AUSTRALIAN PRODUCT INFORMATION - VPRIV® (velaglucerase alfa ghu) powder for solution for infusion

1 NAME OF THE MEDICINE

Velaglucerase alfa ghu

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VPRIV is supplied in 400 U/vial (10 mg) of velaglucerase alfa ghu.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

VPRIV is a sterile, white to off-white, preservative-free lyophilised powder in single-use vials.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VPRIV is indicated for long-term enzyme replacement therapy (ERT) for paediatric and adult patients with type 1 Gaucher disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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 practising 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 ERT 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 Section 5.2 Pharmacokinetic Properties).

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.

Method of administration

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

Use aseptic technique.

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. Each vial is reconstituted with 4.3 mL Sterile Water for Injections and the reconstituted vial has an extractable volume of 4.0 mL with a concentration of 100 U/mL.

   Table 1: Reconstitution instructions:

Solution	400 U/vial
Sterile Water for Injections	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 intravenous administration. Mix gently. DO NOT SHAKE. Slight flocculation (described as white irregular shaped particles) may occasionally occur.
5. Administer VPRIV 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 the 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.

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

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 reactions

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

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

Infusion-related reactions

Infusion-related reactions 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. Additional infusion-related reactions of chest discomfort, dyspnoea, pruritus, and vomiting have been reported in post-marketing experience. Serious infusion-related 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 (see Section 4.8 Adverse Effects (Undesirable Effects): Immunogenicity).

Use in hepatic impairment

There are no clinical data on the use of VPRIV in patients with hepatic insufficiency.

Use in renal impairment

There are no clinical data on the use of VPRIV in patients with renal insufficiency.

Use in the elderly

In clinical studies, a total of 56 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 paediatric and adult patients.

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.

Effects 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been conducted.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data included.

Use in pregnancy

Pregnancy Category B2

There are no data from studies in pregnant women and there are limited 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. 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.

Use in lactation

There is insufficient information on the excretion of velaglucerase alfa ghu or its metabolites in human milk. Because many medicines are excreted in human milk, caution should be exercised when prescribing to a lactating woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 5 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 (see Section 4.4 Special Warnings and Precautions for Use). 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 2 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), Uncommon (≥1/1000 to <1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reactions derived from post-marketing reports other than interventional clinical trials are printed in italic.

Table 2: Adverse Drug Reactions Associated with VPRIV in Patients with Type 1 Gaucher's Disease

Italic text denotes post-marketing reaction. Frequencies were determined from cases seen in clinical studies.

System/Organ Class	Incidence Category	Adverse Drug Reactions
Nervous system disorders	Very common	Headache, dizziness
Gastrointestinal disorders	Very common	Abdominal pain/abdominal pain upper
	Common	Nausea
	Uncommon	*Vomiting*
Musculoskeletal and connective tissue disorders	Very common	Bone pain, arthralgia, back pain
Investigations	Common	Activated partial thromboplastin time prolonged, neutralising antibody positive[§]
General disorders and administration site conditions	Very common	Infusion-related reactions[†], asthenia/fatigue, pyrexia/body temperature increased
	Common	*Chest discomfort*
Vascular disorders	Common	Flushing[§], hypertension, hypotension
Cardiac disorders	Common	Tachycardia
Respiratory, thoracic and mediastinal disorders	Common	*Dyspnoea*
Skin and subcutaneous tissue disorders	Common	Rash, urticaria, *pruritus*
Immune system disorders	Common	Hypersensitivity reactions (includes dermatitis allergic and *anaphylactic*/anaphylactoid reaction)

[§] See Immunogenicity
[†] Reactions occurring up to 24 hours after the start of the infusion

Vomiting

In some cases vomiting can be serious (reported from post-marketing experience).

Table 3 includes a listing of adverse events observed in Study 039 in at least 2 patients treated with 60 U/kg of either VPRIV or imiglucerase.

Table 3: 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)
Nasopharyngitis	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 versicolor	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)

Immunogenicity

In the registration enabling 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. One additional patient developed IgG antibodies to velaglucerase alfa ghu that were reported as having neutralising activity during an extension study (study 044). No adverse events considered related to velaglucerase alfa ghu 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.

