SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Replagal 1 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 1 mg of agalsidase alfa*. Each vial of 3.5 ml of concentrate contains 3.5 mg of agalsidase alfa.

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

Excipient(s) with known effect

This medicinal product contains 14.2 mg sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion. A clear and colourless solution.

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 physician experienced in the management of patients with Fabry Disease or other inherited metabolic diseases.

Posology

Replagal is administered at a dose of 0.2 mg/kg body weight every other week by intravenous infusion over 40 minutes.

Special populations

Elderly patients

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

The safety and efficacy of Replagal in children aged 0-6 years has not yet been established. Currently available data are described in section 5.1 but no recommendation on posology can be made.

In clinical studies of children (7-18 years) who received Replagal 0.2 mg/kg every other week, no unexpected safety issues were encountered (see section 5.1).

Method of administration

For instructions on dilution of the medicinal product before administration, see section 6.6.

Administer the infusion solution over a period of 40 minutes using an intravenous line with an integral filter. Do not infuse Replagal concomitantly in the same intravenous line with other agents.

4.3 Contraindication

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 batch number of the administered product should be clearly recorded.

Idiosyncratic infusion related reactions

13.7% of adult patients treated with Replagal in clinical trials have experienced idiosyncratic infusion related reactions. Four of 17 (23.5%) paediatric patients ≥7 years of age enrolled in clinical trials experienced at least one infusion reaction over a period of 4.5 years of treatment (mean duration of approx. 4 years). Three of 8 (37.5%) paediatric patients <7 years of age experienced at least one infusion related reaction over a mean observation time of 4.2 years. 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 hemodynamic 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. These effects have decreased with time. 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 symptomatic treatment was required.

Hypersensitivity reactions

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.

Antibodies to the protein

As with all protein pharmaceutical products, patients may develop 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% were antibody negative throughout. In paediatric patients >7 years of age, 1/16 male patients tested positive for IgG anti- agalsidase alfa antibodies during the study. No increase in the incidence of adverse events was detected for this patient. In paediatric patients <7 years of age, 0/7 male patients tested positive for IgG anti-agalsidase alfa antibodies. IgE antibody positivity not associated with anaphylaxis has been reported in clinical trials in a very limited number of patients.

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 medicinal product 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 medicinal products and other forms of interaction

Replagal should not be co-administered with chloroquine, amiodarone, benoquin 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 drug-drug 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is very limited data on pregnancies exposed to Replagal. Animal studies do not indicate direct or indirect harmful

effects with respect to pregnancy or embryonic/fetal development when exposed during organogenesis (see Section 5.3). Caution should be exercised when prescribing to pregnant women.

Breast-feeding

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

Fertility

No effects on male fertility were seen in reproductive studies in male rats.

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	
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	

See also section 4.4.

Description of selected adverse reactions

Infusion related reactions reported in the postmarketing 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, dyspnea, tremor and pruritus. Infusion-related symptoms may also include dizziness, hyperhidrosis, hypotension, cough, vomiting and fatigue. Hypersensitivity, including anaphylaxis, has been reported.

Paediatric 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 (pyrexia, dyspnoea, chest pain) and pain exacerbation occurred more frequently.

Other special populations
Patients with renal disease

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

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

In clinical trials doses up to 0.4 mg/kg weekly were used, and their safety profile was not different from the recommended dose of 0.2 mg/kg biweekly.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products - Enzymes.

ATC code: A16AB03.

Mechanism of action

Fabry Disease is a glycosphingolipid storage disorder that is caused by deficient activity of the lysosomal enzyme α-galactosidase A, resulting in accumulation of globotriaosylceramide (Gb3 or GL- 3, also known as ceramidetrihexoside (CTH)), the glycosphingolipid substrate for this enzyme. Agalsidase alfa catalyses the hydrolysis of Gb3, cleaving a terminal galactose residue from the molecule. Treatment with the enzyme has been shown to reduce accumulation of Gb3 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 can influence uptake by mannose-6- phosphate receptors on the surface of target cells. The selection of 0.2 mg/kg dose (infused over 40 minutes) for the registration clinical studies was intended to temporarily saturate the ability of the mannose-6- phosphate receptors to internalize the agalsidase alfa in the liver and allow distribution of enzyme to other relevant organ tissues. Data with patients indicates that at least 0.1mg/kg is required to achieve a pharmacodynamics response.

Clinical efficacy and safety

The safety and efficacy of Replagal 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 Replagal. 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 Replagal 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. In subsequent studies, in male paediatric patients above the age of 7, a reduction in pain was observed after 9 and 12 months of Replagal 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 Replagal resulted in improvement in quality of life (QoL), as measured by validated instruments.

