

## PRODUCT MONOGRAPH

**Pr Replagal<sup>®</sup>**

**agalsidase alfa**

**1 mg/mL concentrate for solution for infusion**

**Gene-Activated  $\alpha$ -Galactosidase A for  
Enzyme Replacement Therapy of Fabry Disease**

**Replagal shows promising preliminary evidence of efficacy for the treatment of patients with Fabry Disease; however, the optimal individual dose requires further investigation. Studies are underway to evaluate more frequent and/or higher doses of Replagal therapy than used in clinical trials to date.”**

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**This product has been approved under the  
Notice of Compliance with Conditions (NOC/c)  
policy for one or all of its indicated uses.**

### **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 include the following:

- Dosage and Administration;
- Pharmacokinetics;
- Clinical Trials;
- Detailed Pharmacology;
- Insert for Patients

### **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 Health Product Safety Information Division 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.

## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>4</b>
<b>SUMMARY PRODUCT INFORMATION.....</b>	<b>4</b>
<b>INDICATIONS AND CLINICAL USE.....</b>	<b>4</b>
<b>CONTRAINDICATIONS.....</b>	<b>4</b>
<b>WARNINGS AND PRECAUTIONS.....</b>	<b>5</b>
<b>ADVERSE REACTIONS.....</b>	<b>6</b>
<b>DRUG INTERACTIONS.....</b>	<b>10</b>
<b>NOC/c  DOSAGE AND ADMINISTRATION.....</b>	<b>11</b>
<b>OVERDOSAGE.....</b>	<b>11</b>
<b>ACTION AND CLINICAL PHARMACOLOGY.....</b>	<b>11</b>
<b>STORAGE AND STABILITY.....</b>	<b>13</b>
<b>SPECIAL HANDLING INSTRUCTIONS.....</b>	<b>13</b>
<b>DOSAGE FORMS, COMPOSITION AND PACKAGING.....</b>	<b>14</b>
<b>PART II: SCIENTIFIC INFORMATION.....</b>	<b>15</b>
<b>PHARMACEUTICAL INFORMATION.....</b>	<b>15</b>
<b>NOC/c  CLINICAL TRIALS.....</b>	<b>17</b>
<b>NOC/c  DETAILED PHARMACOLOGY.....</b>	<b>18</b>
<b>TOXICOLOGY.....</b>	<b>18</b>
<b>NOC/c  PART III: CONSUMER INFORMATION.....</b>	<b>20</b>

**Replagal®**  
agalsidase alfa

**PART I: HEALTH PROFESSIONAL INFORMATION**

**Replagal shows promising preliminary evidence of efficacy for the treatment of patients with Fabry Disease; however, the optimal individual dose requires further investigation. Studies are underway to evaluate more frequent and/or higher doses of Replagal therapy than used in clinical trials to date.**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Pharmaceutical Form/Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Intravenous (IV)	1 mg/mL concentrate for solution for infusion	None

**INDICATIONS AND CLINICAL USE**

Replagal (agalsidase alfa) is indicated for:

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

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

(See Part II: Scientific Information, Clinical Trials for clinical information.)

**CONTRAINDICATIONS**

- Life-threatening hypersensitivity (anaphylactic reaction) to the active substance or any of the excipients.
- Replagal should not be co-administered with chloroquine, amiodarone, benoquin or gentamicin since these substances have the potential to inhibit intra-cellular  $\alpha$ -galactosidase activity.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

#### General

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

#### Carcinogenesis and Mutagenesis

See Part II: Scientific Information, Toxicology for animal data.

#### Hepatic

No studies have been performed in patients with hepatic impairment.

#### Immune

In approximately 10% of patients, Replagal has been associated with mild, acute idiosyncratic infusion reactions, during or within one hour following infusion. The most common symptoms have been chills and facial flushing. Severe infusion reactions have been reported uncommonly. Symptoms reported include nausea, pyrexia, rigors, tachycardia, urticaria and vomiting. Such reactions have generally occurred within the first 2-4 months after initiation of treatment with Replagal. 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 pre-treatment, generally with oral antihistamines and corticosteroids, from 1 to 3 hours prior to infusion has prevented subsequent reactions in those cases where symptomatic treatment was required.

