



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Velaglucerase alfa (ghu)

Proprietary Product Name: VPRIV

Sponsor: Shire Australia Pty Ltd

May 2012

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New Chemical Entity (Biological)
<i>Decision:</i>	Approved
<i>Date of decision:</i>	23 February 2012
<i>Active ingredient:</i>	Velaglucerase alfa (ghu)
<i>Product name:</i>	VPRIV®
<i>Sponsor's name and address:</i>	Shire Australia Pty Ltd Level 3, 78 Waterloo Road North Ryde NSW 2113
<i>Dose form:</i>	Lyophilised powder, which requires reconstitution and dilution
<i>Strength:</i>	400 Units
<i>Container:</i>	Glass vial with rubber stopper
<i>Pack size:</i>	Single carton containing one vial of 400 Units of velaglucerase alfa powder for solution for infusion
<i>Approved therapeutic use:</i>	Long-term enzyme replacement therapy for paediatric and adult patients with Type 1 Gaucher disease associated with at least one of the following clinical manifestations: anaemia, thrombocytopenia, hepato-splenomegaly.
<i>Route of administration:</i>	Intravenous (IV) infusion
<i>Dosage:</i>	60 Units/kg administered every other week as a 60 minute intravenous infusion
<i>ARTG number:</i>	180965

Product background

VPRIV®, velaglucerase alfa, 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. VPRIV is used to treat Gaucher's Disease (GaD), an autosomal recessive storage disorder resulting from a deficiency in the lysosomal enzyme, beta-glucocerebrosidase. GaD is the most frequent lysosomal storage disease presenting in all populations.

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

VPRIV is indicated for long term enzyme replacement therapy (ERT) for paediatric and adult patients with Type 1 GaD (GaD1), an autosomal recessive metabolism disorder caused by mutations in the glucocerebrosidase (also known as glucosylceramide or acid beta-glucosidase, GBA) gene on chromosome 1q21 affecting the recycling of cellular glycolipids.

Gaucher's disease (GaD)

GaD is an inborn error of metabolism that affects the recycling of cellular glycolipids. Glucocerebrosidase (also called glucosylceramide) and several related compounds that are ordinarily degraded to glucose and lipid components accumulate within the lysosomes of cells.

GaD is one of the few inherited metabolic disorders that can be treated by replacement of the deficient enzyme (enzyme replacement therapy). Because early treatment can prevent development of irreversible complications, early identification is crucial to improving ultimate outcome.

Epidemiology

GaD is the most common lysosomal storage disease. It occurs in approximately 1/75,000 births worldwide, but is more prevalent in individuals of Ashkenazi Jewish descent. There are approximately 20,000 individuals with GaD in the United States, based upon a gene frequency study, two-thirds of whom are Ashkenazi Jews.

Approximately 90 percent of patients have GaD1, which is the non neuronopathic form. This type is most common in the Ashkenazi Jewish population, in which the carrier frequency is approximately 1 in 12 and the frequency of disease associated genotypes is calculated at 1 in 850. The incidence of GaD1 is much lower in non Jewish populations, occurring in approximately 1 in 40,000 to 1 in 86,000 live births.

Type 2 Gaucher's disease (GaD2, also called acute neuronopathic GaD, infantile cerebral GaD, or perinatal lethal GaD) is the rarest form, with an incidence estimated at 1 in 150,000.

The estimated incidence of Type 3 GaD (GaD3) is 1 in 200,000. GaD3 is panethnic, but with well studied clusters in Northern Europe, Egypt and East Asia.

Genetics

GaD is an autosomal recessive disorder caused by mutations in the glucocerebrosidase (GBA) gene located on chromosome 1q21. More than 200 distinct mutations are reported. However three mutant alleles account for most cases: c.1226A>G (N370S), c.1448T>C (L444P), and c.84dupG (84GG). The prevalence of these alleles varies with ethnicity. The c.1226A>G mutation is encountered commonly in non Jewish Europeans and Ashkenazi Jews, whereas c.1448T>C is relatively common in Sweden and Northern Europe. Disease onset, severity, and clinical manifestations vary with the genotype, although the genotype-phenotype correlation is not entirely consistent.

Pathogenesis

GaD results from deficiency of a lysosomal enzyme GBA. GBA is a glycoprotein enzyme whose major substrate is glucocerebrosidase, a component of the cell membrane that is distributed widely in many organs. In the normal lysosome, the protein saposin C is thought to present glucocerebrosidase to GBA and thereby activate the enzyme.

In affected patients, the deficiency of GBA leads to accumulation of glucocerebrosidase and other glycolipids within the lysosomes of macrophages. The tissue levels of these compounds may be increased 20 to 100 times. The deacylated form of glucosylceramide,

glucosylsphingosine, is particularly elevated in neuronopathic disease and may have a role in the pathogenesis of neurodegeneration.

