Summary Report of Benefit-Risk Assessment

REPLAGAL CONCENTRATE FOR SOLUTION FOR INFUSION 1 MG/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Agalsidase alfa
Product Registrant	Takeda Pharmaceuticals (Asia Pacific) Pte. Ltd.
Product Registration Number	SIN16197P
Application Route	Abridged evaluation
Date of Approval	17 May 2021

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A INTRODUCTION

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

The active substance, agalsidase alfa, is human α-galactosidase A produced by genetic engineering technology in a human cell line. It has been developed as an enzyme replacement therapy (ERT) for the treatment of Fabry disease, caused by deficiency of activity of the lysosomal enzyme α-galactosidase A.

Replagal is available as a concentrate for solution for infusion containing 1 mg/mL of agalsidase alfa. Other ingredients include sodium phosphate monobasic monohydrate, polysorbate 20, sodium chloride, sodium hydroxide and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, agalsidase alfa, is manufactured at Shire Human Genetic Therapies, Lexington, USA and Shire Human Genetic Therapies, Cambridge, USA. The drug product, Replagal concentrate for solution for infusion, is manufactured at Cangene Biopharma LLC, Maryland, USA and Vetter Pharma-Fertigung GmbH & Co. KG, Langenargen, Germany.

Drug substance:

Adequate controls have been presented for the reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturers are compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented were sufficient to support the approved storage condition and shelf-life. The packaging is a 2L USP Class VI polycarbonate bottle closed with silicone rubber lined white polypropylene closure. The drug substance is approved for storage at -75 ± 10°C with a shelf life of 36 months.

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines.

Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were sufficient to support the approved shelf-life of 24 months when stored at 5 ± 3ºC. The shelf life after dilution is not more than 24 hours, when stored at or below 25ºC and this is supported with appropriate data. The container closure system is a 5mL Type I, Class A untreated flint borosilicate glass vial with grey fluoro-resin laminated butyl rubber stopper, aluminium seal and a plastic flip-off cap.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of agalsidase alfa in the long-term enzyme replacement therapy in patients with Fabry disease was based primarily on data from two double-blind, placebo-controlled Phase II studies (TKT003, TKT005) and one Phase III study (TKT010), and supported by 5 open-label extension studies (TKT006, TKT011, TKT007, TKT013, TKT015) and a patient registry Fabry Outcome Survey (FOS). In addition, there were 4 studies which supported the use of agalsidase alfa in special populations, including paediatrics (TKT023 and TKT029), females (TKT014), and patients who had end stage renal disease (ESRD) requiring dialysis or had a history of renal transplantation (HORT) (TKT019).

Study TKT003

Study TKT003 was a Phase II, single-centre, randomised, double-blind, placebo-controlled study of agalsidase alfa replacement therapy in adult patients with Fabry disease. A total of 26 patients in the study were randomised in a 1:1 ratio to receive 0.2 mg/kg agalsidase alfa or placebo intravenously every other week for a total of 24 weeks.

The primary efficacy endpoint was change in “pain at its worst scores” while off pain medications, as measured using the Brief Pain Inventory (BPI) based on area under the curve (AUC) calculation. Secondary efficacy endpoints were BPI severity mean score, BPI interference mean score, pain medication usage, renal structure as assessed by kidney pathology, kidney ceramide trihexoside (CTH) and urine sediment CTH. Tertiary efficacy endpoints included creatinine clearance based on 24-hour urine collections, measured glomerular filtration rate (GFR) based on inulin clearance and plasma CTH.

The full analysis set population comprised 14 patients in the agalsidase alfa arm and 12 patients in the placebo arm. The mean age was 34 years (range 19 to 48 years), all patients were male and majority of patients (92%) were Caucasian. The mean duration of illness at baseline (time from the diagnosis) was comparable for patients in the agalsidase alfa arm (12.8 years) and the placebo arm (12.1 years). The majority of patients in both treatment arms had 4-6 organ systems involved. Baseline BPI scores for the pain at its worst item, both on and off pain medication, tended to be higher in the placebo arm. The mean baseline BPI score for the pain at its worst item while on pain medication was 4.2 and 6.3 in the agalsidase alfa arm and

the placebo arm, respectively; while the mean baseline BPI score for the pain at its worst item while off pain medication was 6.2 and 7.3 in the agalsidase alfa arm and the placebo arm, respectively. The number of neuropathic pain medications used on a continuous basis at baseline was in the range of 1-3 medications for 100% of the patients in the placebo arm and for 71% of patients in the agalsidase alfa arm; there were 4 patients in the agalsidase alfa arm with no reported continuous neuropathic pain medication use at baseline.

