PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrREPLAGAL®

agalsidase alfa for injection

1 mg/mL Concentrate for solution for intravenous infusion

Enzyme Replacement Therapy

REPLAGAL, indicated for
- the long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency)

has been issued marketing authorization with conditions, pending the results of a trial to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for REPLAGAL please refer to Health Canada's Notice of Compliance with conditions – drug products website.

Takeda Canada Inc.
22 Adelaide Street West, Suite 3800
Toronto Ontario M5H 4E3

Date of Initial Approval:
February 10, 2017

Date of Revision:
February 19, 2021

Submission Control No: 243618

This product has been authorized under the Notice of Compliance with Conditions (NOC/c)

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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PrREPLAGAL ®

agalsidase alfa for injection

PART I: HEALTH PROFESSIONAL INFORMATION

REPLAGAL, indicated for
- the long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency)

has been issued marketing authorization with conditions, pending the results of a trial to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for REPLAGAL please refer to Health Canada's Notice of Compliance with conditions – drug products website.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant nonmedicinal Ingredients
Intravenous (IV)	Concentrate for solution for intravenous infusion 1 mg/mL	None *For complete listing see Dosage Forms, Composition and Packaging section.*

NOC/c

INDICATIONS AND CLINICAL USE

REPLAGAL (agalsidase alfa) is indicated for:

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

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

Geriatrics (>65 years of age)
Studies specifically in patients over 65 years of age have not been performed and no dosage regimen can presently be recommended in these patients as safety and efficacy have not yet been established.

Pediatrics (<18 years of age)
The experience in children is limited. In children in clinical studies (7-18 years) who received REPLAGAL 0.2 mg/kg every other week for one to 4 years no unexpected safety issues were encountered. The safety and efficacy of REPLAGAL in children ages 0-6 years has not yet been established.

NOC/c CONTRAINDICATIONS

- Severe allergic reactions to the active substance or to any ingredient in the formulation or components of the container of REPLAGAL. For a complete listing, see **Dosage Forms, Composition and Packaging**.

NOC/c WARNINGS AND PRECAUTIONS

Immune

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. (see **Adverse Reactions**)

Idiosyncratic infusion-related reactions
In adult and pediatric patients treated with REPLAGAL in clinical studies idiosyncratic infusion-related reactions were very commonly reported. 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 edema with throat tightness, stridor and swollen tongue. Other infusion-related symptoms may include dizziness and hyperhidrosis. 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. (see **Adverse Reactions**)

Antibodies to the protein
As with all protein pharmaceutical products, patients may develop antibodies to the protein. A low titre anti-drug antibody response has been observed in approximately 9.4% of male patients treated

with REPLAGAL after 12 months of treatment. (see **Adverse Reactions, Immunogenicity**)

Renal

No dose adjustment is necessary in patients with renal impairment. The presence of extensive renal damage (eGFR < 60 mL/min) 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 the disease. Limited data are available in patients on dialysis or post-kidney transplantation, no dose adjustment is required.

Hepatic

No studies have been performed in patients with hepatic impairment.

General

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

Special Populations

Pregnant Women
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 embryonal/fetal development when exposed during organogenesis. (see **Toxicology, Reproduction and Teratology Studies**)

Nursing Women
It is not known whether REPLAGAL is excreted in human milk. Caution should be exercised when prescribing REPLAGAL to nursing mothers.

Pediatrics (<18 years of age)
The experience in children is limited. In clinical studies of children (7-18 years of age) who received REPLAGAL 0.2 mg/kg every other week for one to 4 years, no unexpected safety issues were encountered.

Geriatrics (>65 years of age)
Studies specifically in patients over the age of 65 years old have not been performed and no dosage regimen can presently be recommended in these patients as safety and efficacy have not yet been established.

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse drug reactions (occurring in at least 10% of subjects) reported in

patients treated with REPLAGAL in these and other clinical studies were headache, flushing, nausea, rigors, pyrexia, pain and fatigue.

