ANNEX I

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.

Excipients with known effect

This medicinal product contains 14.2 mg sodium per vial.
This medicinal product contains 0.836 mg of polysorbate 20 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.

Replagal home infusion, and administration by the patient in presence of a responsible adult or administration by the patient's caregiver (self-administration), may be considered for patients who are tolerating their infusions well. The decision to have a patient move to home infusion and/or self-administration should be made after evaluation and recommendation by the treating physician.

Appropriate training should be given by the treating physician and/or nurse to the patient and/or caregiver prior to initiation of self-administration. Dose and infusion rate should remain constant while at home, and not be changed without supervision of a healthcare professional. Self-administration should be closely followed by the treating physician.

Any patients experiencing adverse events during the home infusion/self-administration need to immediately stop the infusion process and seek the attention of a healthcare professional. Subsequent infusions may need to occur in a clinical setting.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and 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.

Polysorbate 20

This medicinal product contains 0.836 mg of polysorbate 20 in each vial which is equivalent to 0.22 mg/ml. Polysorbates may cause allergic reactions.

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/foetal 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 98 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			

Table 1				
System organ class	**Adverse reaction**			
	Very common	**Common**	**Uncommon**	**Not known**
Nervous system disorders	headache, dizziness, neuralgia, 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, cardiac failure, ventricular extrasystoles
Vascular disorders		hypertension, hypotension, flushing		
Respiratory, thoracic, and mediastinal disorders	dyspnoea, cough, nasopharyngitis, pharyngitis	dysphonia, throat tightness, rhinorrhoea	oxygen saturation decreased, increased upper airway secretion	
Gastrointestinal disorders	vomiting, nausea, abdominal pain, diarrhoea	abdominal discomfort		
Skin and subcutaneous tissue disorders	rash	urticaria, erythema, pruritus, acne, hyperhidrosis	angioedema, livedo reticularis	
Musculoskeletal, connective tissue and bone disorders	arthralgia, pain in extremity, 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, chills, pyrexia, pain, asthenia, fatigue	chest discomfort, fatigue, 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 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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 0.1 mg/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 Gb3 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 minutes intravenous infusions while female patients received 0.2 mg enzyme per kg body weight as 40 minutes 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.

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 Gb3 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 (E339)
Polysorbate 20 (E432)
Sodium chloride
Sodium hydroxide (E524)
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

3 years.

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.

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 sizes of 1, 4 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

- Calculate the dose and number of Replagal vials needed.
- Any dose change should occur only at the direction of the treating physician.
- 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 (see section 6.3).
- 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 Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50–58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/189/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03/08/2001
Date of last renewal: 28/07/2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Shire Human Genetic Therapies Inc.,
205 Alewife Brook Parkway
Cambridge, MA 02138
USA

Shire Human Genetic Therapies Inc.,
400 Shire Way
Lexington, MA 02421
USA

Name and address of the manufacturers responsible for batch release

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50–58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

Shire Pharmaceuticals Ireland Limited
Block 2 & 3 Miesian Plaza
50–58 Baggot Street Lower
Dublin 2
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates of submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH must agree on the content and format of the educational materials for use of Replagal in self-administration, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority.

The educational materials for the use of Replagal are aimed at providing guidance on how to manage risks of infusion related reactions and medication errors due to self-administration/home infusion.

The MAH shall ensure that in each Member State where Replagal is marketed, all healthcare professionals, and patients/carers who are expected to prescribe, dispense or use Replagal have access to/are provided with the following educational package:
- HCP Guide for Self-administration of Replagal;
- Patient/Caregiver/HCP Guide for Self-administration of Replagal;

The HCP Guide for Self-Administration of Replagal should contain the following key elements:
- Checklist to determine patient eligibility prior to initiation of self-administration of the home infusion.
    - Patient has had a sufficient number of consecutive well-tolerated infusions (no IRRs) in the clinic.
    - Patient considered medically stable.
    - Patient has a history of adherence to infusion schedule.
    - Patient has agreed to receive Replagal at home.
    - The patient and/or caregiver have been trained about the associated risks, the possible complications, and the requirement to maintain open communication with the treating physician, including emergency contact details.
    - The patient and/or caregiver appear adequately trained and aware of the risks of self-administration.
    - The patient’s home is safe (clean, hygienic, storage area for supplies, drug and emergency medication) and adequately equipped.
    - Rapid and reliable communication measures have been established, just in case problems occur.

- The HCP should ensure that the medications are prescribed and readily available to mitigate any risk that occur in case of an emergency, if necessary, and the patient/caregiver knows how to utilise.
- The importance of the patient always having a caregiver or responsible adult nearby who is capable of alerting you, the treating physician or emergency medical care if needed.

- Provide the patient/caregiver with detailed training on how to identify and manage IRRs, hypersensitivity reactions, medication errors and AEs.
- Provide the patient/caregiver detailed training about the administration procedures of Replagal as well as, the dosage and infusion rate which must be included in the Infusion Diary.
- Emphasize the need for the patient/caregiver to communicate to you, the treating physician, any events during and after the infusion, and to update the Infusion Diary.
- The Infusion Diary must be used as a back and forth communication tool throughout the course of self-administration of Replagal.

