ANNEX I

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

Elfabrio 2 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20 mg of pegunigalsidase alfa in a volume of 10 mL or 5 mg of pegunigalsidase alfa in a volume of 2.5 mL, at a concentration of 2 mg/mL.

The strength indicates the quantity of the pegunigalsidase alfa with consideration of the pegylation.

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).

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 5.1.

Excipient with known effect

Each 10 mL vial contains 46 mg sodium.
Each 2.5 mL vial contains 11.5 mg sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of 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 4.4).

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 6.6.

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 populations
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 5.1.

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.

Method 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 6.6.

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 4.4.

Further details on how to handle Elfabrio before administration, see section 6.6.

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 4.4)

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 4.4).
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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

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 4.8). 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 4.2).

Hypersensitivity

Hypersensitivity reactions have been reported in patients in clinical studies (see section 4.8). 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 4.8).

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 4.8). 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 10 mL vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This medicinal product contains 11.5 mg sodium per 2.5 mL vial, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and 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 5.3). As a precautionary measure, it is preferable to avoid the use of Elfabrio during pregnancy unless clearly necessary.

Breast-feeding

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 5.3). 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 5.3).

4.7 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.

4.8 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	

System organ class	Frequency	
	Common	**Uncommon**
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 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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code: A16AB20.

Mechanism of action

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 and safety

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 -0.759 [-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

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

5.2 Pharmacokinetic properties

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 ($t_{1/2}$) ranging from 53-134 hours across dose groups and visit day. The mean value for $AUC_{0-\infty}$ increased with increasing dose on Day 1 and throughout the study. Mean values for dose-normalized AUC_{0-2wk} 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 $t_{1/2}$ and $AUC_{0-\infty}$ with increasing duration of treatment and corresponding decreases in Cl and V_z, 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.

5.3 Preclinical safety 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate tribasic dihydrate
Citric acid
Sodium chloride

6.2 Incompatibilities

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

6.3 Shelf life

4 years.

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.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL vial (15R clear glass) closed with coated rubber stopper and sealed with aluminium flip off cap.
2.5 mL vial (6R 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.

6.6 Special precautions for disposal and other 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).
   - In this example, 4 vials of the 10 mL vial (or 16 vials of the 2.5 mL vial) are needed.

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.

7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1724/001
EU/1/23/1724/002
EU/1/23/1724/003
EU/1/23/1724/004
EU/1/23/1724/005
EU/1/23/1724/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 May 2023

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Protalix Ltd.
2 Snunit St., Science Park,
Carmiel 2161401
Israel

Name and address of the manufacturer responsible for batch release

Chiesi Farmaceutici S.p.A.
Via San Leonardo 96
43122 Parma
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the use of Elfabrio in each Member State in the home setting the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Elfabrio is marketed, all Healthcare Professionals (HCP) who are expected to prescribe Elfabrio are provided with the following educational pack, which includes:

- An HCP brochure providing relevant information for the HCP to train the patient and/or caregiver to administer the product at home, which describes the following key elements:
    - ✓ checklist with eligibility criteria for home infusion
    - ✓ the need for prescribing medication to treat IRRs and that the patient/caregiver should be able to use them
    - ✓ the need for premedication if necessary (with antihistamines and/or corticosteroids) in those patients where symptomatic treatment was required.
    - ✓ the training of the person who will infuse pegunigalsidase alfa on how to identify IRRs
    - ✓ the training of the person who will infuse pegunigalsidase alfa about the preparation and administration of the product and the use of the logbook
    - ✓ the need of the logbook and its function in communication with the treating physician
    - ✓ describe the importance of the presence of a caregiver in case emergency medical care is needed

- A patient/ caregiver/ HCP guide for the administration at home which describe the following key elements:
    - ✓ Step by step instructions on the preparation and administration technique including proper aseptic technique
    - ✓ the dosing and infusion rate which will be determined by the treating physician
    - ✓ signs and symptoms of IRRs and how to treat or manage them
    - ✓ the importance of the presence of a caregiver to monitor the patient in case emergency medical care is needed
    - ✓ medication prescribed by the treating physician for IRRs or pre-medication should be available at home and should be used accordingly
    - ✓ the logbook should be used to record the infusion and any IRR, and taken to the treating physician visits

