PRODUCT MONOGRAPH

Pr VPRIV®

velaglucerase alfa

Powder for Solution for Injection
400 U/vial

Enzyme Replacement Therapy
ATC code: A16AB10

Shire Human Genetic Therapies, Inc.
300 Shire Way
Lexington, MA USA 02421 www.shire.com

Importer/Distributor:
Shire Pharma Canada ULC
22 Adelaide Street West, Suite 3800
Toronto, Ontario
Canada
M5H 4E3

Date of Initial Approval:
October 1, 2010

Date of Revision:
July 30, 2019

Submission Control No: 227923

Table of Contents

Pr VPRIV®
velaglucerase alfa

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous (IV)	Powder for solution for injection/ 400 U/vial	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

After reconstitution with sterile water for injection, each vial contains 100 U/mL. VPRIV is dosed by units (U/kg), where one unit (U) of enzyme activity is defined as the quantity of enzyme required to convert one micromole of p-nitrophenyl-ß-D-glucopyranoside to p-nitrophenol per minute at 37ºC.

DESCRIPTION
Velaglucerase alfa is produced by gene activation technology in a human cell line. Velaglucerase alfa is a glycoprotein with the same amino acid sequence as the naturally occurring human enzyme, glucocerebrosidase. Velaglucerase alfa catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide in the lysosome.

INDICATIONS AND CLINICAL USE

VPRIV (velaglucerase alfa) is indicated for

- long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **Dosage Forms, Composition and Packaging**.

WARNINGS AND PRECAUTIONS

General

No studies of VPRIV on the effects on the ability to drive and use machines have been performed.

Hypersensitivity Reactions

Immune

Hypersensitivity reactions including symptoms consistent with anaphylaxis have been reported in patients in clinical studies and in post-marketing experience. As with any intravenous protein product, hypersensitivity reactions are possible, therefore appropriate medical support should be readily available when VPRIV is administered. If a severe reaction occurs, current medical standards for emergency treatment are to be followed.

Treatment with VPRIV should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the active ingredient or excipients in the drug product or to other enzyme replacement therapy.

Infusion-Related Reactions

Infusion-related reactions, the most commonly observed adverse reactions in patients treated with VPRIV in clinical studies, occurred in 28/54 (51.9%) of patients who were naïve to therapy and in 9/40 (22.5%) of patients who switched from imiglucerase to VPRIV. Most of the infusion-related reactions were mild. The most commonly observed symptoms of infusion-related reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia, and pyrexia/body temperature increased. In treatment-naïve patients, the majority of infusion-related reactions occurred during the first 6 months of treatment with VPRIV. Additional infusion-related reactions of chest discomfort, dyspnea, and pruritis have been reported in post-marketing experience.

The management of infusion-related reactions should be based on the severity of the reaction, e.g. slowing the infusion rate, treatment with medications such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with increased infusion time.

Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Patients were not routinely pre-medicated prior to infusion of VPRIV during clinical studies.

Immunogenicity

In clinical studies, 1 of 94 (1%) patients treated with VPRIV developed IgG-class antibodies to velaglucerase alfa. In this one event the antibodies were determined to be neutralizing in an in vitro assay. No infusion-related reactions were reported for this patient. It is unknown if the presence of IgG antibodies to velaglucerase alfa is associated with a higher risk of infusion

reactions. No patients developed IgE antibodies to velaglucerase alfa.

Carcinogenesis and Mutagenesis

See **Toxicology**.

Hepatic/ Biliary/Pancreatic

No studies have been performed in patients with hepatic impairment.

Renal

No studies have been conducted in patients with renal impairment.

Special Populations

Pregnant Women
There are no data from studies in pregnant women and there are limited data from the use of VPRIV in pregnant women. It is not known whether VPRIV would cause fetal harm when administered to a pregnant woman or would affect reproductive capacity. VPRIV should be administered during pregnancy only when clearly needed.

In Segment I, II, and III animal reproductive and developmental toxicology studies (see **Toxicology**) in rats and rabbits, the no observed effect level/no observed adverse effect level (NOEL/NOAEL) for velaglucerase alfa was the maximum dose evaluated: 17 mg/kg/dose for rats and 20 mg/kg/dose in rabbits, equal to 11-fold and 13-fold the maximum human dose of 60 U/kg on a milligrams-per-kilogram (mg/kg) basis. Velaglucerase alfa showed no evidence of impaired fertility or maternal or developmental treatment-related effects.

Nursing Women
There are no data from studies in lactating women. It is unknown if VPRIV is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VPRIV is administered to a lactating woman.

Pediatrics (2 - 17 years of age)
Twenty (20) of the 94 patients (21%) who received VPRIV during clinical studies were in the pediatric age range (2 to 17 years). No data are available from children under the age of 4 years. The safety and efficacy profiles were similar between pediatric and adult patients.

Table 1 - Age Distribution of Pediatric Patients (2 to 17 years) by Clinical Trial

	Study		
Age (years)	**032**	**034**	**039**
4	1		
6	2		
7	1		1
9	1	1	1
10		1	
12		1	
13		2	
14		3	2
15	1		
16	1	1	

Geriatrics (>65 years of age)

In clinical studies, a total of 57 patients 65 years of age or older were treated with velaglucerase alfa. Among 205 patients who participated in a clinical safety study and switched from imiglucerase to velaglucerase alfa, 52 patients were 65 years of age or older. The safety profile in elderly patients was consistent with that previously observed across pediatric and adult patients.

Monitoring and Laboratory Tests

No special laboratory tests are required for patients receiving VPRIV other than the usual tests that are required for monitoring patients with type 1 Gaucher disease.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse drug reactions (incidence ≥ 10%) reported in the clinical trials were abdominal pain/abdominal pain upper, arthralgia, asthenia/fatigue, back pain, bone pain, dizziness, headache, infusion-related reactions, pyrexia/body temperature increased, and upper respiratory tract infections. The only adverse reaction leading to discontinuation of VPRIV was an infusion-related reaction.