The most serious adverse drug reactions include abdominal pain/discomfort, anaphylactic reaction, arthralgia, chest pain, chest tightness, cough, dyspnea, erythema, hypersensitivity, hypertension, hypoesthesia, palpitations, pyrexia, tachycardia, throat tightness, tremor, and vomiting.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The most common adverse drug reactions reported in the clinical studies were infusion-related reactions, which occurred very commonly (13.7% of patients) in adults patients treated with REPLAGAL. (see **Warnings and Precautions**)

Adverse drug reactions reported for REPLAGAL in clinical studies are presented in Table 1:

Table 1 Adverse Drug Reactions Reported for REPLAGAL in Clinical Studies

Body System	Incidence Category	Adverse Drug Reaction
Cardiac disorders	Common	Tachycardia, palpitations
Ear and labyrinth disorders	Common	Tinnitus, tinnitus aggravated
Eye disorders	Common	Lacrimation increased
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhea, vomiting, abdominal pain / discomfort
General disorders and administration site conditions	Very common	Rigors, pyrexia, pain and discomfort, fatigue
	Common	Fatigue aggravated, feeling hot, feeling cold, asthenia, chest pain, chest tightness, influenza-like illness, injection site rash, malaise
Immune system disorders	Uncommon	Anaphylactic reaction, hypersensitivity
Investigations	Common	Corneal reflex decreased
	Uncommon	Oxygen saturation decreased
Metabolism and nutritional disorders	Common	Peripheral edema
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal discomfort, myalgia, back pain, limb pain, peripheral swelling, arthralgia, joint swelling
	Uncommon	Sensation of heaviness

Table 1 Adverse Drug Reactions Reported for REPLAGAL in Clinical Studies		
Body System	**Incidence Category**	**Adverse Drug Reaction**
Nervous system disorders	Very common	Headache
	Common	Dizziness, dysgeusia, neuropathic pain, tremor, hypersomnia, hypoesthesia, paraesthesia
	Uncommon	Parosmia
Respiratory, thoracic and mediastinal disorders	Common	Cough, hoarseness, throat tightness, dyspnea, nasopharyngitis, pharyngitis, throat secretion increased, rhinorrhea
Skin and subcutaneous tissue disorders	Common	Acne, erythema, pruritus, rash, livedo reticularis
	Uncommon	Angioneurotic edema, urticaria
Vascular disorders	Very common	Flushing
	Common	Hypertension

Adverse reactions reported in pediatric patients in clinical studies were generally similar to those reported in adults. However, infusion-related reactions occurred more frequently in pediatric patients than in adults. (see **Warnings and Precautions**)

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

Immunogenicity

As with all protein pharmaceutical products, patients may develop antibodies to the protein. A low titer anti-drug antibody response has been observed in approximately 9.4% of male patients treated with REPLAGAL after 12 months of treatment. These anti-drug antibodies appeared to develop following approximately 6-12 months of treatment. After 18 to 24 months of therapy, 6.3% of REPLAGAL-treated patients were still antibody positive. In other studies, after 12 to 54 months of therapy, 17% of REPLAGAL-treated patients were still antibody-positive. Borderline IgE antibody positivity not associated with anaphylaxis has been reported in clinical trials in a very limited number of patients. (see **Warnings and Precautions**)

Post-Market Adverse Drug Reactions

Infusion-related reactions may include cardiac events such as cardiac arrhythmias (atrial fibrillation, ventricular extrasystoles, tachyarrhythmia), myocardial ischemia and heart failure in patients with Fabry disease involving 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. (see **Warnings and Precautions**)

DRUG INTERACTIONS

Drug-Drug Interactions

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

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

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

NOC/c

DOSAGE AND ADMINISTRATION

Dosing Considerations

- REPLAGAL is intended for long-term, chronic use
- REPLAGAL treatment should be supervised by a physician experienced in the management of patients with Fabry Disease or other inherited metabolic diseases
- Infusion of REPLAGAL at home may be considered for patients who are tolerating their infusions well.

