▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
ELFABRIO® (pegunigalsidase alfa)

1 NAME OF THE MEDICINE

Pegunigalsidase alfa

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20 mg of pegunigalsidase alfa in a volume of 10 mL (2 mg/mL).

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Concentrated injection.

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.

4.2 DOSE 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Administration of ELFABRIO should be carried out by a healthcare professional with the ability to manage ERT and medical emergencies.

Dosage

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

Patients switching treatment from agalsidase alfa or beta

For the initial 3 months (6 infusions) of treatment with ELFABRIO, pre-treatment regimen should be continued with stepwise discontinuation of pre-treatment as appropriate based on the patient's tolerance to treatment.

Special populations

Renal or hepatic impairment

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

Elderly (≥65 years old)

The safety and efficacy of ELFABRIO in patients older than 65 years has not been established.

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.

Instructions for dilution

Vials are for single use only. Aseptic technique to be used.

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 (approximately 30 minutes).

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 0.9% (9 mg/mL) solution for infusion from the infusion bag.

4. Withdraw the required volume of ELFABRIO solution from the vials, and dilute with sodium chloride 0.9% (9 mg/mL) solution for infusion, to a total volume based on patient weight (Table 1).

5. 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.

Table 1. 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

Infusion rate and duration of infusion

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

Table 2. 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/h)
70-100	250 mL	not less than 3 hours	1.39 mL/min (83.33 mL/h)
>100	500 mL	not less than 3 hours	2.78 mL/min (166.67 mL/h)
Maintenance infusion 1 mg/kg of body weight every 2 weeks The target infusion duration can be reduced based patient's tolerability. The increase in the infusion rate should be achieved gradually starting from the rate given at the first infusion.			
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/h)
70-100	250 mL	not less than 1.5 hours	2.78 mL/min (166.67 mL/h)
>100	500 mL	not less than 1.5 hours	5.56 mL/min (333.33 mL/h)

*Infusion rate may be adjusted in case of infusion reaction (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

If the patient experiences an infusion-related reaction (IRR), 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Home administration

Infusion of ELFABRIO at home may be considered if the patient is tolerating their infusions well and has no history of moderate or severe IRRs for at least 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. Appropriate support should be available.

Home infusions should be administered by a healthcare professional able to assess and manage infusion reactions (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The dose and infusion rate used in the home setting should remain the same as was used in the hospital setting and should be changed only under the supervision of the treating physician.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

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 (IRRs)

IRRs are 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 ADVERSE EFFECTS (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 4.2 DOSE AND METHOD OF ADMINISTRATION).

Hypersensitivity

Hypersensitivity reactions have been reported in patients in clinical studies (see section 4.8 ADVERSE EFFECTS (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 should be followed.

In patients who have experienced severe hypersensitivity reactions during ELFABRIO infusion or previous ERT, caution should be exercised upon re-challenge, including considering slowing infusion rates and 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

The presence of ADAs to ELFABRIO may be associated with a higher risk of IRRs, 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 (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). This event led to a temporary decline in renal function, which improved upon discontinuation of the medicinal product. It is recommended to monitor serum creatinine and urinary protein to creatinine ratio. Discontinue ELFABRIO if glomerulonephritis is suspected, until a diagnostic evaluation can be conducted.

Excipients

This medicinal product contains 48 mg sodium per vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Use in the elderly

See section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

See section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no studies assessing the potential effect of pegunigalsidase alfa on fertility in humans. No effect on fertility or reproductive performance was observed in male and female rats given pegunigalsidase alfa IV prior to mating through implantation at exposures ≤4-fold the anticipated clinical exposure (based on AUC).

Use in pregnancy (Category B3)

There are no or limited amount of data from the use of pegunigalsidase alfa in pregnant women.

Animal reproduction studies have been conducted with pegunigalsidase alfa in pregnant rats and rabbits administered pegunigalsidase alfa IV twice weekly through organogenesis. Placental transfer of pegunigalsidase alfa was demonstrated in rats. No adverse effects on embryofetal development were observed in pregnant rats at exposures ≤4-fold the anticipated clinical exposure (based on AUC). Fetotoxicity (including abortions, increased late resorptions, number of does with resorptions, increased post-implantation loss and/or decreased fetal body weights) was observed in pregnant rabbits at clinically relevant exposures (based on AUC). There was no increase in fetal external, skeletal, or visceral malformations, however, the incidence of skeletal alterations (including dumb-bell thoracic vertebral centra in rats and extra lumbar vertebral centra in rabbits) was increased in both species at dose levels corresponding to 3.6-fold (rats) and 0.5-fold (rabbits) the anticipated clinical exposure (based on AUC).

As a precautionary measure, it is preferable to avoid the use of ELFABRIO during pregnancy unless clearly necessary.