The most serious adverse drug reactions in patients in clinical trials were arthralgia, hypersensitivity reactions, and urticaria. Serious adverse drug reactions observed post-market were anaphylactic reaction, chest discomfort, dyspnea, pruritis, 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 data described below reflect exposure of 94 patients with type 1 Gaucher disease who received VPRIV at doses ranging from 15 to 60 U/kg every other week in 5 clinical studies. Fifty-four (54) patients were naïve to ERT and 40 patients switched from imiglucerase to VPRIV. Patients were between 4 and 71 years old at the time of first treatment with VPRIV, and included 46 male and 48 female patients.

The most serious adverse reactions in patients in clinical trials were hypersensitivity reactions. See **Warnings and Precautions, Immune** and **Adverse Reaction Overview**, Table 2.

Adverse drug reactions considered related to VPRIV are shown in **Table 2**. Information is presented by system organ class and frequency (very common ≥10%; common ≥1% and <10%;).

Table 2 - Adverse Drug Reactions Reported in Patients with Type 1 Gaucher Disease Treated With VPRIV During Clinical Trials

System Organ Class Preferred Term (Incidence Category)	Naïve to ERT N = 54	Switched from imiglucerase to VPRIV N = 40
	Number of Patients (%)	
Cardiac disorders		
Tachycardia (Common)	2 (3.7)	0 (0.0)
Gastrointestinal disorders		
Abdominal pain/abdominal pain upper (Very common)	10 (18.5)	6 (15)
Nausea (Common)	3 (5.6)	4 (10.0)
General disorders and administration site conditions		
Infusion-related reaction† (Very common)	28 (51.9)	9 (22.5)
Asthenia/fatigue (Very common)	8 (14.8)	5 (12.5)
Pyrexia/body temperature increased (Very common)	14 (25.9)	5 (12.5)
Immune system disorders		
Hypersensitivity reactions§ (Common)	2 (3.7)	1 (2.5)
Infections and Infestations		
Upper respiratory tract infections (Very common)	17 (31.5)	12 (30.0)
Investigations		
Activated partial thromboplastin time prolonged (Common)	6 (11.1)	2 (5.0)

Neutralizing antibody positive* (Common)	1 (1.9)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Bone pain (Very common)	13 (24.1)	1 (2.5)
Arthralgia (Very common)	12 (22.2)	9 (22.5)
Back pain (Very common)	9 (16.7)	7 (17.5)
Nervous system disorders		
Headache (Very common)	19 (35.2)	12 (30.0)
Dizziness (Very common)	12 (22.2)	3 (7.5)
Skin and subcutaneous tissue disorders		
Rash (Common)	2 (3.7)	1 (2.5)
Urticaria (Common)	2 (3.7)	1 (2.5)
Vascular disorders		
Hypertension (Common)	4 (7.4)	3 (7.5)
Hypotension (Common)	4 (7.4)	0 (0.0)
Flushing* (Common)	0 (0.0)	1 (2.5)

* See **Warnings and Precautions, Immune**
† Reactions occurring up to 24 hours after the start of the infusion
§ Includes dermatitis and anaphylactoid reaction

In clinical studies, 1 of 94 patients treated with VPRIV developed IgG-class antibodies to velaglucerase alfa. In this one event the antibodies were determined to be neutralizing in an in vitro assay. No infusion-related reactions were reported for this patient. It is unknown if the presence of IgG antibodies to velaglucerase alfa is associated with a higher risk of infusion reactions. No patients developed IgE antibodies to velaglucerase alfa.

Post-market Adverse Drug Reactions

The following adverse reactions have been identified during post approval use of VPRIV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Vomiting *
General Disorders and Administration Site Conditions: Chest discomfort
Immune System Disorders: Anaphylactic reaction
Respiratory, Thoracic and Mediastinal Disorder: Dyspnea
Skin and Subcutaneous Tissue Disorders: Pruritis

** In some cases vomiting can be serious.*

DRUG INTERACTIONS

No serious drug interactions have been reported.

Overview

Velaglucerase alfa is a purified form of the naturally occurring enzyme glucocerebrosidase; it is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

Drug-Drug Interactions

Interactions with other drugs have not been established.

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

VPRIV should be administered under the supervision of a healthcare professional. Home administration may be considered for patients who are tolerating their infusions well.

- Patients currently being treated with other enzyme replacement therapy for type 1 Gaucher disease may be switched to VPRIV using the same dose and frequency.

Recommended Dose and Dosage Adjustment

The recommended dose is 60 U/kg administered every other week as a 60-minute intravenous (IV) infusion.

Dosage adjustments can be made on an individual basis based on achievement and maintenance of therapeutic goals. Clinical studies have evaluated doses ranging from 15 to 60 U/kg every other week.

Missed Dose

If a scheduled infusion is missed, administer the dose as soon as possible if it can be given at least 7 days before the next scheduled dose.

Administration

VPRIV should be administered by IV infusion over a period of 60 minutes.

Reconstitution:
VPRIV should be prepared by and administered under the supervision of a healthcare professional.

Use aseptic technique.

VPRIV is a lyophilized powder, which requires reconstitution and dilution, and is intended for intravenous infusion only. VPRIV contains no preservatives and vials are single-use only. Discard any unused solution. VPRIV should be prepared as follows:

1. Determine the number of vials to be reconstituted based on the individual patient's weight and the prescribed dose. Follow the instructions in **Table 4** for reconstitution.