Recommended Dose and Dosage Adjustment

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

Administration

1. Calculate the dose and number of REPLAGAL vials needed.
2. 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.

3. The solution should be inspected visually for particulate matter and discoloration 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. After dilution, the product should be administered immediately.
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.

OVERDOSAGE

No case of overdose has been reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

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 (also referred to as Gb_3 or CTH), the glycosphingolipid substrate for this enzyme. Agalsidase alfa catalyzes the hydrolysis of Gb_3, cleaving a terminal galactose residue from the molecule. Treatment with the enzyme has been shown to reduce accumulation of Gb_3 in many cell types including endothelial and parenchymal cells. Agalsidase alfa has been produced in a human cell line to provide for a human glycosylation profile that influences biodistribution to allow preferential uptake by target cells.

Pharmacodynamics

Agalsidase alfa is a human α-galactosidase A produced in a human cell line by genetic engineering technology. Agalsidase alfa is a homodimer which consists of 2 approximately 50,000 Dalton subunits, with each subunit consisting of 398 amino acids. The product is post-translationally modified by the removal of a signal sequence of 31 residues and by the addition of carbohydrate chains to 3N-linked glycosylation sites.

Agalsidase alfa is targeted to its lysosomal site of action by mannose-6-phosphate (M6P) residues on the agalsidase alfa molecule. The M6P moiety binds to a specific M6P receptor on

the cell surface and is thus directed to the lysosomes. Many cells in the body contain M6P receptors, and agalsidase alfa has been shown to be taken up by the liver, kidney, heart, and blood vessels.

Agalsidase alfa is a highly purified preparation. Biological activity of agalsidase alfa is measured using the water soluble substrate 4-methylumbelliferyl-α-D-galactopyranoside (4-MUF-gal), and biological potency is measured based on its ability to be taken up by normal human cells.

Pharmacokinetics

REPLAGAL 0.2 mg per kg body weight were administered to 17 adult male patients with Fabry Disease as 40-minute intravenous infusions. Following the infusion, agalsidase alfa had a biphasic distribution and elimination profile from the circulation. The median clearance of agalsidase alfa normalized for body weight was 3.4 mL/min/kg (range: 0.6, 85.5 mL/min/kg). The median volume of distribution was 203 mL/kg (range: 89, 6778 mL/kg), and the median elimination half-life was 54.7 min (range: 28.5, 654.2 min).

Based on the analysis of pre- and post-dose liver biopsies in males with Fabry Disease treated with agalsidase alfa manufactured using a different method, 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 at the therapeutic dose level of 0.2 mg/kg.

In three studies with pharmacokinetic evaluations in Fabry patients receiving REPLAGAL 0.2 mg/kg body weight every other week, 4 of 17 adult male Fabry patients, 4 of 14 pediatric Fabry patients, and 2 of 10 adolescent / young adult Fabry patients tested positive for anti-agalsidase alfa antibodies (6 patients were IgM+; 4 patients were IgG+). Of the 6 IgM+ patients, 1 tested positive for neutralizing antibodies. Of the 4 IgG+ patients, 3 tested positive for neutralizing antibodies. Following six months of REPLAGAL treatment, some male patients showed altered pharmacokinetics including an apparent increase in clearance. These changes were associated with the development of low titer antibodies to agalsidase alfa.

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.

Special Populations and Conditions

Pediatrics: In 14 pediatric Fabry patients (7 to <18 years old), median clearance of REPLAGAL was 4.7 mL/min/kg (range: 2.1, 8.2 mL/min/kg). The mean (SD) volume of distribution was 128 mL/kg (51 mL/kg) and the mean (SD) elimination half-life was 32 min (9 min). In a separate long-term pediatric study of 10 adolescents / young adults with Fabry disease (15 to 23 years old), median clearance of REPLAGAL was 3.1 mL/min/kg (range: 1.2, 20 mL/min/kg).

Gender: Pharmacokinetic parameters were not significantly different between men and women.

Race: Formal pharmacokinetic studies for race have not been conducted.

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. (see **Warnings and Precautions, Renal**).

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.

STORAGE AND STABILITY

Store in a refrigerator (2 - 8ºC).

