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RESEARCH**

APPLICATION NUMBER:

22-575

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VPRIV safely and effectively. See full prescribing information for VPRIV.

VPRIV™ (velaglucerase alfa for injection)

Initial U.S. Approval: 2010

INDICATIONS AND USAGE

VPRIV (velaglucerase alfa for injection) is a hydrolytic lysosomal glucocerebrosidase-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease (1).

DOSAGE AND ADMINISTRATION

- 60 Units/kg administered every other week as a 60-minute intravenous infusion (2).
- Patients currently being treated with imiglucerase for Gaucher disease can be switched to VPRIV. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with VPRIV at that same dose when they switch from imiglucerase to VPRIV (2).
- Physicians can make dosage adjustments based on achievement and maintenance of each patient's therapeutic goals. Clinical trials have evaluated doses ranging from 15 Units/kg to 60 Units/kg every other week (2).

DOSAGE FORMS AND STRENGTHS

- Lyophilized powder to be reconstituted and diluted for infusion (3).
- Available in 200 Units and 400 Units single-use vials (3).

CONTRAINDICATIONS

- None (4).

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions: Treatment with VPRIV should be carefully re-evaluated in the presence of significant evidence of hypersensitivity to the product (5.1).
- Infusion-related reactions (5.2).

ADVERSE REACTIONS

- The most common adverse reactions during clinical studies were infusion-related reactions (5.2, 6.1).
- Other commonly observed adverse reactions in ≥ 10% of patients were: headache, dizziness, abdominal pain, nausea, back pain, joint pain, upper respiratory tract infection, activated PTT prolonged, fatigue/asthenia, and pyrexia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Shire Human Genetic Therapies, Inc. at the OnePathSM phone # 1-866-888-0660 or MedInfoGlobal@Shire.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See Section 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2010

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VPRIV™ (velaglucerase alfa for injection)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VPRIV (velaglucerase alfa for injection) is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose is 60 Units/kg administered every other week as a 60-minute intravenous infusion.

Patients currently being treated with imiglucerase for type 1 Gaucher disease may be switched to VPRIV. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with VPRIV at that same dose when they switch from imiglucerase to VPRIV.

Dosage adjustments can be made based on achievement and maintenance of each patient's therapeutic goals. Clinical studies have evaluated doses ranging from 15 Units/kg to 60 Units/kg every other week.

VPRIV should be administered under the supervision of a healthcare professional.

2.2 Preparation and Administration Instructions

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:

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 Instructions

	200 Units/vial	400 Units/vial
Volume of Sterile Water for Injection, USP, for reconstitution	2.2 mL	4.3 mL
Concentration after reconstitution	100 Units/mL	100 Units/mL
Withdrawal volume	2 mL	4 mL

Upon reconstitution, mix vials gently. DO NOT SHAKE. 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 particulate matter is present. 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.

VPRIV should be administered over 60 minutes. 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. The diluted solution should be filtered through an in-line low protein-binding 0.2µm filter during administration.

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). Do not freeze. Protect from light. The infusion should be completed within 24 hours of reconstitution of vials.

3 DOSAGE FORMS AND STRENGTHS

VPRIV is a sterile, white to off-white, lyophilized powder for reconstitution with Sterile Water for Injection, USP, to yield a final concentration of 100 Units/mL.

VPRIV is available as 200 Units and 400 Units single-use vials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients in clinical studies with VPRIV [*see Adverse Reactions (6.1)*]. 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.

5.2 Infusion-related Reactions

Infusion-related reactions were the most commonly observed adverse reactions in patients treated with VPRIV in clinical studies. The most commonly observed symptoms of infusion-related reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia, and pyrexia. Generally the infusion-related reactions were mild and, in treatment-naïve patients, onset occurred mostly during the first 6 months of treatment and tended to occur less frequently

with time.

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.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The data described below reflect exposure of 94 patients with type 1 Gaucher disease who received VPRIV at doses ranging from 15 Units/kg to 60 Units/kg every other week in 5 clinical studies. Fifty-four (54) patients were naïve to ERT and received VPRIV for 9 months and 40 patients switched from imiglucerase to VPRIV treatment and received VPRIV for 12 months [see *Clinical Studies (14)*]. Patients were between 4 and 71 years old at time of first treatment with VPRIV, and included 46 male and 48 female patients.

The most serious adverse reactions in patients treated with VPRIV were hypersensitivity reactions [see *Warnings and Precautions (5.1)*].