Table 4 - Reconstitution Instructions

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
400 U/vial	4.3 mL	4.0 mL	100 U/mL

2. Upon reconstitution, mix vials gently. DO NOT SHAKE.
3. Prior to further dilution, visually inspect the solution in the vials; the solution should be clear to slightly opalescent and colorless; do not use if the solution is discolored or if foreign particles are present.
4. Withdraw the calculated volume of drug from the appropriate number of vials and dilute the total volume required in 100 mL of 0.9% sodium chloride solution suitable for IV administration. Mix gently. DO NOT SHAKE. Slight flocculation (described as white irregularly shaped particles) may occasionally occur.

VPRIV should be administered through a 0.2 μm in-line filter over a period of 60 minutes. The infusion should be completed within 24 hours of reconstitution of vials. VPRIV should not be infused with other products in the same infusion tubing as the compatibility in solution with other products has not been evaluated.

OVERDOSAGE

There is no experience with overdosage of VPRIV in humans.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Gaucher disease is an autosomal recessive disorder caused by mutations in the GBA gene which results in a deficiency of the lysosomal enzyme beta-glucocerebrosidase. This enzymatic deficiency causes an accumulation of glucocerebroside primarily in macrophages, giving rise to foam cells or "Gaucher cells". In this lysosomal storage disorder (LSD), clinical features are reflective of the distribution of Gaucher cells in the liver, spleen, bone marrow, skeleton, and lungs. The accumulation of glucocerebrosidase in the liver and spleen leads to organomegaly. Bone involvement results in skeletal abnormalities and deformities as well as bone pain crises. Deposits in the bone marrow and splenic sequestration lead to clinically significant anemia and thrombocytopenia.

Velaglucerase alfa, the active ingredient in VPRIV, supplements or replaces beta-glucocerebrosidase, the enzyme that catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside and correcting the pathophysiology of Gaucher disease.

Pharmacodynamics

The active ingredient of VPRIV is velaglucerase alfa which is produced by gene activation technology in a human cell line. Velaglucerase alfa is a glycoprotein; the monomer is approximately 63 kDa, has 497 amino acids, and the same amino acid sequence as the naturally occurring human enzyme glucocerebrosidase.

Velaglucerase alfa is manufactured to contain predominantly high mannose-type N-linked glycans. There are 5 potential N-linked glycosylation sites; four of these sites are occupied. This modification facilitates internalization of the enzyme by the phagocytic target cells via the mannose receptor. Velaglucerase alfa catalyzes the hydrolysis of the glycolipid glucocerebrosidase to glucose and ceramide in the lysosome.

Pharmacokinetics

The pharmacokinetic (PK) characteristics of VPRIV at doses of 15, 30, 45, and 60 U/kg were evaluated in a total of 37 patients with type 1 Gaucher disease receiving 60-minute intravenous infusions every other week (EOW) in 3 clinical studies for up to 2 years (see **Table 5**).

At all doses, velaglucerase alfa serum concentrations rose rapidly for the first 20 minutes of the

60-minute infusion before leveling off, and C_{max} was typically attained between 40 and 60 minutes after the start of the infusion. T_{max} values for individual subjects ranged from 20 to 65 minutes after the start of infusion with one exception; one subject had an anomalous pharmacokinetic profile with a T_{max} of 5 minutes. After the end of the infusion, velaglucerase alfa serum concentrations fell rapidly in a monophasic or biphasic fashion with a mean $t_{1/2}$ ranging from 5 to 12 minutes for the 15, 30, 45, and 60 U/kg doses.

Velaglucerase alfa exhibited an approximately linear (i.e., first-order) pharmacokinetic profile, and C_{max} and AUC increased approximately proportional to the dose. The high clearance of velaglucerase alfa from serum (mean 6.7 to 7.6 mL/min/kg in Study 032) is consistent with the rapid uptake of velaglucerase alfa into macrophages via mannose receptors.

For the 2 dose groups in Study 032, the range of velaglucerase alfa clearance in pediatric patients (n=7, age range 4 to 17 years) was contained within the range of clearance values in adult patients (n=15, age range 19 to 62 years). Additionally, there were no apparent pharmacokinetic differences between male and female patients with type 1 Gaucher disease in this study.

None of the subjects were positive for anti-velaglucerase alfa antibodies on the days of pharmacokinetic evaluation. Therefore, it was not possible to evaluate the effect of antibody response on the pharmacokinetic profile of velaglucerase alfa.

Table 5 - Pharmacokinetic Profile of Velaglucerase alfa in Treatment-Naïve Patients with Type 1 Gaucher Disease

Study	Dose (EOW)	Total Weeks on Treatment	N	$t_{1/2}$ (min)	CL (mL/min/kg)	V_{ss} (% B.W.)
025	15 U/kg	1	3	5.3 ± 1.3	10.1 ± 2.3	7.5 ± 0.9
	30 U/kg	3	2	10.3 ± 1.0	13.1 ± 4.9	19.7 ± 8.9
	60 U/kg	1 or 5	11	9.8 ± 2.8	12.6 ± 3.7	17.5 ± 5.1
	60 U/kg	37 or 39	8	6.8 ± 1.5	5.6 ± 4.0	5.4 ± 3.7
025EXT	30 U/kg	105	9	8.9 ± 2.2	6.5 ± 2.0	8.3 ± 2.0
032	45 U/kg	1	10	12.4 ± 3.1	7.0 ± 2.6	10.4 ± 6.6
	45 U/kg	37	10	11.9 ± 5.5	7.6 ± 3.6	10.8 ± 5.9*
	60 U/kg	1	12	11.5 ± 3.5	7.2 ± 3.5	10.6 ± 6.0
	60 U/kg	37	12	11.4 ± 3.2	6.7 ± 2.9	8.2 ± 3.9

Values are mean ± SD
* n=9

STORAGE AND STABILITY

VPRIV should be stored in a refrigerator at 2 to 8ºC (36 to 46ºF).