The primary analysis of AUC of the change in "pain at its worst scores" while off pain medications did not meet statistical significance but demonstrated a numerically greater improvement in pain score in the agalsidase alfa arm compared to the placebo arm (-22.4 pain unit weeks vs -1.0 pain unit weeks; p=0.195, t-test). The post-hoc analysis of covariance (ANCOVA) analysis which incorporated the baseline pain score into the calculation demonstrated a trend for the effect of agalsidase alfa (p=0.081, ANCOVA). In terms of absolute change in pain score, there was a 1.9 unit decrease in the level of pain in the agalsidase alfa arm and a 0.5 unit decrease in the placebo arm. Both the repeated measures ANOVA analysis (which incorporated the total treatment effect over time) and the post-hoc analysis of the change from baseline to the final pain score using ANCOVA suggested benefits with agalsidase alfa treatment (p=0.021 and p=0.047 respectively).

While statistical significance was not met for the primary endpoint of the change in "pain at its worst scores", numerical benefit was considered clinically meaningful and these results were supported by other pain-related endpoints. There were numerically greater improvements in pain severity mean scores (-1.14 vs -0.7) and pain interference mean scores (-1.1 vs -0.6) from baseline in the agalsidase alfa treatment arm compared to the placebo arm. There were significant differences in days off pain medications (93.5 days for agalsidase alfa vs 25.4 days for placebo, p=0.013) and time to permanent discontinuation of chronic neuropathic mediations (p=0.031). A post-hoc analysis, including only those patients with neuropathic pain medication use, similarly showed a significant difference in days off pain medications between arms (74.5 days for agalsidase alfa vs 12.9 days for placebo, p=0.022).

After 24 weeks of treatment, the 24-hour urine creatinine clearance was stabilised in the agalsidase alfa arm (minimal change of -0.4 ml/min) while there was an average of 18.5 ml/min (or 17%) decline in the creatinine clearance in the placebo arm (p=0.051). After the exclusion of a patient with loss of renal function due to renal biopsy procedure, the agalsidase alfa arm showed significant improvements in creatinine clearance compared to the placebo arm (increase of 3.4 ml/min in the agalsidase alfa arm vs 18.5 ml/min decline in the placebo arm; p=0.016). Similarly for GFR, the mean change in GFR from baseline was a 19.8 ml/min (or 22%) decline from a baseline of 91 ml/min in the placebo arm and a 6.2 ml/min (or 8%) decline from a lower baseline of 77 ml/min in the agalsidase alfa arm (p=0.168).

The kidney pathology changes correlated with the changes in renal function. Kidney biopsy specimens revealed a significant increase in the fraction of normal glomeruli (8.2% increase in the agalsidase alfa arm vs 15.9% decrease in the placebo arm, p=0.012) and a significant decrease in the fraction of glomeruli with mesangial widening in patients treated with agalsidase alfa compared to the patients treated with placebo (12.5% decrease in the agalsidase alfa arm vs 16.5% increase in the placebo arm, p=0.010).

There was a numerically greater decrease in the urine sediment CTH (685.6 nmol/g or 29% decrease in agalsidase alfa arm vs 332.7 nmol/g or 15% increase in placebo arm, p=0.053) and kidney CTH (3.98 nmol/mg decrease in the agalsidase alfa arm vs 0.87 nmol/mg decrease in the placebo arm, p=0.272) in the agalsidase alfa arm compared to the placebo arm.

Treatment with agalsidase alfa resulted in significant metabolic correction of plasma CTH content at all 3 postbaseline evaluations compared to placebo ($p<0.005$).

