AUSTRALIAN PRODUCT INFORMATION

REPLAGAL® (agalsidase alfa ghu)

1 NAME OF THE MEDICINE

Agalsidase alfa ghu

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3.5 mL vial of REPLAGAL contains 3.5 mg of agalsidase alfa ghu.

Agalsidase alfa ghu is a human α-galactosidase A produced by genetic engineering technology. Agalsidase alfa ghu is a homodimer comprised of 2 approximately 50,000 dalton subunits, with each subunit containing 398 amino acid residues. The product is synthesised by a human cell line and has the identical amino acid sequence as that of α-galactosidase A produced in human tissues. REPLAGAL is now manufactured using a serum-free bioreactor process.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

REPLAGAL is provided as a sterile, clear and colourless solution intended for intravenous (IV) administration. A minute amount of fine particulate matter, causing the solution to appear slightly hazy, may be present.

REPLAGAL contains no antimicrobial agent. It is supplied in a single-dose vial.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REPLAGAL (agalsidase alfa ghu) is indicated for long-term enzyme replacement therapy of patients with Fabry Disease (α-galactosidase A deficiency).

4.2 DOSE AND METHOD OF ADMINISTRATION

In adults and children 6.5 years of age and older, REPLAGAL is administered at a dose of 0.2 mg/kg body weight every 2 weeks by intravenous infusion over a period of 40 minutes. Therapy with REPLAGAL should only be initiated or continued by a physician with expertise in the treatment of Fabry Disease (see Section 4.4 Special warnings and precautions for use). Infusion of REPLAGAL at home may be considered for patients who have been stabilised in a controlled hospital setting and are tolerating their infusions well. REPLAGAL is not recommended in children below 6.5 years of age.

Instruction for use/handling

REPLAGAL for patient administration should be prepared by slowly mixing the appropriate amount of REPLAGAL into 100 mL of normal saline (0.9% sodium chloride) suitable for IV administration. Once diluted into normal saline, the solution should be rocked gently to mix, but not shaken. To reduce potential microbiological hazard, REPLAGAL diluted into normal saline

should be used as soon as practicable after preparation as the product does not contain any bacteriostatic preservatives. However, when prepared under aseptic conditions, the diluted product may be stored for 24 hours at 2-8ºC. The diluted solution must be administered via an IV line, which contains a standard 0.2 micron filter. Do not mix REPLAGAL with or administer in conjunction with other drug solutions.

The chemical and physical stability of the diluted solution has been demonstrated for 24 hours at 25ºC.

4.3 CONTRAINDICATIONS

Life-threatening hypersensitivity (anaphylactic reaction) to the active substance or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

The diagnosis, assessment and management of Fabry Disease should only be undertaken by physicians with experience and training in the treatment of inherited diseases of metabolism. REPLAGAL therapy should only be initiated or continued under the ongoing supervision of a physician with such expertise in the treatment of Fabry Disease.

Hypersensitivity

Hypersensitivity reactions have been reported. If severe hypersensitivity or anaphylactic reactions occur, the administration of REPLAGAL should be discontinued immediately and appropriate treatment initiated. The current medical standards for emergency treatment are to be observed.

Idiosyncratic infusion related reactions

In 13.7% of adult patients, REPLAGAL has been associated with mild, acute idiosyncratic infusion reactions. Overall the percentage of infusion related reactions was lower in females than males. The most common symptoms have been rigors, headache, nausea, pyrexia, flushing and fatigue. Serious infusion reactions have been reported uncommonly; symptoms reported include pyrexia, rigors, tachycardia, urticaria, nausea/vomiting, angioneurotic oedema with throat tightness, stridor and swollen tongue. Other infusion related symptoms may include dizziness and hyperhidrosis. A review of cardiac events showed that infusion reactions may be associated with haemodynamic stress triggering cardiac events in patients with pre-existing cardiac manifestations of Fabry Disease. The onset of infusion related reactions has generally occurred within the first 2-4 months after initiation of treatment with REPLAGAL although later onset (after 1 year) has been reported as well. If mild or moderate acute infusion reactions occur, medical attention must be sought immediately and appropriate actions instituted. The infusion can be temporarily interrupted (5 to 10 minutes) until symptoms subside and the infusion may then be restarted. Mild and transient effects may not require medical treatment or discontinuation of the infusion. In addition, oral or intravenous pre-treatment, with antihistamines and/or corticosteroids, from 1 to 24 hours prior to infusion may prevent subsequent reactions in those cases where prophylaxis was felt to be indicated.

