swissmedic

Date: 7 November 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Elfabrio

International non-proprietary name: pegunigalsidase alfa
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 20 mg/10 mL
Route(s) of administration: intravenous
Marketing authorisation holder: Chiesi SA
Marketing authorisation no.: 69257
Decision and decision date: approved on 11 September 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
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)
GI	Gastrointestinal
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 non-proprietary 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 new active substance status for pegunigalsidase alfa in the above-mentioned medicinal product.

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 27 February 2023.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Elfabrio is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).

2.2.2 Approved indication

Elfabrio is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of pegunigalsidase alfa is 1 mg/kg of body weight administered once every 2 weeks.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	21 April 2023
Formal control completed	4 May 2023
Preliminary decision	3 July 2023
Response to preliminary decision	17 July 2023
Final decision	11 September 2023
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the publicly available assessment report Elfabrio, Procedure No. EMEA/H/C/005618/0000, 23 February 2023 issued by the EMA.

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3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Elfabrio, Procedure No. EMEA/H/C/005618/0000, 23 February 2023 issued by the EMA.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Elfabrio, Procedure No. EMEA/H/C/005618/0000, 23 February 2023 issued by the EMA.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Elfabrio, Procedure No. EMEA/H/C/005618/0000, 23 February 2023 issued by the EMA.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken 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. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. 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 that occur in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Elfabrio 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 valid and relevant reference document 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. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼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.

ELFABRIO

Composition

Active substances

Pegunigalsidase alfa

Pegunigalsidase alfa is produced in tobacco cells (Nicotiana tabacum BY2 cells) using recombinant DNA technology.

The active substance, pegunigalsidase alfa, is a covalent conjugate of prh-alpha-GAL-A with polyethylene glycol (PEG).

Excipients

Sodium citrate dihydrate, citric acid, sodium chloride, water for injection.

Each vial contains 46 mg sodium.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion

Clear, colourless, solution

Each vial contains 20 mg of pegunigalsidase alfa in a volume of 10 mL at a concentration of 2 mg/mL. The strength indicates the quantity of the pegunigalsidase alfa with consideration of the pegylation.

The potency of this medicinal product should not be compared to the one of another pegylated or non- pegylated protein of the same therapeutic class. For more information, see section Properties/Effects.

Indications/Uses

Elfabrio is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).

Dosage/Administration

Elfabrio treatment must be managed by a physician experienced in the treatment of patients with Fabry disease.

Appropriate medical support measures should be readily available when Elfabrio is administered to patients who have not had treatment before, or who have experienced severe hypersensitivity reactions to Elfabrio in the past.

Pre-treatment with antihistamines and/or corticosteroids may be advisable for patients who had previously experienced hypersensitivity reactions to Elfabrio or to another enzyme replacement therapies (ERT) treatment (see section Warnings and precautions).

Posology

The recommended dose of pegunigalsidase alfa is 1 mg/kg of body weight administered once every two weeks.

For instructions on reconstitution, see section Other information.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Patients switching treatment from agalsidase alfa or beta
For the initial 3 months (6 infusions) of treatment with Elfabrio, pre-treatment regimen should be preserved with stepwise discontinuation of pre-treatment based on appropriate tolerability of the patients.

Special patient groups

Renal or hepatic impairment

No dose adjustment is needed in patients with renal or hepatic impairment.

Elderly (≥ 65 years old)

Safety and efficacy of Elfabrio in patients older than 65 years have not been evaluated and no alternative dose regimens can be recommended for these patients. Elderly patients may be treated with the same dose as other adult patients, see section Properties/Effects.

Paediatric population

The safety and efficacy of Elfabrio in children and adolescents aged 0-17 years have not yet been established. No data are available.

Mode of administration

For intravenous infusion use only.

Elfabrio must not be infused in the same intravenous line with other products.

For instructions on dilution of the medicinal product before administration, see section Other Information.