The Patient/Caregiver/HCP Guide for Self-administration of Replagal should contain the following key elements:

- The importance of the patient always having a caregiver or responsible adult nearby who is capable of alerting the treating physician or emergency medical care if needed.
- A description of the correct preparation and administration technique for Replagal, including proper aseptic technique.
- Importance of adhering to the dosing and infusion rate prescribed by the physician.
- Any medication prescribed by your physician for pre-medication or treatment of any IRRs should be available at home. Importance to follow on any instructions regarding pre-medication or treatment of serious IRRs.
- Information on signs and symptoms related to infusion-related reactions and recommended actions for the management of the adverse drug reactions (ADRs) when symptoms occur.
- The Infusion diary must serve as a record of the recommended Replagal infusions and facilitate regular monitoring of the patient's health status to document any product related IRRs, including allergic-type hypersensitivity reactions before, during or after the infusion and any medication errors.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON / 3.5 ML VIAL

1. NAME OF THE MEDICINAL PRODUCT

Replagal 1 mg/ml concentrate for solution for infusion
agalsidase alfa

2. STATEMENT OF ACTIVE SUBSTANCE

One vial contains 3.5 mg of agalsidase alfa.

3. LIST OF EXCIPIENTS

Sodium phosphate monobasic, monohydrate (E339), polysorbate 20 (E432), sodium chloride, sodium hydroxide (E524), water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 x 3.5 ml per vial concentrate for solution for infusion
4 x 3.5 ml per vial concentrate for solution for infusion
10 x 3.5 ml per vial concentrate for solution for infusion

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50–58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/01/189/001 1 vial
EU/1/01/189/002 4 vials
EU/1/01/189/003 10 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Replagal

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL 3.5 ML PRESENTATION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Replagal 1 mg/ml sterile concentrate
agalsidase alfa
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3.5 ml

6. OTHER

Store in a refrigerator.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Replagal 1 mg/ml concentrate for solution for infusion
agalsidase alfa

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Replagal is and what it is used for
2. What you need to know before you are given Replagal
3. How Replagal is given
4. Possible side effects
5. How to store Replagal
6. Contents of the pack and other information

1. What Replagal is and what it is used for

The active substance in Replagal is agalsidase alfa (1 mg/ml). Agalsidase alfa is a form of the human enzyme α-galactosidase. It is produced by switching on the gene for α-galactosidase A in cells. The enzyme is then removed from the cells and made into a sterile concentrate for solution for infusion.

Replagal is used to treat adult patients, as well as adolescents and children from the age of 7, with confirmed diagnosis of Fabry Disease. It is used as long-term enzyme replacement therapy when the level of enzyme in the body is absent or lower than normal as in Fabry Disease.

After 6 months of therapy Replagal significantly reduced pain in patients when compared to placebo (dummy) treated patients. Replagal reduced left ventricle mass in treated patients compared to placebo treated patients. These results suggest the symptoms of the disease are improving or the disease is becoming stable.

2. What you need to know before Replagal is given

You must not be given Replagal

- if you are allergic to agalsidase alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before Replagal is used.

If you notice any of these effects during or after an infusion you should tell your doctor immediately:
- high fever, chills, sweating, fast heart rate.
- vomiting.
- light-headedness.
- hives.

- swelling in your hands, feet, ankles, face, lips, mouth or throat which may cause difficulty in swallowing or breathing.

Your doctor may stop the infusion temporarily (5-10 min) until the symptoms go away and then begin the infusion again.

Your doctor may also treat the symptoms with other medicines (antihistamines or corticosteroids). Most of the time you can still be given Replagal even if these symptoms occur.

If you experience a severe allergic (anaphylactic-type) reaction, the administration of Replagal will be immediately discontinued and an appropriate treatment will have to be initiated by your doctor.

If treatment with Replagal makes your body produce antibodies this will not stop Replagal from working and the antibodies may disappear with time.

If you have advanced renal disease, you may find that your Replagal treatment has a limited effect on your kidneys. Talk to your doctor or pharmacist before using Replagal.

Children

The experience in children 0-6 years old is limited and therefore no dose can be recommended for this age group.

Other medicines and Replagal

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you use any medicines containing chloroquine, amiodarone, benoquin or gentamicin. There is a theoretical risk of decreased agalsidase alfa activity.

Pregnancy and breast feeding

Very limited clinical data on pregnancies exposed to Replagal have shown no adverse effects on the mother and newborn child.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

You may drive and use machines whilst on Replagal.

Replagal contains sodium

This medicine contains 14.2 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.7% of the recommended maximum daily dietary intake of sodium for an adult.

Replagal contains polysorbate 20

This medicine contains 0.836 mg of polysorbate 20 in each vial which is equivalent to 0.22 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you or your child have any known allergies.

Keeping a record

In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded by your healthcare professional. Speak with your healthcare professional if you are not sure.

3. How Replagal is given

This medicine should be applied and supervised by appropriately trained personnel, who will also calculate the dose that you will be given. While remaining under the physician's supervision, Replagal can be self-administered (by you or your caregiver) after appropriate training by the treating physician and/or nurse. Self-administration should occur in the presence of a responsible adult.

