PRODUCT INFORMATION

VPRIV® (velaglucerase alfa ghu)

NAME OF THE MEDICINE

VPRIV powder for solution for infusion.

Active Ingredient: velaglucerase alfa ghu

CAS number: 37228-64-1

DESCRIPTION

Velaglucerase alfa ghu is a glycoprotein produced by gene-activation technology in a human cell line. The monomer is approximately 63 kDa, has 497 amino acids and the same amino acid sequence as the naturally occurring human enzyme, glucocerebrosidase. There are 5 potential N-linked glycosylation sites, four of which are occupied. Velaglucerase alfa ghu is manufactured to contain predominantly high-mannose-type glycans to facilitate internalisation of the enzyme by the phagocytic target cells via the mannose receptor.

VPRIV is supplied in 400 U/vial (10 mg) of velaglucerase alfa ghu. VPRIV is a sterile, preservative free lyophilised powder in single-use vials which requires reconstitution and dilution, and is intended for intravenous infusion only. VPRIV contains the following excipients: sucrose, sodium citrate, citric acid monohydrate and polysorbate 20.

PHARMACOLOGY

General

Gaucher disease is an autosomal recessive disorder caused by mutations in the GBA gene which results in a deficiency of the lysosomal enzyme, beta-glucocerbrosidase. This enzymatic deficiency causes an accumulation of glucocerebroside primarily in macrophages, giving rise to foam cells or “Gaucher cells”. In this lysosomal storage disorder, clinical features are reflective of the distribution of Gaucher cells in the liver, spleen, bone marrow, skeleton, and lungs. The accumulation of glucocerbroside 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 anaemia and thrombocytopaenia.

Pharmacodynamic properties

Velaglucerase alfa ghu, the active ingredient in VPRIV, supplements or replaces beta-glucocerebrosidase, the enzyme that catalyses the hydrolysis of glucocerebroside to glucose and ceramide in the lysosome, reducing the amount of accumulated glucocerebroside and correcting the pathophysiology of Gaucher disease. VPRIV increases haemoglobin concentration and platelet counts and reduces spleen volumes in patients with type 1 Gaucher disease. It also reduces liver volumes.

Pharmacokinetics

The pharmacokinetic properties 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 in 3 clinical studies for up to 2 years.

At all doses, velaglucerase alfa ghu serum concentrations rose rapidly for the first 20 minutes of the 60 minute infusion before levelling off, and C_{max} was typically attained between 40 and 60 minutes after the start of the infusion. After the end of the infusion, velaglucerase alfa ghu serum concentrations fell rapidly in a monophasic or biphasic fashion with a mean $t_{½}$ ranging from 5 to 12 minutes for the 15, 30, 45 and 60 U/kg doses.

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

For the two dose groups in Study 032, the range of velaglucerase alfa ghu clearance in paediatric 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 ghu 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 ghu.

CLINICAL TRIALS

The safety and efficacy of VPRIV were assessed in 5 clinical studies in a total of 94 patients with type 1 Gaucher disease, age 2 years and older. Studies 025, 032, and 039 were conducted in patients naïve to enzyme replacement therapy (ERT). 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 switched from imiglucerase treatment to VPRIV. (see Table 1)

In all studies, 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 were offered home therapy. In Study 025EXT, 7 of the 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.

Table 1: Study Demographics and Trial Design

Study #	Trial Design, Dose and Duration	Inclusion Criteria, Disease	Study Subjects[a]	Mean Age (Range)	Gender