As with any intravenous protein product, allergic-type hypersensitivity reactions are possible. A severe infusion reaction has been reported in a clinical trial post-approval. Symptoms reported were pyrexia, rigors, tachycardia, nausea and vomiting. If severe allergic or anaphylactic-type

reactions occur, the administration of REPLAGAL should be discontinued immediately and appropriate treatment initiated. The current medical standards for emergency treatment are to be observed.

Infusion reactions were more commonly reported in a paediatric study, affecting 8 out of 14 (57.1%) patients. Most reactions were mild to moderate.

Antibodies to protein

As with all protein pharmaceutical products, patients may develop IgG antibodies to the protein. A low titre IgG antibody response has been observed in approximately 24% of the male patients treated with REPLAGAL. Based on limited data this percentage has been found to be lower (7%) in the male paediatric population (2 out of 28 patients). These IgG antibodies appeared to develop following approximately 3-12 months of treatment. After 12 to 54 months of therapy, 17% of REPLAGAL treated patients were still antibody positive whereas 7% showed evidence for the development of immunologic tolerance, based on the disappearance of IgG antibodies over time. The remaining 76% remained antibody negative throughout. Borderline IgE antibody positivity not associated with anaphylaxis has been reported in clinical trials in a very limited number of patients.

Use in hepatic impairment

As metabolism is expected to occur by peptide hydrolysis, an impaired liver function is not expected to affect the pharmacokinetics of REPLAGAL in a clinically significant way.

Use in renal impairment

Renal elimination of REPLAGAL is considered to be a minor pathway for REPLAGAL clearance.

The presence of extensive renal damage 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.

Use in the elderly

Patients with Fabry Disease in the elderly age group were not available for clinical studies.

Paediatric use

The experience in children is limited. Studies in children (0-6 years) have not been performed and no dosage regimen can presently be recommended in these patients as safety and efficacy have not yet been established. Limited clinical data in children (6.5-18 years) do not permit the recommendation of an optimal dosage regimen presently (see Section 5.2 Pharmacokinetic properties). Because no unexpected safety issues were encountered in the 6 month study with REPLAGAL administered at 0.2 mg/kg in this population, this dose regimen is suggested for children between 6.5-18 years of age (see Section 4.2 Dose and method of administration).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

REPLAGAL should not be co-administered with chloroquine, amiodarone, benoquin or gentamicin to patients who require treatment with these drugs because they have the potential to inhibit intra-cellular α-galactosidase activity.

No formal drug interaction studies have been conducted with REPLAGAL. As α-galactosidase A is itself an enzyme, it would be an unlikely candidate for cytochrome P450 mediated drug-drug interactions. In the placebo-controlled studies, neuropathic pain medications were administered concurrently to most patients. No unexpected adverse events were associated with these concomitant therapies.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Male and female fertility was not affected in rats at up to 1 mg/kg IV, corresponding to approximately 2 times the expected human exposure, based on AUC. No clinical studies have investigated the effects of agalsidase alfa ghu on fertility in humans.

Use in pregnancy (Category B2)

Studies with agalsidase alfa ghu in pregnant rats and rabbits showed no evidence of embryonic or foetal damage at IV doses up to 1 mg/kg, with exposures approximately 2 times the expected human exposure, based on AUC. The effects of agalsidase alfa ghu on parturition and post-natal development have not been studied in animals.