After preparation, the dilution should be administered via intravenous infusion and filtered through an in-line low protein-binding 0.2 µm filter.

The patient should be observed for infusion-related reactions (IRRs) for two hours after the infusion; see section Warnings and precautions.

Further details on how to handle Elfabrio before administration, see section Other information.

Home administration

Infusion of Elfabrio at home may be considered if the patient is tolerating his infusions well and have no history of moderate or severe IRRs for a few months.

The decision to move to home infusion should be made after evaluation and recommendation by the treating physician. The patient should be medically stable. Home infusion infrastructure, resources, and procedures, including training, must be established and available to the healthcare professional in charge of home infusion.

The healthcare professional should be available at all times during the home infusion and for a specified time after infusion.

Appropriate training should be given by the treating physician and/or nurse to the patient and/or caregiver prior to initiation of home infusion. The dose and infusion rate used in the home setting should remain the same as was used in the hospital setting; they should be changed only under the supervision of the treating physician.

Infusion rate and duration of infusion

Table 1: Recommended dose and infusion time for intravenous administration of Elfabrio

Initial infusion 1 mg/kg of body weight every 2 weeks			
Body weight (Kg)	**Total volume (mL)**	**Infusion time**	**Infusion rate***
up to 70	150 mL	not less than 3 hours	0.83 mL/min (50 mL/hr)
70-100	250 mL	not less than 3 hours	1.39 mL/min (83.33 mL/hr)
> 100	500 mL	not less than 3 hours	2.78 mL/min (166.67 mL/hr)
Maintenance infusion The target infusion duration can be achieved pending patient's tolerability. The increase in the infusion rate should be achieved gradually starting from the rate given at the first infusion.			
1 mg/kg of body weight every 2 weeks			
Body weight (Kg)	**Total volume (mL)**	**Infusion time**	**Infusion rate***
up to 70	150 mL	not less than 1.5 hours	1.68 mL/min (100 mL/hr)
70-100	250 mL	not less than 1.5 hours	2.78 mL/min (166.67 mL/hr)
> 100	500 mL	not less than 1.5 hours	5.56 mL/min (333.33 mL/hr)

*infusion rate may be adjusted in case of infusion reaction (see section Warnings and precautions)

If patients experience infusion-related reactions, including hypersensitivity reactions or anaphylactic reactions during the infusion, the infusion must be immediately stopped and appropriate medical treatment should be initiated (see section Warnings and precautions).
Any patients experiencing adverse events during the home infusion need to immediately stop the infusion process and seek the attention of a healthcare professional. Subsequent infusions may need to occur in a clinical setting.

Contraindications

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

Warnings and precautions

Infusion related reactions

Infusion-related reactions (IRRs), defined as any related adverse events with onset after start of infusion and up to 2 hours after end of infusion have been reported (see section Undesirable effects). The most commonly observed symptoms of IRRs were hypersensitivity, itching, nausea, dizziness, chills and muscular pain.

The management of IRRs must be based on the severity of the reaction, and include slowing the infusion rate and treatment with medicinal products such as antihistamines, antipyretics and/or corticosteroids, for mild to moderate reactions. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required, although IRRs occurred in some patients after receiving pre-treatment (see section Dosage/Administration).

Hypersensitivity

Hypersensitivity reactions have been reported in patients in clinical studies (see section Undesirable effects). As with any intravenous protein product, allergic-type hypersensitivity reactions may manifest and can include localised angioedema (including swelling of the face, mouth, and throat), bronchospasm, hypotension, generalised urticaria, dysphagia, rash, dyspnoea, flushing, chest discomfort, pruritus, and nasal congestion. If a severe allergic or anaphylactic-type reactions occur, immediate discontinuation of Elfabrio is recommended and current medical standards for emergency treatment are to be followed. In patients who have experienced severe hypersensitivity reactions during Elfabrio infusion, caution should be exercised upon re-challenge and appropriate medical support should be readily available.
Moreover, for patients who experienced severe hypersensitivity reactions with ERT infusion including Elfabrio, appropriate medical support should be readily available.