		Characteristics	(N)		
025	Phase I/II, Single center; Open label; 15 U/kg to 60 U/kg[b] velaglucerase alfa ghu EOW, IV infusion 9 months	Patients with Type 1 Gaucher disease who had received no treatment within 12 months prior to study entry; patients exhibited anemia, thrombocytopaenia, deficient GCB activity as measured in leukocytes. Patients with splenectomy were excluded.	12	41.7 (18.8 - 69.8)	Male and Female
025EXT	Phase I/II, Multicenter; 60 U/kg-30 U/kg velaglucerase alfa ghu EOW, IV infusion 60 months[c]	Open label extension study of patients completing week 41 in TKT025	10	38.8 (18 - 63)	Male and Female
032	Phase III, Multicenter, Randomised, Double-blind, Parallel group, Controlled; 45 U/kg or 60 U/kg velaglucerase alfa ghu EOW, IV infusion 12 months	Patients with Type 1 Gaucher disease who had received no treatment within 30 months prior to study entry; patients had deficient GCB activity as measured in leukocytes or by genotype analysis; patients exhibited decreased haemoglobin and platelet counts and increased spleen and liver volume. Patients with splenectomy were excluded.	25	26.0 (4.0 - 62)	Male and Female
039	Phase III, Multicenter, Randomised, Double-blind, Active comparator, Controlled; 60 U/kg velaglucerase alfa ghu EOW, IV infusion for 60 minutes 60 U/kg imiglucerase EOW, IV infusion for 1-2 hours 9 months	Patients with Type 1 Gaucher disease who had received no treatment within 12 months prior to study entry; patients had deficient GCB activity as measured in leukocytes or by genotype analysis; patients exhibited decreased haemoglobin and platelet counts and increased spleen and liver volume.	35	29.7 (3.0 - 73)	Male and Female
034	Phase II/III, Multicenter, Open	Patients previously treated for a minimum	40	35.6 (9.0 - 71)	Male and

	label; analysis15 U/kg to 60 U/kg velaglucerase alfa ghu EOW, IV infusion 12 months	of 30 months with imiglucerase at the same dose for the 6 months prior to study entry; patients had deficient GCB activity as measured in leukocytes or by genotype; patients were excluded for unstable hemoglobin, platelet count, clinically significant spleen infarction, or worsening bone necrosis on prior imiglucerase.			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
[c] Ongoing

Studies in Treatment Naïve Patients

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

Clinically meaningful and statistically significant improvements from baseline were observed in haemoglobin 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 patients who completed Study 025, enrolled in an open-label extension 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 two of the four "Year 1" therapeutic goals of ERT for type 1 Gaucher disease. Patients received VPRIV at doses ranging from 34 to 60 U/kg (median dose of 35 U/kg) every other week for up to 60 months. VPRIV continued to demonstrate sustained clinical activity during 5 years of treatment as observed by improvements in haemoglobin concentrations and platelet counts and reduced liver and spleen volumes. (see Table 2)

Table 2: Median observed values and mean change or mean percent change from Baseline from the start of Study 025 to 5 years of treatment with VPRIV in Study 025EXT

Clinical Parameters	Median Observed Values [Range]	Mean Change or Mean % Change from Baseline ± SE (95% CI)

	Baseline*	**5 years**
N	10	10
Haemoglobin concentration (g/dl)	10.9 [10.0, 13.5]	2.38 ± 0.344 (1.60, 3.16)
Platelet count (x 10^9/L)	55.5 [37.0, 80.0]	85.1 ± 11.2 (59.8, 110.4)
Liver volume (% Body weight)	4.40 [2.6, 5.8]	-38.8% ± 4.55% (-49.1%, -28.5%)
Spleen volume** (% Body weight)	3.80 [2.2, 6.5]	-74.0% ± 6.66% (-89.3%, -58.6%)

* Baseline is defined as data collected at the baseline visit in Study 025

** 1 splenectomised patient was excluded

Study 032 was a 12-month, randomised, double-blind, parallel-group efficacy study in 25 patients aged 2 years and older who were naïve to ERT. In this study, naïve patients were defined as having not been treated with ERT for at least 30 months prior to study entry. Patients were required to have Gaucher disease-related anaemia and either thrombocytopaenia or organomegaly. Patients were randomised 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 favour of 60 U/kg was observed in relation to the 45 U/kg dose group after 12 months of treatment (see Table 3).