Use in lactation

Prenatal and postnatal developmental toxicity studies were not performed with pegunigalsidase alfa. Thus, the risks for fetus and pups during the late pregnancy and lactation are unknown. Milk excretion of pegunigalsidase alfa was demonstrated in rats.

It is unknown whether pegunigalsidase alfa and/or its metabolites are excreted in human milk. A risk to newborns or infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue ELFABRIO therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

BALANCE clinical trial

The safety of ELFABRIO in adults with confirmed Fabry disease who had been previously treated with agalsidase beta was evaluated in the BALANCE trial in patients with Fabry disease. Patients

received 1 mg/kg of ELFABRIO or 1 mg/kg agalsidase beta given intravenously every 2 weeks for at least 104 weeks.

The most common adverse reactions (≥15%) reported with ELFABRIO were infusion-related reactions which occurred in 17 patients (32%); followed by, nasopharyngitis and headache each in 11 patients (21%); diarrhoea in 10 patients (19%); fatigue and nausea each in 9 patients (17%); and back pain, pain in extremity, and sinusitis each in 8 patients (15%).

One ELFABRIO-treated patient experienced a severe hypersensitivity reaction during the first infusion. The patient withdrew from the trial following a moderate hypersensitivity reaction during the second infusion.

The adverse events reported in at least 5% of ELFABRIO-treated patients in the BALANCE trial are listed in Table 3.

Table 3. Adverse events which occurred in at least 5% of ELFABRIO-treated patients in the BALANCE trial

Adverse Events	ELFABRIO N=52 n (%)	Agalsidase beta N=25 n (%)
Nasopharyngitis	11 (21)	4 (16)
Headache	11 (21)	5 (20)
Diarrhoea	10 (19)	6 (24)
Fatigue	9 (17)	4 (16)
Nausea	9 (17)	3 (12)
Back pain	8 (15)	5 (20)
Pain in extremity	8 (15)	4 (16)
Sinusitis	8 (15)	3 (12)
Upper respiratory tract infection	6 (12)	4 (16)
Urinary tract infection	6 (12)	3 (12)
Vomiting	6 (12)	3 (12)
Dizziness	6 (12)	2 (8)
Abdominal pain	6 (12)	0 (0)
Proteinuria	6 (12)	0 (0)
Cough	6 (12)	5 (20)
Bronchitis	5 (10)	5 (20)
Pyrexia	5 (10)	3 (12)
Muscle spasms	5 (10)	3 (12)
Rash	5 (10)	2 (8)
Upper respiratory tract congestion	4 (8)	0 (0)
Neuralgia	4 (8)	0 (0)
Anaemia	4 (8)	3 (12)
Oedema peripheral	4 (8)	3 (12)
Arthralgia	4 (8)	2 (8)
Atrial fibrillation	4 (8)	1 (4)
Seasonal allergy	4 (8)	1 (4)
Oropharyngeal pain	3 (6)	3 (12)
Viral infection	3 (6)	3 (12)
Palpitations	3 (6)	2 (8)
Musculoskeletal pain	3 (6)	2 (8)
Vertigo	3 (6)	1 (4)

Adverse Events	**ELFABRIO N=52 n (%)**	**Agalsidase beta N=25 n (%)**
Gastroesophageal reflux disease	3 (6)	1 (4)
Respiratory tract infection	3 (6)	1 (4)
Nasal congestion	3 (6)	1 (4)
Peripheral neuropathy	3 (6)	0 (0)
Sciatica	3 (6)	0 (0)
Infusion site extravasation	3 (6)	0 (0)
Haematuria	3 (6)	0 (0)
Urine protein/creatinine ratio increased	3 (6)	0 (0)

Tabulated summary of adverse reactions

The data described in Table 4 reflects data from 141 patients with Fabry disease who received ELFABRIO in 8 clinical studies, following the IV administration 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 classified by system organ class and preferred term according to the MedDRA frequency convention. 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 4. Adverse reactions reported during treatment with ELFABRIO

System organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Common	hypersensitivity*, type I hypersensitivity*
Psychiatric disorders	Common	agitation*
	Uncommon	insomnia
Nervous system disorders	Common	paraesthesia*, dizziness*, headache*
	Uncommon	restless legs syndrome, peripheral neuropathy, neuralgia, burning sensation, tremor*
Ear and labyrinth disorders	Common	vertigo
Cardiac disorders	Common	supraventricular extrasystoles
	Uncommon	bradycardia*, left ventricular hypertrophy
Vascular disorders	Uncommon	flushing, hypotension*, hypertension*, lymphoedema
Respiratory, thoracic and mediastinal disorders	Uncommon	bronchospasm*, dyspnoea*, throat irritation*, nasal congestion*, sneezing*
Gastrointestinal disorders	Common	nausea*, abdominal pain*, diarrhoea, vomiting*
	Uncommon	gastro-oesophageal reflux disease, gastritis, dyspepsia, flatulence
Skin and subcutaneous issue disorders	Common	rash*, erythema*, pruritus*
	Uncommon	hypohidrosis
Musculoskeletal and connective tissue disorders	Common	arthralgia, musculoskeletal pain*
Renal and urinary disorders	Uncommon	glomerulonephritis membranoproliferative, chronic kidney disease, proteinuria
Reproductive system and breast disorders	Uncommon	nipple pain