Immunogenicity

In clinical studies, treatment-induced anti-drug antibodies (ADA) development has been observed (see section Undesirable effects).

The presence of ADAs to Elfabrio may be associated with a higher risk of infusion-related reactions, and severe IRRs are more likely to occur in ADA positive patients. Patients who develop infusion or immune reactions with Elfabrio treatment should be monitored.

Additionally, patients who are ADA positive to other enzyme replacement therapies, who have experienced hypersensitivity reactions to Elfabrio and patients who are switching to Elfabrio should be monitored.

Glomerulonephritis membranoproliferative

Depositions of immune complexes can potentially occur during treatment with ERTs, as a manifestation of immunological response to the product. A single case of glomerulonephritis membranoproliferative was reported during the clinical development of Elfabrio, due to immune depositions in the kidney (see section Undesirable effects). This event led to a temporary decline in renal function, which improved upon discontinuation of the medicinal product.

Excipients of known effect

This medicinal product contains 46 mg sodium per vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

No interaction studies and no *in vitro* metabolism studies have been performed. Based on its metabolism, pegunigalsidase alfa is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.
Elfabrio is a protein and is expected to be metabolically degraded through peptide hydrolysis.

Pregnancy, lactation

Pregnancy

There are no or limited amount of data from the use of pegunigalsidase alfa in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section Preclinical data). As a precautionary measure, it is preferable to avoid the use of Elfabrio during pregnancy unless clearly necessary.

Lactation

It is unknown whether pegunigalsidase alfa/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of Elfabrio in milk (for details see section Preclinical data). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Elfabrio therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no studies assessing the potential effect of pegunigalsidase alfa on fertility in humans. Animal studies show no evidence of impaired fertility (see section Preclinical data).

Effects on ability to drive and use machines

Dizziness or vertigo were observed in some patients following Elfabrio administration. These patients should refrain from driving or the use of machines until symptoms have subsided.

Undesirable effects

Summary of the safety profile

The most common adverse reactions were infusion-related reactions reported in 6.3% of patients, followed by hypersensitivity and asthenia reported each by 5.6% of patients.

In clinical studies, 5 patients (3.5%) experienced a serious reaction that was considered related to Elfabrio. Four of these reactions were confirmed IgE-mediated hypersensitivity (bronchospasm, hypersensitivity) that occurred at the first infusion of Elfabrio and resolved within the day after occurrence.

Tabulated summary of adverse reactions

The data described below reflects data from 141 patients with Fabry disease who received Elfabrio in 8 clinical studies, following the posology of 1 mg/kg every two weeks or 2 mg/kg every four weeks for a minimum of 1 infusion up to 6 years.

Adverse reactions are listed in Table 2. Information is presented by system organ class. Frequencies are 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); frequency not known (cannot be estimated from available data).

Table 2: Adverse reactions reported during treatment with Elfabrio

System organ class	Frequency	
	Common	**Uncommon**
Immune system disorders	hypersensitivity* type I hypersensitivity*	
Psychiatric disorders	agitation*	insomnia
Nervous system disorders	paraesthesia* dizziness* headache*	restless legs syndrome peripheral neuropathy neuralgia burning sensation tremor*
Ear and labyrinth disorders	vertigo	
Vascular disorders		flushing hypotension* hypertension* lymphoedema
Respiratory, thoracic and mediastinal disorders		bronchospasm* dyspnoea* throat irritation* nasal congestion* sneezing*
Gastrointestinal disorders	nausea* abdominal pain* diarrhoea vomiting*	gastrooesophageal reflux disease gastritis dyspepsia flatulence
Skin and subcutaneous issue disorders	rash* erythema* pruritus*	hypohidrosis
Musculoskeletal and connective tissue disorders	arthralgia musculoskeletal pain*	
Renal and urinary disorders		glomerulonephritis membranoproliferative chronic kidney disease proteinuria
Reproductive system and breast disorders		nipple pain
General disorders and administration site conditions	asthenia* chills* chest pain* pain*	infusion site extravasation oedema influenza-like illness infusion site pain