Do not use VPRIV after the expiration date on the vial. Do not freeze. Protect from light.

SPECIAL HANDLING INSTRUCTIONS

VPRIV should be administered through a 0.2µm in-line filter over a period of 60 minutes. The infusion should be completed within 24 hours of reconstitution of vials. VPRIV should not be infused with other products in the same infusion tubing as the compatibility in solution with other products has not been evaluated.

As VPRIV contains no preservatives, once reconstituted the product should be used immediately. If immediate use is not possible, the reconstituted or diluted product may be stored for up to 24 hours at 2 to 8ºC (36 to 46ºF). The infusion should be completed within 24 hours of reconstitution of vials.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VPRIV is a sterile, preservative free, lyophilized powder requiring reconstitution and further dilution prior to use (see **Special Handling Instructions**). It is supplied in individually packaged glass vials, which are closed with a butyl rubber stopper with a fluoro-resin coating and are sealed with an aluminum overseal with a flip-off plastic cap. The vials are intended for single use only.

VPRIV is available in vials containing 400 U each.

VPRIV is available in a pack size of 1 vial per carton.

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

Citric acid monohydrate.
Polysorbate 20.
Sodium citrate dihydrate.
Sucrose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: velaglucerase alfa

Chemical name: glucocerebrosidase, β-D-glucosyl-N-acylsphingosine glucohydrolase, acid-β-glucosidase

Molecular formula and molecular mass: Velaglucerase alfa is a glycoprotein; the monomer is approximately 63 kDa, has 497 amino acids, and the same amino acid sequence as the naturally occurring human enzyme, glucocerebrosidase.

Structural formula: Velaglucerase alfa is human glucocerebrosidase secreted from a transfected continuous human cell line (HT-1080), generated using gene activation technology. Velaglucerase alfa is manufactured to contain predominantly high mannose-type N-linked glycans. There are 5 potential N-linked glycosylation sites; four of these sites are occupied.

Amino Acid Sequence of Secreted Velaglucerase alfa using Three-letter Code

1 Ala Arg Pro **Cys** Ile Pro Lys Ser Phe Gly Tyr Ser Ser Val Val **Cys** Val **Cys** Asn Ala 20
21 Thr Tyr **Cys** Asp Ser Phe Asp Pro Pro Thr Phe Pro Ala Leu Gly Thr Phe Ser Arg Tyr 40
41 Glu Ser Thr Arg Ser Gly Arg Arg Met Glu Leu Ser Met Gly Pro Ile Gln Ala Asn His 60
61 Thr Gly Thr Gly Leu Leu Leu Thr Leu Gln Pro Glu Gln Lys Phe Gln Lys Val Lys Gly 80
81 Phe Gly Gly Ala Met Thr Asp Ala Ala Ala Leu Asn Ile Leu Ala Leu Ser Pro Pro Ala 100
101 Gln Asn Leu Leu Leu Lys Ser Tyr Phe Ser Glu Glu Gly Ile Gly Tyr Asn Ile Ile Arg 120
121 Val Pro Met Ala Ser **Cys** Asp Phe Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro Asp 140
141 Asp Phe Gln Leu His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys Leu Lys Ile Pro Leu 160
161 Ile His Arg Ala Leu Gln Leu Ala Gln Arg Pro Val Ser Leu Leu Ala Ser Pro Trp Thr 180
181 Ser Pro Thr Trp Leu Lys Thr Asn Gly Ala Val Asn Gly Lys Gly Ser Leu Lys Gly Gln 200
201 Pro Gly Asp Ile Tyr His Gln Thr Trp Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala Tyr 220
221 Ala Glu His Lys Leu Gln Phe Trp Ala Val Thr Ala Glu Asn Glu Pro Ser Ala Gly Leu 240
241 Leu Ser Gly Tyr Pro Phe Gln **Cys** Leu Gly Phe Thr Pro Glu His Gln Arg Asp Phe Ile 260
261 Ala Arg Asp Leu Gly Pro Thr Leu Ala Asn Ser Thr His His Asn Val Arg Leu Leu Met 280
281 Leu Asp Asp Gln Arg Leu Leu Leu Pro His Trp Ala Lys Val Val Leu Thr Asp Pro Glu 300
301 Ala Ala Lys Tyr Val His Gly Ile Ala Val His Trp Tyr Leu Asp Phe Leu Ala Pro Ala 320
321 Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe Pro Asn Thr Met Leu Phe Ala Ser Glu 340

341 Ala **Cys** Val Gly Ser Lys Phe Trp Glu Gln Ser Val Arg Leu Gly Ser Trp Asp Arg Gly 360

361 Met Gln Tyr Ser His Ser Ile Ile Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr Asp 380

381 Trp Asn Leu Ala Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg Asn Phe Val Asp Ser 400

401 Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe Tyr Lys Gln Pro Met Phe Tyr His Leu 420

421 Gly His Phe Ser Lys Phe Ile Pro Glu Gly Ser Gln Arg Val Gly Leu Val Ala Ser Gln 440

441 Lys Asn Asp Leu Asp Ala Val Ala Leu Met His Pro Asp Gly Ser Ala Val Val Val Val 460

461 Leu Asn Arg Ser Ser Lys Asp Val Pro Leu Thr Ile Lys Asp Pro Ala Val Gly Phe Leu 480

481 Glu Thr Ile Ser Pro Gly Tyr Ser Ile His Thr Tyr Leu Trp Arg Arg Gln 497

Asn = potential N-linked glycosylation site
Cysteine residues are highlighted

Physicochemical properties: Velaglucerase alfa drug substance is a frozen liquid, formulated in 50 mM sodium citrate at pH 6.0 containing 0.01% (vol/vol) polysorbate 20. The specific activity is 40 U/mg.