System organ class	Frequency	Adverse reaction
General disorders and administration site conditions	Common	asthenia*, chills*, chest pain*, pain*
	Uncommon	infusion site extravasation, oedema, influenza-like illness, infusion site pain
Investigations	Uncommon	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	Common	infusion-related reaction*

The following preferred terms have been grouped in Table 4:
- 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 IRRs (see Description of selected adverse reactions)

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 a Phase 1/2 trial in ERT-naïve patients or patients who did not receive ERT for 26 weeks, 4 out of 14 ELFABRIO-treated patients who were IgG anti-pegunigalsidase alfa antibodies (anti-drug antibodies or ADA) negative at baseline became ADA positive during ELFABRIO treatment. The onset of ADA positivity in 3 of these patients occurred within 26 weeks after starting ELFABRIO treatment. Two patients had ADA prior to receiving their first ELFABRIO dose, one of these patients remained ADA positive after receiving ELFABRIO treatment (this patient had boosted antibody titers during ELFABRIO treatment).

In the BALANCE trial in ERT-experienced patients with Fabry disease who switched from

agalsidase beta, 3 out of the 34 ELFABRIO-treated patients who were ADA negative at baseline became ADA positive during ELFABRIO treatment. The onset of ADA positivity occurred within 26 weeks after starting ELFABRIO treatment in 1 patient and more than 52 weeks in the remaining 2 patients. Eighteen ELFABRIO-treated patients had ADA prior to receiving their first ELFABRIO dose of which 17 (94%) patients remained ADA positive after receiving ELFABRIO treatment at one or more timepoints; and 3 (17%) patients had boosted ADA titers during ELFABRIO treatment.

Across all 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 ADAs. IRRs occurred more frequently in ELFABRIO-treated patients who were IgG ADA positive compared to those that were IgG ADA negative (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

Fabry disease is caused by deficiency of the lysosomal enzyme alpha-galactosidase A. 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 α-galactosyl moieties of oligosaccharides and polysaccharides in the lysosome, where it is thought to exert enzymatic activity and reduce accumulated globotriaosylceramide (Gb3).

Clinical trials

Disease substrate

An open-label dose-ranging Phase 1/2 trial in adults diagnosed with Fabry disease enrolled 18 patients who were ERT-naïve or who had not received ERT for more than 26 weeks and had a negative test for anti-pegunigalsidase alfa IgG antibodies prior to enrollment. Two patients in the 1 mg/kg treatment group discontinued the trial after their first infusion; one of them discontinued due to severe hypersensitivity reaction. Among the remaining 16 patients who completed the trial, 9 (56%) were males and 7 (44%) were females ranging in age 17-54 years with a median age of 30 years. The median baseline eGFR and proteinuria was 115 mL/min/1.73 m^2 and 0.11 g/g, respectively. Among the male patients, the median value of residual alpha-galactosidase A activity was 2.4% (range 0.0%-9.3%) in plasma and 1.3% (range 0.0%-3.4%) in leukocytes.

The average number of globotriaosylceramide (Gb3) inclusions per renal peritubular capillary (PTC) in renal biopsy specimens of patients was assessed by light microscopy using the quantitative Barisoni Lipid Inclusion Scoring System (BLISS). Evaluable renal biopsies were obtained at baseline and at 26 weeks of treatment in 14 of the 16 patients who completed the trial. The changes from baseline to 26 weeks in the BLISS score (average number of Gb3 inclusions per renal PTC) for these 14 ELFABRIO-treated patients is shown in Table 5.

Table 5. Summary of the renal biopsy BLISS Score[1] of Gb3 inclusions at baseline and after 26 weeks of ELFABRIO treatment in adults with Fabry disease

Median (range)	**All Patients (N = 14)**	**Males (N = 8)**	**Females (N = 6)**
Baseline	3.2 (0.4, 9.0)	6.8 (0.4, 9.0)	1.2 (0.8, 3.3)
Week 26	0.7 (0.3, 2.5)	0.7 (0.3, 2.5)	0.7 (0.3, 1.4)
Change at week 26	-2.5 (-8.5, 0.5)	-5.3 (-8.5, 0.5)	-0.7 (-2.5, 0.1)
Mean change at week 26 (95% CI)	**-3.1 (-4.8, -1.4)**	**-4.7 (-7.1, -2.3)**	**-1.0 (-2.1, 0.1)**

[1]The BLISS methodology counts the number of Gb3 inclusions in each renal PTC contained in a biopsy specimen. For each biopsy specimen (slide), approximately 300 renal PTCs were scored, and the final biopsy score for each patient was determined as the average number of Gb3 inclusions per PTC.