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*).*

In a second study, fifteen patients with left ventricular hypertrophy completed a 6 month placebo- controlled study and entered an extension study. Treatment with Replagal 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, Replagal effected a significant reduction in cardiac mass after 12 to 18 months of maintenance therapy (p<0.001). Replagal 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 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 meaningful symptom improvement as measured using the NYHA and CCS in Fabry patients with severe heart failure or anginal symptoms at baseline.

Compared with placebo, treatment with Replagal also reduced accumulation of Gb3. After the first 6 months of therapy mean decreases of approximately 20 - 50 % were observed in plasma, urine sediment, 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 Replagal, treatment with the enzyme reduced accumulation of Gb3 in many cell types, including renal glomerular and tubular epithelial cells, renal capillary endothelial cells (cardiac

and dermal capillary endothelial cells were not examined) and cardiac myocytes. In male paediatric Fabry patients plasma Gb_3 decreased 40-50% after 6 months of Replagal therapy 0.2 mg/kg and this reduction persisted after a total 4 years of treatment in 11 patients.

Infusion of Replagal at home may be considered for patients who are tolerating their infusions well.

Paediatric population

In male paediatric Fabry patients ≥ 7 years of age, hyperfiltration can be the earliest manifestation of renal involvement in the disease. Reduction in their hypernormal eGFRs was observed within 6 months of initiating Replagal therapy. After one year of treatment with agalsidase alfa 0.2 mg/kg every other week, the abnormally high eGFR decreased from 143.4 ± 6.8 to 121.3 ± 5.6 mL/min/1.73 m^2 in this subgroup and these eGFRs stabilized in the normal range during 4 years of Replagal 0.2 mg/kg therapy, as did the eGFRs of the non-hyperfiltrators.

In male paediatric patients ≥ 7 years of age, heart rate variability was abnormal at baseline and 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 long-term extension study in 9 boys. Among 9 boys with left ventricular mass (LVMI) indexed 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 left ventricular hypertrophy (LVH) threshold throughout the 6.5 years of treatment. In a second study, in 14 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.

For patients between 0 and 7 years of age, limited data indicate no specific safety issues.

Study in patients switching from agalsidase beta to Replagal (agalsidase alfa)

100 patients [(naïve (n=29); or previously treated with agalsidase beta who switched to Replagal (n=71)) were treated for up to 30 months in an open label, uncontrolled study. An analysis showed that serious adverse events were reported in 39.4% of those patients who switched from agalsidase beta compared to 31.0% in those who were naïve to therapy prior to study entry. Patients switched from agalsidase beta to Replagal had a safety profile consistent with that observed in other clinical experience. Infusion related reactions have been experienced by 9 patients of the naïve population (31.0%) compared to 27 patients of the switched population (38.0%).

Study with various dosing regimen

In an open-label randomised study, there were no statistically significant differences between adult patients treated for 52 weeks with 0.2 mg/kg intravenously every other week (n=20) and those treated with 0.2 mg/kg weekly (n=19) in mean change from baseline LVMI or other endpoints (cardiac functional status, renal function, and pharmacodynamic activity). In each treatment group, LVMI remained stable over the treatment period of the study. The overall incidence of SAEs by treatment group did not show any obvious effect of treatment regimen on the SAE profile of the different treatment groups.

Immunogenicity

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 $\pm$ 17 minutes in males compared to 89 $\pm$ 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.

Following six months of Replagal 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. It is not expected to bind to proteins. It is expected that its metabolic degradation will follow the pathways of other proteins, i.e. peptide hydrolysis. Agalsidase alfa is unlikely to be a candidate for drug-drug interactions.

Renal impairment

Renal elimination of agalsidase alfa is considered to be a minor clearance pathway since pharmacokinetic parameters are not altered by impaired renal function.

Hepatic impairment

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.

Paediatric population

In 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 Gb_3 are more or less comparable between adolescents and young children (see section 5.1).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity. Genotoxic and carcinogenic potential are not expected. Reproduction toxicity studies in female rats and rabbits have shown no effect on pregnancy or the developing foetus. No studies have been conducted with respect to parturition or peri/post-natal development. It is not known whether Replagal crosses the placenta.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic, monohydrate
Polysorbate 20
Sodium chloride
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

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, unless dilution has taken place in controlled and validated aseptic conditions. The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

6.5 Nature and contents of container

3.5 ml of concentrate for solution for infusion in a 5 ml vial (Type I glass) with a stopper (fluoro-resin coated butyl rubber), a one piece seal (aluminium) and flip-off cap. Pack size of 1vial.

6.6 Special precautions for disposal and other handling

- 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.

- Since no preservative is present, it is recommended that administration is started as soon as possible after dilution.
- The solution should be inspected visually for particulate matter and discolouration prior to administration.
- For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Israel Ltd.,25 Efal

st.,Petach Tikva 4951125

8. Manufacturer

Shire Human Genetic Therapies INC., USA

300 Shire Way, Lexington, MA 02421, USA

9. Registration number

124-32-30382

This leaflet was revised in Jan 2021 according to MOHs guidelines