CLINICAL TRIALS

Study demographics and trial design

Table 6 - Summary of patient demographics for clinical trials in specific indication

Study #	Trial Design	Dosage, Route of Administration, Duration	Study Subjects[a] (N)	Mean Age (Range)	Gender
025	Phase I/II, Single center, Open label	15 U/kg to 60 U/kg[b] velaglucerase alfa EOW, IV infusion 9 months	12	41.7 (18.8 - 69.8)	Male and Female
025EXT	Phase I/II, Multicenter, Open label extension	60 U/kg-30 U/kg velaglucerase alfa EOW, IV infusion 60 months	10	38.8 (19 - 63)	Male and Female
032	Phase III, Multicenter, Randomized, Double-blind, Parallel group, Controlled	45 U/kg or 60 U/kg velaglucerase alfa EOW, IV infusion 12 months	25	26.0 (4.0 - 62)	Male and Female
039	Phase III, Multicenter, Randomized, Double-blind, Active comparator, Controlled	60 U/kg velaglucerase alfa EOW, IV infusion for 60 minutes 60 U/kg imiglucerase EOW, IV infusion for 1-2 hours 9 months	34	29.7 (3.0 - 73)	Male and Female
034	Phase II/III, Multicenter, Open label	15 U/kg to 60 U/kg velaglucerase alfa EOW, IV infusion 12 months	40	35.6 (9.0 - 71)	Male and Female
044	Phase I/II, Multicenter, Open-label extension	15 U/kg to 60 U/kg velaglucerase alfa EOW, IV infusion	95	30 (4.0-72)	Male and Female
058	Phase III Open-label Treatment Protocol	15 U/kg to 60 U/kg velaglucerase alfa EOW, IV infusion	211	50.6 (6-89)	Male and Female

[a] Number of patients dosed

[b] The first patient dosed with VPRIV in the dose-escalation phase received two 15-U/kg doses and then one 30-U/kg escalation dose. Based on acceptable safety evaluations, all 3 patients in the dose-escalation cohort had their doses increased to 60 U/kg. All subsequent patients in this study received 60 U/kg every other week for the entire study

The safety and efficacy of VPRIV (velaglucerase alfa) were assessed in 5 clinical studies in a total of 94 patients with type 1 Gaucher disease who were age 2 years and older. Studies 025, 032, and 039 were conducted in patients naïve to enzyme replacement therapy. Study 025EXT was an extension to Study 025. A treatment-naïve patient was defined differently for each study. Study 034 was conducted in patients who were receiving imiglucerase treatment. Study 044 was an extension study of patients from Studies 032, 039, and 034.

In both treatment-naïve patients and patients switched from imiglucerase to VPRIV, VPRIV was administered every other week at doses ranging from 15 to 60 U/kg. Of the 54 treatment-naïve

patients who received VPRIV, 41 (76%) received a starting dose of 60 U/kg every other week. VPRIV was administered by IV infusion over 60 minutes.

In Studies 025EXT and 034, patients for whom VPRIV was well-tolerated were offered home therapy under the direction of the Investigator. In Study 025EXT, 7 of 10 patients (70%) received home therapy at least once during 60 months of treatment. In Study 034, 25 of 40 patients (63%) received home therapy at least once during the 12-month study.

Study results

Studies in Treatment Naïve Patients

Study 025 was a 9-month, open-label study in 12 adult (≥18 years) patients who were naïve to enzyme replacement therapy (defined as having not been treated with enzyme replacement therapy for at least 12 months prior to study entry). VPRIV was initially administered in a dose-escalating fashion in the first 3 patients (15, 30, 60 U/kg) and the 9 remaining patients began treatment with 60 U/kg.

Clinically meaningful and statistically significant improvements from baseline were observed in hemoglobin concentration and platelet counts as early as 3 months and in liver and spleen volumes at both 6 months and 9 months following the initiation of treatment with VPRIV.

Ten (10) of the patients who completed Study 025 enrolled in an open-label extension study (**Study 025EXT**). After a minimum of 12 months of continuous treatment with VPRIV, all patients qualified to have the dose of VPRIV reduced in a step-wise fashion from 60 to 30 U/kg after achieving at least 2 of the 4 "Year 1" therapeutic goals of ERT for type 1 Gaucher disease. Patients received VPRIV at a median dose of 35 U/kg (34 to 60 U/kg) every other week for up to 84 months (7 years). VPRIV continued to demonstrate sustained clinical activity during treatment observed by improvements in hemoglobin concentrations and platelet counts and reduced liver and spleen volumes (see **Table 7**).

Table 7 – Median observed values and mean change from baseline in Study 025 EXT – ITT population

Clinical Parameters	**Median Observed Values Baseline * [Range]**	**Median Observed Values 7 Years § [Range]**	**Mean Change from Baseline (95% CI) 7 years §**
N	10	10	10
Hemoglobin concentration (g/dL)	11.10 [9.8, 12.9]	13.40 [11.6, 16]	2.0 (1.4, 2.6)
Platelet count (x 10^9/L)	62.25 [37.0, 98.5]	122.0 [88, 166]	63.9 (45.7, 82.1)
Liver volume†	4.40 [2.6, 5.8]	2.30 [1.6, 4.0]	-1.8 (-2.5, -1.2)
Spleen volume†	3.80 [2.2, 6.5]	0.50 [0.4, 4.9]	-3.0 (-3.9, -2.2)

* Baseline is defined as data collected at the baseline visit in Study 025
§ The last MRI assessment in the study was at 81 months of observation
† Normalized % of body weight

For the 10 patients in Study 025EXT, the liver multiple of normal was 1.760 [range: 1.04, 2.32] and 0.920 [range: 0.64, 1.6] at baseline (in Study 025) and 7 years, respectively. The spleen multiple of normal was 19.00 [range: 11.00, 32.50] and 2.5 [range: 2, 24.5] at baseline (in Study 025) and 7 years, respectively.