As with any intravenous protein product, allergic-type hypersensitivity reactions are possible. If severe allergic or anaphylactic-type reactions occur, the administration of Replagal should be discontinued immediately and appropriate treatment initiated. The current medical standards for emergency treatment are to be observed.

As with all protein pharmaceutical products, patients may develop antibodies to the protein. A low titre IgG antibody response has been observed in approximately 55% of the patients treated with Replagal. The antibodies appear to develop following approximately 3 months of treatment. After 12 to 18 months of therapy, 60% of patients are antibody free and >80% of patients who were antibody positive showed evidence for the development of immunologic tolerance, based on the reduction of antibody titres over time.

(See Adverse Reactions section.)

## **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. Limited data are available in patients on dialysis or post-kidney transplantation, no dose adjustment is required.

## **Special Populations:**

**Pregnant Women:** For Replagal, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development when exposed during organogenesis. See Part II Toxicology for animal data.

**Nursing Women:** It is not known whether Replagal is excreted in human milk.

## **Pediatrics (0 - 17 years of age) and Geriatrics (> 65 years of age):**

Replagal has been found to be safe and well tolerated following 12 months of therapy in children with Fabry disease and there is no evidence of any difference in the safety profile compared to the larger experience in treating adult patients. In the first six children studied there have been no reports of significant infusion related symptoms and no patients have developed IgG anti-agalsidase alfa antibodies following 12 months of therapy. Studies in patients over the age of 65 have not been performed.

The benefit versus risk balance should be considered carefully before prescribing Replagal to pregnant or nursing women, children or the elderly.

## **Monitoring and Laboratory Tests**

No special laboratory tests are required for patients receiving Replagal, other than the usual tests that are required for monitoring patients with Fabry Disease.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The most commonly reported undesirable effects were associated with infusion reactions which occurred in approximately 10% of patients treated in clinical trials. Most undesirable effects were mild to moderate in severity and the majority were consistent with the natural course of Fabry Disease.

### **Adverse Drug Reactions**

Table 1 lists those adverse drug reactions (ADRs) reported for the 55 patients treated with agalsidase alfa in clinical trials where causality is at least suspected in one or more cases (see Part II: Scientific Information, Clinical Trials section). Information is presented by system organ class and frequency (very common >1/10; common >1/100 and <1/10). The occurrence of an event in a single patient is defined as common in view of the number of patients treated. A single patient could be affected by several ADRs.

**Table 1. Adverse Drug Reactions in Clinical Trials**

		<b>Replagal (n= 55)</b>	
		<b>Patients (n)</b>	<b>%</b>
<b>Metabolism and nutrition disorders</b>			
<i>Common</i>	edema	1	1.8
	peripheral edema	1	1.8
<b>Psychiatric disorders</b>			
<i>Common</i>	panic attack	1	1.8
<b>Nervous system disorders</b>			
<i>Very Common</i>	headache	6	10.9
<i>Common</i>	dizziness	5	9.1
	dysgeusia	3	5.5
	neuropathic pain	3	5.5
	tremor	2	3.6
	hypersomnia	1	1.8
	hypoesthesia	1	1.8
	paraesthesia	1	1.8
	parosmia	1	1.8
	somnolence	1	1.8
<b>Eye disorders</b>			
<i>Common</i>	lacrimation increased	1	1.8
	periorbital edema	1	1.8
<b>Ear and labyrinth disorders</b>			
<i>Common</i>	vertigo	1	1.8
<b>Cardiac disorders</b>			
<i>Common</i>	tachycardia	2	3.6
	chest pain	1	1.8
<b>Vascular disorders</b>			
<i>Very Common</i>	flushing	13	23.6
<i>Common</i>	hypertension	2	3.6
	peripheral coldness	1	1.8