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Elfabrio 2 mg/mL concentrate for solution for infusion
pegunigalsidase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 20 mg of pegunigalsidase alfa in 10 mL (2 mg/mL)
One vial contains 5 mg of pegunigalsidase alfa in 2.5 mL (2 mg/mL)

3. LIST OF EXCIPIENTS

Sodium citrate tribasic dihydrate
Citric acid
Sodium chloride
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion

20 mg/10 mL
5 mg/2.5 mL
1 vial
5 vials
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1724/001
EU/1/23/1724/002
EU/1/23/1724/003
EU/1/23/1724/004
EU/1/23/1724/005
EU/1/23/1724/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Elfabrio 2 mg/mL concentrate for solution for infusion
pegunigalsidase alfa
IV after dilution

2. METHOD OF ADMINISTRATION

Read the package leaflet before use
Intravenous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg/10 mL
5 mg/2.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Elfabrio 2 mg/mL concentrate for solution for infusion
pegunigalsidase alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Elfabrio is and what it is used for

Elfabrio contains the active substance pegunigalsidase alfa, and is used as enzyme replacement therapy in adult patients with confirmed Fabry disease. Fabry disease is a rare genetic disease that can affect many parts of the body. In patients with Fabry disease, a fat substance is not removed from the cells of their body, and builds up in the walls of blood vessels which can cause organ failure. This fat builds up in the cells of these patients because they do not have enough of an enzyme called α-galactosidase-A, the enzyme responsible for breaking it down Elfabrio is used long-term to supplement or replace this enzyme in adult patients who have confirmed Fabry disease.

2. What you need to know before you are given Elfabrio

Do not use Elfabrio
- if you are severely allergic to pegunigalsidase alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before Elfabrio is used.

If you are treated with Elfabrio, you may experience a side effect during or immediately following the drip (infusion) used to give the medicine (see section 4). This is known as an **infusion-related reaction** and can sometimes be severe.

- Infusion-related reactions include dizziness, headache, nausea, low blood pressure, tiredness and fever. If you experience an infusion-related reaction, **you must tell your doctor immediately**.
- If you have an infusion-related reaction you may be given additional medicines to treat or help prevent future reactions. These medicines may include medicines used to treat allergies

(antihistamines), medicines used to treat fever (antipyretics) and medicines to control inflammation (corticosteroids).
- If the infusion-related reaction is severe, your doctor will stop the infusion immediately and start giving you appropriate medical treatment or slow down treatment rate.
- If the infusion-related reactions are severe and/or there is a loss of effect from this medicine, your doctor will perform a blood test to check for antibodies that might affect the outcome of your treatment.
- Most of the time you can still be given Elfabrio even if you experience an infusion-related reaction.

In very rare cases, your immune system may not be able to recognise Elfabrio, leading to an immunological kidney disease (glomerulonephritis membranoproliferative). During the clinical studies, only one case occurred, and the only symptoms reported were a temporary decline of renal functions with excess proteins in the urine. The symptoms resolved upon discontinuation of the treatment.

Children and adolescents
This medicine should not be used in children and adolescents. The safety and efficacy of Elfabrio in children and adolescents aged 0-17 years have not been established.

Other medicines and Elfabrio
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
You should not use Elfabrio if you are pregnant, since there is no experience with Elfabrio in pregnant women. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

It is unknown whether Elfabrio is excreted in human milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding or stop taking Elfabrio, considering the benefit of breast-feeding for your baby and the benefit of Elfabrio for you.

Driving and using machines
Elfabrio may cause dizziness or vertigo. If you feel dizzy or vertigo on the day of treatment with Elfabrio, do not to drive or use machines until you feel better.

Elfabrio contains sodium
This medicine contains 46 mg sodium (main component of cooking/table salt) in each 10 mL vial. This is equivalent to 2% of the recommended maximum daily dietary intake of sodium for an adult.
This medicine contains 11.5 mg sodium (main component of cooking/table salt) in each 2.5 mL vial. This is equivalent to 1% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Elfabrio is given

This medicine is only to be used under the supervision of a doctor experienced in the treatment of Fabry disease or other similar diseases and should only be given by a healthcare professional.

