SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

REPLAGAL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE

1 ml of concentrate for solution for infusion contains 1 mg of agalsidase alfa.

Each 5 ml vial of concentrate contains 3,5 mg/3,5 ml of agalsidase alfa.

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

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion contains 1 mg of agalsidase alfa.

Appearance

A clear and colourless solution and essentially free of particles. Finished product may develop a minute amount of fine particulate matter during storage

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

REPLAGAL is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).

4.2 Posology and method of administration

REPLAGAL treatment should be supervised by a medical doctor experienced in the management of patients with Fabry disease or other inherited metabolic diseases. Infusion of REPLAGAL at home may be considered for patients who are tolerating their infusions well.

Posology

REPLAGAL is administered at a dose of 0,2 mg/kg body weight every other week by intravenous infusion over 40 minutes. In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

Special populations

Patients 65 years and above

Studies in patients over the age of 65 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.

Patients with hepatic impairment

No studies have been performed in patients with hepatic impairment.

Patients with renal impairment

No dose adjustment is necessary in patients with renal impairment.

The presence of extensive renal damage (eGFR <60ml/min) may limit the renal response to enzyme replacement therapy. Limited data are available in patients on dialysis or post-kidney transplantation, no dose-adjustment is recommended.

Paediatric population

Paediatric Patients

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 the patients as safety and efficacy have not yet been established. Limited clinical data in children (7-18 years) do not permit to recommend an optimal dosage regimen presently (see section '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 dosage regimen is suggested for children between 7– 18 years of age.

Method of administration

- Calculate the dose and number of REPLAGAL vials needed.

- Dilute the total volume of REPLAGAL concentrate required in 100 ml of 9 mg/ml (0,9 %) sodium chloride solution for infusion. Care must be taken to ensure the sterility of the prepared solutions since REPLAGAL does not contain any preservative or bacteriostatic agent; aseptic technique must be observed. Once diluted, the solution should be mixed gently but not shaken.
- The solution should be inspected visually for particulate matter and discolouration prior to administration.
- Administer the infusion solution over a period of 40 minutes using an intravenous line with an integral filter. Since no preservative is present, it is recommended that administration is started as soon as possible.
- Do not infuse REPLAGAL concomitantly in the same intravenous line with other agents.
- For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

4.4 Special warnings and precautions for use

Traceability

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

Idiosyncratic infusion-related reactions

13,7 % of patients treated with REPLAGAL in clinical trials have experienced idiosyncratic infusion-related reactions. Overall, the percentage of infusion-related reactions was significantly lower in females than in males. The most common symptoms reported 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.

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. These effects usually decrease with time. If any 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 symptomatic treatment was required.

Allergic-type hypersensitivity reactions

Allergic-type hypersensitivity reactions may occur. 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.

IgG antibodies to the protein

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. 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. No IgE antibodies have been detected in any patient receiving REPLAGAL.

Patients with renal impairment

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.

Sodium

This medicine contains 14.2 mg sodium per vial, equivalent to 0.7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

REPLAGAL should not be co-administered with chloroquine, amiodarone, or gentamicin since these substances have the potential to inhibit intra-cellular α-galactosidase activity.

As α-galactosidase A is itself an enzyme, it would be an unlikely candidate for cytochrome P450 mediated interactions. In clinical studies, neuropathic pain medicinal products (such as carbamazepine, phenytoin and gabapentin) were administered concurrently to most patients without any evidence of interaction.

Incompatibilities:

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

4.6 Fertility, pregnancy and lactation

Very limited clinical data on pregnancies exposed to REPLAGAL (n=4) have shown no adverse effects on the mother and newborn child.

It is not known whether REPLAGAL is excreted in human milk. Caution should be exercised when prescribing to pregnant or breast-feeding women

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

Summary of safety profile

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

Tabulated list of adverse reactions

Table 1 lists adverse reactions reported for the 344 patients treated with Replagal in clinical trials, including 21 patients with history of end stage renal disease, 30 paediatric patients (≤18 years of age) and 17 female patients, and from post-marketing spontaneous reports. Information is presented by system organ class and frequency (very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100). The adverse reactions categorized as incidence "not known (cannot be estimated from the available data)" are derived from post-marketing spontaneous reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. 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 adverse reactions.