**Table 1. Adverse Drug Reactions in Clinical Trials**

		<b>Replagal (n= 55)</b>	
		<b>Patients (n)</b>	<b>%</b>
<b>Respiratory, thoracic and mediastinal disorders</b>			
<i>Common</i>	hoarseness	3	5.5
	throat tightness	3	5.5
	cough	2	3.6
	dyspnea	2	3.6
	nasopharyngitis	2	3.6
	pharyngitis	2	3.6
	nasal congestion	1	1.8
	snoring	1	1.8
	throat irritation	1	1.8
<b>Gastrointestinal disorders</b>			
<i>Common</i>	nausea	5	9.1
	diarrhea	2	3.6
	vomiting	2	3.6
	abdominal pain	1	1.8
	dyspepsia	1	1.8
	gastrointestinal upset	1	1.8
	stomach cramps	1	1.8
	stomach discomfort	1	1.8
<b>Skin and subcutaneous tissue disorders</b>			
<i>Common</i>	acne	5	9.1
	erythema	4	7.3
	mottled skin	2	3.6
	pruritus	2	3.6
	dry skin	1	1.8
	eczema	1	1.8
	itchy rash	1	1.8
	rash	1	1.8
<b>Musculoskeletal, connective tissue and bone disorders</b>			
<i>Common</i>	myalgia	3	5.5
	musculoskeletal discomfort	1	1.8
	back pain	1	1.8
	limb pain	1	1.8

**Table 1. Adverse Drug Reactions in Clinical Trials**

		Replagal (n= 55)	
		Patients (n)	%
<b>General disorders and administrative site conditions</b>			
<i>Very Common</i>	rigors	11	20
	pyrexia	11	20
	infusion related reactions (see below)	7	12.7
<i>Common</i>	fatigue	5	9.1
	chest tightness	4	7.3
	pain and discomfort	4	7.3
	fatigue aggravated	4	7.3
	feeling hot	2	3.6
	asthenia	1	1.8
	chest pain	1	1.8
	influenza like illness	1	1.8
	edema	1	1.8

In pre-approval clinical trials approximately 10% of agalsidase alfa treated patients have experienced idiosyncratic infusion-reactions (see Warnings and Precautions section). These effects have decreased with time. Symptoms have included predominantly rigors (chills) and facial flushing with a few patients experiencing headache, dyspnea, abdominal pain, nausea or chest pain. All symptoms resolved with appropriate intervention, such as, stopping the infusion prior to restarting or medical therapy with antihistamines and corticosteroids. Severe infusion reactions have been reported uncommonly. Symptoms reported include nausea, pyrexia, rigors, tachycardia, urticaria and vomiting.

Considering the rarity of Fabry Disease and the relatively limited number of patients exposed to agalsidase alfa to date, health-care professionals should be aware of the occurrence of the following very common adverse events observed in this patient population that were considered unrelated to agalsidase alfa: anorexia, insomnia, anxiety, depression, headache, dizziness, neuropathic pain, hypoesthesia, paraesthesia, syncope, vision blurred, vertigo, hypoacusis, ear pain, tinnitus, palpitations, nausea, diarrhoea, vomiting, abdominal pain, gastrointestinal upset, flatulence, abdominal distension, flu like illness, dyspnea, erythema, rash, contusion, musculoskeletal pain, pain exacerbated, chest pain, rigors, pyrexia, asthenia, malaise, peripheral edema, generalized infections, dysuria. An increase in the frequency of some events considered unrelated to treatment was reported following 6 to 12 months of therapy, none were considered serious. Most events were associated with Fabry Disease such as gastrointestinal disorders, changed temperature sensation / heat intolerance and dyspnea. Events that were not reported in placebo controlled trials but were observed after longer term treatment include asthenia.

### **Post-Market Adverse Drug Reactions**

The safety experience with the use of commercial Replagal is similar to that which has been reported in clinical trials. The most commonly reported adverse drug reactions have been infusion related reactions or infusion associated symptoms and were mild to moderate in severity. Symptoms have predominantly included chills (rigors) and facial flushing with a small number of patients experiencing headache, dyspnea, fever, urticaria and diarrhea. All symptoms resolved either with or without intervention. Reported intervention has included temporarily stopping the infusion for a few minutes prior to restarting, restarting the infusion at a slower rate, medical treatment with analgesics, antipyretics, antihistamines and or corticosteroids. In some cases subsequent infusions were premedicated, which after a limited period was successfully withdrawn.

### **DRUG INTERACTIONS**

<b>Serious Drug Interactions</b>
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#### **Overview**

Replagal should not be co-administered with chloroquine, amiodarone, benoquin or gentamicin since these substances have the potential to inhibit intra-cellular  $\alpha$ -galactosidase activity.

As  $\alpha$ -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.

