

## **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 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 vial contains 48 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

Pegunigalsidase alfa 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 pegunigalsidase alfa is administered to patients who have not had treatment before, or who have experienced severe hypersensitivity reactions to pegunigalsidase alfa in the past.

Pre-treatment with antihistamines and/or corticosteroids may be advisable for patients who had previously experienced hypersensitivity reactions to pegunigalsidase alfa 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.

The treatment can be also administered at the dose of 2 mg/kg of body weight once every four weeks in patients stable with an ERT treatment (see section 4.4 Treatment monitoring).

For instructions on reconstitution, see section 6.6.

#### Patients switching treatment from agalsidase alfa or beta

For the initial 3 months of treatment with pegunigalsidase alfa, pre-treatment regimen should be preserved with stepwise discontinuation of pre-treatment based on appropriate tolerability of the patients.

#### Special populations

##### *Hepatic impairment*

No dose adjustment is needed in patients with hepatic impairment.

##### *Renal impairment*

No dose adjustment is needed in patients with renal impairment.

Renal function should be evaluated regularly during pegunigalsidase alfa treatment (see section 4.4).

### *Elderly ( $\geq 65$ years old)*

Safety and efficacy of pegunigalsidase alfa 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 pegunigalsidase alfa 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.

Pegunigalsidase alfa 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  $\mu\text{m}$  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 pegunigalsidase alfa before administration, see section 6.6.

### Home administration

Infusion of pegunigalsidase alfa at home may be considered if the patient is tolerating infusions well and has 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 1 mg/kg of body weight of pegunigalsidase alfa every 2 weeks**

<b><i>Initial infusion 1 mg/kg of body weight every 2 weeks</i></b>			
<b>Body weight (Kg)</b>	<b>Total volume (ml)</b>	<b>Infusion time</b>	<b>Infusion rate*</b>
<70	150 ml	≥ 3 hours	0.83 ml/min (50 ml/hr)
70-100	250 ml	≥ 3 hours	1.39 ml/min (83.33 ml/hr)
> 100	500 ml	≥ 3 hours	2.78 ml/min (166.67 ml/hr)
<b><i>Maintenance infusion</i></b> 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.			
<b><i>1 mg/kg of body weight every 2 weeks</i></b>			
<b>Body weight (Kg)</b>	<b>Total volume (ml)</b>	<b>Infusion time</b>	<b>Infusion rate*</b>
<70	150 ml	≥ 1.5 hours	1.68 ml/min (100 ml/hr)
70-100	250 ml	≥ 1.5 hours	2.78 ml/min (166.67 ml/hr)
> 100	500 ml	≥ 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)

**Table 2: Recommended dose and infusion time for intravenous administration of 2 mg/kg of body weight of pegunigalsidase alfa every 4 weeks**

<i>Initial infusion 2 mg/kg of body weight every 4 weeks</i>			
<b>Body weight (Kg)</b>	<b>Total volume (ml)</b>	<b>Infusion time</b>	<b>Infusion rate*</b>
< 70	150 ml	≥ 4.5 hours	0.56 ml/min (33.33 ml/hr)
70-100	250 ml	≥ 4.5 hours	0.93 ml/min (55.56 ml/hr)
> 100	500 ml	≥ 6 hours	1.39 ml/min (83.33 ml/hr)
<b><i>Maintenance infusion</i></b>			
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.			
<i>2 mg/kg of body weight every 4 weeks</i>			
<b>Body weight (Kg)</b>	<b>Total volume (ml)</b>	<b>Infusion time</b>	<b>Infusion rate*</b>
< 70	150 ml	≥ 2 hours	1.25 ml/min (75 ml/hr)
70-100	250 ml	≥ 2 hours	2.08 ml/min (125 ml/hr)
> 100	500 ml	≥ 3 hours	2.78 ml/min (166.67 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.

### Treatment monitoring

For patients switched to pegunigalsidase alfa 2 mg/kg body weight once every 4 weeks, regular monitoring (e.g.: after 3, 6, 12, 18 and 24 months) should be performed. Monitoring should include at least the evaluation of lyso-Gb3, renal (eGFR, proteinuria), cardiac (LVMi, NT-proBNP, troponin or ECG), and biochemical parameters. A change in any individual parameter should be interpreted in the context of the patient's overall clinical status, and clinically relevant deterioration should prompt re-evaluation of the treatment regimen.

### 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, nausea, chills and nasal congestion. If a severe allergic or anaphylactic-type reactions occur, immediate discontinuation of pegunigalsidase alfa is recommended and current medical standards for emergency treatment are to be followed.

In patients who have experienced severe hypersensitivity reactions during pegunigalsidase alfa 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 pegunigalsidase alfa, 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 pegunigalsidase alfa 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 pegunigalsidase alfa treatment should be monitored.

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

#### Membranoproliferative glomerulonephritis

Depositions of immune complexes can potentially occur during treatment with ERTs, as a manifestation of immunological response to the product. A single case of membranoproliferative glomerulonephritis was reported during the clinical development of pegunigalsidase alfa, 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.