Study TKT005

Study TKT005 was a Phase II, single-centre, randomised, double-blind, placebo-controlled study of agalsidase alfa replacement therapy in adult patients with Fabry disease. A total of 15 patients in the studies were randomised in a 1:1 ratio to receive 0.2 mg/kg agalsidase alfa or placebo intravenously every other week for a total of 24 weeks.

The primary efficacy endpoint was change from baseline in cardiac CTH content. Secondary efficacy endpoints included left ventricular cardiac mass, left ventricular end diastolic volume, left ventricular end diastolic diameter and interventricular septal thickness, QRS complex duration, GFR, 24-hour urine creatinine clearance, serum creatinine, blood urea nitrogen (BUN), urine sediment CTH, plasma CTH, effects on pain, and quality of life measured using Profile of Mood States questionnaire and the Fabry Symptom Scale.

The full analysis set population comprised 7 patients in the agalsidase alfa arm and 8 patients in the placebo arm. The number of patients randomised in the study was less than the number of patients (n=24) required based on the sample size calculation. This was due to the rarity of Fabry disease and the stringent inclusion criterion requiring patients to have left ventricular enlargement. The mean age of the randomised patients was 37 years (range 22 to 50 years), all patients were male and majority of patients (93%) were Caucasian. In line with the inclusion criterion of left ventricular enlargement, all patients had a significantly elevated cardiac mass (mean cardiac mass was 276.2 g in the agalsidase alfa arm and 248.2 g in the placebo arm).

The primary analysis of the change from baseline to Week 24 in cardiac CTH favoured the agalsidase alfa arm numerically (0.132 nmol/µg or 19% decrease in the agalsidase alfa arm vs 0.053 nmol/µg or 9% increase in the placebo arm). The difference between the two arms was not statistically significant (p=0.423), and this could be due to the insufficient power of the study to demonstrate a significant difference between arms as a result of the reduced sample size (n=15).

The analysis of the change from baseline to Week 24 demonstrated a significant decrease in left ventricular mass of 11.48 g or 4.2% in the agalsidase alfa arm as compared to an increase of 21.82 g or 8.8% in the placebo arm (p=0.041). There were numerical reductions in left ventricular end diastolic volume, left ventricular end diastolic diameter and interventricular septal thickness, as well as numerical reduction in QRS complex duration with agalsidase alfa therapy. The results suggest that agalsidase alfa therapy reduces cardiac size and improves cardiac conduction.

While both arms showed a decline in creatine clearance at Week 24 compared to baseline, the decline was lesser in the agalsidase alfa arm compared to the placebo arm (-13.1 ml/min in the agalsidase alfa arm vs -24.2 ml/min in the placebo arm). The slower decline of creatine clearance in the agalsidase alfa arm was also associated with numerical improvements in GFR, serum creatinine and BUN at Week 24 compared to the placebo arm (GFR: 25.4 ml/min vs 14.3 ml/min; serum creatinine: -8.2 µmol/l vs 28.0 µmol/l; BUN: -0.24 mmol/l vs 1.16 mmol/l, for agalsidase alfa vs placebo arms, respectively). In general, the results showed that agalsidase alfa therapy resulted in a stabilisation or improvement in renal function, while placebo was associated with a decline in renal function. In the agalsidase alfa arm, there was an approximately 50% decline in the plasma CTH level and urine sediment CTH level.

The interpretation of the effects of agalsidase alfa therapy on pain was limited by the small number of patients who reported pain at baseline. Only 4 out of 15 patients in the study were taking 1 pain medication on a continuous basis at baseline, and 5 patients in the study reported baseline pain at its worst scores of 0. There were also no differences in quality of life between arms due to the relative lack of pain in this study population and the small study population.

Study TKT010

Study TKT010 was a Phase III, multi-centre, randomised, double-blind, placebo-controlled study of agalsidase alfa replacement therapy in adult patients with Fabry disease. A total of 80 patients in the studies were randomised in a 1:1 ratio to receive 0.2 mg/kg agalsidase alfa or placebo intravenously every other week for a total of 24 weeks.

