

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrVPRIV®**

velaglucerase alfa

Powder for Solution for Injection  
400 U/vial, Intravenous

Enzyme Replacement Therapy  
ATC code: A16AB10

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

Date of Initial Approval:  
October 1, 2010

Date of Revision:  
December 21, 2020

Submission Control No: 241844

VPRIV® and the VPRIV Logo® are registered trademarks of Shire Human Genetic Therapies, Inc.  
TAKEDA™ and the TAKEDA Logo® are trademarks of Takeda Pharmaceutical Company Limited, used under license.

**RECENT MAJOR LABEL CHANGES**

Warnings and Precautions, Immunogenicity (8)	9/2020
Warnings and Precautions, Infusion-Related Reactions (8)	9/2020
Warnings and Precautions, Breast-feeding (8.1.2)	9/2020

**TABLE OF CONTENTS**

<b>PART I: HEALTH PROFESSIONAL INFORMATION</b> .....	<b>4</b>
<b>1 INDICATIONS</b> .....	<b>4</b>
<b>2 CONTRAINDICATIONS</b> .....	<b>4</b>
<b>4 DOSAGE AND ADMINISTRATION</b> .....	<b>4</b>
4.1 Dosing Considerations.....	4
4.2 Recommended Dose and Dosage Adjustment.....	4
4.3 Administration.....	4
4.4 Reconstitution.....	4
4.5 Missed Dose.....	5
<b>5 OVERDOSAGE</b> .....	<b>5</b>
<b>6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING</b> .....	<b>5</b>
<b>7 DESCRIPTION</b> .....	<b>6</b>
<b>8 WARNINGS AND PRECAUTIONS</b> .....	<b>6</b>
8.1 Special Populations.....	7
8.1.1 Pregnant Women.....	7
8.1.2 Breast-feeding.....	8
8.1.3 Pediatrics.....	8
8.1.4 Geriatrics.....	8
<b>9 ADVERSE REACTIONS</b> .....	<b>8</b>
9.1 Adverse Reaction Overview.....	8
9.2 Clinical Trial Adverse Reactions.....	9
9.6 Post-Market Adverse Reactions.....	10
<b>10 DRUG INTERACTIONS</b> .....	<b>10</b>
10.1 Serious Drug Interactions Box.....	10
10.2 Overview.....	11
10.3 Drug-Drug Interactions.....	11
10.4 Drug-Food Interactions.....	11
10.5 Drug-Herb Interactions.....	11
10.6 Drug-Laboratory Test Interactions.....	11
<b>11 ACTION AND CLINICAL PHARMACOLOGY</b> .....	<b>11</b>
11.1 Mechanism of Action.....	11
11.2 Pharmacodynamics.....	11
11.3 Pharmacokinetics.....	12
<b>12 STORAGE, STABILITY AND DISPOSAL</b> .....	<b>13</b>
<b>13 SPECIAL HANDLING INSTRUCTIONS</b> .....	<b>13</b>

**PART II: SCIENTIFIC INFORMATION ..... 14**

**14 PHARMACEUTICAL INFORMATION..... 14**

**15 CLINICAL TRIALS..... 15**

    15.1 Trial Design and Study Demographics ..... 15

    15.2 Study Results ..... 16

    15.3 Comparative Bioavailability Studies..... 19

**17 NON-CLINICAL TOXICOLOGY ..... 19**

**PATIENT MEDICATION INFORMATION ..... 21**

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

VPRIV (velaglucerase alfa) is indicated for

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

### 2 CONTRAINDICATIONS

VPRIV is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 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.

#### 4.2 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.

#### 4.3 Administration

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

#### 4.4 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 1** for reconstitution.

#### **Table 1 - Reconstitution**

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.

#### 4.5 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.

### 5 OVERDOSAGE

There is limited information available regarding overdose with VPRIV. However, in the event of accidental or intentional overdose, patients should be carefully observed and treatment should be symptomatic and supportive. There is no antidote available.

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

### 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

**Table 2 – Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous (IV)	Powder for solution for injection/ 400 U/vial	Citric acid monohydrate Polysorbate 20 Sodium citrate dihydrate Sucrose

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.

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- $\beta$ -D-glucopyranoside to p-nitrophenol per minute at 37°C.