REPLAGAL diluted into normal saline should be used as soon as practicable after preparation, as the product does not contain any bacteriostatic preservatives. However, when prepared under aseptic conditions, the diluted product may be stored for 24 hours at 2 to 8 ºC.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each vial of 3.5 mL concentrate for solution for infusion contains 3.5 mg of agalsidase alfa.

The concentrate must be diluted further prior to administration. (see **Dosage and Administration, Administration)**.

REPLAGAL concentrate for solution for intravenous infusion contains the following excipients: polysorbate 20, sodium chloride, sodium hydroxide, sodium phosphate monobasic monohydrate, and water for injection.

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

Pack size of 1 vial per carton.

PART II: SCIENTIFIC INFORMATION

REPLAGAL, indicated for
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PHARMACEUTICAL INFORMATION

Drug Substance

Proper name (USAN/INN): agalsidase alfa

Chemical name: agalsidase alfa

Other name: Gene-activated α-galactosidase A

Molecular formula and molecular mass:
The mature enzyme is a glycoprotein which consists of a homodimer of 2 approximately 50,000 dalton molecular weight subunits, each consisting of 398 amino acids.

Structural formula:
Agalsidase alfa is the active pharmaceutical ingredient in the drug product REPLAGAL, and is the human protein α-galactosidase A produced by a well-characterized human cell line by genetic engineering technology. Agalsidase alfa is post-translationally modified by the removal of a signal sequence of 31 residues and by the addition of carbohydrate chains to 3 N-linked glycosylation sites (circled in illustration).

Physicochemical properties:
Agalsidase alfa drug substance is a clear colorless solution. As formulated in sodium phosphate and sodium chloride, agalsidase alfa has a pH of 6.0±0.5).