The primary efficacy endpoint was initially based on the effect on serious, debilitating pain, but was subsequently amended to the change in GFR to provide an assessment of the effect on renal function. GFR was measured with chromium-51 ethylenediamine tetraacetic acid (EDTA) or technetium-99m diethylene-triamine-pentaacetate (DTPA). Secondary efficacy endpoints were estimated creatinine clearance based on Cockcroft-Gault method, estimated GFR based on Modification of Diet in Renal Disease (MDRD) 6 variable equation, 24-hour urine creatinine clearance and urine sediment CTH level.

The full analysis set population comprised 40 patients in the agalsidase alfa arm and 40 patients in the placebo arm. The mean age of the randomised patients was 33 years (range 18 to 54 years), all patients were male and majority of patients (91%) were Caucasian. The mean baseline GFR was 89.6 ml/min in the agalsidase alfa arm and 82.9 ml/min in the placebo arm.

In terms of the primary efficacy endpoint, there were no statistically or clinically significant differences in change from baseline in renal function at Week 24 between the agalsidase alfa arm and placebo arm, as measured by GFR (-4.70 ml/min/1.73 m^2 in the agalsidase alfa arm vs -3.50 ml/min/1.73 m^2 in the placebo arm; p=0.739). Similarly, no significant differences were observed with several other secondary efficacy endpoints, including estimated creatinine clearance, estimated GFR, and 24-hour urine creatinine clearance. This could be attributed to the normal renal function at baseline in most patients (63%) who would have little change in renal function over the 24-week study duration. Nevertheless, pre-specified subgroup analyses in patients with reduced GFR (<80 ml/min/1.73m^2) at baseline showed improvement in GFR with agalsidase alfa arm, whereas patients receiving placebo showed a decline (1.38 ml/min/1.73 m^2 in the agalsidase alfa arm vs -3.30 ml/min/1.73 m^2 in the placebo arm. Within the baseline renal dysfunction subgroup, patients over the age of 30 years tended to show more benefit (2.41 ml/min/1.73 m^2 in the agalsidase alfa arm vs -4.40 ml/min/1.73 m^2 in the placebo arm).

Agalsidase alfa treatment demonstrated significant decline in CTH levels from baseline to Week 24 among agalsidase alfa-treated patients compared with placebo-treated patients, in both plasma and urine sediment. Agalsidase alfa-treated patients experienced a 21% decrease in mean urine sediment CTH level and a 52% decrease in plasma CTH level, compared with 0.7% increase and 14% decrease, respectively, in placebo-treated patients.

Summary of primary efficacy endpoints in the placebo-controlled studies

Efficacy endpoints	Agalsidase alfa	Placebo	p-value
Study TKT003			
Changes in BPI "pain at its worst" scores while off pain medications			
Baseline, mean	6.2	7.3	
AUC of change, mean	-22.4	-1.0	0.195[1], 0.081[2]
Change from baseline to Week 24, mean	-1.9	-0.4	0.021[3], 0.047[4]
Study TKT005			
Changes in CTH content (nmol/µg protein)			
Baseline, mean ± SE	0.712 ± 0.179	0.581 ± 0.075	
Change from baseline to Week 24, mean ± SE (% change)	-0.132 ± 0.164 (-19%)	0.053 ± 0.084 (+9%)	0.423
Studies TKT010			
GFR (ml/min/1.73m^2)			
Baseline, mean ± SE	89.63 ± 4.244	82.89 ± 4.671	
Change from baseline to Week 24, mean ± SE	-4.70 ± 2.113	-3.50 ± 1.892	0.739

[1] t-test; primary analysis
[2] ANCOVA; post-hoc analysis
[3] Repeated measures ANOVA; pre-specified analysis
[4] ANCOVA; post-hoc analysis

The open-label extension studies (TKT006, TKT011, TKT007, TKT013, TKT015) with a follow-up period of up to 4.5 years of agalsidase alfa treatment demonstrated consistent benefits of agalsidase alfa treatment in stabilising renal function, especially in those with baseline renal dysfunction. In addition, there were reduced levels of the biochemical marker CTH in urine sediment, kidney and plasma, which is the primary glycosphingolipid product that accumulate in multiples tissues and organs and ultimately lead to progressive tissue damage and end organ dysfunction in Fabry disease, although the use of CTH as a surrogate endpoint remains to be validated.