Investigations		body temperature increased* hepatic enzyme increased urine protein/creatinine ratio increased white blood cells urine positive blood uric acid increased weight increased
Injury, poisoning and procedural complications	infusion related reaction*	
Cardiac disorders	supraventricular extrasystoles	bradycardia* left ventricular hypertrophy
The following preferred terms have been grouped in Table 2: • hypersensitivity includes: drug hypersensitivity • agitation includes: nervousness • abdominal pain includes: abdominal discomfort • rash includes: rash maculo-papular and rash pruritic • musculoskeletal stiffness recorded as musculoskeletal pain includes: myalgia • asthenia includes: malaise and fatigue • chest pain includes: chest discomfort and non-cardiac chest pain • pain includes: pain in extremity • oedema peripheral recorded as oedema		

* Preferred terms considered as IRR as described in the section below.

Description of selected adverse reactions

Infusion related reactions (adverse reactions within 2 hours of infusion)
IRRs were reported in a total of 32 patients (22%): 26 patients (23%) treated with 1 mg/kg every two weeks and 6 patients (20%) treated with 2 mg/kg every four weeks. The most commonly reported symptoms associated with IRRs reported for 1 mg/kg dosage were: hypersensitivity, chills, dizziness, rash and itching. For the 2 mg/kg dose the most commonly reported symptom was pain. IRRs were mostly mild or moderate in intensity and resolved with continuous treatment; however, 5 patients (all male, 1 mg/kg dose) experienced 5 severe IRRs. These 5 IRRs were also serious. Four of these events were confirmed type I hypersensitivity reactions and 3 led to the discontinuation from the study.
Another patient was later withdrawn from the study, after the occurrence of another moderate IRR. All 5 patients however recovered within the day after of occurrence with appropriate treatment. IRRs predominantly occurred within the first year of treatment with Elfabrio and no serious IRR was observed during the second year and beyond.

Immunogenicity
In clinical studies, 17 out of 111 of patients (16%) treated with 1 mg/kg Elfabrio every two weeks and 0 out of 30 patients treated with 2 mg/kg Elfabrio every four weeks developed treatment-induced anti-drug antibodies (ADAs).

Glomerulonephritis membranoproliferative
During the clinical development of Elfabrio, one patient out of 136 reported a severe event of glomerulonephritis membranoproliferative after receiving treatment for more than 2 years. The patient was ADA positive at the start of the infusions. The event led to a transitory reduction in the eGFR and an increase on the level of proteinuria, with no additional signs or symptoms. A biopsy revealed the immune-complex mediated nature of this event. Upon discontinuation of the treatment, the eGFR values stabilised and the glomerulonephritis was reported as resolving.

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 are no reports of overdose of Elfabrio during clinical studies. The maximum dose of Elfabrio studied was 2 mg/kg body weight every two weeks and no specific signs and symptoms were identified following the higher doses. The most common adverse reactions reported were infusion related reaction and pain in extremity. If overdose is suspected, seek emergency medical attention.

Properties/Effects

ATC code

A16AB20

Mechanism of action

Pharmacodynamics

The active substance of Elfabrio is pegunigalsidase alfa. Pegunigalsidase alfa is a pegylated recombinant form of human α-galactosidase-A. The amino acid sequence of the recombinant form is similar to the naturally occurring human enzyme.

Pegunigalsidase alfa supplements or replaces α-galactosidase-A, the enzyme that catalyses the hydrolysis of the terminal α-galactosyl moieties of oligosaccharides and polysaccharides in the lysosome, reducing the amount of accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (Lyso-Gb3).