The most commonly reported adverse reactions (occurring in $\geq 10\%$ of patients) that were considered related to VPRIV are shown in Table 2. The most common adverse reactions were infusion-related reactions.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 2: Adverse Reactions Observed in $\geq 10\%$ of Patients with Type 1 Gaucher Disease Treated with VPRIV

System Organ Class Preferred Term	Naïve to ERT N = 54	Switched from imiglucerase to VPRIV N = 40
	Number of Patients (%)	
Nervous system disorders		
Headache	19 (35.2)	12 (30)
Dizziness	12 (22.2)	3 (7.5)
Gastrointestinal disorders		
Abdominal pain	10 (18.5)	6 (15)
Nausea	3 (5.6)	4 (10)
Musculoskeletal and connective tissue disorders		
Back pain	9 (16.7)	7 (17.5)
Joint pain (knee)	8 (14.8)	3 (7.5)
Infections and infestations		
Upper respiratory tract infection	17 (31.5)	12 (30)
Investigations		
Activated partial thromboplastin time prolonged	6 (11.1)	2 (5)
General disorders and administration site conditions		
Infusion-related reaction*	28 (51.9)	9 (22.5)
Pyrexia	12 (22.2)	5 (12.5)
Asthenia/Fatigue	7 (13)	5 (12.5)
*Denotes any event considered related to and occurring within up to 24 hours of VPRIV infusion		

Less common adverse reactions affecting more than one patient ($>3\%$ in the treatment-naïve group and $>2\%$ in patients switched from imiglucerase to VPRIV treatment) were bone pain, tachycardia, rash, urticaria, flushing, hypertension, and hypotension.

Pediatric Patients

All adult adverse reactions to VPRIV are considered relevant to pediatric patients (ages 4 to 17 years). Adverse reactions more commonly seen in pediatric patients compared to adult patients include ($>10\%$ difference): upper respiratory tract infection, rash, aPTT prolonged, and pyrexia.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In clinical studies, 1 of 54 treatment-naïve patients treated with VPRIV developed IgG class antibodies to VPRIV.

In this patient, 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 VPRIV is associated with a higher risk of infusion reactions. Patients with an immune response to other enzyme replacement therapies who are switching to VPRIV should continue to be monitored for antibodies.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VPRIV with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category B

Reproduction studies with velaglucerase alfa have been performed in pregnant rats at intravenous doses up to 17 mg/kg/day (102 mg/m²/day, about 1.8 times the recommended human dose of 60 Units/kg/day or 1.5 mg/kg/day or 55.5 mg/m²/day based on the body surface area). Reproduction studies have been performed in pregnant rabbits at intravenous doses up to 20 mg/kg/day (240 mg/m²/day, about 4.3 times the recommended human dose of 60 Units/kg/day based on the body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to velaglucerase alfa.

A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at doses up to 17 mg/kg (102 mg/m²/day, about 1.8 times the recommended human dose of 60 Units/kg/day based on the body surface area). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VPRIV should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

There are no data from studies in lactating women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VPRIV is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of VPRIV have been established in patients between 4 and 17 years of age. Use of VPRIV in this age group is supported by evidence from adequate and well-controlled studies of VPRIV in adults and pediatric [20 of 94 (21%)] patients. The safety and efficacy profiles were similar between pediatric and adult patients [*see Adverse Reactions (6.1) and Clinical Studies (14)*]. The safety of VPRIV has not been established in pediatric patients

younger than 4 years of age.

8.5 Geriatric Use

During clinical studies 4 patients aged 65 or older were treated with VPRIV. Clinical studies of VPRIV did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be approached cautiously, considering potential comorbid conditions.

10 OVERDOSAGE

There is no experience with overdose of VPRIV.

11 DESCRIPTION

The active ingredient of VPRIV is velaglucerase alfa, which is produced by gene activation technology in a human fibroblast cell line. Velaglucerase alfa is a glycoprotein of 497 amino acids; with a molecular weight of approximately 63 kDa. Velaglucerase alfa has the same amino acid sequence as the naturally occurring human enzyme, glucocerebrosidase. Velaglucerase alfa contains 5 potential N-linked glycosylation sites; four of these sites are occupied by glycan chains. Velaglucerase alfa is manufactured to contain predominantly high mannose-type N-linked glycan chains. The high mannose type N-linked glycan chains are specifically recognized and internalized via the mannose receptor present on the surface on macrophages, the cells that accumulate glucocerebroside in Gaucher disease. Velaglucerase alfa catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide in the lysosome.

VPRIV is dosed by Units/kg, where one Unit of enzyme activity is defined as the quantity of enzyme required to convert one micromole of p-nitrophenyl β -D-glucopyranoside to p-nitrophenol per minute at 37°C.