Animal reproduction studies are not always predictive of the human response and there are no adequate and well-controlled clinical studies in pregnant women. There is very limited data on pregnancies exposed to REPLAGAL. REPLAGAL should be used during pregnancy only if clearly needed.

Use in lactation

There were no studies in lactating animals. It is not known whether REPLAGAL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REPLAGAL is administered to a nursing mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

REPLAGAL has no influence on the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most commonly reported undesirable effects were infusion reactions which occurred in 13.7% of patients treated with REPLAGAL in clinical trials. Most undesirable effects were mild to moderate in severity.

Table 1 lists adverse drug reactions (ADRs) reported for patients treated with REPLAGAL in clinical trials and from post-marketing reports. Information is presented by system organ class and frequency (very common ≥1/10; common ≥1/100, <1/10; uncommon ≥1/1000, <1/100). The

occurrence of an event in a single patient is defined as uncommon in view of the number of patients treated. A single patient could be affected by several ADRs.

The most common ADRs observed in the clinical trials (occurring in at least 10% of subjects) were headache, nausea, fatigue, diarrhoea, cough, vomiting, dizziness, arthralgia, back pain, pyrexia, nasopharyngitis, paraesthesia, abdominal pain, dyspnoea, pain in limb, chest pain, palpitations, pain, myalgia, hypoesthesia, pharyngitis, asthenia, rigors, neuropathic pain, rash, peripheral oedema, tinnitus, and tremor.

Table 1. Adverse Drug Reactions Associated with REPLAGAL *(italic text denotes post-marketing event)*	
Cardiac disorders	
Very common	Palpitations
Common	*Atrial fibrillation*[§], tachycardia
Uncommon	*Tachyarrhythmia*[§]
Not known*	*Heart failure, myocardial ischaemia, ventricular extrasystoles*[§]
Ear and labyrinth disorders	
Very common	Tinnitus
Common	Tinnitus aggravated
Eye disorders	
Common	Lacrimation increased
Gastrointestinal disorders	
Very common	Vomiting, diarrhoea, abdominal pain, nausea
Common	Abdominal discomfort
General disorders and administration site conditions	
Very common	Chest pain, rigors, pyrexia, pain, asthenia, fatigue
Common	Chest tightness, fatigue aggravated, feeling hot, feeling cold, influenza-like illness, discomfort, malaise
Uncommon	Injection site rash
Immune system disorders	
Common	Hypersensitivity
Uncommon	Anaphylactic reaction
Investigations	
Uncommon	Oxygen saturation decreased, corneal reflex decreased
Metabolism and nutrition disorders	
Very common	Peripheral oedema
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, pain in limb, myalgia, back pain
Common	Peripheral swelling, joint swelling, musculoskeletal discomfort
Uncommon	Sensation of heaviness
Nervous system disorders	
Very common	Headache, dizziness, neuropathic pain, tremor, hypoesthesia, paraesthesia
Common	Dysgeusia, hypersomnia
Uncommon	Parosmia
Respiratory, thoracic and mediastinal disorders	
Very common	Dyspnoea, cough, nasopharyngitis, pharyngitis
Common	Throat tightness, hoarseness, rhinorrhoea
Uncommon	Throat secretion increased

Skin and subcutaneous tissue disorders	
Very common	Rash
Common	Urticaria, erythema, pruritus, acne, *hyperhidrosis*
Uncommon	Angioneurotic oedema, livedo reticularis
Vascular disorders	
Common	Hypertension, *hypotension*, flushing

Incidence rates are based on clinical trial data.

*Incidence of ADRs identified from post-marketing sources only is 'Not known'.

§Atrial fibrillation, heart failure, myocardial ischaemia, tachyarrhythmias, and ventricular extrasystoles have been reported as infusion related reactions in patients with Fabry Disease involving heart structures.