The recommended dose is an infusion of 0.2 mg for every kg you weigh. This would be about 14 mg or 4 vials (glass bottles) of Replagal for an average size (70 kg) individual.

Use in children and adolescents

For children and adolescents 7-18 years old a dose of 0.2 mg/kg every other week may be used.

Children and adolescents may be more likely than adults to experience an infusion related reaction. Tell your doctor if you experience any side effects whilst having the infusion.

Method of administration

Replagal has to be diluted in 9 mg/ml (0.9%) sodium chloride solution before use. After dilution Replagal is given in a vein. This will usually be in your arm.

The infusion will be given every two weeks.

Each time you are treated it will take 40 minutes for Replagal to be given to you in a vein. Your treatment will be supervised by a doctor who specialises in the treatment of Fabry Disease.

For self-administration, the dose and rate of infusion given should not be changed without the agreement of the treating physician.

If you use more Replagal than you should

If you believe you have used more Replagal than you should, please contact your doctor.

If you use less Replagal than you should

If you believe you have used less Replagal than you should, please contact your doctor.

If you forget to use Replagal

If you have missed an infusion of Replagal, please contact your doctor.

If you stop using Replagal

Do not stop using Replagal without contacting your doctor. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience a severe allergic (anaphylactic-type) reaction, the administration of Replagal will be immediately discontinued and an appropriate treatment will have to be initiated by your doctor.

Most side effects are mild to moderate. More than 1 in 10 people (frequency "very common") may have a reaction during or following an infusion of Replagal (infusion related reaction). These effects include chills, headache, nausea, fever, tiredness, unsteadiness, difficulty breathing, shaking, cough and vomiting. However, some effects may be serious and may need treatment. Infusion related reactions involving the heart including heart muscle ischemia and heart failure, may occur in patients with Fabry disease involving the heart structures (frequency "not known" (cannot be estimated from the available data)). Your doctor may stop the infusion temporarily (5-10 min) until the symptoms go away and then begin the infusion again. Your doctor may also treat the symptoms with other medicines (antihistamines or corticosteroids). Most of the time you can still be given Replagal even if these symptoms occur.

List of other side effects:

Very common (may affect more than 1 in 10 people):
- swelling in the tissue (e.g., legs, arm)
- tingling or numbness or pain in fingers or toes
- ear ringing
- palpitations
- Sore throat
- abdominal pain, diarrhoea
- rash
- back or limb pain, muscle pain, joint pain
- chest pain, cold symptoms, fever, feeling sick

Common (may affect up to 1 in 10 people):
- change in the taste of food, prolonged sleep
- eyes tearing
- increased ear ringing
- increased heart rate, heart rhythm problems
- increased blood pressure, low blood pressure, facial flushing (redness)
- hoarseness, or tight throat, runny nose
- abdominal discomfort
- acne, red or itchy or mottled skin, excessive sweating
- muscle and bone discomfort, swelling of the extremities or joints
- hypersensitivity
- chest tightness, increased feeling lack of energy, feeling cold or hot, flu-like symptoms, discomfort

Uncommon (may affect up to 1 in 100 people):
- severe allergic (anaphylactic-type) reaction
- blink reflex abnormal
- increased heart rate
- low level of oxygen in your blood and sticky throat secretions
- sense of smell is different)
- collection of fluid under the skin may lead to swelling of body parts, lace-like discoloration of the skin e.g., in the leg
- sensation of heaviness
- injection site rash

Children and adolescents

Side effects reported in children were, in general, similar to those reported in adults. However, infusion related reactions (fever, difficulty breathing, chest pain) and pain aggravated occurred more frequently.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Replagal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).

Do not use Replagal if you notice that there is discolouration or other foreign particles present.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Replagal contains

- The active substance is agalsidase alfa. Each ml of Replagal contains 1 mg of agalsidase alfa.
- The other ingredients are sodium phosphate monobasic, monohydrate (E339), polysorbate 20 (E432), sodium chloride, sodium hydroxide (E524), water for injections. See section 2 “Replagal contains sodium” and “Replagal contains polysorbate 20”.

What Replagal looks like and contents of the pack

Replagal is a concentrate for solution for infusion. Your medicine is available in vials containing 3.5 mg/ 3.5 ml of agalsidase alfa. Pack sizes of 1, 4 or 10 vials are available. Not all pack sizes may be marketed.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for medical or healthcare professionals only:

Instructions for use, handling, and disposal

Replagal treatment should be supervised by a physician experienced in the management of patients with Fabry Disease or other inherited metabolic diseases.

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

1. Calculate the dose and number of Replagal vials needed.

2. Dilute the total volume of Replagal concentrate required in 100 ml 9 mg/ml sodium chloride solution for infusion (0.9% w/v). 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.

3. The solution should be inspected visually for particulate matter and discolouration prior to administration.

4. 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. However, the chemical and physical stability of the diluted solution has been demonstrated for 24 hours at 25 °C.

5. Do not infuse Replagal concomitantly in the same intravenous line with other agents.

6. For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.