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

Your doctor may advice that you can be treated at home provided you meet certain criteria. Please contact your doctor if you would like to be treated at home.

See information for healthcare professionals at the end of this package leaflet.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects occur during the infusion or shortly after ("infusion-related reaction", see section 2 "Warnings and precautions").

While under treatment with Elfabrio, you may experience some of the following reactions:

Serious side effects

Common side effects (may affect up to 1 in 10 people)
- hypersensitivity and serious allergic reaction (symptoms including excessive and prolonged contraction of the airway muscles causing breathing difficulty (bronchospasm), swelling of the face, mouth and throat, wheezing, low blood pressure, hives, difficulty swallowing, rash, shortness of breath, flushing, chest discomfort, itchiness, sneezing and nasal congestion)

If these side effects happen, immediately seek medical attention and stop the infusion. Your doctor will give you medical treatment if required.

Other side effects include

Common (may affect up to 1 in 10 people)
- infusion related reactions
- weakness
- feeling sick (nausea)
- rash
- abdominal pain
- dizziness
- pain
- chest pain
- headache
- muscle and joint pain
- sensations like numbness, tingling, or pins and needles (paraesthesia)
- itching (pruritus)
- diarrhoea
- vomiting
- chills
- redding of the skin (erythema)
- a spinning sensation (vertigo), arousal, irritability or confusion
- alteration of the normal heart rhythm
- agitation

Uncommon (may affect up to 1 in 100 people)
- shaking (tremor)
- high blood pressure (hypertension)
- bronchospasm (contraction of the bronchial muscles causing obstruction of breathing airways) and difficult breathing
- throat irritation
- increased body temperature
- difficulty sleeping (insomnia)
- restless legs syndrome
- nerve damage in arms and legs causing pain or numbness, burning and tingling (peripheral neuropathy)
- nerve pain (neuralgia)
- burning sensation

- flushing
- disease where stomach acid goes upwards into the oesophagus (gastro-oesophageal reflux disease)
- inflammation of the stomach lining (dyspepsia)
- indigestion
- gas (flatulence)
- diminished sweating (hypohydrosis)
- immunological kidney disease causing excess protein in the urine and renal malfunctioning (glomerulonephritis membranoproliferative)
- chronic kidney disease
- excess protein in the urine (proteinuria)
- tissue damage because the medicine that is normally infused into a vein leaks or is accidentally infused into the surrounding tissue (infusion site extravasation)
- swelling of lower legs or hands (oedema)
- swelling of arms or legs
- influenza-like illness
- nasal congestion and sneezing
- infusion site pain
- increased liver enzymes and uric acid in the blood, increased urine protein/creatinine ratio, white blood cells in the urine, as tested in the laboratory
- weight increase
- low blood pressure (hypotension)
- slow heart rate (bradycardia)
- thickening of the wall within the ventricle in the heart

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Elfabrio

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C-8 °C).

After dilution, the diluted solution should be used immediately. If not used immediately, the diluted solution should be stored for no longer than 24 hours in a refrigerator (2 °C-8 °C) or for no longer than 8 hours at room temperature (below 25 °C).

Do not use this medicine if you notice particles or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Elfabrio contains
- The active substance is pegunigalsidase alfa. Each vial contains 20 mg pegunigalsidase alfa in 10 mL or 5 mg pegunigalsidase alfa in 2.5 mL (2 mg/mL)

- The other ingredients are: tribasic dihydrate sodium citrate, citric acid, and sodium chloride (see section 2 “Elfabrio contains sodium”).

What Elfabrio looks like and contents of the pack
Clear and colourless solution in clear glass vial with a rubber stopper and sealed with aluminium flip off cap.

Pack sizes: 1, 5 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
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Manufacturer
Chiesi Farmaceutici S.p.A.
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Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Dilution (using aseptic technique)

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).
   - In this example, 4 vials of the 10 mL vial (or 16 vials of the 2.5 mL vial) are needed.

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 the table below.

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.