In clinical trials 13.7% of REPLAGAL treated adult patients have experienced idiosyncratic infusion reactions. The percentage of patients affected was lower in females than males. These effects have decreased with time, the majority of them being reported within the first 6 months of treatment. Symptoms have included predominantly rigors (chills), headache, nausea, pyrexia, flushing and fatigue with patients commonly experiencing pain/discomfort including exacerbated neuropathic pain, vomiting and chest or throat tightness. Other infusion related symptoms may include dizziness and hyperhidrosis. All symptoms resolved with appropriate intervention, such as, stopping the infusion prior to restarting or medical therapy with antihistamines and/or corticosteroids. Serious infusion reactions have been reported uncommonly; symptoms reported include pyrexia, rigors, tachycardia, urticaria, nausea/vomiting, angioneurotic oedema with throat tightness, stridor and swollen tongue. Infusion related reactions may also include cardiac events such as cardiac arrhythmias (atrial fibrillation, ventricular extrasystoles, tachyarrhythmia), myocardial ischaemia and heart failure in patients with Fabry Disease involving the heart structures (see Section 4.4 Special warnings and precautions for use – Idiosyncratic infusion related reactions).

Adverse drug reactions reported in patients with history of end stage renal disease were similar to those reported in the general population.

Adverse drug reactions reported in the paediatric population (children and adolescents) were, in general, similar to those reported in adults. However, infusion related reactions and pain exacerbation occurred more frequently; being observed in 10/55 patients (18.2%). The most frequent were mild infusion related reactions that mainly included rigors, pyrexia, flushing, headache, nausea, and dyspnoea.

In the post-marketing setting, infusion related reactions (see Section 4.4 Special warnings and precautions for use – Idiosyncratic infusion related reactions) may also include cardiac events such as cardiac arrhythmias (atrial fibrillation, ventricular extrasystoles, tachyarrhythmia), myocardial ischaemia and heart failure in patients with Fabry Disease involving structures. The most common infusion related reactions were mild and include rigors, pyrexia, flushing, headache, nausea, dyspnoea, tremor and pruritus. Infusion related symptoms may also include dizziness, hyperhidrosis, hypotension, cough, vomiting and fatigue. Hypersensitivity including anaphylaxis has been reported. Borderline IgE antibody positivity not associated with anaphylaxis has been reported in clinical trials in a very limited number of patients.

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no experience with overdosage of REPLAGAL.

For information on the management of overdose, contact the Poisons Information Centre on 131126 in Australia, or the National Poisons Centre on 0800 POISON (0800 764766) in New Zealand.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Fabry Disease is a glycosphingolipid storage disorder that is caused by deficient activity of the lysosomal enzyme α-galactosidase A. Globotriaosylceramide (Gb3, also known as ceramide trihexoside, CTH), which is the glycosphingolipid substrate for this enzyme, progressively accumulates within vulnerable cells and tissues of affected patients. Endothelial, perithelial, and smooth muscle cells of the vascular system, renal epithelial cells, myocardial cells, dorsal root ganglia, and cells of the autonomic nervous system are selectively damaged by Gb3. The disease typically is characterised by recurrent episodes of severe pain in the extremities, heat intolerance, gastrointestinal distress and associated malabsorption, hypohidrosis, characteristic cutaneous lesions known as angiokeratomas, and a distinctive but asymptomatic corneal dystrophy. Vital organs are affected, and renal failure, myocardial infarctions, and cerebrovascular events are common clinical sequelae, commonly resulting in life expectancy to the fourth or fifth decade.

REPLAGAL catalyses the hydrolysis of Gb3, cleaving a terminal galactose residue from the molecule. Agalsidase alfa ghu has been produced in a human cell line to provide for a human glycosylation profile that determines biodistribution to allow preferential uptake by target cells. The hydrolysis of Gb3 in affected individuals causes a reduction in the amount of Gb3 in many cell types in the body, including cells of the liver, heart, kidney, and blood vessels, and in the plasma. As a result, REPLAGAL causes an improvement in or stabilisation of renal function and structure, a reduction in pain, a decrease in pain medication usage, an improvement in pain related quality of life, and a decrease in cardiac mass with an associated improvement in cardiac function.