Human α-Galactosidase A Sequence

1 Leu Asp Asn Gly Leu Ala Arg Thr Pro Thr Met Gly Trp Leu His Trp Glu

18 Arg Phe Met Cys Asn Leu Asp Cys Gln Glu Glu Pro Asp Ser Cys Ile Ser

35 Glu Lys Leu Phe Met Glu Met Ala Glu Leu Met Val Ser Glu Gly Trp Lys

52 Asp Ala Gly Tyr Glu Tyr Leu Cys Ile Asp Asp Cys Trp Met Ala Pro Gln

69 Arg Asp Ser Glu Gly Arg Leu Gln Ala Asp Pro Gln Arg Phe Pro His Gly

86 Ile Arg Gln Leu Ala Asn Tyr Val His Ser Lys Gly Leu Lys Leu Gly Ile

103 Tyr Ala Asp Val Gly (Asn) Lys Thr Cys Ala Gly Phe Pro Gly Ser Phe Gly

120 Tyr Tyr Asp Ile Asp Ala Gln Thr Phe Ala Asp Trp Gly Val Asp Leu Leu

137 Lys Phe Asp Gly Cys Tyr Cys Asp Ser Leu Glu Asn Leu Ala Asp Gly Tyr

154 Lys His Met Ser Leu Ala Leu (Asn) Arg Thr Gly Arg Ser Ile Val Tyr Ser

171 Cys Glu Trp Pro Leu Tyr Met Trp Pro Phe Gln Lys Pro (Asn) Tyr Thr Glu

188 Ile Arg Gln Tyr Cys Asn His Trp Arg Asn Phe Ala Asp Ile Asp Asp Ser

205 Trp Lys Ser Ile Lys Ser Ile Leu Asp Trp Thr Ser Phe Asn Gln Glu Arg

222 Ile Val Asp Val Ala Gly Pro Gly Gly Trp Asn Asp Pro Asp Met Leu Val

239 Ile Gly Asn Phe Gly Leu Ser Trp Asn Gln Gln Val Thr Gln Met Ala Leu

256 Trp Ala Ile Met Ala Ala Pro Leu Phe Met Ser Asn Asp Leu Arg His Ile

273 Ser Pro Gln Ala Lys Ala Leu Leu Gln Asp Lys Asp Val Ile Ala Ile Asn

290 Gln Asp Pro Leu Gly Lys Gln Gly Tyr Gln Leu Arg Gln Gly Asp Asn Phe

307 Glu Val Trp Glu Arg Pro Leu Ser Gly Leu Ala Trp Ala Val Ala Met Ile

324 Asn Arg Gln Glu Ile Gly Gly Pro Arg Ser Tyr Thr Ile Ala Val Ala Ser

341 Leu Gly Lys Gly Val Ala Cys Asn Pro Ala Cys Phe Ile Thr Gln Leu Leu

358 Pro Val Lys Arg Lys Leu Gly Phe Tyr Glu Trp Thr Ser Arg Leu Arg Ser

375 His Ile Asn Pro Thr Gly Thr Val Leu Leu Gln Leu Glu Asn Thr Met Gln

392 Met Ser Leu Lys Asp Leu Leu

NOC/c CLINICAL TRIALS

Efficacy Studies

Study demographics and study design

Table 2 Summary of Patient Demographics and Study Design for Clinical Studies in Adults					
Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects receiving Replagal (n=number)**	**Mean age (Range)**	**Gender**
TKT 028	Multicenter,open-label randomized study to evaluate safety and efficacy of 3 REPLAGAL dose regimens in adults with Fabry disease	0.2mg/kg EOW, 0.2mg/kg weekly, and 0.4mg/kg weekly by i.v. infusion 12 months	META-ANALYSIS OF ADULT PATIENTS FOR CARDIAC PARAMETERS n = 153 Mean age: 47.3 yrs (19-84 yrs) Male: 58% Female: 42%		
HGT-REP-060	Open-label, multicenter, extension of study TKT 028 to evaluate safety and efficacy of REPLAGAL in adults with Fabry disease	0.2mg/kg EOW by i.v. infusion 12 months			
HGT-REP-059	Open-label, multicenter, single-arm study to evaluate safety of REPLAGAL in adults with Fabry disease	0.2mg/kg EOW by i.v. infusion 24 months	META-ANALYSIS OF ADULT PATIENTS FOR RENAL PARAMETERS n = 183 Mean age: 48.6 yrs (20-84 yrs) Male: 51% Female: 49%		
CFDI-001	Open-label, multicenter observational study to evaluate the effects of enzyme replacement therapy in Canadian patients with Fabry disease (*interim report including patients receiving REPLAGAL)*	0.2mg/kg EOW or 0.2mg/kg weekly by i.v. infusion 10 years			

EOW = every other week

Table 3	**Summary of Patient Demographics and Study Design for Clinical Studies in Pediatric Patients**				
Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects receiving REPLAGAL (n=number)**	**Mean age (Range)**	**Gender**
HGT-REP-084	Open-label, multicenter study to evaluate safety of REPLAGAL in pediatric patients with Fabry disease who are enzyme replacement treatment-naïve.	0.2mg/kg EOW by i.v. infusion 12 months	n=14	12.16 yrs (6.7-15.9 yrs)	Male: 35.7% Female: 64.3%

EOW = every other week

Study results

A summary of the results of the meta-analysis of cardiac and renal parameters from REPLAGAL (agalsidase alfa) studies in adult patients with Fabry Disease who were treatment-naïve at baseline are presented in Table 4.

Table 4	**Results of Meta-analysis of Studies in Adult patients with Fabry Disease treated with REPLAGAL 0.2 mg/kg EOW who were Treatment-naïve at Baseline**	
Primary analysis	**Mean baseline value (SD)**	**Adjusted Annualized Rate of Change using a Random Coefficient Model (AARC by RIS) (95% CI)**
Left ventricular mass index (LVMI) ($g/m^{2.7}$) (n=30)	56.1 (23.39)	0.32 (-2.07, 2.71)
Estimated glomerular filtration rate (eGFR) ($mL/min/1.73m^2$) (n=38)	79.0 (27.34)	-0.85 (-3.85, 2.15)

CI = Confidence interval; SD = Standard deviation; EOW = every other week

Cardiac Effects

The annual rate of change (95% CI) of LVMI in adult treatment-naïve patients (n=30), treated with REPLAGAL 0.2 mg/kg administered EOW over a mean of 1.95 (0.9 - 3.1) years, was 0.32 (-2.07, 2.71) $g/m^{2.7}$ demonstrating the stabilizing effect of REPLAGAL on this parameter (see

Table 4). This was further corroborated by the average annual rates of change for interventricular septum end-diastole thickness (IVSTd) and posterior wall thickness (PWTd).