#### **Drug-Drug Interactions**

Replagal should not be co-administered with chloroquine, amiodarone, benoquin or gentamicin since these substances have the potential to inhibit intra-cellular  $\alpha$ -galactosidase activity.

#### **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 (agalsidase alfa) is intended for long term, chronic use under the guidance and supervision of a physician; however, home infusion is permitted.
- Replagal is administered at a dose of 0.2 mg/kg body weight every other week by intravenous infusion over 40 minutes.
- For preparation and administration instructions, see Special Handling Instructions section.

### **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. Replagal shows promising preliminary evidence of efficacy for the treatment of patients with Fabry Disease; however, the optimal individual dose requires further investigation. Studies are underway to evaluate more frequent and/or higher doses of Replagal therapy than used in clinical trials to date.

### **Administration**

See Special Handling Instructions section for method of dilution.

## **OVERDOSAGE**

No case of overdose has been reported.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Fabry Disease is a glycosphingolipid storage disorder that is caused by deficient activity of the lysosomal enzyme  $\alpha$ -galactosidase A, resulting in accumulation of globotriaosylceramide (also referred to as Gb<sub>3</sub> or CTH), the glycosphingolipid substrate for this enzyme. Agalsidase alfa catalyzes the hydrolysis of Gb<sub>3</sub>, cleaving a terminal galactose residue from the molecule. Treatment with the enzyme has been shown to reduce accumulation of Gb<sub>3</sub> 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.

### **Pharmacodynamics**

Agalsidase alfa is a human  $\alpha$ -galactosidase A produced by Gene Activation technology. Agalsidase alfa is a homodimer comprising 2 approximately 50,000 Dalton subunits, with each subunit containing 398 amino acid residues. The product is synthesized by a human cell line and has the identical amino acid sequence as that of  $\alpha$ -galactosidase A produced in human tissues.

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- $\alpha$ -D-galactopyranoside (4-MUF-gal), and biological potency is measured based on its ability to be taken up by normal human cells.

Agalsidase alfa catalyzes the hydrolysis of Gb<sub>3</sub>, cleaving a terminal galactose residue from the molecule. The hydrolysis of Gb<sub>3</sub> in affected individuals causes a reduction in the amount of Gb<sub>3</sub> in many cell types in the body, including cells in the liver, heart, kidney, and blood vessels, and in the plasma.

### NOC/c    Pharmacokinetics

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 (1.8 hours) in males compared to 89±28 minutes (1.5 hours) in females and volume of distribution was approximately 17% body weight in both sexes. Clearance normalized 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.

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

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

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

A short-term study is being initiated to assess the pharmacodynamic and pharmacokinetic effects as well as the safety of alternative dosing regimens of Replagal in comparison to the current dosing regimen of 0.2 mg/kg every 2 weeks. Replagal doses between 0.1 and 0.4 mg/kg will be studied with weekly and biweekly infusions.

## **STORAGE AND STABILITY**

Store at 2 to 8 °C (in a refrigerator).

Replagal has a shelf life of 3 years.

After dilution, the product should be administered immediately (within 3 hours). The product does not contain any bacteriostatic preservative therefore storage of the diluted solution is not recommended; however, when prepared under aseptic conditions, the chemical and physical stability of the diluted solution has been demonstrated for 24 hours at 25 °C.

## **SPECIAL HANDLING INSTRUCTIONS**

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. After dilution, the product should be administered immediately (within 3 hours). The product does not contain any bacteriostatic preservative therefore storage of the diluted solution is not recommended; however, when prepared under aseptic conditions, the chemical and physical stability of the diluted solution has been demonstrated for 24 hours at 25 °C.
5. Do not infuse Replagal concomitantly in the same intravenous line with other agents.
6. For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL contains 1.0 mg of agalsidase alfa.

Agalsidase alfa is the human protein  $\alpha$ -galactosidase A produced by Gene Activation technology in a human cell line.

The concentrate must be diluted further, see Special Handling Procedures section.

1 mL of concentrate for solution for infusion in 3 mL vial (Type 1 glass) with a fluoro-resin coated butyl rubber stopper, a one piece aluminum seal and flip-off cap.

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

Pack sizes of 1, 4 or 10 vials per carton. Not all pack sizes may be marketed.