Clinical trials

Phase I/II studies

The safety and efficacy of REPLAGAL (original roller bottle process) has been assessed in two pivotal studies in a total of 40 symptomatic adult male patients and a number of open-label studies in adult male as well as female and paediatric patients with Fabry Disease. Treatment was for up to 3 years at a dose of 0.2 mg/kg every other week. Alternative dosing regimens were investigated in one small open-label study in 21 adult males which suggested similar efficacy and safety outcomes with different doses.

Effect on pain

In the first pivotal study, 26 adult patients received infusions of either 0.2 mg/kg of REPLAGAL or placebo every 2 weeks for 6 months. Twenty-five patients completed the study and entered a maintenance study. The outcome assessments included change in serious, debilitating pain as assessed by the Brief Pain Inventory (a validated pain measurement scale), measurements of renal structure and function, biochemical markers and other measures of pain including pain medication usage and pain related quality of life.

Compared with placebo, treatment with REPLAGAL effected comprehensive and statistically significant changes in pain in patients with Fabry Disease. Patients generally began to show significant decreases in their level of pain by 8 to 16 weeks of therapy. Pain at its worst scores were reduced in 9/14 patients on agalsidase alfa ghu and 5/12 patients on placebo. Mean pain at its worst scores while off pain medication were 6.2 at baseline and 4.3 at week 24 for patients given agalsidase alfa ghu *versus* 7.3 at baseline and 6.8 at week 24 for patients on placebo. The difference in change in mean pain scores was statistically significant using Repeat Measure and ANCOVA analyses, p=0.021 and p=0.047 respectively. Pain severity and pain interference scores were not significantly different comparing week 24 to baseline by ANCOVA, but were significantly different using Repeat Measure analysis. There were statistically significant differences in days off pain medication (74.5 days agalsidase alfa ghu *versus* 12.9 placebo; p=0.013) and mean time to permanent discontinuation (30.5 days agalsidase alfa *versus* no placebo patient permanently discontinuing pain medication p=0.013).

Effect on renal function

After 6 months of therapy REPLAGAL stabilised renal function compared with a decline in placebo treated patients. Kidney biopsy specimens revealed a significant increase in the fraction of normal glomeruli and a significant decrease in the fraction of glomeruli with mesangial widening in patients treated with REPLAGAL in contrast to the patients treated with placebo. After 12 to 18 months of maintenance therapy, REPLAGAL improved renal function as measured by inulin based glomerular filtration rate by 8.7 ± 3.7 mL/min (p=0.030). Longer term therapy (48-54 months) resulted in stabilisation of GFR in male patients with normal baseline (GFR > 90 mL/min/1.73 m^2) and with mild to moderate renal dysfunction (GFR 60 to < 90 mL/min/1.73 m^2), and in slowing of the rate of decline in renal function and progression to end-stage renal disease in male Fabry patients with more severe renal dysfunction (GFR 30 to < 60 mL/min/1.73 m^2).

Cardiac effects

In the second pivotal study in adults who were administered 0.2 mg/kg of REPLAGAL or Placebo every 2 weeks for 6 months, 15 patients with left ventricular hypertrophy completed the 6 month placebo controlled study and entered an open-label extension study. The outcome assessments included measurements of cardiac mass, renal function and biochemical markers, including cardiac Gb3. Treatment with REPLAGAL for 6 months resulted in an 11.5 g decrease in left ventricular mass as measured by magnetic resonance imaging (MRI), while patients receiving placebo exhibited an increase in left ventricular mass of 21.8 g (p=0.041). Treatment with REPLAGAL showed a trend in reducing cardiac Gb3 whilst other measures of effects on cardiac function were not associated with statistically significant changes. In addition, in the first study involving 25 patients, REPLAGAL effected a significant reduction in cardiac mass after 12 to 18 months of maintenance therapy (p<0.001). REPLAGAL was also associated with a decrease in mean QRS duration and a concomitant decrease in septal thickness on echocardiography. Two patients with right bundle branch block in the studies conducted reverted to normal following therapy with REPLAGAL. Subsequent open-label studies demonstrated significant reduction