The annual rates of change (95% CI) for cardiac parameters in adult patients treated with REPLAGAL 0.2 mg/kg administered EOW regardless of treatment at baseline (n=153) were:

- 0.31 (-0.77, 1.38) $g/m^{2.7}$ for LVMI from a mean (SD) at baseline of 62.5 (26.6) $g/m^{2.7}$,
- 0.009 (-0.014, 0.031) cm for IVSTd from a mean (SD) at baseline of 1.41 (0.47) cm, and
- -0.014 (-0.032, 0.005) cm for PWTd from a mean (SD) at baseline of 1.31 (0.38) cm.

In a subset of patients with left-ventricular hypertrophy at baseline (n=98) the average annual rates of change (95% CI) for cardiac parameters in patients on treatment with REPLAGAL were close to zero, further supporting a positive treatment effect:

- -0.12 (-1.67, 1.43) $g/m^{2.7}$ for LVMI from a mean (SD) at baseline of 76.3 (23.3) $g/m^{2.7}$,
- -0.002 (-0.026, 0.021) cm for IVSTd from a mean (SD) at baseline of 1.63 (0.44) cm, and
- -0.033 (-0.059, -0.007) cm for PWTd from a mean (SD) at baseline of 1.48 (0.35) cm.

Effects on Renal Function

The annual rate of change (95% CI) of eGFR in adult treatment-naïve patients (n=38), treated with REPLAGAL 0.2 mg/kg administered EOW over a mean of 1.97 (0.9 – 3.1) years, was -0.85 (-3.85, 2.15) $mL/min/1.73m^2$, thus providing a strong indication of a reduction of decline in renal function in patients with Fabry disease (see Table 4).

The annual rate of change (95% CI) of eGFR in adult patients treated with REPLAGAL 0.2 mg/kg administered EOW regardless of treatment at baseline (n=183), with a mean (SD) eGFR at baseline of 81.2 (26.32) $mL/min/1.73m^2$, was -3.26 (-4.36, -2.17) $mL/min/1.73m^2$.

In a subset of these patients with baseline eGFR below normal values, the annual rates of changes (95% CI) for eGFR in patients on treatment with REPLAGAL further demonstrated REPLAGAL's effect on the reduction of decline in renal function:

- -2.25 (-3.54, -0.96) $mL/min/1.73m^2$ for eGFR in patients with CKD Stage 2 at baseline (n=78) with a mean baseline (SD) eGFR of 75.6 (8.01) $mL/min/1.73m^2$, and
- -2.95 (-5.19, -0.71) $mL/min/1.73m^2$ for eGFR in patients with CKD Stage 3 at baseline (n=24) with mean baseline (SD) eGFR of 45.9 (9.6) $mL/min/1.73m^2$.

Results in Pediatric Patients

In a 55-week open-label multicenter study to evaluate the safety of REPLAGAL in pediatric patients with Fabry disease who are enzyme replacement treatment-naïve, an additional primary objective was to assess the changes in heart rate variability (HRV) (as an assessment of cardiac autonomic function) with LVMI and eGFR among secondary endpoints. The analyses of HRV indicated that time domain HRV indices remained stable or trended towards improvement. The baseline LVMI values for males and females were within the normal range (<51 $g/m^{2.7}$ for males and <48 $g/m^{2.7}$ for females) and overall, the mean baseline LVMI was 35.37 $g/m^{2.7}$. At Week 55, the mean LVMI changed by 0.16 $g/m^{2.7}$. Taken together, the study results indicated a potential stabilization or trend toward improvement in the cardiac function when treatment was started as soon as children with Fabry disease had low or abnormal HRV and before they developed left-

ventricular hypertrophy. Overall and by sex, assessments of renal function remained stable over the course of REPLAGAL treatment. The mean baseline eGFR was 117.50 mL/min/1.73 m^2 and none of the patients had eGFR ≤60 mL/min/1.73 m^2 at baseline. The mean change in eGFR from baseline at Week 55 was 0.15 mL/min/1.73 m^2.