With respect to cerebrovascular involvement, comparison of the data on sentinel events in the combined studies TKT003, TKT006, and TKT011 to historical control showed that the incidence of stroke reported (12% or 3 of 25 patients) over 4 to 4.5 years of agalsidase alfa treatment was half of the 24% reported in the literature for untreated patients with Fabry disease.

The results of the open-label study TKT014 in women with Fabry disease were consistent with that in male patients. Data from the FOS registry showed that treatment with agalsidase alfa for up to 5 years demonstrated consistent benefits on stabilisation of renal function, improvement of left ventricular mass, and improvement in Fabry-associated pain in male and female patients with Fabry disease.

In patients with ESRD on dialysis and HORT (study TKT019), no change in renal function was observed, and reduced plasma CTH levels were observed. These observations were not unexpected.

Data in the paediatric patients aged 7 to 18 years were based on the open-label, 26-week study TKT023 (n=24) and its extension study TKT029 with a follow-up period of up to 237 weeks as of data cut-off. The majority of patients had a normal calculated GFR at baseline. While no clinically significant changes from baseline in GFR were seen in the overall

population, among patients with evidence of hyperfiltration at baseline (GFR>135 ml/min/1.73 m^2), improvements to normal range of GFR were seen by Week 9 (125 ml/min/1.73 m^2), which persisted through Week 26. For patients with GFR between 60 and 90 ml/min/1.73 m^2 at baseline, mean GFR also increased significantly by 12.62 ml/min/1.73m^2 to normal range by Week 26. All patients had normal left ventricular mass index at baseline and there were no significant changes in left ventricular mass index over the 26-week study period. However, among 3 patients with high normal left ventricular mass index (>40 g/$m^{2.7}$) at baseline, decreases in left ventricular mass index ranging from 7.2% to 21.4% were seen at Week 26. Treatment with agalsidase alfa reduced plasma CTH levels by 42% in male patients, whereas plasma CTH levels in female patients which were within normal range at baseline had little change over 26 weeks. Urine sediment CTH levels also decreased in both male and female patients (median decrease of 78% and 37%, respectively). In terms of the BPI "pain at its worst scores", change from baseline was -1.35 at Week 26. In the extension study TKT029, the results demonstrated that continued treatment with agalsidase alfa resulted in stabilisation of renal function, reduction in left ventricular mass index, and maintained reductions in plasma and urine sediment CTH levels.

Patients enrolled in the studies had deficiency of α-galactosidase A enzyme activity ranging from 0 to 15% of controls. While the studies did not specifically include patients with classic Fabry disease, classic Fabry disease and late-onset Fabry disease are managed similarly with respect to the use of ERT although late-onset Fabry disease have more variable presentation and rate of progression than classic Fabry disease. In addition, given that the mechanism of action of agalsidase alfa is based on replacement of the deficient α-galactosidase A enzyme, agalsidase alfa is expected to be efficacious as an enzyme replacement therapy in Fabry disease without regard to the subtypes. Therefore, a broad indication of long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency) is considered acceptable.