VPRIV is supplied as a sterile, preservative free, lyophilized powder in single-use vials. Following reconstitution with Sterile Water for Injection, USP, the solution contains the components listed in Table 3.

Table 3: VPRIV Composition Following Reconstitution

	Extractable 200 Units/vial	Extractable 400 Units/vial
Active Ingredient		
velaglucerase alfa	200 Units	400 Units
Inactive Ingredients		
citric acid, monohydrate	2.52 mg	5.04 mg
polysorbate 20	0.22 mg	0.44 mg
sodium citrate, dihydrate	25.88 mg	51.76 mg
sucrose	100 mg	200 mg

12 CLINICAL PHARMACOLOGY

12.1 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. Glucocerebrosidase catalyzes the conversion of the sphingolipid glucocerebroside into glucose and ceramide. The enzymatic deficiency causes an accumulation of glucocerebroside primarily in the lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells". In this lysosomal storage disorder (LSD), clinical features are reflective of the accumulation of Gaucher cells in the liver, spleen, bone marrow, and other organs. The accumulation of Gaucher cells in the liver and spleen leads to organomegaly. Presence of Gaucher cells in the bone marrow and spleen lead to clinically significant anemia and thrombocytopenia.

Velaglucerase alfa catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside.

12.3 Pharmacokinetics

In a multicenter study conducted in pediatric (N=7, 4 to 17 years old) and adult (N=15, 19 to 62 years old) patients with type 1 Gaucher disease, pharmacokinetic evaluations were performed at Weeks 1 and 37 following 60-minute intravenous infusions of VPRIV 60 Units/kg every other week. Serum velaglucerase alfa concentrations declined rapidly with a mean half life of 11 to 12 minutes. The mean velaglucerase alfa clearance ranged from 6.72 to 7.56 mL/min/kg. The mean volume of distribution at steady state ranged from 82 to 108 mL/kg (8.2% to 10.8% of body weight). However, because an inadequately validated analytical assay method was used in the evaluations, the accurate and definitive pharmacokinetic parameter values are not currently available.

No accumulation or change in velaglucerase alfa pharmacokinetics over time from Weeks 1 to 37 was observed upon multiple-dosing 60 Units/kg every other week.

Based on the limited data, there were no notable pharmacokinetic differences between male and female patients in this study. The effect of age on pharmacokinetics of velaglucerase alfa was inconclusive.

The effect of anti-drug antibody formation on the pharmacokinetic parameters of velaglucerase alfa is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with velaglucerase alfa.

In a male and female fertility study in rats, velaglucerase alfa did not cause any significant adverse effect on male or female fertility parameters up to a maximum dose of 17 mg/kg/day (102 mg/m²/day, about 1.8 times the recommended human dose of 60 Units/kg/day based on the

body surface area).

14 CLINICAL STUDIES

The efficacy of VPRIV was assessed in three clinical studies in a total of 99 patients with type 1 Gaucher disease: 82 patients age 4 years and older received VPRIV and 17 patients age 3 years and older received imiglucerase. Studies I and II were conducted in patients who were not currently receiving Gaucher disease-specific therapy. Study III was conducted in patients who were receiving imiglucerase treatment immediately before starting VPRIV. In these studies, VPRIV was administered intravenously over 60 minutes at doses ranging from 15 Units/kg to 60 Units/kg every other week.

14.1 Studies of VPRIV as Initial Therapy

Study I was a 12-month, randomized, double-blind, parallel-dose-group, multinational study in 25 patients age 4 years and older with Gaucher disease-related anemia and either thrombocytopenia or organomegaly. Patients were not allowed to have had disease-specific therapy for at least the previous 30 months; all but one had no prior therapy. The mean age was 26 years and 60% were male. Patients were randomized to receive VPRIV at a dose of either 45 Units/kg (N=13) or 60 Units/kg (N=12) every other week.

At baseline, mean hemoglobin concentration was 10.6 g/dL, mean platelet count was $97 \times 10^9/L$, mean liver volume was 3.6 % of body weight (% BW), and mean spleen volume was 2.9 % BW. For all studies, liver and spleen volumes were measured by MRI. The changes in clinical parameters after 12 months of treatment are shown in Table 4. The observed change from baseline in the primary endpoint, hemoglobin concentration, was considered to be clinically meaningful in light of the natural history of untreated Gaucher disease.