Table 3: Mean Change from Baseline to 12 Months for Key Efficacy Parameters in Treatment-naïve Patients with Type 1 Gaucher Disease in Study 032

	Mean change from baseline ± SE p-value*	
Clinical Parameters	**VPRIV 60 U/kg every other week**	**VPRIV 45 U/kg every other week**
N	12	13
Haemoglobin 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 (% Body weight)	-0.84 ± 0.33 p = 0.0282	-0.30 ± 0.29 p = 0.3149
Spleen volume** (% Body weight)	-1.92 ± 0.51 p = 0.0032**	-1.87 ± 0.60 p = 0.0085**

* p-value based on paired t-test

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

The reductions in liver and spleen volumes were larger in the 60 U/kg dose group. In the 60 U/kg 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, randomised, double-blind, non-inferiority, active-comparator (imiglucerase) controlled, parallel-group efficacy study in 34 patients aged 2 years and older who were naïve to ERT. In this study, naïve patients were defined as having not been treated with ERT for at least 12 months prior to study entry. Patients were required to have Gaucher disease-related anaemia and either thrombocytopaenia 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 haemoglobin concentrations was 1.624 g/dL (± 0.223 SE) following 9 months of treatment with VPRIV. This increase in haemoglobin 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 in the time to first haemoglobin response (defined as 1 g/dL increase from baseline).

Study in patients switching from imiglucerase to VPRIV

Study 034 was a 12-month, open-label safety study in 40 patients aged 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 enrolment. Treatment with VPRIV was administered as the same number of units and regimen as their imiglucerase dose. Haemoglobin 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, haemoglobin concentrations and platelet counts were sustained at therapeutic levels through 12 months of treatment. The median value for haemoglobin 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).

Paediatric population

Use in the age group 4 to17 is supported by evidence from controlled studies in adults and paediatric [20 of 94 (21%)]. The safety and efficacy profiles were similar between paediatric and adult patients. The studies allowed the inclusion of patients 2 years and older and the safety and efficacy profiles are expected to be similar down to the age of 2 years. However, no data are available for children under the age of 4 years.

INDICATIONS

VPRIV is indicated for long-term enzyme replacement therapy (ERT) for paediatric and adult patients with type 1 Gaucher disease associated with at least one of the following clinical manifestations: anaemia, thrombocytopaenia, hepato-splenomegaly.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

There is no clinical experience with the use of VPRIV in patients with type 2 or 3 Gaucher disease. Patients with respiratory symptoms should be evaluated for the presence of pulmonary hypertension.

Hypersensitivity

Hypersensitivity reactions have been reported in patients in clinical studies. 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 other enzyme replacement therapy.

Infusion reactions

Infusion-related reactions were the most commonly reported adverse reactions, occurring in approximately 62% (58/94) of patients treated with VPRIV in clinical studies. 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 six months of treatment with VPRIV. Serious infusion reactions of hypersensitivity have been reported and included anaphylactoid reaction and allergic dermatitis in one patient each.

The management of infusion-related reactions should be based on the severity of the reaction, and include 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

Antibodies may play a role in treatment-related reactions found with the use of velaglucerase alfa ghu. To further evaluate the relationship, in cases of severe infusion-related reactions and in cases of lack or loss of effect, patients should be tested for the presence of antibodies and the results reported to the company.

In clinical studies 1 of 94 patients (1%) treated with VPRIV developed IgG-class antibodies to velaglucerase alfa ghu. In this one event, the antibodies were determined to be neutralising 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 ghu is

associated with a higher risk of infusion reactions. No patients developed IgE antibodies to velaglucerase alfa ghu.

Use in pregnancy – (Category B2)

There are no data from the use of velaglucerase alfa ghu in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

Use in lactation

There were no data from studies in lactating women. It is not known whether velaglucerase alfa ghu is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when prescribing to a lactating woman.

Carcinogenicity

As velaglucerase alfa ghu is similar to the naturally occurring human enzyme, glucocerebrosidase, VPRIV is not expected to be carcinogenic. Carcinogenicity studies have not been conducted with VPRIV.

Genotoxicity

As velaglucerase alfa ghu is similar to the naturally occurring human enzyme, glucocerebrosidase, VPRIV is not expected to be mutagenic. Mutagenicity studies have not been conducted with VPRIV.

Paediatric use

Twenty of the 94 patients (21%) who received VPRIV during clinical studies were in the paediatric age range (4 to ≤ 17 years). The safety and efficacy profiles were similar between paediatric and adult patients.

Elderly patients

Four of the 94 patients (5%) who received VPRIV during clinical studies were age 65 years or older. The safety and efficacy profiles were similar between elderly and other patients.