from baseline in left ventricular mass by echocardiography in both male and female Fabry patients over 24 to 36 months of REPLAGAL treatment. The reductions in LV mass observed by echocardiography in both male and female Fabry patients over 24 to 36 months of REPLAGAL treatment were associated with a meaningful symptom improvement. The functional assessments for symptoms of cardiovascular disease were conducted with the New York Heart Association (NYHA) classes for heart failure and the Canadian Cardiovascular Society (CCS) classes for angina. In a pooled, post hoc analysis of open-label studies, 21 patients (10 males and 11 females) improved to a better NYHA class, 16 patients (7 males and 9 females) had no change and no patient worsened. Twenty-three patients (12 males and 11 females) improved to a better CCS class, 13 patients had no change (5 males, 8 females) and two patients (2 females) worsened. The results, being based on a pooled, post hoc analysis of open-label studies, should be interpreted with caution.

Effects on accumulation of Gb3

Mean Gb3 decreases in plasma, urine sediment and liver, kidney and heart biopsy samples revealed a range of approximately 20 to 50 % decline. These decreases may represent a reasonable estimate of the total body burden of stored Gb3 mobilised by 6 months treatment with agalsidase alfa ghu.

Other findings

Twelve to 18 months of treatment with REPLAGAL resulted in improvement in quality of life (QoL), as measured by validated instruments. The improvement was statistically significant in patients who had impaired QoL at the start of treatment.

There are limited data on the effects of REPLAGAL on sentinel clinical events such as transient ischaemic attack, stroke, myocardial infarction, heart failure and initiation of renal dialysis. There are limited pharmacokinetic and long-term data on the use of REPLAGAL in females and children with Fabry Disease. Data in adult males indicate that generally, REPLAGAL is safe to use as continuation therapy at home after adequate trials of administration in the hospital setting.

Paediatric population

In an open-label study of 25-week duration in 24 paediatric patients aged 7 to 17 who were administered REPLAGAL 0.2 mg/kg every 2 weeks and a follow-on study in which 11 patients were followed up for up to 6.5 years, 17 male patients experienced a reduction in pain reaching statistical significance after 9 and 12 months of REPLAGAL therapy compared to pre-treatment baseline. The mean pain score for female paediatric patients at baseline was lower and therefore the lower magnitude of improvement is not unexpected. In male paediatric Fabry patients, hyperfiltration can be the earliest manifestation of renal involvement in the disease. While most of the 24 patients had normal renal function at baseline, 7 males were observed to have hyperfiltration. Following REPLAGAL therapy, a reduction in their hypernormal eGFR was observed within 6 months with the mean eGFR of this group decreased from 149.4 ± 7.5 to 127.8 ± 7.6 mL/min/1.73 m^2 approaching statistical significance (p=0.078). After 6.5 years of REPLAGAL therapy, 3 of the 4 patients with hyperfiltration at baseline and normalisation on therapy resumed (2 transiently) hyperfiltration and 1 progressed to CKD Stage 1/2. Five of 6 male patients who had normal (>90 and ≤135mL/min/1.73m^2) or below normal eGFR at baseline maintained baseline eGFR status.

In male paediatric patients ≥7 years of age, heart rate variability was abnormal at baseline and on average improved after 6 months of REPLAGAL therapy in 15 boys and the improvement was