Overall, although statistical significance for the primary endpoints was not met in studies TKT003 and TKT005, the effects of agalsidase alfa on the primary endpoints, reduction in "pain at its worst" scores and reduction in cardiac CTH, respectively, were considered clinically meaningful. While no improvement in renal function was demonstrated in study TKT010, which could be attributed to the majority of patients having normal renal functions at baseline, subgroup analyses showed improvement in GFR in those with abnormal renal function at baseline. Furthermore, data across other studies and from the FOS registry have demonstrated consistent benefits of agalsidase alfa in stabilising renal function, reducing left ventricular mass, and reducing the accumulation of CTH in urine sediment, kidney and plasma, all of which were important clinical aspects of Fabry disease. Although it is currently not known how the improvement in left ventricular mass and reduced CTH levels could translate into clinical benefit, it was observed that patients treated with agalsidase alfa had lower incidence of stroke compared to historical control of untreated patients, and data from the FOS registry also showed a correlation between left ventricular hypertrophy and clinical events (including cardiac, cardiovascular or composite events). Although the efficacy of agalsidase alfa was primarily based on descriptive results in the studies with small sample sizes, considering the rarity of disease and the totality of data, the data were considered adequate to support the efficacy of agalsidase alfa in in the long-term enzyme replacement therapy in patients with Fabry disease.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of agalsidase alfa for the long-term enzyme replacement therapy in patients with Fabry disease was based primarily on data from 153 patients which comprised the Main Safety Analysis Population, including 121 patients which comprised the Placebo-controlled Population, as well as post-marketing data. In the Main Safety Analysis Population, patients were treated with agalsidase alfa for a median of 16.2 months, and at least 20 (13.1%) patients have been treated for up to 4 years. The patient population exposed to agalsidase alfa in the post-marketing setting included over 2600 patients for over 10 years.

Overview of safety profile in the Main Safety Analysis Population

Adverse event (AE)	**Agalsidase alfa (N=153)**
AE	151 (98.7%)
Treatment-related AE	108 (70.6%)
Serious AE (SAE)	56 (36.6%)
Treatment-related SAE	4 (2.6%)
Discontinuations due to AE	5 (3.3%)
Deaths due to TEAE	6 (3.9%)

Overview of safety profile in the Placebo-Controlled Population

Adverse event (AE)	**Agalsidase alfa (N=61)**	**Placebo (N=60)**
AE	61 (100.0%)	59 (98.3%)
Treatment-related AE	42 (68.9%)	32 (53.3%)
Serious AE (SAE)	9 (14.8%)	7 (11.7%)
Treatment-related SAE	4 (6.6%)	0
Discontinuations due to AE	0	0
Deaths due to TEAE	0	1 (1.7)

In the placebo-controlled studies, treatment-related AEs were more commonly reported in the agalsidase alfa arm (68.9%) than in the placebo arm (53.3%). Treatment-related AEs reported in at least 5% more patients in the agalsidase alfa arm than in the placebo arm were nausea (18.0% vs 5.0%), infusion-related reaction (14.8% vs 6.7%), chills (14.8% vs 8.3%), pyrexia (8.2% vs 1.7%), and rash (6.6% vs 0%). Most AEs were mild or moderate in severity.

The incidence of SAEs was higher in the agalsidase alfa arm (14.8%) than in the placebo arm (11.7%). Four patients (6.6%) in the agalsidase alfa arm experienced treatment-related SAEs. Three patients had infusion-related reactions and 1 patient had pyrexia. There were no patients in either arm who discontinued due to AEs during the placebo-controlled studies.

In the Main Safety Analysis Population, 5 patients discontinued because of an AE. Four of these patients had an SAE with an outcome of death, and 1 had a non-serious, non-fatal AE of infusion-related reaction. Six patients died while receiving agalsidase alfa treatment and 1 while receiving placebo treatment. All events were considered not related to study treatment.

Infusion-associated AEs, identified as AEs that started on the day of or the day after infusion, occurred in 49.0% of patients. Infusion-related reactions, a subset of infusion associated AEs, which were AEs that started within 24 hours of infusion and were determined related to the infusion, occurred in 19.6% of patients. Treatment-related SAEs of infusion-related reactions were reported in 3 patients (4.9%), and discontinuation due to infusion-related reaction was only reported for 1 patient.

With regard to anti-agalsidase alfa IgG antibody status, 118 (77.1%) patients were antibody negative, 13 (8.5%) patients were transiently positive, and 22 (14.4%) patients were persistently positive. All antibody positive patients were male. No female patients were tested

positive for anti-agalsidase alfa antibodies, likely due to the presence or residual α-galactosidase A enzyme in the circulation of heterozygous females. No correlation was observed between the presence of antibodies and efficacy outcomes. A causal relationship between the presence of antibodies and the occurrence of infusion reactions could not be established.