The effect of VPRIV on bone parameters, including bone marrow burden (BMB) assessed by magnetic resonance imaging and bone mineral density (BMD) assessed by dual x-ray absorptiometry, was examined in this study. The median BMB score at baseline was 6.0. At month 9, the median BMB was 3.5. By month 57, 8 patients remained in 025EXT and had achieved a clinically meaningful reduction from baseline of at least 2 points in the lumbar spine BMB score. The mean change from baseline after 7 years of treatment with VPRIV for the lumbar spine and femoral neck BMDs (Z-score) were 0.7 (95%CI: 0.4, 1.0) and 0.5 (95%CI: 0.2, 0.7), respectively. Z-score changes in the lumbar spine and femoral neck were clinically meaningful and statistically significant by 24 and 33 months, respectively.

Study 032 was a 12-month, randomized, double-blind, parallel-group efficacy study in 25 patients age 2 years and older who were naïve to enzyme replacement therapy (defined as having not been treated with enzyme replacement therapy for at least 30 months prior to study entry). Patients were required to have Gaucher disease-related anemia and either thrombocytopenia or organomegaly. Patients were randomized to receive VPRIV at a dose of either 45 U/kg (N=13) or 60 U/kg (N=12) every other week. A dose-related effect in favor of 60 U/kg was observed in relation to the 45 U/kg dose group after 12 months of treatment (see **Table** 8). There were no data to suggest that there were any clinically significant differences between the 60 U/kg and 45 U/kg dose groups in terms of safety.

Table 8 - Mean change from baseline to 12 months for key efficacy parameters in treatment-naïve patients with Type 1 Gaucher disease in Study 032

Clinical Parameters	Mean Change from Baseline ± SE p-value[1]	
	VPRIV 60 U/kg EOW	VPRIV 45 U/kg EOW
N	12	13
Hemoglobin Concentration (g/dL)	2.43 ±0.32 p<0.0001	2.44±0.44 p=0.0001**
Platelet count (x 10^9/L)	50.9 ±12.2 p=0.0016**	40.9 ±13.6 p=0.0111**
Liver volume (% B.W.)	-0.84 ±0.33 p=0.0282	-0.30 ±0.29 p=0.3149
Spleen volume (% B.W.)	-1.92 ±0.51 p=0.0032**	-1.87 ±0.60 p=0.0085**

[1] p-value based on paired t-test

** Statistically significant after adjusting for performing multiple tests [on the following endpoints: mean within patient changes in hemoglobin concentration (45 U/kg arm only), platelet counts, and liver and spleen volumes from baseline to Month 12 separately for each randomized treatment group.]

The reductions in liver and spleen volumes were larger in the 60 U/kg VPRIV dose group. In this group, liver volume was reduced from 1.46 to 1.22 times normal (mean reduction of 17%) and spleen volume was reduced from 14.0 to 5.75 times normal (mean reduction of 50%). In the 45 U/kg group, liver volume was reduced from 1.40 to 1.24 times normal (mean reduction of 6%) and spleen volume was reduced from 14.5 to 9.50 times normal (mean reduction of 40%).

Study 039 was a 9-month, randomized, double-blind, active-comparator (imiglucerase) controlled, non-inferiority, parallel-group efficacy study in 34 patients age 2 years and older who were naïve to enzyme replacement therapy (defined as having not been treated with enzyme replacement therapy for at least 12 months prior to study entry). Patients were required to have Gaucher disease-related anemia and either thrombocytopenia or organomegaly. Patients received either 60 U/kg of VPRIV (N=17) or 60 U/kg of imiglucerase (N=17) every other week.

The mean absolute increase from baseline in hemoglobin concentrations was 1.624 g/dL (±0.223 SE) following 9 months of treatment with VPRIV. This increase in hemoglobin concentration was demonstrated to be clinically and statistically non-inferior to imiglucerase (mean treatment difference of change from baseline to 9 months [VPRIV – imiglucerase]: 0.135 g/dL). There were no statistically significant differences between VPRIV and imiglucerase in changes in platelet counts and liver and spleen volumes after 9 months of VPRIV treatment, and the time to first hemoglobin response (defined as 1g/dL increase from baseline).

Study in Patients Switching from Imiglucerase Treatment to VPRIV

Study 034 was a 12-month, open-label safety study in 40 patients age 2 years and older who had been receiving treatment with imiglucerase at doses ranging between 15 to 60 U/kg for a minimum of 30 consecutive months. Patients were required to have a stable dose of imiglucerase for at least 6 months prior to study enrollment. Treatment with VPRIV was administered as the same number of units and regimen as their imiglucerase dose. Hemoglobin concentration and platelet counts were evaluated as changes from baseline, which was defined as the end of the patient's treatment with imiglucerase.

In patients who switched from imiglucerase to VPRIV, hemoglobin concentrations and platelet counts were sustained at therapeutic levels through 12 months of treatment. The median value for hemoglobin concentrations at baseline was 13.8 g/dL (range: 10.4, 16.5) and after 12 months of treatment with VPRIV the median value was 13.5 g/dL (range: 10.8, 16.1). The median value for platelet counts at baseline was 162 x 10^9/L (range: 29.0, 399.0) and after 12 months of treatment with VPRIV the median value was 174 x 10^9/L (range: 24.0, 408.0).