Table 4: Mean Change from Baseline to Month 12 for Clinical Parameters in Patients with Type 1 Gaucher Disease Initiating Therapy with VPRIV in Study I

Clinical Parameter	Mean Changes from Baseline \pm Std. Err. of the Mean	
	VPRIV Dose (given every other week)	
	45 Units/kg N = 13	60 Units/kg N = 12
Hemoglobin concentration change (g/dL)	2.4 \pm 0.4*	2.4 \pm 0.3**
Platelet count change ($\times 10^9/L$)	41 \pm 14*	51 \pm 12*
Liver volume change (% BW)	-0.30 \pm 0.29	-0.84 \pm 0.33
Spleen volume change (% BW)	-1.9 \pm 0.6*	-1.9 \pm 0.5*

** Primary study endpoint was hemoglobin concentration change in the 60 Unit/kg group, $p < 0.001$

* Statistically significant changes from baseline after adjusting for performing multiple tests

Study II was a 9-month, randomized, double-blind, active-controlled (imiglucerase), parallel-group, multinational study in 34 patients age 3 years and older. Patients were required to have Gaucher disease-related anemia and either thrombocytopenia or organomegaly. Patients were

not allowed to have had disease-specific therapy for at least the previous 12 months. The mean age was 30 years and 53% were female; the youngest patient who received VPRIV was age 4 years. Patients were randomized to receive either 60 Units/kg of VPRIV (N=17) or 60 Units/kg of imiglucerase (N=17) every other week.

At baseline, the mean hemoglobin concentration was 11.0 g/dL, mean platelet count was $171 \times 10^9/L$, and mean liver volume was 4.3 % BW. For the patients who had not had splenectomy (7 in each group) the mean spleen volume was 3.4 % BW. After 9 months of treatment, the mean absolute increase from baseline in hemoglobin concentration was $1.6 \text{ g/dL} \pm 0.2 \text{ (SE)}$ for patients treated with VPRIV. The mean treatment difference in change from baseline to 9 months [VPRIV – imiglucerase] was $0.1 \text{ g/dL} \pm 0.4 \text{ (SE)}$.

In Studies I and II, examination of age and gender subgroups did not identify differences in response to VPRIV among these subgroups. The number of non-Caucasian patients in these studies was too small to adequately assess any difference in effects by race.

14.2 Study in Patients Switching from Imiglucerase Treatment to VPRIV

Study III was a 12-month, open-label, single-arm, multinational study in 40 patients age 9 years and older who had been receiving treatment with imiglucerase at doses ranging between 15 Units/kg to 60 Units/kg for a minimum of 30 consecutive months. Patients also were required to have a stable biweekly dose of imiglucerase for at least 6 months prior to enrollment. The mean age was 36 years and 55% were female. Imiglucerase therapy was stopped, and treatment with VPRIV was administered every other week at the same number of units as the patient's previous imiglucerase dose. Adjustment of dosage was allowed by study criteria if needed in order to maintain clinical parameters.

Hemoglobin concentrations and platelet counts remained stable on average through 12 months of VPRIV treatment. After 12 months of treatment with VPRIV the median hemoglobin concentration was 13.5 g/dL (range: 10.8, 16.1) vs. the baseline value of 13.8 g/dL (range: 10.4, 16.5), and the median platelet count after 12 months was $174 \times 10^9/L$ (range: 24, 408) vs. the baseline value of $162 \times 10^9/L$ (range: 29, 399). No patient required dosage adjustment during the 12-month treatment period.

15 REFERENCES

1. Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic Goals in the Treatment of Gaucher Disease. *Semin Hematol.* 2004; 41(4 Suppl 5):4-14.

16 HOW SUPPLIED/STORAGE AND HANDLING

VPRIV is a sterile, preservative free, lyophilized powder requiring reconstitution and further dilution prior to use. 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 as: 200 Units/vial NDC 54092-701-02 and 400 Units/vial NDC 54092-701-04.

16.1 Storage

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 vial from light.

17 PATIENT COUNSELING INFORMATION

- VPRIV should be administered under the supervision of a healthcare professional. VPRIV is a treatment that is given intravenously (by IV) every other week. The infusion typically takes up to 60 minutes.
- Patients should be advised that VPRIV may cause hypersensitivity reactions or infusion-related reactions. Infusion-related reactions can usually be managed by 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. Treatment with VPRIV should be carefully re-evaluated in the presence of significant evidence of hypersensitivity to the product [*see Warnings and Precautions (5.1, 5.2)*].

Rx Only

VPRIV is manufactured by:

Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, MA 02139

OnePath is a service mark and VPRIV is a trademark of Shire Human Genetic Therapies, Inc.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22575

ORIG-1

SHIRE HUMAN
GENETIC
THERAPIES INC

VELAGLUCERASE ALFA

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/s/

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02/26/2010