Clinical efficacy

The efficacy and safety of pegunigalsidase alfa were evaluated in 142 patients (94 males and 48 females), of which 112 receiving pegunigalsidase alfa 1 mg/kg every other week (EOW).

Disease substrate

Analyses of kidney biopsies from naïve patients treated with pegunigalsidase alfa in a phase 1/2 study exhibited a reduction of the globotriaosylceramide (Gb3) substrate from the renal peritubular capillaries, measured with BLISS (Barisoni Lipid Inclusion Scoring System) of 68% in the overall population (including females, classic males and non-classic males exposed to different tested doses; n=13) after 6 months of treatment. Additionally, 11 out of 13 subjects with available biopsies had substantial reduction (≥50%) in their BLISS score following 6 months of treatment. Plasma Lyso-Gb3 decreased by 49% after 12 months of treatment (n=16) and by 83% after 60 months of treatment (n=10). In a phase 3 study, where patients were switching from agalsidase beta to pegunigalsidase alfa, plasma Lyso-Gb3 values stayed stable after 24 months of treatment (+3.3 nM mean value, n=48).

Renal function

The renal function was evaluated through the estimated glomerular filtration rate (eGFR – CKD-EPI equation) and its annualised measurement slope was the primary endpoint for efficacy in two phase 3 studies in previously ERT-treated adult Fabry patients: BALANCE (main study), a randomized, double

blinded, head-to-head comparison with agalsidase beta, after switch from agalsidase beta at month 12 (primary analysis) and month 24, and an open label single arm study, after switch from agalsidase alfa, both followed by a long-term extension study.

No final conclusion on non-inferiority over agalsidase beta as measured by the annualised eGFR can be retrieved from the main study given that the data for the primary endpoint comparison at month 12 was not on its own sufficiently informative due to the design and size of the trial. Nevertheless, the median eGFR slopes from baseline to month 24 of pegunigalsidase and the comparator agalsidase beta appeared close. At month 12, the mean slopes for eGFR were -2.507 mL/min/1.73 m²/year for the pegunigalsidase alfa arm and -1.748 for the agalsidase beta arm (difference -0.749 [-3.026, 1.507]. At month 24, the median slopes for eGFR were -2.514 [-3.788; -1.240] mL/min/1.73 m²/year for the pegunigalsidase alfa arm and -2.155 [-3.805; -0.505] for the agalsidase beta arm (difference -0.359 [-2.444; 1.726]).

Paediatric population

See section Dosage/Administration for information on paediatric use.

Pharmacokinetics

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

Absorption

n.a.

Distribution

n.a.

Metabolism

n.a.

Elimination

Plasma pharmacokinetic (PK) profiles of pegunigalsidase alfa were characterized during the course of the clinical development at 0.2, 1, and 2 mg/kg administered every two weeks in adult patients with Fabry disease. The pharmacokinetic results for all three dose levels demonstrated that the enzyme was available throughout the 2-week intervals with a plasma half-life (t1/2) ranging from 53-134 hours across dose groups and visit day. The mean value for AUC0-∞ increased with increasing dose on Day 1 and throughout the study. Mean values for dose-normalized AUC0-2wk were similar for all dose levels, indicating linear dose-proportionality. For patients who received 1 and 2 mg/kg Elfabrio, there were increases in mean t1/2 and AUC0-∞ with increasing duration of treatment and corresponding decreases in Cl and Vz, suggesting a saturated clearance.

Pegunigalsidase alfa is a protein and is expected to be metabolically degraded through peptide hydrolysis. Consequently, impaired liver function is not expected to affect the pharmacokinetics of Elfabrio in a clinically significant way. The molecular weight of pegunigalsidase alfa is ~116 KDa, which is twice the cut-off value for glomerular filtration, thus excluding filtration and/or proteolytic degradation in kidneys.