The following adverse reactions have been identified for agalsidase alfa:

Table 1

System organ class	**Adverse reaction**			
	Very common	**Common**	**Uncommon**	**Not known**
Metabolism and nutrition disorders	peripheral oedema			
Nervous system disorders	headache, dizziness, neuropathic pain, tremor, hypoesthesia, paraesthesia	dysgeusia, hypersomnia,	parosmia	
Eye disorders		lacrimation increased	corneal reflex decreased,	

Table 1				
System organ class	**Adverse reaction**			
	Very common	**Common**	**Uncommon**	**Not known**
Ear and labyrinth disorders	tinnitus	tinnitus aggravated		
Cardiac disorders	palpitations	tachycardia, atrial fibrillation	Tachyarrhythmia	myocardial ischaemia, heart failure, ventricular extrasystoles,
Vascular disorders		hypertension, hypotension, flushing		
Respiratory, thoracic and mediastinal disorders	dyspnoea, cough, nasopharyngitis, pharyngitis	hoarseness, throat tightness, rhinorrhoea	oxygen saturation decreased, Throat secretion increased	
Gastrointestinal disorders	vomiting, nausea, abdominal pain, diarrhoea	abdominal discomfort		
Skin and subcutaneous tissue disorders	rash	Urticaria, erythema, pruritus, acne, hyperhidrosis	angioneurotic oedema, livedo reticularis	
Musculoskeletal, connective tissue and bone disorders	arthralgia, pain in limb, myalgia, back pain	musculoskeletal discomfort, peripheral swelling, joint swelling	sensation of heaviness	
Immune system disorders		hypersensitivity	anaphylactic reaction,	
General disorders and administration site conditions	chest pain, rigors, pyrexia, pain, asthenia, fatigue	chest tightness, fatigue aggravated, feeling hot, feeling cold, influenza like illness, discomfort, malaise	injection site rash	

181 See also section 4.4.

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183 Description of selected adverse reactions

Infusion related reactions reported in the post marketing setting (also see section 4.4) may include cardiac events such as cardiac arrhythmias (atrial fibrillation, ventricular extrasystoles, tachyarrhythmia), myocardial ischemia, and heart failure in patients with Fabry disease involving the heart 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.

Side effects reported in patients with history of end-stage renal disease were similar to those reported in the general patient population.

Side effects 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. The most frequent were mild infusion-related reactions that mainly included rigors, pyrexia, flushing, headache, nausea, and dyspnoea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No case of overdose has been reported. Treatment is symptomatic and supportive

5. PHARMACOLOGICAL PROPERTIES

Pharmacological class

A.31 Enzymatic Preparations

General

Agalsidase alfa is human protein α-galactosidase A produced in a human cell line by genetic engineering technology.

5.1 Pharmacodynamic properties

Fabry disease is a glycosphingolipid storage disorder caused by deficient activity of the lysosomal enzyme α-galactosidase A, resulting in accumulation of globotriaosylceramide (also referred to as Gb_3 or CTH), the glycosphingolipid substrate for this enzyme. Agalsidase alfa catalyses the hydrolysis of Gb_3, cleaving a terminal galactose residue from the molecule.

Treatment with the enzyme has been shown to reduce accumulation of Gb_3 in many cell types including endothelial and parenchymal cells. Agalsidase alfa has been produced in a human cell line to provide for a human glycosylation profile that influences biodistribution allowing preferential uptake by target cells.

The safety and efficacy of agalsidase alfa was assessed in two randomised, double blind, placebo controlled studies and open label extension studies, in a total of forty patients with a diagnosis of Fabry disease based on clinical and biochemical evidence. Patients received the recommended dosage of 0,2 mg/kg of agalsidase alfa. Twenty-five patients completed the first study and entered an extension study. After 6 months of therapy there was a significant reduction in pain in the agalsidase alfa treated patients compared with placebo (p=0,021), as measured by the Brief Pain Inventory (a validated pain measurement scale). This was associated with a significant reduction in chronic neuropathic pain medication use and number of days on pain medication. This reduction in the severity of neuropathic pain was maintained over two years of agalsidase alfa treatment. In subsequent studies, in male paediatric patients above the age of 7, a reduction in pain was observed after 9 and 12 months of agalsidase alfa therapy compared to pre-treatment baseline. This pain reduction persisted through 4 years of Replagal therapy in 9 patients (in patients 7 – 18 years of age).

Twelve to 18 months of treatment with agalsidase alfa resulted in improvement in quality of life (QoL), as measured by validated instruments.

After 6 months of therapy agalsidase alfa stabilised renal function compared with a decline in renal function 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 agalsidase alfa in contrast to the patients treated with placebo. After 12 to 18 months of maintenance therapy, agalsidase alfa 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).

In male paediatric Fabry patients, hyperfiltration can be the earliest manifestation of renal involvement in the disease. Reduction in their hypernormal eGFRs was observed within 6 months of initiating agalsidase alfa therapy.