## 7 DESCRIPTION

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

## 8 WARNINGS AND PRECAUTIONS

### **Carcinogenesis and Mutagenesis**

See **NON-CLINICAL TOXICOLOGY**.

### **Driving and Operating Machinery**

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

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

### **Hepatic/Biliary/Pancreatic**

No studies have been performed in patients with hepatic impairment.

### **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.

### **Immunogenicity**

In clinical studies, 1 of 94 (1%) patients treated with VPRIV developed IgG-class antibodies to velaglycerase 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. One additional patient developed IgG antibodies to velaglycerase alfa that were reported as having neutralizing activity

during an extension study. No adverse events considered related to velaglucerase alfa 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.

### **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, pruritis, and vomiting 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.

### **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.

### **Renal**

No studies have been conducted in patients with renal impairment.

### **Sexual Health**

#### ***Fertility***

See Special Populations: Pregnant Women

## **8.1 Special Populations**

### **8.1.1 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 **NON-CLINICAL 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.

### 8.1.2 Breast-feeding

There is insufficient information on the excretion of VPRIV or its metabolites in human milk. Because many drugs are excreted in human milk, caution should be exercised when VPRIV is administered to a lactating woman.

### 8.1.3 Pediatrics

**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). The studies allowed inclusion of patients 2 years and older; however, 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 3 - Age Distribution of Pediatric Patients (2 to 17 years) by Clinical Trial**

Age (years)	Study		
	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	

### 8.1.4 Geriatrics

**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.

## 9 ADVERSE REACTIONS

### 9.1 Adverse Reaction Overview

The most common adverse drug reactions (incidence  $\geq$  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.



## 9.2 Clinical Trial Adverse 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 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 4.

Adverse drug reactions considered related to VPRIV are shown in **Table 4**. Information is presented by system organ class and frequency (very common  $\geq 10\%$ ; common  $\geq 1\%$  and  $< 10\%$ ).

**Table 4 - 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 (%)	
<b>Cardiac disorders</b>		
Tachycardia (Common)	2 (3.7)	0 (0.0)
<b>Gastrointestinal disorders</b>		
Abdominal pain/abdominal pain upper (Very common)	10 (18.5)	6 (15)
Nausea (Common)	3 (5.6)	4 (10.0)
<b>General disorders and administration site conditions</b>		
Infusion-related reaction <sup>†</sup> (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)
<b>Immune system disorders</b>		
Hypersensitivity reactions <sup>§</sup> (Common)	2 (3.7)	1 (2.5)
<b>Infections and Infestations</b>		
Upper respiratory tract infections (Very common)	17 (31.5)	12 (30.0)
<b>Investigations</b>		
Activated partial thromboplastin time prolonged (Common)	6 (11.1)	2 (5.0)
Neutralizing antibody positive* (Common)	1 (1.9)	0 (0.0)

<b>Musculoskeletal and connective tissue disorders</b>		
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)
<b>Nervous system disorders</b>		
Headache (Very common)	19 (35.2)	12 (30.0)
Dizziness (Very common)	12 (22.2)	3 (7.5)
<b>Skin and subcutaneous tissue disorders</b>		
Rash (Common)	2 (3.7)	1 (2.5)
Urticaria (Common)	2 (3.7)	1 (2.5)
<b>Vascular disorders</b>		
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. One additional patient developed IgG antibodies to velaglucerase alfa that were reported as having neutralizing activity during an extension study. No adverse events considered related to velaglucerase alfa 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.

## 9.6 Post-Market Adverse 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.*

## 10 DRUG INTERACTIONS

### 10.1 Serious Drug Interactions Box

No serious drug interactions have been reported.

## 10.2 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.

## 10.3 Drug-Drug Interactions

Interactions with other drugs have not been established.

## 10.4 Drug-Food Interactions

Interactions with food have not been established.

## 10.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

## 10.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

# 11 ACTION AND CLINICAL PHARMACOLOGY

## 11.1 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.

## 11.2 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.

### 11.3 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

### Non-clinical Pharmacokinetics

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 in a dose-dependent manner, limited by mannose receptors. 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.

## **12 STORAGE, STABILITY AND DISPOSAL**

VPRIV should be stored in a refrigerator at 2 to 8°C (36 to 46°F).