Impaired renal or hepatic function

There is no clinical experience in patients with renal or hepatic insufficiency.

Effects on ability to drive and use machines

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

Effect on Laboratory Tests

Thrombocytopaenia and prolonged activated partial thromboplastin time (aPTT) are common in Type 1 Gaucher disease. Treatment with velaglucerase alfa ghu generally results in increased platelet count. In clinical trials, three patients had mild to moderate thrombocytopaenia thought to be related to treatment. One patient had aPTT of 129.6

sec. Velaglucerase alfa ghu was continued and the aPTT was found to be 40.9 sec at the next assessment.

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been conducted.

ADVERSE EFFECTS

Clinical trial experience

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 five clinical studies. Fifty-four patients were naïve to ERT and 40 patients switched from imiglucerase to VPRIV.

No treatment-naïve patient treated with velaglucerase alfa ghu discontinued due to an adverse event while one treatment naïve patient on imiglucerase withdrew consent due to adverse events. Only one patient who transitioned from imiglucerase discontinued due to an adverse event.

The most serious adverse reactions in patients in clinical trials were hypersensitivity reactions. One serious anaphylactoid reaction occurred during the first VPRIV infusion, resolved upon discontinuation of infusion and treatment with diphenhydramine and hydrocortisone. The patient had switched from imiglucerase therapy. One additional serious report of hypersensitivity was allergic dermatitis 7 months after initiation of VPRIV and 1 week after the latest infusion, which was considered to be related to VPRIV. Therapy with VPRIV was continued with added premedications of antihistamines and corticosteroids; concomitant medication was indomethacin. No antibodies specific to velaglucerase alfa ghu were detected in these two patients.

The most common adverse reactions were infusion-related reactions. The most commonly observed symptoms of infusion-related reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia and pyrexia/body temperature increased. The only adverse reaction leading to discontinuation of treatment was an infusion-related reaction.

Patients were offered home administration during clinical trials. No serious infusion-related adverse events involving hypersensitivity, anaphylaxis, or any anaphylactoid reaction were associated with a home infusion, including over 5 years exposure in study TKT025EXT.

The adverse reactions described in Table 4 are listed by system organ class and frequency according to MedDRA convention. Frequency is described as Very Common (≥ 1/10), Common (≥ 1/100 to < 1/10), and Not Known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Adverse Drug Reactions Associated with VPRIV in Patients with Type 1 Gaucher's Disease

	Adverse reaction

System organ class			
	Very common	**Common**	**Not Known**
Immune system disorders			hypersensitivity reactions*
Nervous system disorders	headache, dizziness		
Cardiac disorders		tachycardia	
Vascular disorders		hypertension, hypotension	flushing*
Gastrointestinal disorders		abdominal pain/abdominal pain upper, nausea	
Skin and subcutaneous tissue disorders		rash, urticaria	
Musculoskeletal and connective tissue disorders	bone pain, arthralgia, back pain		
General disorders and administration site conditions	infusion-related reaction, asthenia/fatigue, pyrexia/body temperature increased		
Investigations		activated partial thromboplastin time prolonged	neutralizing antibody positive**

* Events of anaphylactoid reaction and allergic dermatitis have been observed in one patient each in clinical trials; therefore, the frequency cannot be reliably ascertained.
**A laboratory finding; not reported as an adverse event.

Table 5 includes a listing of adverse events observed in 039 in at least 2 patients treated with 60 U/kg of either VPRIV or imiglucerase.

Table 5: The Most Common (≥10% of Patients) Treatment emergent Adverse Events in a Randomised, Double-Blind, Parallel-Group Study of VPRIV Compared with Imiglucerase in Patients with Type 1 Gaucher's Disease

Adverse Events	VPRIV 60 U/ kg N=17	Imiglucerase 60 U/kg N=17
Infections and Infestations		
Influenza	3 (17.6)	4 (23.5)
Nasopharygitis	3 (17.6)	3 (17.6)
Rhinitis	3 (17.6)	1 (5.9)
Bronchitis	1 (5.9)	2 (11.8)
Cystitis	2 (11.8)	1 (5.9)
Tinea versicolour	2 (11.8)	0
Urinary tract infection	2 (11.8)	0
Immune system disorders		
Hypersensitivity	2 (11.8)	0
Nervous System disorders		