Other Studies

Extension Study 044 [032, 034 and 039]

A total of 95 adult and pediatric patients, who received VPRIV in Studies 032, 034, and 039 enrolled in this open-label extension study. Fifty-seven (57) patients were treatment-naïve and 22 were 17 years of age or younger. All patients received at least 2 years of enzyme replacement therapy and were followed for a mean of 4.5 years (min 2.3 yrs, max 5.8 yrs). In this study, in treatment-naïve patients after 24 months of VPRIV treatment versus baseline the mean hemoglobin concentration increased by 2.75 g/dL (95% CI: 2.28, 3.22), mean platelet count increased by 87.85 X10^9/L (95% CI: 72.69, 103.00), normalized liver volume decreased by 1.21 (95% CI: -1.50, -0.91) and normalized spleen volume decreased by 2.66 (95% CI: -3.50, -1.82). In patients who switched from imiglucerase to VPRIV, hemoglobin concentrations and platelet counts were sustained through 24 months of treatment with a mean change from baseline in hemoglobin of -0.05 g/dL (95% CI: -0.34, 0.25) and a mean change from baseline in platelet count of 9.03 X 10^9/L (95% CI: -2.60, 20.66). Normalized liver and spleen volumes were also sustained, with a mean change from baseline in normalized liver volume of -0.026% body weight (CI: -0.10, 0.047) and a mean change in normalized spleen volume of -0.11% body weight (CI: -0.191, -0.029). In children, increases in the mean height Z-score were seen through 60 months of treatment in the overall treatment-naïve population. Similar treatment effects were seen through 48 months in children who received 9 months of imiglucerase followed by VPRIV. Treatment effects on hemoglobin, platelet count, organ volumes, bone mineral density and height were maintained through the end of the study. The safety profile observed in the extension study is consistent with that observed in other studies.

Study 058

In this study, which enrolled both treatment-naïve and patients transitioning from imiglucerase, the safety profile in 205 patients previously treated with imiglucerase was similar to that observed in other clinical trials. Observation regarding treatment goals suggests that an apparent

increase from baseline in hemoglobin concentration and platelet count was observed in the 4 treatment-naïve patients with post-baseline data. Among previously treated patients mean hemoglobin concentration and platelet count were maintained throughout the study and remained within the normal range.

Comparative Bioavailability Studies

No comparative bioavailability studies have been performed with VPRIV.

DETAILED PHARMACOLOGY

A series of studies were performed comparing the biological and biochemical effects of velaglucerase alfa and imiglucerase in a mouse model of Gaucher disease (9V/null mouse) following repeat administration of both enzymes (5, 15, or 60 U/kg). Results showed that velaglucerase alfa and imiglucerase similarly restored normal lipid (glucocerebroside) content in the liver, while the lipid content in the spleen was unaffected in comparison to wild-type controls. Neither enzyme affected the lipid content of the lung. Both enzymes comparably reduced the number of Gaucher cells in liver.

A series of nonclinical pharmacokinetic studies in rats, dogs, and rhesus monkeys demonstrated that velaglucerase alfa was distributed into the tissue by 1st order elimination kinetics. The serum elimination half-life of velaglucerase alfa at a low-dose of 0.84 mg/kg was approximately 2, 4, and 5 minutes in rats, dogs, and rhesus monkeys, respectively. In rhesus monkeys, the elimination half-lives increased from 5 minutes at 0.84 mg/kg to 11 minutes at the maximum dose of 17 mg/kg. C_{max} was proportional to dose in all 3 species evaluated, whereas AUC was not dose-proportional. Serum clearance mechanisms (presumably via mannose receptors) appear to become saturated at dose levels >3 mg/kg.

A tissue biodistribution study in rats using ^{125}I-labeled velaglucerase alfa demonstrated that the greatest amount of administered dose was found in the liver 20 minutes after dosing (~70% at a dose of 1.1 mg/kg) with lesser amounts localized in other organs (1.5% in spleen, 3.0% in kidney, and 0.5% in bone/bone marrow). Tissue elimination from the liver and spleen, organs associated with Gaucher disease, was biphasic. Initial half-lives were approximately 1 hour in both organs and elimination half-lives ranged from 13 hours (spleen) to 17 hours (liver), suggesting that velaglucerase alfa would not be expected to accumulate in these organs following repeated, every other week, IV dosing.

TOXICOLOGY

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, repeated dose toxicity, and developmental and reproductive toxicology studies. The only treatment-related finding was observed in the rat repeat-dose and reproduction studies, manifesting as swelling and/or redness of the face and/or paws. Swelling

was transient, lasting for 1 to 4 hours post-dosing. Histamine monitoring revealed increased values at 15 minutes post-treatment, whereas complement levels were unaffected. However, a similar response was not observed for rabbits, dogs or monkeys. Hence, the post-dosing swelling was considered to be a rat-specific response to velaglucerase alfa. Genotoxic and carcinogenic potential are not expected.

Acute Toxicity Studies

The acute toxicity of velaglucerase alfa was evaluated in rats. Doses of velaglucerase alfa up to 23 mg/kg, 15-fold the recommended dose in humans, have been tested without any adverse toxicity.

Repeat-dose Toxicity Studies

Nonclinical data reveal no special hazard for humans based on 3- and 6-month, repeat-dose toxicology studies in rats and a 6-month, repeat-dose toxicity study in rhesus monkeys. The maximum no observed effect level of at least 17 mg/kg velaglucerase alfa was established, providing safety margins (on a mg/kg basis) of approximately 44-fold for the lowest human dose (0.38 mg/kg, 15 U/kg) and 11-fold for the highest human dose (1.5 mg/kg; 60 U/kg).

Reproduction and Teratology

A series of developmental and reproductive toxicology studies were conducted in rats and rabbits. These studies included a Segment I study in rats (male and female fertility and early embryonic development), Segment II studies in rats and rabbits (embryo-fetal development; dose-range finding and definitive studies), and a Segment III study in rats (pre- and post-natal development and maternal function).

Reproductive toxicity studies performed in male and female rats included doses up to 17 mg/kg, or 11-fold the maximum human dose of 60 U/kg on a mg-per-kg basis, and revealed no evidence of impaired male or female fertility. Developmental toxicity studies performed in female rats and rabbits at maximum doses of 17 and 20 mg/kg, or 11-fold and 13-fold the maximum human dose of 60 U/kg on a mg-per-kg basis, resulted in no maternal or developmental treatment-related effects.