The following is a list of excipients used in the Replagal formulation:

Polysorbate 20;

Sodium chloride;

Sodium hydroxide;

Sodium phosphate monobasic monohydrate;

Water for Injection

## PART II: SCIENTIFIC INFORMATION

**Replagal shows promising preliminary evidence of efficacy for treatment of patients with Fabry Disease; however, the optimal individual dose requires further investigation. Studies are underway to evaluate more frequent and/or higher doses of Replagal therapy than used in clinical trials to date.**

### PHARMACEUTICAL INFORMATION

#### Drug Substance

**Proper name:** agalsidase alfa

**Chemical name:**  $\alpha$ -galactosidase A

#### **Molecular formula and molecular mass:**

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

#### **Structural formula:**

This molecule consists of 398 amino acids. Agalsidase alfa is human  $\alpha$ -Galactosidase A manufactured by gene activation technology in a continuous human cell line. The amino acid sequence of agalsidase alfa, determined by mass spectroscopy, peptide mapping, and sequencing of the cDNA in the Master Cell Bank, Working Cell Bank, and End of Production cells, is illustrated below. The three sites of N-linked glycosylation are circled.

## Human $\alpha$ -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

### Physicochemical properties:

Replagal is a clear, colorless solution. A minute amount of fine particulate matter may cause the solution to appear slightly hazy. As supplied, Replagal has a pH of  $6.0 \pm 0.5$ .

### NOC/c CLINICAL TRIALS

#### Study demographics and trial design

Table 2- Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
TKT003	Pivotal, Phase II, randomized, double-blind, placebo controlled	0.2 mg/kg Replagal or placebo intravenously every other week for 24 weeks (total of 12 doses)	n=26	Replagal (n=14): $34.0 \pm 2.26$ (19-48)  Placebo (n=12): $34.4 \pm 2.22$ (23-45)	Male
TKT005	Pivotal, Phase II, randomized, double-blind, placebo controlled	0.2 mg/kg Replagal or placebo intravenously every other week for 24 weeks (total of 12 doses)	n=15	Replagal (n=7): $36.4 \pm 3.81$ (22-50)  Placebo (n=8): $36.9 \pm 2.80$ (26-49)	Male

### STUDY RESULTS

The safety and efficacy of Replagal was assessed in two randomized, 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 dosage of

0.2 mg/kg of Replagal. Twenty-five patients completed the first study and entered an extension study.

In a second study, fifteen patients with left ventricular hypertrophy completed a 6 month placebo-controlled study and entered an extension study. Two patients with right bundle branch block in the studies conducted reverted to normal following therapy with Replagal.

Compared with placebo, treatment with Replagal reduced accumulation of Gb<sub>3</sub> in plasma and urine sediment. Treatment with Replagal also reduced accumulation of Gb<sub>3</sub> in many cell types, including renal glomerular and tubular epithelial cells, renal capillary endothelial cells and cardiac myocytes. Serial examination of 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 patients treated with placebo.

Antibodies to agalsidase alfa have not been shown to be associated with any clinically significant effects on safety.

## **NOC/c DETAILED PHARMACOLOGY**

Agalsidase alfa was evaluated for pharmacological effect in a “knockout” mouse model of  $\alpha$ -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<sub>3</sub> in the liver, heart, and kidney. Multiple injections of 0.1 and 1.0 mg/kg restored liver to almost normal levels of Gb<sub>3</sub> and significantly improved the reduction of Gb<sub>3</sub> 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**

Preclinical 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 agalsidase alfa crosses the placenta.

### **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 planned clinical dose, have been tested without any adverse toxicity.

### **Multidose 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.

Antibodies to the human protein were detected in the majority of rats, and in all rabbits. No antibodies were detected in monkeys.

### Reproduction and Teratology:

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 IV 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 IV dosing of agalsidase alfa on maternal reproductive performance as indicated by mating index, fertility index, pre- and post-implantation losses, or by 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.

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 Studies:

Mutagenicity studies were not conducted, since proteins, in general, are not mutagenic compounds. This is consistent with the ICH Guidelines; “S1A Guidelines on the Need for Carcinogenicity Studies of Pharmaceuticals”.

### Carcinogenicity Studies:

Carcinogenicity studies were not conducted which is consistent with the ICH Guidelines; “S1A Guidelines on the Need for Carcinogenicity Studies of Pharmaceuticals”.