#### Patients with renal impairment

The presence of extensive renal damage (eGFR < 60 ml/min) may limit the renal response to enzyme replacement therapy, possibly due to underlying irreversible pathological changes. In such cases, the loss of renal function remains within the expected range of the natural progression of disease. Regular evaluation of changes in the estimated glomerular filtration rate (eGFR) during pegunigalsidase alfa treatment is recommended.

#### 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.

Pegunigalsidase alfa 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 pegunigalsidase alfa 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 pegunigalsidase alfa 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 pegunigalsidase alfa 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, syncope or vertigo were observed in some patients following pegunigalsidase alfa 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 7.8% of patients, followed by nausea and asthenia, both reported in 5.6% of patients and headache, reported in 4.2% of patients.

In clinical studies, 5 patients (3.5%) experienced a serious reaction that was considered related to pegunigalsidase alfa. Four of these reactions were confirmed IgE-mediated hypersensitivity (bronchospasm, hypersensitivity) that occurred at the first infusion of pegunigalsidase alfa 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 pegunigalsidase alfa 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 7 years.

Adverse reactions are listed in Table 3. Information is presented by system organ class. Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ); rare ( $\geq 1/10\ 000$  to

< 1/1 000); very rare (< 1/10 000); frequency not known (cannot be estimated from available data).

**Table 3: Adverse reactions reported during treatment with pegunigalsidase alfa**

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* syncope*
Ear and labyrinth disorders	vertigo	
Vascular disorders		flushing hypotension* hypertension* lymphoedema
Respiratory, thoracic and mediastinal disorders		bronchospasm* sneezing* nasal congestion* dyspnoea* throat irritation* throat tightness
Gastrointestinal disorders	nausea* abdominal pain* diarrhoea vomiting*	gastroesophageal 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		Membranoproliferative glomerulonephritis chronic kidney disease proteinuria
Reproductive system and breast disorders		nipple pain
General disorders and administration site conditions	asthenia* chills* chest pain* pain*	influenza-like illness infusion site extravasation infusion site pain oedema

System organ class	Frequency	
	Common	Uncommon
Investigations		body temperature 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	
<p>The following preferred terms have been grouped in Table 3:</p> <ul style="list-style-type: none"> <li>• hypersensitivity includes: drug hypersensitivity</li> <li>• agitation includes: nervousness</li> <li>• abdominal pain includes: abdominal discomfort</li> <li>• rash includes: rash maculo-papular and rash pruritic</li> <li>• musculoskeletal stiffness recorded as musculoskeletal pain includes: myalgia</li> <li>• asthenia includes: malaise and fatigue</li> <li>• chest pain includes: chest discomfort and non-cardiac chest pain</li> <li>• pain includes: pain in extremity</li> <li>• oedema peripheral recorded as oedema</li> </ul>		

\* 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 36 patients (25%): 26 patients (23%) treated with 1 mg/kg every two weeks and 10 patients (34%) 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 symptoms were pain, headache and nausea. 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 pegunigalsidase alfa 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 pegunigalsidase alfa every two weeks and 1 out of 30 patients (3.4%) treated with 2 mg/kg pegunigalsidase alfa every four weeks developed treatment-induced anti-drug antibodies (ADAs).

### Membranoproliferative glomerulonephritis

During the clinical development of pegunigalsidase alfa, one patient out of 141 reported a severe event of membranoproliferative glomerulonephritis 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:

Yellow Card Scheme Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## **4.9 Overdose**

There are no reports of overdose of pegunigalsidase alfa during clinical studies. The maximum dose of pegunigalsidase alfa 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.

## **5.1 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  $\alpha$ -galactosidase-A. The amino acid sequence of the recombinant form is similar to the naturally occurring human enzyme.

Pegunigalsidase alfa supplements or replaces  $\alpha$ -galactosidase-A, the enzyme that catalyses the hydrolysis of the terminal  $\alpha$ -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 141 patients. Among these patients, the efficacy was evaluated in 111 receiving pegunigalsidase alfa 1 mg/kg once every two weeks (E2W), and in 29 receiving pegunigalsidase alfa 2 mg/kg body weight once every four weeks (E4W).

### Disease substrate

Analyses of kidney biopsies from naïve patients treated with pegunigalsidase alfa at a dosage of 1 mg/kg body weight E2W 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 ( $\geq 50\%$ ) 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 at a dosage of 1 mg/kg body weight E2W, plasma lyso-Gb3 values stayed stable after 24 months of treatment (+3.3 nM mean value, n=48).

In an open-label Phase 3 study in 29 patients with stable Fabry disease on ERT (agalsidase alfa or agalsidase beta), lyso-Gb3 values were evaluated prior to and after treatment conversion into pegunigalsidase alfa at a dosage of 2 mg/kg body weight E4W. The observed median (Q1, Q3) plasma lyso-Gb3 levels at baseline were 17.2 (12.1, 32.8) nmol/l for male study patients (n= 23) and 4.4 (2.9, 5.9) nmol/l for female study patients (n=6). In men, the median (Q1, Q3) changes in lyso-Gb3 levels after 1, 2, and 4 years compared to baseline were respectively +5.1 (0.3, 7.8), +4.5 (-0.1, 9.4), and +2.7 (-2.0, 7.4) nmol/l. In women, the median (Q1, Q3) changes in lyso-Gb3 levels after 1, 2, and 4 years compared to baseline were respectively -0.1 (-0.4, 0.2), +0.2 (-0.2, 0.7), and -0.3 (-1.0, 1.2) nmol/l.