Preclinical data

There are no animal studies to assess the carcinogenic or mutagenic potential of Elfabrio.

In the 6-month chronic toxicity study in mice, an increased incidence and/or mean severity of multifocal nephropathy and interstitial lymphocytic infiltration in the kidneys, hepatocytic vacuolation and hepatocyte necrosis in the liver, were confined to males and females administered the high-dose of 40 mg/kg/injection (3.2-fold human exposure, in terms of AUC, following a dose of 1 mg/kg); in monkeys, an increased incidence of Kupffer cell hypertrophy was noted in the liver (7.6-fold above AUC reached in humans following a dose of 1 mg/kg); all findings resolved during the recovery period. Animal studies demonstrated low systemic exposure in foetus (between 0.005 and 0.025% of dams' systemic exposure) and suckling pups (maximum 0.014% compared to mother's systemic exposure) following repeated treatment of the dams or mothers with pegunigalsidase alfa. Fertility and embryofoetal developmental toxicity studies did not show evidence of impaired fertility, embryotoxicity or teratogenicity. However, prenatal and postnatal developmental toxicity studies were not performed with pegunigalsidase alfa and the risks for foetus and pups during the late pregnancy and lactation are unknown.

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.

Diluted solution for infusion

Chemical and physical in use stability has been demonstrated for 72 hours both at 2 °C-8 °C and below 25 °C.
From a microbiological point of view, the 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 in the refrigerator (2 °C-8 °C) or 8 hours if stored below 25 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Store refrigerated (2°C - 8°C).
For storage conditions after dilution of the medicinal product, see section Shelf life.

Instructions for handling

Elfabrio is for intravenous infusion only. Aseptic technique to be used. Vials are for single use only.

If contamination is suspected, the vial has not to be used. Shaking or agitating this medicinal product must be avoided.

Filter needles do not have to be used during the preparation of the infusion.
The number of vials to be diluted should be determined based on the individual patient's weight and the required vials should be removed from the refrigerator in order to allow them to reach room temperature (in approximately 30 minutes).

Dilution

1) Determine the total number of vials required for the infusion.

   The number of vials required is based on the total dose required for each individual patient and requires calculation for weight-based dosing.

   An example calculation for total dose in an 80 kg patient prescribed 1 mg/kg is as follows:
   - Patient weight (in kg) ÷ 2 = Volume of dose (in mL)
   - Example: 80 kg patient ÷ 2 = 40 mL (volume to be withdrawn).
   - Given that 10 mL can be withdrawn from each vial, 4 vials are needed in this example.

2) Allow the required number of vials to reach room temperature prior to dilution (approximately 30 minutes).

   Visually inspect the vials. Do not use if cap is missing or broken. Do not use if there is particulate matter or if it is discoloured.
   Avoid shaking or agitating the vials.

3) Remove and discard the same volume as calculated in step 1 of sodium chloride 9 mg/mL (0.9%) solution for infusion from the infusion bag.

4) Withdraw the required volume of Elfabrio solution from the vials, and dilute with sodium chloride 9 mg/mL (0.9%) solution for infusion, to a total volume based on patient weight specified in Table 4 below.

Table 4: Minimum total infusion volume for patients by body weight

Patient weight	Minimum total infusion volume
< 70 kg	150 mL
70–100 kg	250 mL
> 100 kg	500 mL

Inject the Elfabrio solution directly into the infusion bag. Do NOT inject in the airspace within the infusion bag.
Gently invert the infusion bag to mix the solution, avoiding vigorous shaking and agitation. The diluted solution should be administered using an inline low protein binding 0.2 µm filter.

Disposal

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

Authorisation number

69257

Packs

10 mL vial (15R clear glass) closed with coated rubber stopper and sealed with aluminium flip off cap.

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

Marketing authorisation holder

Chiesi SA, Villars-sur-Glâne.

Date of revision of the text

June 2023