Post-marketing experience

The safety profile of VPRIV in the post-marketing experience reflected that observed in clinical trials.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is limited information available regarding overdose with velaglucerase alfa ghu. 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 information on the management of overdose, contact the Poisons Information Centre on 131126 in Australia, or the National Poisons Centre on 0800 POISON (0800 764766) in New Zealand.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Alimentary tract and metabolism products, enzymes; ATC code: A16AB10

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, clinical features are reflective of the distribution of Gaucher cells in the liver, spleen, bone marrow, skeleton, and lungs. The accumulation of glucocerebroside 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 effects

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.

Clinical trials

The safety and efficacy of VPRIV were assessed in 5 clinical studies that enrolled a total of 94 patients with type 1 Gaucher disease, age 4 years and older. Studies 025, 032, and 039 were conducted in patients naïve to 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 4).

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 (EOW). VPRIV was administered by intravenous 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 4: Study Demographics and Trial Design

Study #	Trial Design, Dose and Duration	Inclusion Criteria, Disease Characteristics	Study Subjects[a] (N)	Mean Age (Range)	Gender
025	Phase I/II, Single center; Open-label; 15 U/kg to 60 U/kg[b] velaglucerase alfa 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 anaemia, 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	39.8 (20 - 64)	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-label; analysis 15 U/kg to 60 U/kg velaglucerase alfa ghu EOW, IV infusion, 12 months	Patients previously treated for a minimum 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 haemoglobin, platelet count, clinically significant spleen infarction, or worsening bone necrosis on prior imiglucerase.	40	35.6 (9.0 - 71)	Male and Female

[a] Number of patients dosed

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

[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 of the 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 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 7 years of treatment as observed by improvements in haemoglobin concentrations and platelet counts and reduced liver and spleen volumes (see Table 5).

Table 5: Median Observed Values and Mean Change from Baseline in Study 025EXT – ITT Population

Clinical Parameters	**Median Observed Values Baseline***	**Median Observed Values 7 years[§]**	**Mean Change from Baseline (95%CI) 7 years[§]**
N	10	10	10
Haemoglobin concentration (g/dL)	11.10	13.40	2.0 (1.4, 2.6)
Platelet count (x 10^9/L)	62.25	122.0	63.9 (45.7, 82.1)
Liver volume[#]	4.40	2.30	-1.8 (-2.5, -1.2)
Spleen volume[#]	3.80	0.50	-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 81 months of observation [#] Normalised % of body weight (BW)			

For the 10 patients in 025EXT receiving VPRIV, 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.

An exploratory analysis was performed to study 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. The median BMB score at baseline was 6.0. At month 9, the median BMB was 3.5. At month 33, the median BMB was 1 and this score was maintained through month 81. By month 57, eight patients remained in 025EXT and had achieved a reduction from baseline of at least 2 points in the lumbar spine BMB score.

WHO classification based on T-scores of BMD improved and remained normal in 2 patients with baseline osteopenia of the lumbar spine and 1 patient with baseline osteopenia of the femoral neck. One patient each with baseline osteoporosis and osteopenia in the femoral neck initially improved but returned to baseline status by the end of the study. After 7 years of treatment with VPRIV, no patients were classified at a more severe WHO classification

compared to baseline. See Table 6 for BMD Z-score results in the lumbar spine and femoral neck. Z-score changes in the lumbar spine and femoral neck were statistically significant by 24 and 33 months, respectively.

Table 6: Mean Observed Values and Mean Change from Baseline in Study 025EXT – ITT Population

Clinical Parameters	Mean Observed Values (95% CI) Baseline	Mean Observed Values (95% CI) 7 Years§	Mean Change from Baseline (95% CI) 7 Years§
Lumbar spine BMD* (Z-score)	-1.6 (-2.2, -1.0)	-0.9 (-1.5, -0.3)	0.7 (0.4, 1.0)
Femoral neck BMD* (Z-score)	-1.5 (-2.1, -0.8)	-1.0 (-1.8, -0.2)	0.5 (0.2, 0.7)
* BMD measured using dual x-ray absorptiometry § The last MRI in the study was at 81 months			

Study 032 was a 12-month, randomised, double-blind, parallel-group efficacy study that enrolled 25 patients aged 4 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 7).

Table 7: 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*	
	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 (%BW)	-0.84 ± 0.33 p = 0.0282	-0.30 ± 0.29 p = 0.3149
Spleen volume** (%BW)	-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 that enrolled 34 patients aged 4 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 that enrolled 40 patients aged 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 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).