Headache	3 (17.6)	3 (17.6)
Dizziness	1 (5.9)	2 (11.8)
Paraesthesia	2 (11.8)	1 (5.9)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2 (11.8)	2 (11.8)
Epistaxis	2 (11.8)	2 (11.8)
Gastrointestinal Disorders		
Abdominal pain upper	1 (5.9)	3 (17.6)
Diarrhoea	3 (17.6)	1 (5.9)
Abdominal Pain	1 (5.9)	2 (11.8)
Vomiting	1 (5.9)	2 (11.8)
Skin and Subcutaneous tissue disorders		
Urticaria	2 (11.8)	1 (5.9)
Pruritus	2 (11.8)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (23.5)	3 (17.6)
Bone pain	2 (11.8)	3 (17.6)
Back Pain	2 (11.8)	2 (11.8)
Muscle spasm	1 (5.9)	2 (11.8)
Myalgia	2 (11.8)	1 (5.9)
Neck pain	2 (11.8)	1 (5.9)
General Disorders and Administration Site Conditions		
Pyrexia	4 (23.5)	2 (11.8)
Oedema peripheral	3 (17.6)	0
Influenza like illness	1 (2.4)	2 (11.8)

Postmarketing experience

The safety profile of VPRIV in the postmarketing experience reflected that observed in clinical trials.

DOSAGE AND ADMINISTRATION

VPRIV treatment should only be initiated or continued by a physician experienced in the management of patients with Gaucher disease. VPRIV should be administered under the supervision of a healthcare professional. Home administration may be considered for patients who have received at least three infusions in hospital and are tolerating their infusions well. Home infusions should only be provided by healthcare professionals trained in recognising and medically managing serious infusion related reactions under the direction of a practicing physician.

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

Dose 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.

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.

Impaired renal or hepatic function

There is no clinical experience in patients with renal or hepatic insufficiency. However, no dosing adjustment is recommended in patients with renal or hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of velaglucerase alfa ghu (see Pharmacokinetics).

Elderly population

Four of the 94 patients (5%) who received velaglucerase alfa ghu during clinical studies were age 65 years and older. The limited data do not indicate a need for a dose adjustment in this age group.

Paediatric population

Twenty of the 94 patients (21%) who received VPRIV during clinical studies were in the paediatric age range (4 to ≤ 17 years). The safety and efficacy profiles were similar between paediatric and adult patients.

Instructions for use

VPRIV is a lyophilised powder, which requires reconstitution and dilution, and is intended for intravenous infusion only.

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. See Table 6 for instructions on reconstitution.

Table 6: Reconstitution instructions:

Solution	**400 U/vial**
Sterile Water for Injection	4.3 mL
Extractable volume	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 colourless; do not use if the solution is discoloured or if foreign particulate matter is 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 irregular shaped particles) may occasionally occur.
5. The infusion should be completed within 24 hours of reconstitution of the vials.

VPRIV should be administered through a 0.2 µm in line filter over a period of 60 minutes.

VPRIV contains no preservatives and vials are for single-use in one patient, on one occasion only. Discard any unused solution.

OVERDOSAGE

There is no experience with overdosage of VPRIV.

For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

Presentation

VPRIV is a sterile, preservative free lyophilised powder which requires reconstitution and dilution, and is intended for intravenous infusion only. Vials are single-use only.

VPRIV is supplied in a glass vial (type I glass) with a stopper (fluoro-resin coated butyl rubber) one piece overseal and flip-off plastic cap.

Pack size: Single carton containing one vial of 400 Units of velaglucerase alfa ghu powder for solution for infusion.

Storage

VPRIV vials should be stored at 2-8°C. Do not freeze. Keep the vial in the outer carton in order to protect it from light.

To reduce potential microbiological hazard, the reconstituted and diluted solution should be used immediately. However, when prepared under aseptic conditions, the reconstituted and/or diluted solution may be stored at 2-8°C under protection from light for 24 hours. The infusion should be initiated within 24 hours from the time of reconstitution and/or dilution.

NAME AND ADDRESS OF SPONSOR

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Australia

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

29th February 2012