The safety profile for children was consistent with that observed for the adult population. The findings from post-marketing data of over 10 years' duration and the FOS registry were consistent with that observed in the clinical studies.

Overall, agalsidase alfa presented an acceptable safety profile for the target population. The package insert has included adequate warnings and information on management of the AEs.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Fabry disease is a rare, X-linked glycosphingolipid storage disorder caused by a deficiency in or absence of the lysosomal hydrolase α-galactosidase A, presenting with a spectrum of clinical manifestations, ranging from the severe classic phenotype in hemizygous males and asymptomatic to full presentation in heterozygous females. Once organ involvement is established, Fabry disease is progressive and unremitting which could lead to eventual end organ dysfunction and death. In general, timely initiation of ERT is important given that some early pathological changes in Fabry disease are potentially reversible by ERT. There is an unmet medical need as treatment options for Fabry disease are limited. Currently there is only one registered alternative, agalsidase beta, available locally.

Agalsidase alfa treatment had been shown to provide benefits in terms of clinically meaningful improvement in "pain at its worst" scores and reduction in cardiac CTH in studies TKT003 and TKT005 respectively. In addition, agalsidase alfa demonstrated consistent benefits in stabilisation of renal function, reduction in left ventricular mass, and reduction of CTH level in urine sediment, kidney and plasma across all studies. In study TKT010, improvement in GFR was demonstrated in patients with abnormal renal function at baseline.

The safety profile of agalsidase alfa was considered acceptable relative to the benefits. The safety concerns were mostly related to infusion-related reactions and antibody formation. These risks have been adequately addressed in the package insert.

Taking into consideration the rarity of disease and the unmet medical need in Fabry disease, the overall evidence presented was sufficient to conclude that the benefit-risk profile of agalsidase alfa for the long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency) was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Replagal for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency) was deemed favourable and approval of the product registration was granted on 17 May 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

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.

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 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 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

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. Borderline 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.

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.

4.6 Effects on ability to drive and use machines

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

4.7 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 177 patients treated with Replagal in clinical trials, including 21 patients with history of end stage renal disease, 24 paediatric patients (7 to 17 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, dysgeusia, neuropathic pain, tremor, hypersomnia, hypoesthesia, paraesthesia	Parosmia	
Eye disorders		Corneal reflex decreased, lacrimation increased		
Ear and labyrinth disorders		Tinnitus, tinnitus aggravated		
Cardiac disorders		Tachycardia, palpitations		Cardiac arrhythmias (atrial fibrillation, ventricular extrasystoles, tachyarrhythmia), Myocardial ischaemia, heart failure
Vascular disorders	Flushing	Hypertension		Hypotension
Respiratory, thoracic and mediastinal disorders		Cough, hoarseness, throat tightness, dyspnoea, nasopharyngitis, pharyngitis, throat secretion increased, rhinorrhoea	Oxygen saturation decreased	
Gastrointestinal disorders	Nausea	Diarrhoea, vomiting, abdominal pain/discomfort		
Skin and subcutaneous tissue disorders		Acne, erythema, pruritus, rash, livedo reticularis	Angioneurotic oedema, urticaria	Hyperhidrosis
Musculoskeletal, connective tissue and bone disorders		Musculoskeletal discomfort, myalgia, back pain, limb pain, peripheral swelling, arthralgia, joint swelling	Sensation of heaviness	
Immune system disorders			Anaphylactic reaction, hypersensitivity	

Table 1				
System organ class	**Adverse reaction**			
	Very common	**Common**	**Uncommon**	**Not known**
General disorders and administration site conditions	Rigors, pyrexia, pain and discomfort, fatigue	Fatigue aggravated, feeling hot, feeling cold, asthenia, chest pain, chest tightness, influenza like illness, injection site rash, malaise		

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

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.

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.

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.

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 ($\geq$ 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 ± 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 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
Sodium hydroxide
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

2 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°C 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). Store in the original package to protect from light.

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 and 4 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.
- 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. PRODUCT OWNER

Shire Human Genetic Therapies AB
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8. DATE OF REVISION

May 2021