefore no dedicated studies on excretion were conducted.

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In pregnant rats and rabbits, exposure increased dose-proportionally at gestation day (GD) 6, but a high drop in exposure was measured on GD 16 due to the presence of ADAs in all animals.
Toxicokinetics was not measured in fertility and early embryonic development (FEED) and pre- and post-natal (PPND) studies.
Excretion in milk was not measured in nonclinical species.
Antibodies against velmanase alfa developed across all toxicity studies, including the 26-week study with Tg+/α-mKO mice, which were expected to be immune tolerant. ADAs affected $T_{½}$ and exposure to velmanase alfa.

5.3 Toxicology

Mouse, rat, rabbit and cynomolgus monkey were selected as relevant species based on the pharmacology data of similar cellular (fibroblasts) uptake of velmanase alfa and the highly conserved interspecies sequence homology of the enzyme. Repeated-dose toxicity was assessed in Tg+/a-mKO mice (26-week study) and cynomolgus monkeys (up to 13 weeks), with bi-weekly dosing up to ~1300 U/kg (~50 mg/kg) in both species. Rats and rabbits were used for reproduction toxicity testing. The duration of the repeated-dose studies is considered short to support chronic use, but was accepted considering the high immunogenicity of velmanase alfa and the absence of toxicities. The IV route of administration corresponded to the intended clinical route of administration.
After single dosing in rats, swollen feet/limbs, swollen muzzles, piloerection and excessive grooming were observed across the studies. These findings were dose-dependent (> 164 U/kg; 6.7 mg/kg) and considered to be associated with the high immunogenicity in this species. There were no adverse treatment-related changes associated with velmanase alfa in the pivotal repeated-dose studies in mice and monkeys. The only observation was increased salivation and reduced food consumption in the dose escalation study in monkeys at ≥ 466 U/kg. The NOAELs in pivotal studies are considered the highest doses tested, associated with exposure 121-fold and 229-fold the clinical exposure at the maximum recommended human dose (MRHD) in mice and monkeys, respectively.
No genotoxicity and carcinogenicity studies were conducted, which is in line with ICH S6(R1).There were no adverse effects of velmanase alfa on fertility parameters and pregnancy outcome. Fetus examination revealed abnormalities in four fetuses in the 20 mg/kg group (duplicated sternebrae, cleft palate and palantine, severely bent scapula). No historical data were submitted, which was accepted considering that the product is an enzyme replacement with a high safety margin (>20-fold the clinical exposure at the MRHD) and no treatment-related findings were observed in the study in rabbits.
In the pre- and post-natal development study in rats dosed up to 30 mg/kg every other day from GD 6 to lactation day 20, maternal toxicity was observed at all dose levels in terms of prolonged adverse clinical signs (clonic convulsions, piloerection, decreased activity, slow breathing), necessitating premature euthanasia. A NOAEL for maternal toxicity was not established. No adverse effects were observed with regard to duration of gestation or pup survival, clinical condition and development. All parameters assessed (learning and memory, motor activity, auditory function, vaginal opening or balanopreputial separation) showed values comparable with controls. All F1 animals mated within four days of pairing and pregnancy data were similar. Thus, the NOAEL for the F1 generation was 30 mg/kg.
Overall, based on the results of the reproductive toxicity studies, the risk for adverse effects on male and female fertility, pregnancy performance, embryo-fetal development and offspring development at clinically relevant exposures is considered low. There were no findings in juvenile toxicity study.
There is no concern with respect to excipients and impurities.
The description of the safety findings from the nonclinical studies and their evaluation in Module SII of the RMP is accepted.
A significant risk for the environment resulting from introduction of velmanase alfa to the market is not expected.

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5.4 Nonclinical Conclusions

Overall, the pharmacology and toxicological profile of velmanase alfa were adequately characterised in the nonclinical studies. From the nonclinical side, the application can be approved.

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6 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by EMA. The available assessment report and respective product information from EMA were used as a basis for the clinical and clinical pharmacology evaluation.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the Information for healthcare professionals relating to Lamzede was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the Information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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Placeholder for text approval stamp

▼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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Lamzede is temporarily authorised – see "Properties/Effects" section

Lamzede 10 mg powder for solution for infusion

Composition

Active substances

Velmanase alfa

Excipients

Disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, mannitol, glycine.
Sodium content: 0.817 mg per vial.

Pharmaceutical form and active substance quantity per unit

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

Indications/Uses

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

Dosage/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. For infusion rate see section “Method of administration”.

Special patient groups

Renal or hepatic impairment

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

Elderly patients

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

Children and adolescents
No dose adjustment is necessary for the paediatric population.

Mode of administration

For intravenous infusion use only. For instructions on reconstitution of the medicinal product before administration, see section “Instructions for reconstitution and administration” in section “Other information”.

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 “Instructions for reconstitution and administration”.
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 “Warnings and precautions”.

Contraindications

Severe allergic reaction to the active substance or to any of the excipients listed in section “Composition”.

Warnings and precautions

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 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 “Undesirable effects”). 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 3 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. 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 medication contains less than 1 mmol (23 mg) of sodium per dose, i.e. it is essentially "sodium-free".

Interactions

No interaction studies have been performed.

Pregnancy, 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 "Preclinical data"). As velmanase alfa aims at normalizing alpha-mannosidase in alpha-mannosidosis patients, Lamzede should be used during pregnancy only when strictly needed.

Lactation

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.

Effects on ability to drive and use machines

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

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.

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. The adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows:
"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/ 1,000)
"very rare" (<1/10,000)
"not known" (frequency cannot be estimated from the available data)

Table 1: Adverse reactions reported in clinical studies in patients with alpha-mannosidosis 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
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
	Cyanosis(1)	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	Arthralgia	Common

tissue disorders	Back pain	Common
	Joint stiffness	Common
	Myalgia	Common
	Pain in extremity	Common
Renal and urinary disorders	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
	Malaise[(1)]	Common
Investigations	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 specific adverse reactions and additional information

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 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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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 “Warnings and precautions” and “Undesirable effects”.

Properties/Effects

ATC code

A16AB15

Mechanism of action

Pharmacodynamics

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

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)	

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

Paediatrics

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 concomitant 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 young 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.

Temporary authorisation

The medicinal product Lamzede has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation

Pharmacokinetics

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). 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 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).

Kinetics in specific patient groups

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.

Preclinical 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.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.
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.

Special precautions for storage

Store and transport refrigerated (2°C - 8°C).
Store in the original package in order to protect from light.

Instructions for 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. 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 "Dosage/Administration"). 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
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

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
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

49	24.5	25	59
50	25	25	60

97	48.5	25	116
98	49	25	118

Authorisation number

68591

Packs

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

Marketing authorisation holder

Chiesi SA, Villars-sur-Glâne.

Date of revision of the text

July 2022