**NOC/c PART III: CONSUMER INFORMATION**

**What is a Notice of Compliance with Conditions**

**Replagal shows promising preliminary evidence of efficacy for the treatment of patients with Fabry Disease; however, the optimal individual dose requires further investigation. Studies are underway to evaluate more frequent and/or higher doses of Replagal therapy than used in**

**(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.

**Replagal®**  
agalsidase alfa

This leaflet is part III of a three-part "Product Monograph" published when Replagal was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Replagal. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**

What the medication is used for:

Replagal is used to treat Fabry Disease. Replagal is intended for long term use. Replagal treatment should initially be supervised by a physician experienced in the management of patients with Fabry Disease or other inherited metabolic diseases; however, infusions can be given in the patient's home.

What it does:

Replagal is used as enzyme replacement therapy when the level of enzyme in the body is lower than normal as in Fabry Disease.

When it should not be used:

If you are allergic (hypersensitive) to agalsidase alfa or any of the other ingredients of Replagal.

What the medicinal ingredient is:

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

What the important nonmedicinal ingredients are:

The other ingredients are polysorbate 20, sodium chloride, sodium hydroxide, sodium phosphate monobasic monohydrate, and water for injections.

What dosage forms it comes in:

1 mg/mL concentrate for solution for infusion

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions**

Approximately 10% of patients had reactions during or within one hour following infusion of Replagal. Most reactions were mild. The most common symptoms were chills and facial flushing (warmth and redness). These reactions have generally first happened 2-4 months after the start of treatment and decreased over time. Most of the time you can still be given Replagal even if the symptoms occur.

If you experience an allergic side effect following the administration of Replagal, you should immediately contact your doctor.

If symptoms occur during your infusion:

- Your doctor may stop the infusion temporarily (5-10 min) until the symptoms go away and then begin the infusion again.
- Your doctor may also treat the symptoms with other medicines (antihistamines or corticosteroids).

It is possible that treatment with Replagal will make your body produce antibodies. This will not stop Replagal from working and the antibodies are likely to disappear with time.

If severe allergic (anaphylactic-type) reactions occur, immediate discontinuation of the administration of Replagal may be considered and an appropriate treatment will have to be initiated by your doctor.

### INTERACTIONS WITH THIS MEDICATION

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

### PROPER USE OF THIS MEDICATION

#### Dose:

The dose is an infusion of 0.2 mg for every kg you weigh. This would be about 14 mg or four 5 mL vials (glass bottles) of Replagal for an average size (70 kg) individual. The infusion will be given every other week.

More frequent and/or higher doses are being studied.

#### Overdose:

There is no experience of overdose with Replagal.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Replagal can have side effects. Most side effects are mild to moderate and include headache, tingling, numbness, tremors, fatigue, change in temperature sensation, increased blood pressure, upset stomach, diarrhea, coughing, sore throat, difficulty sleeping, change in the taste of food, change in smell, difficulty speaking, acne, dry skin and eye problems. About 1 out of 10 patients may have a reaction during or shortly after infusion of Replagal. These effects include

chills and facial flushing (warmth and redness). However some effects may be serious and may need treatment.

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Tell your doctor immediately if you notice any of these effects which may be serious:

- Swelling in your hands, feet, ankles, face, lips, mouth or throat which may cause difficulty in swallowing or breathing
- Fever
- Rash
- Itching

Tell your doctor as soon as possible if you notice any of the following:

- Signs of infection
- Shortness of breath
- Changes in the way your heart beats (for example, if you notice it beating faster)
- Pain or tenderness in chest, muscles or joints
- Light-headedness

If you notice any side effects not mentioned in this leaflet, please inform your doctor.

*This is not a complete list of side effects. For any unexpected effects while taking Replagal, contact your doctor or pharmacist.*

### HOW TO STORE IT

Store at 2 to 8 °C (in a refrigerator).

### **REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax 866-678-6789

By email: [cadmp@hc-sc.gc.ca](mailto:cadmp@hc-sc.gc.ca)

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness  
Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa ON K1A 0K9

*NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.*

### **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be requested by contacting Paladin Labs Inc., at: 1-888-550-6060.

This leaflet was prepared by Shire Human Genetic Therapies, Inc.

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