Effects on Plasma Gb3 Levels
The effect of REPLAGAL on plasma Gb3 was analyzed in treatment-naïve male patients receiving 0.2 mg/kg administered EOW in an open-label study. Plasma Gb3 levels generally decreased over time. At baseline, the mean (SD) plasma Gb3 was 19.0 (9.84) nmol/mL. After 12 months (n=9), 18 months (n=8), and 24 months (n=3) of treatment, the mean change (SD) in plasma Gb3 from baseline was -8.2 (5.01) nmol/mL, -9.8 (10.04) nmol/mL, and -10.5 (1.95) nmol/mL, respectively.

Post-market experience
Total worldwide exposure to REPLAGAL, as of July 31, 2015, was estimated to be 14,683 patient-years.

DETAILED PHARMACOLOGY

Agalsidase alfa was evaluated for pharmacological effect in a "knockout" mouse model of α-galactosidase A deficiency.

Immunostaining of tissues from mice treated with a single dose of agalsidase alfa at 1.0 mg/kg provided direct evidence that intravenously administered agalsidase alfa was taken up by liver, heart, and kidney cells. A single dose of 0.2 mg/kg was sufficient to catabolize stored Gb_3 in the liver, heart, and kidney. Multiple injections of 0.1 and 1.0 mg/kg restored liver to almost normal levels of Gb_3 and significantly improved the reduction of Gb_3 in heart and kidney. The results of this study have shown that intravenously dosed agalsidase alfa is effectively targeted to key tissues that show storage induced pathology in Fabry Disease, indicating that it reaches the lysosomes in an active form.

TOXICOLOGY

Acute Toxicity Studies

The acute toxicity of agalsidase alfa was evaluated in rats. Doses of up to 10 mg/kg body weight, representing 50 times the recommended clinical dose, have been tested without any adverse toxicity.

Subacute and Subchronic Toxicity Studies

Multiple dose toxicity of agalsidase alfa was evaluated using rats, rabbits and monkeys. Doses of up to five times the recommended clinical dose and at twice the dosing frequency were tested

for 13 and 26 weeks in rats, and 13 weeks in monkeys. No adverse toxicity was observed. No toxicity was observed in a 14-day, daily-dosing, range finding study in rabbits.

Reproduction and Teratology Studies

A reproductive study in male rats used a maximum dose of 1.0 mg/kg and a dosing frequency of 3 times per week. There were no adverse effects of intravenous dosing of agalsidase alfa on male reproductive organs or on any assessment of male reproduction.

A combined fertility/teratology study in female rats used a maximum dose of 1.0 mg/kg body weight with daily dosing from pre-mating, through mating and day 17 of gestation. There were no adverse effects of intravenous dosing of agalsidase alfa on maternal reproductive performance as indicated by mating index, fertility index, pre- and post-implantation losses, or by fetal sex ratio. There were no treatment related changes in the frequency of major malformations, minor external or visceral abnormalities, or skeletal abnormalities in the examined fetuses. A teratology study in rabbits was also conducted using intravenous doses up to 1.0 mg/kg body weight per day from days 7 through 19 of gestation. There were no adverse maternal or fetal development effects observed.

It is not known whether agalsidase alfa crosses the placenta.

Both males and females were used for the majority of the studies and no sex related differences were observed in toxicity or in pharmacokinetics.

Mutagenicity and Carcinogenicity Studies

Mutagenicity and carcinogenicity studies were not conducted, however genotoxic and carcinogenic potential are not expected.

Read this for safe and effective use of your medicine

PART III: PATIENT MEDICATION INFORMATION

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

REPLAGAL is used to
- treat patients with a confirmed diagnosis of Fabry Disease.