Other studies

Extension study 044 [032, 034 and 039]

A total of 95 adult and paediatric patients, who received VPRIV in studies 032, 034 and 039 enrolled in this open-label extension study. Two (2) of the 95 patients were not included in the ITT analysis because they were confirmed to carry only one mutant glucocerebrosidase allele. Fifty-seven (57) patients were treatment-naïve (i.e. from 032 and 039) and 22 were 17 years of age or younger. All patients received at least 2 years of ERT and were followed for a mean of 4.5 years (minimum 2.3 years, maximum 5.8 years).

Efficacy data collected in 044 were analysed for 3 mutually exclusive groups of patients:

- Treatment-naïve patients randomised to VPRIV (referred to as Overall VELA) in the parent study 032 and 039 and continued to receive VPRIV in study 044 (n=39)
- Treatment-naïve patients randomised to imiglucerase in the parent study 039 and switched to VPRIV in study 044 (IMI →VELA) (n=16)
- Patients who had switched from long-term ERT with imiglucerase to VPRIV in study 034 and continued to receive VPRIV in study 044 (034 VELA) (n=38)

In this study, haemoglobin concentration, platelet count, liver volume and spleen volume were assessed in treatment-naïve patients after 24 months of treatment. In the Overall VELA group

(n=39), the mean haemoglobin concentration increased from baseline by 2.75 g/dL (95% CI: 2.28, 3.22), and the mean platelet count increased from baseline by 87.85 x 10^9/L (95% CI: 72.69, 103.00). Normalised liver volume was decreased from baseline by a mean of 1.21 (95% CI: -1.50,-0.91) and normalised spleen volume decreased from baseline by a mean of 2.66 (95% CI: -3.50, -1.82). See Table 8 for observed values and change from baseline.

Table 8: Observed Values and Change from Baseline – Study 044 Overall VELA ITT Population

Clinical Parameters	Mean observed values Baseline*	Mean observed values 24 months	Mean change from Baseline (95%CI) 24 months
Haemoglobin concentration (g/dL) n=39	11.04	13.74	2.75 (2.28, 3.22)
Platelet count (x 10^9/L) n=39	108.65	196.77	87.85 (72,69, 103.00)
Normalised liver volume (%BW) n=39	4.03	2.82	-1.21 (-1.50, -0.91)
Normalised spleen volume (%BW) n=30**	3.85	1.18	-2.66 (-3.50, -1.82)
* Baseline is defined as data collected at the baseline visit in studies 032 or 039 ** Excludes patients with splenectomy			

At 24 months, patients who were treated with imiglucerase for 9 months in study 039 followed by VPRIV for 15 months had mean increases in haemoglobin (2.00 g/dL, 95% CI: 1.25, 2.75) and platelet counts (160.94 x 10^9/L, 95% CI: 117.22, 204.66) and mean decreases in normalised liver volume of (-1.69 %BW, 95% CI: -2.16, -1.21) and in normalised spleen volume (-3.63 %BW, 95% CI: -7.25, -0.02) (see Table 9).

Table 9: Observed Values and Change from Baseline – Study 044 IMI→VELA ITT population

Clinical Parameters	Mean observed values Baseline*	Mean observed values 24 months	Mean change from Baseline (95%CI) 24 months
Overall Population (VPRIV 45-60 U/kg)			
Haemoglobin concentration (g/dL) n=16	10.58	12.53	2.00 (1.25, 2.75)
Platelet count (x 10^9/L) n=16	186.25	347.63	160.94 (117.22, 204.66)
Normalised liver volume (%BW) n=16	4.21	2.52	-1.69 (-2.16, -1.21)
Normalised spleen volume (%BW) n=6**	4.70	1.07	-3.63 (-7.25, -0.02)
* Baseline is defined as data collected at the baseline visit in Study 039 ** Excludes patients with splenectomy			

In patients who switched from imiglucerase in Study 034 to VPRIV, haemoglobin concentrations and platelet counts were sustained through 24 months of treatment with a mean change from baseline haemoglobin of -0.05 g/dL (95% CI: -0.34, 0.25) and a mean change from baseline in platelet count of 9.03 x 10^9/L (95% CI: -2.60, 20.66). Normalised liver and spleen volumes were also sustained with a mean change from baseline in normalised liver volume of -0.026 %BW (95% CI: -0.10, 0.047) and a mean change in normalised spleen volume of -0.11 %BW (95% CI: -0.191, -0.029) (see Table 10).