### 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 several phase 3 studies.

Two phase 3 studies evaluated pegunigalsidase alfa 1 mg/kg E2W 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 -

2.5 ml/min/1.73 m<sup>2</sup>/year for the pegunigalsidase alfa arm and -1.7 for the agalsidase beta arm (difference -0.8 [-3.0, 1.5]). At month 24, the median slopes for eGFR were -2.5 [-3.8; -1.2] ml/min/1.73 m<sup>2</sup>/year for the pegunigalsidase alfa arm and -2.2 [-3.8; -0.5] for the agalsidase beta arm (difference -0.36 [-2.4; 1.7]).

The renal function was also evaluated through the annualised eGFR slope in a phase 3 study that investigated pegunigalsidase alfa 2 mg/kg E4W in previously ERT-treated adult Fabry patients: this study was an open label single arm study, after switch from agalsidase beta or agalsidase alfa, followed by a long-term extension study.

The mean (SD) annualized eGFR slope in the efficacy population was -1.8 (3.7) and -2.0 (2.1) ml/min/1.73 m<sup>2</sup>/year respectively at pre-treatment baseline and during treatment over  $\geq 4$  years of treatment with pegunigalsidase alfa 2 mg/kg E4W.

### 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 and 2 mg/kg every four weeks in adult patients with Fabry disease. The pharmacokinetic results (non-compartmental PK analysis) for all dose levels demonstrated that the enzyme was available throughout the whole dosing intervals with a plasma half-life ( $t_{1/2}$ ) ranging from 53-134 hours across dose groups and visit day.

In adult ERT-naïve patients, on Day 1, the mean values for dose-normalized AUCs were similar for all dose levels, indicating linear dose-proportionality in the range of tested doses (0.2, 1 and 2 mg/kg E2W). At 3, 6 and 12 Months, the mean values for AUCs and  $C_{last}$  increased more than as per dose-proportionality with relatively high inter-subject variability in 0.2 mg/kg group and at some visits in 1 and 2 mg/kg dose groups. For patients who received 1 and 2 mg/kg pegunigalsidase alfa, there were increases in mean  $t_{1/2}$  and  $AUC_{0-2wk}$  with increasing duration of treatment and corresponding decreases in CL and  $V_z$ , suggesting a saturated clearance.

In adult ERT-experienced patients, for 1 mg/kg E2W dosing regimen, mean  $C_{max}$  ranged from 21.2 to 23.3 mcg/mL, while mean  $AUC_{last}$  ranged from 972 to 1156 mcg·h/mL. All the observations on the PK parameters indicate a consistent PK profile of pegunigalsidase alfa throughout the 2-years study treatment duration.

For 2 mg/kg E4W dosing regimen, mean  $C_{max}$  ranged from 36 to 47 mcg/mL, while mean  $AUC_{last}$  ranged from 1648 to 2179 mcg·h/mL. There appears to be no time effect on the PK.

Population PK modelling indicates that steady state is effectively achieved within the first month of treatment, with negligible accumulation, in both ERT-experienced and ERT-naïve patients irrespective of the dosing regimen.

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 pegunigalsidase alfa 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.

The population PK model showed that over a 4-week interval AUC and  $C_{avg}$  are simulated to be similar following 1 mg/kg E2W or 2 mg/kg E4W, whereas  $C_{max}$  is simulated to be 2-fold higher and  $C_{min}$  is simulated to be 0.4-fold lower in the 2 mg/kg E4W regimen. The PK/PD analysis indicated that no clear relationship between pegunigalsidase alfa exposure and Lyso-Gb3 change from baseline at 12 months of treatment or with eGFR annualized slope can be quantified. Despite the fact that the data do not support the quantification of an exposure-response relationship, an overlap in the median [Q1, Q3] lyso-Gb3 concentrations at baseline, 24 months, and 48 months after switching from ERT to 2 mg/kg E4W was observed (see section 5.1).

### 5.3 Preclinical safety data

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

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.

Pack sizes of 1, 5 or 10 vials.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

Pegunigalsidase alfa 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)  $\div$  2 = Volume of dose (in mL)
- Example: 80 kg patient  $\div$  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.

An example calculation for total dose in an 80 kg patient prescribed 2 mg/kg is as follows:

- Patient weight (in kg) = Volume of dose (in mL)
- Example: 80 kg patient = 80 mL (volume to be withdrawn).
- In this example, 8 vials of the 10 mL vial (or 32 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 pegunigalsidase alfa 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 pegunigalsidase alfa 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**

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Manchester  
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## **8      MARKETING AUTHORISATION NUMBER(S)**

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