Renal function

The BALANCE study was a randomised, double-blind, and active-controlled trial in ERT-experienced adults diagnosed with Fabry disease. Eligible patients were treated with agalsidase beta for at least one year prior to trial entry (the mean duration of agalsidase beta treatment prior to enrollment was 5.7 years). Patients were randomised 2:1 to receive ELFABRIO (1 mg/kg intravenous infusion) or agalsidase beta (1 mg/kg intravenous infusion) every 2 weeks for 104 weeks.

A total of 77 patients were randomised and received at least one dose of ELFABRIO (N=52, 68%)

or agalsidase beta (N=25, 32%). Of these patients, 47 (61%) were males and 30 (39%) were females. Patients were 18-60 years with a median age of 46 years at baseline. Forty-one (53%) patients had the classic phenotype. The median baseline eGFR and proteinuria was 75 mL/min/1.73 m^2 and 0.11 g/g, respectively.

The primary efficacy endpoint was the annualised rate of change in eGFR (eGFR slope) assessed over 104 weeks. The estimated median eGFR slopes were -2.514 [95% CI: -3.788; -1.240] mL/min/1.73 m²/year for the pegunigalsidase alfa arm and -2.155 [95% CI: -3.805; -0.505] for the agalsidase beta arm (difference in medians -0.359 [95% CI: -2.444; 1.726]).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

ELFABRIO is administered by intravenous infusion.

Distribution

Plasma pharmacokinetic (PK) profiles of pegunigalsidase alfa were characterised in a dose-ranging Phase 1/2 trial in which ELFABRIO was administered at 0.2, 1 and 2 mg/kg administered every two weeks in adult patients with Fabry disease. The mean maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC) and elimination half-life (t½) of pegunigalsidase alfa increased with increasing duration of treatment (Table 6). There were corresponding decreases in clearance (CL) and terminal volume of distribution (V_z).

Table 6. Pharmacokinetics of pegunigalsidase alfa in adult ERT-naïve patients with Fabry disease following intravenous infusion of ELFABRIO 1 mg/kg every 2 weeks

PK Parameters	Day 1	Week 13	Week 26	Week 52
Mean infusion duration (h)	5.5	4.4	3.9	3.3
C_{max} (µg/mL)	11.1 ± 2.4	11.9 ± 2.4	13.3 ± 3.0	17.3 ± 6.1
AUC_{inf} (µg.h/mL)	391 ± 136	510 ± 174	748 ± 200	1428 ± 875
t½ (h)	78.9 ± 10.3	85.7 ± 28.4	96.5 ± 31.4	121 ± 22
V_z (mL/kg)	321 ± 71	271 ± 89	226 ± 116	186 ± 91
CL (mL/h/kg)	2.9 ± 0.7	2.3 ± 0.8	1.6 ± 0.6	1.1 ± 0.7

[1]Includes patients who had not received ERT for at least 26 weeks and who tested negative for anti-pegunigalsidase alfa antibodies at screening

Metabolism

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.

Excretion

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

Genotoxicity

There have been no studies conducted to assess the mutagenic potential of ELFABRIO.

Carcinogenicity

There have been no studies conducted to assess the carcinogenic potential of ELFABRIO.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium citrate dihydrate
Citric acid
Sodium chloride
Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. ELFABRIO must not be infused in the same intravenous line with other products.

6.3 SHELF LIFE

Unopened vial

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Diluted solution for infusion

From a microbiological point of view, use the diluted solution immediately or it may be stored for 24 hours in the refrigerator (2°C to 8°C) or 6 hours below 25°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze).

6.5 NATURE AND CONTENTS OF CONTAINER

Supplied in a 15R Type I glass vial with a chlorobutyl rubber stopper and sealed with aluminium flip off cap.

Pack sizes of 1, 5 or 10 vials per carton.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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

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

CAS number

1644392-61-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Chiesi Australia Pty Ltd
Level 7, Suite 1, 500 Bourke Street,
Melbourne, VIC 3000.
Email: medinfo.au@chiesi.com

9 DATE OF FIRST APPROVAL

TBC

10 DATE OF REVISION

TBC

Summary table of changes

Section changed	Summary of new information
All	New Product Information