sustained through 6.5 years of REPLAGAL 0.2 mg/kg therapy in an open-label extension study in 9 boys. Among 9 boys with left ventricular mass (LVMI) index to height$^{2.7}$ within the normal range for children (< 39 g/m$^{2.7}$ in boys) at baseline, LVMI remained stable at levels below the LVH threshold throughout the 6.5 years of treatment. In a second open-label study in 14 paediatric patients ≥7 years of age, the results regarding heart rate variability were consistent with previous findings. In this study only one patient had LVH at baseline and remained stable over time.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of REPLAGAL produced through the original roller bottle process have been studied in both adult males and females with Fabry Disease. Six dosages (ranging from 0.01 to 0.2 mg enzyme/kg body weight) were administered to male patients as 20 to 40 minute IV infusions while female patients received 0.2 mg enzyme/kg body weight as 40 minute infusions. The pharmacokinetic properties were essentially unaffected by the dose of the enzyme. Peak plasma concentrations were noted immediately after the completion of the infusions, and the absolute bioavailability of REPLAGAL was estimated to be 100%. Following a single IV dose, REPLAGAL had a biphasic distribution and elimination profile from the circulation. Pharmacokinetic parameters were not significantly different between male and female patients. At 0.2 mg/mL the elimination half-life of the protein from the blood was approximately 108 minutes in males (n=10) and 89 minutes in females. Plasma clearance after IV infusion was approximately 193 mL/minute in males compared with 140 mL/min in females and volume of distribution was approximately 17% of body weight in both sexes. Based on the similarity of pharmacokinetic properties in both males and females, tissue distribution in major tissues and organs is expected to be comparable in male and female patients.

In 24 children (aged 7-18 years), REPLAGAL administered at 0.2 mg/kg was cleared faster from the circulation than in adults. Mean clearance of REPLAGAL in children (aged 7-11 years), in adolescents (aged 12-18 years), and adults was 4.2 mL/min/kg, 3.1 mL/min/kg, and 2.3 mL/min/kg, respectively. Pharmacodynamic data suggest that at a dose of 0.2 mg/kg REPLAGAL, the reductions in plasma Gb3 are more or less comparable between adolescents and young children (see Section 5.1 Pharmacodynamic properties – Clinical trials).

Following 6 months of treatment with REPLAGAL some male patients showed altered pharmacokinetics with reduced plasma half-life and more rapid elimination from the blood with corresponding lower AUC and lower C_{max}. These changes were associated with the development of low titre antibodies to agalsidase alfa ghu, and did not appear to be of clinical consequence. Most patients with low titre antibodies to agalsidase alfa ghu develop immunologic tolerance to the molecule.

Finally, based on the analysis of pre- and post-dose liver biopsies in adults with Fabry Disease, the tissue half-life has been estimated to be in excess of 24 hours.

Distribution

Studies in mice and rats with radio-iodinated agalsidase alfa showed that agalsidase alfa ghu was concentrated into the liver (up to 36% of the administered dose at 4 h). Tissue uptake was 2-10 fold lower for the kidney and spleen and 10-20 fold lower for the heart based on tissue radioactivity concentrations. In humans, it is not possible to fully quantitate uptake, but a combination of histological and biochemical studies indicate that REPLAGAL is taken up by the liver (estimated to be 10% of administered dose), kidney, heart, and blood vessels.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Based on its mechanism of action REPLAGAL is unlikely to be mutagenic. Mutagenicity studies have not been conducted with REPLAGAL.

Carcinogenicity

Based on its mechanism of action REPLAGAL is unlikely to be carcinogenic. Carcinogenicity studies have not been conducted with REPLAGAL.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium phosphate - monobasic monohydrate
Polysorbate 20
Sodium chloride
Sodium hydroxide
Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

REPLAGAL vials should be stored at 2-8°C. Do not use beyond the expiration date stamped on the vial. DO NOT SHAKE VIALS.

REPLAGAL is supplied in single-use vials and contains no antimicrobial agent. The product is for treatment of one patient only on one occasion. Discard any remaining contents.

6.5 NATURE AND CONTENTS OF CONTAINER

REPLAGAL is supplied in a single-dose vial closed with a butyl rubber stopper and sealed with an aluminium overseal with a flip-off plastic cap.

Pack size: x 1 vial (3.5 mL) of REPLAGAL (agalsidase alfa ghu) concentrated injection vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number: 0104138-64-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 39
225 George Street
Sydney NSW 2000
Australia
Telephone: 1800 012 612
www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

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Summary table of changes

Section changed	Summary of new information
1, 7	Minor editorial changes
8	Update of sponsor details
10	Revision of document date