In a second study, fifteen patients with left ventricular hypertrophy completed a 6 month placebo-controlled study and entered an extension study. Treatment with agalsidase alfa resulted in an 11,5 g decrease in left ventricular mass as measured by magnetic resonance imaging (MRI) in the controlled study, while patients receiving placebo exhibited an increase in left ventricular mass of 21,8 g. In addition, in the first study involving 25 patients, agalsidase alfa effected a significant reduction in cardiac mass after 12 to 18 months of maintenance therapy (p<0,001). Agalsidase alfa was also associated with improved myocardial contractility, 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 agalsidase alfa. 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 agalsidase alfa treatment. This reduction was associated with meaningful improvement in heart failure and anginal symptoms.

Compared with placebo, treatment with agalsidase alfa also reduced accumulation of Gb_3. After the first 6 months of therapy mean decreases of approximately 20 - 50 % were observed in plasma, urine sediment and liver, kidney and heart biopsy samples. After 12 to 18 months treatment a reduction of 50 – 80 % was observed in plasma and urine sediment. The metabolic effects were also associated

with clinically significant weight gain, increased sweating and increased energy. Consistent with the clinical effects of agalsidase alfa, treatment with the enzyme reduced accumulation of Gb_3 in many cell types, including renal glomerular and tubular epithelial cells, renal capillary endothelial cells and cardiac myocytes. In male paediatric Fabry patients plasma Gb_3 decreased 40-50 % after 6 months of agalsidase alfa therapy and this reduction persisted after a total of 4 years of treatment in 11 patients. Antibodies to agalsidase alfa have not been shown to be associated with any clinically significant effects on safety (e.g. infusion reactions) or efficacy.

5.2 Pharmacokinetic properties

Single doses ranging from 0,007 – 0,2 mg enzyme per kg body weight were administered to adult male patients as 20 - 40 minute intravenous infusions while female patients received 0,2 mg enzyme per kg body weight as 40 minute infusions. The pharmacokinetic properties were essentially unaffected by the dose of the enzyme.

Following a single intravenous dose of 0,2 mg/kg, agalsidase alfa had a biphasic distribution and elimination profile from the circulation. Pharmacokinetic parameters were not significantly different between male and female patients.

Elimination half-lives were 108 ± 17 minutes in males compared to 89 ± 28 minutes in females and volume of distribution was approximately 17 % body weight in both sexes.

Clearance normalised for body weight was 2,66 and 2,10 ml/min/kg for males and females, respectively. Based on the similarity of pharmacokinetic properties of agalsidase alfa in both males and females, tissue distribution in major tissues and organs is also expected to be comparable in male and female patients.

In children (aged 7-18 years), agalsidase alfa administered at 0,2 mg/kg was cleared faster from the circulation than in adults. Mean clearance of agalsidase alfa 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 agalsidase alfa, the reductions in plasma Gb_3 are more or less comparable between adolescents and young children (see section ‘Pharmacodynamic Properties’).

Following six months of agalsidase alfa treatment 12 of 28 male patients showed altered pharmacokinetics including an apparent increase in clearance. These changes were associated with

the development of low titre antibodies to agalsidase alfa but no clinically significant effects on safety or efficacy were observed in the patients studied.

Based on the analysis of pre- and post-dose liver biopsies in males with Fabry disease, the tissue half-life has been estimated to be in excess of 24 hours and hepatic uptake of the enzyme estimated to be 10 % of administered dose.

Agalsidase alfa is a protein and is therefore: 1) not expected to bind to proteins, 2) expected that metabolic degradation will follow the pathways of other proteins, i.e. peptide hydrolysis, 3) unlikely to be a candidate for medicine-medicine interactions.

Renal elimination of agalsidase alfa is considered to be a minor clearance pathway since pharmacokinetic parameters are not altered by impaired renal function. As metabolism is expected to occur by peptide hydrolysis, impaired liver function is not expected to affect the pharmacokinetics of agalsidase alfa in a clinically significant manner.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate; Polysorbate 20; Sodium chloride; Sodium hydroxide and Water for injection.

6.2 Incompatibilities

Do not infuse REPLAGAL concomitantly in the same intravenous line with other agents

6.3 Shelf life

2 years

Chemical and physical in use stability has been demonstrated for 24 hours at 25°C.

6.4 Special Precautions for Storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

KEEP OUT OF REACH OF CHILDREN

Chemical and physical in use stability has been demonstrated for 24 hours at 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 at 2 to 8 °C.

6.5 Nature and contents of container

3,5 ml of concentrate for solution for infusion in a clear, transparent 5 ml vial (Type I glass) with a grey stopper (fluoro-resin coated butyl rubber), a one-piece seal (aluminium) and white flip-off cap.

Pack sizes of 1, 4 or 10 vials.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Takeda (Pty) Ltd

Monte Circle

64 Monte Casino Boulevard

Fourwarys 2191

8. REGISTRATION NUMBER

43/31/0309

9. DATE OF FIRST AUTHORISATION

26 November 2010

10. DATE OF REVISION

24 July 2024