Table 10: Observed Values and Change from Baseline – Study 044 Switched Patients ITT Population

Clinical Parameters	Mean observed values Baseline*	Mean observed values 24 months	Mean change from Baseline (95%CI) 24 months
Overall Population (VPRIV 45-60 U/kg)			
Haemoglobin concentration (g/dL) n=38	13.82	13.75	-0.05 (-0.34, 0.25)
Platelet count (x 10^9/L) n=38	164.50	173.76	9.03 (-2.60, 20.66)
Normalised liver volume (%BW) n=37	2.06	2.04	-0.026 (-1.00, 0.047)
Normalised spleen volume (%BW) n=34**	0.82	0.71	-0.11 (-0.19, -0.03)
* Baseline is defined as data collected at the baseline visit in study 034 ** Excludes patients with splenectomy			

In this study an exploratory analysis was performed to examine the effect of VPRIV on BMD assessed by using dual x-ray absorptiometry of the lumbar spine and femoral neck. Among the 31 treatment-naïve adult patients treated with VPRIV, the mean lumbar spine BMD Z-score at baseline was -1.82 (95% CI: -2.21, -1.43) (0.845 g/cm^2) and increased by 0.62 (95% CI: 0.39, 0.84) (0.067 g/cm^2, 8%) from baseline following 24 months of treatment with VPRIV. Similar results were seen in the treatment-naïve patients who received 9 months of imiglucerase followed by VPRIV for 15 months. In patients who switched from imiglucerase to VPRIV, VPRIV maintained lumbar spine BMD at 24 months. In contrast to lumbar spine BMD, no significant change in femoral neck BMD was observed.

In children, an exploratory analysis showed an increase in the mean height Z-score (determined by gender and age using WHO 2007 growth reference data) were observed through 60 months of treatment in the overall treatment-naïve population (n=8), suggesting a beneficial treatment effect with VPRIV on linear growth. Similar treatment effects were observed through 48 months in children who received 9 months of imigluerase followed by VPRIV (n=5). Children who switched from imiglucerase to VPRIV in study 034 (n=9) had a greater mean height Z-score at baseline and this remained stable over the duration of study. The numbers of children in each of the subpopulation were small, particularly with regard to long-term follow-up.

The treatment effects on haemoglobin, 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 previous studies. Two patients tested positive for anti-velaglucerase alfa antibodies during the study.

Study 058

Study 058 was an open-label clinical safety study in 211 patients including 205 patients previously treated with imiglucerase and 6 treatment-naïve patients. There were 52 patients aged 65 years or older of whom all had switched from imiglucerase to VPRIV.

This safety study allowed for treatment-naïve patients to receive infusion of VPRIV every other week at a dose of 60 U/kg. In addition, patients transitioning from imiglucerase were offered VPRIV at the same number of units as their imiglucerase dose within the range of 15 to 60 U/kg. If the imiglucerase dose was reduced prior to transition to VPRIV the pre-reduction imiglucerase dose could be used to determine the VPRIV dose. Patients transitioning from a dose of <15 U/kg received a dose of 15 U/kg of VPRIV.

In this study, the safety profile in 205 patients previously treated with imiglucerase was similar to that observed in other clinical studies. Patients previously treated with imiglucerase received a median of 13 VPRIV infusions with a median duration of treatment of 26.0 weeks.

Of the 167 patients with post-Baseline antibody data, including 4 naïve and 163 previously treated patients, 1 patient (0.6%) developed anti-velaglucerase antibodies on treatment.

Observation regarding treatment goals suggests that an apparent increase from baseline in haemoglobin concentration and platelet count was observed in the 4 treatment-naïve patients with post-baseline data. Among previously treated patients mean haemoglobin concentration and platelet were maintained throughout the study and remained within the normal range.

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.

5.2 PHARMACOKINETIC PROPERTIES

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.

There were no apparent pharmacokinetic differences between male and female patients with type 1 Gaucher disease (Study 032).

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.

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).

5.3 PRECLINICAL SAFETY DATA

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Citric acid monohydrate
Polysorbate 20
Sodium citrate dihydrate
Sucrose

6.2 INCOMPATIBILITIES

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.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR 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 completed within 24 hours from the time of reconstitution and/or dilution.

6.5 NATURE AND CONTENTS OF CONTAINER

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.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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.

CAS number

37228-64-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION

12 November 2020

Summary table of changes

Section changed	Summary of new information
5.1	Revision of age of paediatric patients enrolled in the studies; revision of Table 5
8	Update of sponsor details
10	Revision of document date

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