It has been approved *with conditions*. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

PrREPLAGAL®
agalsidase alfa for injection

Read this carefully before you start taking **REPLAGAL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **REPLAGAL**.

What is REPLAGAL used for?

- REPLAGAL is used to treat patients with a confirmed diagnosis of Fabry Disease.

How does REPLAGAL work?

REPLAGAL is a long-term enzyme replacement therapy when the level of enzyme in the body is absent or lower than normal as in Fabry Disease.

What are the ingredients in REPLAGAL?

Medicinal ingredients: agalsidase alfa
Non-medicinal ingredients: polysorbate 20, sodium chloride, sodium hydroxide, sodium phosphate monobasic monohydrate, and water for injection.

REPLAGAL comes in the following dosage forms:

1 mg/mL concentrate for solution for injection.

Do not use REPLAGAL if:

- you are allergic (hypersensitive) to agalsidase alfa, the medicinal ingredient, or to any of the other ingredients in REPLAGAL or its container

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REPLAGAL. Talk about any health conditions or problems you may have, including if:

- you experience any of the following during infusion with REPLAGAL:
  - High fever, chills, sweating, fast heart rate
  - Nausea or are vomiting
  - Headaches, feel light-headedness or fatigue
  - Hives
  - Swelling in your hands, feet, ankles, face, lips, mouth or throat which may cause difficulty in swallowing or breathing

  Your doctor/nurse may stop the infusion temporarily (5 – 10 minutes) 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.

- 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.

- treatment with REPLAGAL makes your body produce antibodies.
- you have advanced renal disease.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with REPLAGAL:

- Chloroquine
- Amiodarone
- Benoquin
- Gentamicin

How to take REPLAGAL:
REPLAGAL treatment should be supervised by a physician experienced in the management of patients with Fabry Disease or other inherited metabolic disease. Infusion of REPLAGAL at home may be considered for patients who are tolerating their infusions well.

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 2 weeks. Each time you are treated, it will take 40 minutes for REPLAGAL to be given to you in a vein. Do not use REPLAGAL if you notice that there is discoloration or other foreign particles present.

Usual dose:
Adults:
The dose is an intravenous infusion (in a vein) of 0.2 mg for every kg you weigh over 40 minutes. This would be about 14 mg or four 5 mL vials (glass bottles) of REPLAGAL for an average size (70 kg) individual. The intravenous infusion will be given every 2 weeks.

Children and adolescents:
For children and adolescents 7-18 years old, a dose of 0.2 mg/kg every 2 weeks may be used.

Overdose:
There is no experience of overdose with REPLAGAL.

If you think you have taken too much REPLAGAL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using REPLAGAL:

These are not all the possible side effects you may feel when taking REPLAGAL. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects with REPLAGAL include headache, flushing, nausea, chills, pain and fatigue.

Serious side effects and what to do about them

Symptom / effect	**Talk to your healthcare professional**		**Stop running infusion and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Pyrexia: fever	√		
COMMON			
Abdominal pain/discomfort	√		
Arthralgia: joint pain	√		
Chest pain		√	√
Chest or throat tightness		√	√
Cough	√		
Dyspnea: trouble breathing		√	√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop running infusion and get immediate medical help**
	Only if severe	**In all cases**	
Erythema: reddening of the skin	√		
Hypertension		√	
Hypoesthesia: loss of sensation		√	
Palpitations: pounding or irregular heartbeat		√	√
Tachycardia: abnormally fast heart rate		√	√
Tremor	√		
Vomiting	√		
UNCOMMON			
Anaphylactic reaction: severe allergic reaction		√	√
Hypersensitivity		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9
    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store REPLAGAL in a refrigerator at 2 to 8°C.

Keep out of reach and sight of children.

If you want more information about REPLAGAL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website (www.takeda.com/en-ca), or by calling 1-800-268-2772.

This leaflet was prepared by:

Takeda Canada Inc.
22 Adelaide Street West, Suite 3800
Toronto Ontario M5H 4E3

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