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

## **13 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 8°C (36 to 46°F). The infusion should be completed within 24 hours of reconstitution of vials.

## PART II: SCIENTIFIC INFORMATION

### 14 PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: velaglucerase alfa

Chemical name: glucocerebrosidase,  $\beta$ -D-glucosyl-N-acylsphingosine glucohydrolase, acid- $\beta$ -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.

## 15 CLINICAL TRIALS

### 15.1 Trial Design and Study Demographics

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

Study #	Trial Design	Dosage, Route of Administration, Duration	Study Subjects <sup>a</sup> (N)	Mean Age (Range)	Sex
025	Phase I/II, Single center, Open label	15 U/kg to 60 U/kg <sup>b</sup> 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
-----	---	--	-----	-------------	-----------------

<sup>a</sup> Number of patients dosed

<sup>b</sup> 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 that enrolled a total of 94 patients with type 1 Gaucher disease who were age 4 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.

## 15.2 Study Results

### Studies in Treatment Naïve Patients

**Study 025** was a 9-month, open-label study in 12 adult ( $\geq 18$  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 <sup>9</sup> /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 that enrolled 25 patients age 4 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 <sup>1</sup>	
	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 <sup>9</sup> /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**

<sup>1</sup> 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 that enrolled 34 patients age 4 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 that enrolled 40 patients age 4 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  $162 \times 10^9/L$  (range: 29.0, 399.0) and after 12 months of treatment with VPRIV the median value was  $174 \times 10^9/L$  (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  $87.85 \times 10^9/L$  (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  $9.03 \times 10^9/L$  (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.

## **15.3 Comparative Bioavailability Studies**

No comparative bioavailability studies have been performed with VPRIV.

## **17 NON-CLINICAL 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.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE****PATIENT MEDICATION INFORMATION****Pr VPRIV®  
velaglucerase alfa**

Read this carefully before you start taking **VPRIV** 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 **VPRIV**.

**What is VPRIV used for?**

VPRIV is an enzyme replacement therapy for pediatric and adult patients with type 1 Gaucher disease.

**How does VPRIV work?**

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.

**What are the ingredients in VPRIV?**

Medicinal ingredients: velaglucerase alfa. Velaglucerase alfa is an enzyme similar to the naturally occurring human enzyme glucocerebrosidase.

Non-medicinal ingredients: citric acid monohydrate, polysorbate 20, sodium citrate dihydrate, and sucrose.

**VPRIV comes in the following dosage forms:**

400 U/vial, packed powder for solution for injection. After reconstitution, each vial contains 100 U/mL.

**Do not use VPRIV if:**

Do not use VPRIV if you are allergic (hypersensitive) to velaglucerase alfa or any of the other nonmedicinal ingredients.

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

**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 VPRIV:**

There is no known interaction of VPRIV with other medicines.

**How to take VPRIV:**

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

After reconstitution, VPRIV has to be diluted in 100 mL 0.9% sodium chloride solution before use. After dilution VPRIV is given through a vein (drip feed).

**Usual dose:**

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). The infusion will normally last for 1 hour and will be given every other week.

**Overdose:**

If you think you have taken too much VPRIV, contact your health care professional, 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.

**What are possible side effects from using VPRIV?**

Like all medicines, VPRIV can cause side effects, although not everybody experiences them. These are not all the possible side effects you may feel when taking VPRIV. If you experience any side effects not listed here, contact your healthcare professional.

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 your 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.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>VERY COMMON</b> Arthralgia: Joint Pain		✓	
<b>COMMON</b> Hypersensitivity Reactions		✓	
Urticaria: Rash/Hives		✓	
<b>UNKNOWN*</b> Anaphylactic Reaction: severe allergic reaction		✓	✓
Chest Discomfort		✓	
Dyspnea: Trouble Breathing		✓	
Pruritis: Itchy Skin		✓	
Vomiting		✓	

\*Frequency of event cannot be determined from available data.

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 report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*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:

Keep out of reach and sight 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.

### 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>); the manufacturer's website ([www.takeda.com/en-ca](http://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

Last Revised December 21, 2020

VPRIV® and the VPRIV Logo® are registered trademarks of Shire Human Genetic Therapies, Inc.

TAKEDA™ and the TAKEDA Logo® are trademarks of Takeda Pharmaceutical Company Limited, used under license.