Mutagenicity and Carcinogenicity Studies

No animal studies have been conducted to assess the mutagenic, genotoxic, and carcinogenic potential for velaglucerase alfa. This is consistent with the ICH guidelines S1A "Guidelines on the Need for Carcinogenicity Studies of Pharmaceuticals" and S6 "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals." As a purified form of the naturally occurring enzyme glucocerebrosidase, such potential is not expected for velaglucerase alfa.

PART III: CONSUMER INFORMATION

Pr VPRIV®
(VEE-priv)
velaglucerase alfa

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

ABOUT THIS MEDICATION

What the medication is used for:
VPRIV is an enzyme replacement therapy for pediatric and adult patients with type 1 Gaucher disease.

What it does:
Gaucher disease is genetic. Patients with Gaucher disease do not produce enough of their own enzyme, glucocerebrosidase, which breaks down a type of lipid (fat) called glucocerebroside. The reduced enzyme levels in patients cause this lipid to collect in white blood cells in some organs including the brain, bone marrow, liver and spleen. Treatment with VPRIV helps replace the low enzyme levels, which helps reduce the lipid deposits.

When it should not be used:
Do not use VPRIV if you are allergic (hypersensitive) to velaglucerase alfa or any of the other nonmedicinal ingredients.

What the medicinal ingredient is:
The active ingredient in VPRIV is velaglucerase alfa. Velaglucerase alfa is an enzyme similar to the naturally occurring human enzyme glucocerebrosidase.

What the important nonmedicinal ingredients are:
The other ingredients are: citric acid monohydrate, polysorbate 20, sodium citrate dihydrate, and sucrose.

What dosage forms it comes in:
400 U/vial, packed powder for solution for injection. After reconstitution, each vial contains 100 U/mL.

WARNINGS AND PRECAUTIONS

BEFORE you use VPRIV talk to your doctor or pharmacist if:

- **You have previously experienced an infusion-related reaction or allergic reaction with other ERT for Gaucher disease.**

Hypersensitivity reactions including symptoms consistent with anaphylaxis (a severe allergic reaction) such as a tightening of the airways going into the lungs and shortness of breath have been observed in some patients treated with VPRIV.

As with any intravenous protein product, allergic reactions are possible.

Appropriate medical support should be readily available when VPRIV is administered.

Treatment with VPRIV should be approached with caution in patients who have had an allergic reaction to the active ingredient or the other medicinal ingredients in the drug product or to other enzyme replacement therapy.

If you are treated with VPRIV you may experience side effects during or following an infusion. This is known as an infusion related reaction and can sometimes be severe.

Infusion related reactions include headache, dizziness, low or high blood pressure, nausea, tiredness, and fever. If you have an infusion-related reaction, tell your doctor immediately.

If you have an infusion-related reaction you may be given additional medicines to treat or help prevent future reactions. These medicines may include antihistamines, antipyretics (for treating fever), and corticosteroids.

If the infusion-related reaction is severe, your doctor will stop the intravenous infusion immediately and start giving you appropriate medical treatment.

Most of the time, you can still be given VPRIV even if these symptoms occur.

INTERACTIONS WITH THIS MEDICATION

There is no known interaction of VPRIV with other medicines.

PROPER USE OF THIS MEDICATION

Treatment with VPRIV should be supervised by a physician or other experienced health care provider.

Usual dose:
After reconstitution, VPRIV has to be diluted in 100 mL 0.9% sodium chloride solution before use. The usual dose is an infusion of 60 U/kg. Doses less than 60 U/kg also have been used (15 U/kg up to 60 U/kg). After dilution VPRIV is given through a vein (drip feed). The infusion will normally last for 1 hour and will be given every other week.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you have missed a dose, please contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, VPRIV can cause side effects, although not everybody experiences them. Most side effects are mild to moderate and generally are associated with the infusion; however some side effects may be serious and may need treatment. Over time the number of these infusion-related reactions generally decreases. If you have any of these side effects talk to you doctor immediately.

Very common side effects (more than 1 per 10 patients) are:

- Headache
- Dizziness
- Bone pain
- Back pain
- Abdominal pain
- Infusion-related reaction
- Weakness/loss of strength/fatigue
- Fever/body temperature increased
- Colds and coughs

Common side effects (more than 1 per 100 patients) are:

- Nausea
- Decreased blood pressure
- Increased blood pressure
- Neutralizing antibody positive
- Flushing
- Rapid heart beat

In clinical trials, the most serious adverse reactions observed were allergic reactions. If you have an allergic reaction following administration of VPRIV, contact your doctor immediately.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common (occurring in ≥10% in clinical studies)	Arthralgia: Joint Pain		✓	
Common (occurring in ≥1% and <10% in clinical studies)	Hypersensitivity Reactions		✓	
	Urticaria: Rash/Hives		✓	

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your
Unknown*	Anaphylactic Reaction: severe allergic reaction		✓	✓
	Chest Discomfort		✓	
	Dyspnea: Trouble Breathing		✓	
	Pruritis: Itchy Skin		✓	
	Vomiting		✓	

**Frequency of event cannot be determined from available data.*
This is not a complete list of side effects. For any unexpected effects while taking VPRIV, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of reach of children. Store under refrigeration at 2°C to 8°C (36°F to 46°F) in the original outer packaging. Do not freeze. Protect from light. Do not use after the expiration date on the vial.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about VPRIV:

- 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 (http://hc-sc.gc.ca/index-eng.php); Shire Canada's website (www.shirecanada.com), or by calling 1-800-268-2772.

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

Last revised: July 30, 2019