The clinical manifestations of GaD are the result of the accumulation of the lipid laden macrophages in the spleen, liver, bone marrow, bone, and other tissues/organs. However, pathologic lipid accumulation in macrophages accounts for less than 2 percent of the additional tissue mass in liver and spleen. The additional increase is attributed to an inflammatory and hyperplastic cellular response. Although the pathogenetic mechanisms are not understood, cells (primarily macrophages) that have an accumulation of glucocerebroside in their lysosomes ('Gaucher cells') and neighbouring macrophages overexpress and secrete lysosomal proteases, such as cathepsins, and inflammatory mediators such as interleukins 6, 8, 10 and macrophage inflammatory proteins. The Gaucher cells exhibit the secretory phenotype of the so called "alternatively activated" macrophage. This phenotype is often associated in other conditions with chronic inflammation, healing, and fibrosis. A mouse model of GaD suggests that other cell types are affected, including thymic T cells, dendritic cells, and osteoblasts.

Several pathologic processes occur within bone: decreased mineral density, marrow infiltration, and infarction of bone. The mechanisms leading to decreased bone mineral density are uncertain but they may involve failure to achieve peak bone mass, abnormal osteoclast regulation, or overproduction of cytokines by activated macrophages. Marrow fibrosis and osteosclerosis result in localised loss of haematopoiesis. In an *in vitro* model of GaD, primitive haematopoiesis and proliferation of mesenchymal progenitors were impaired, suggesting that cytopenias are due an intrinsic defect in addition to hypersplenism and bone marrow infiltration with Gaucher cells. Thrombocytopenia results from splenic sequestration and occasionally marrow failure.

Clinical manifestations

GaD involves the visceral organs, bone marrow, and bone in all affected patients. The presenting features are variable and may occur at any age. GaD is categorised into three clinical types that are distinguished by their clinical features, course, and ethnic predilection. However, there is a broad spectrum of findings and overlap within and between types and intermediate phenotypes are appreciated, suggesting that GaD is a spectrum of disease manifestations, rather than a disorder with three distinct subtypes.

Type 1 GaD (GaD1, MIM #230800) is the most prevalent and occurs with greater frequency in the Ashkenazi Jewish population, although most patients with GaD1 are not Jewish. Types 2 and 3 are less common and occur in all ethnic types. Type 1 GaD is distinguished from type 2 GaD (GaD2, MIM #230900) and type 3 GaD (GaD3, MIM #231000) by the lack of characteristic involvement of the central nervous system, although studies have documented several neurologic features in type 1 patients that are distinct from those observed in types 2 and 3. GaD with neurologic involvement (neuronopathic GaD) is designated as type 2 or 3 based on the acute or chronic nature, respectively.

Presentation

GaD has a variety of presenting features that may occur at any age with varying severity. These include (with percentages from the ICGG Registry Report 2010):

- Splenomegaly (all types; moderate to severe – 85% at presentation)
- Hepatomegaly (all types; moderate to severe – 63% at presentation)
- Anemia (all types; 34% at presentation)
- Thrombocytopenia (all types; moderate to severe – 68% at presentation)
- Bleeding (all types)

- Osteopenia and pathologic fractures (all types; osteopenia 55%, fractures 7%, bone crisis 7% at presentation)
- Bone pain (all types; 33% at presentation)
- Growth retardation (all types; 36%)
- GaD2 constitutes 1% of patients in Registry, GaD3 constitutes 7%
- Developmental delay (GaD2 and GaD3)
- Nonimmune hydrops (GaD2)
- Congenital ichthyosis (GaD2)
- Strabismus or supranuclear gaze palsy (GaD2 and GaD3)
- Progressive dementia, ataxia and myoclonus (GaD3, rare)
- Corneal opacity (GaD3C, rare)
- Cardiovascular calcification (GaD3C, rare)

Patients (usually GaD1) may also present following splenectomy carried out either in the course of investigation of suspected malignancy or following traumatic splenic rupture.

Regulatory status

Velaglucerase alfa was designated an orphan drug by TGA on 8 December 2009. Velaglucerase alfa has received marketing approval in 37 countries including 27 member states of the European Union (as of January 1, 2007) (approved via Centralised Procedure; Iceland, Lichtenstein and Norway approved under the Europe Free Trade Association), the USA, Canada and Switzerland. The current international regulatory status is summarised in Table 1.

Table 1: Summary of international regulatory status of velaglucerase alfa.

Country	Approval Date	Indication
USA	26 Feb 2010	VPRIV (velaglucerase alfa for injection) is a hydrolytic lysosomal glucocerebrosidase specific enzyme indicated for long term ERT for paediatric and adult patients with GaD1.
Switzerland	29 Aug 2011	VPRIV is indicated for long term ERT in patients with GaD1.
EU	26 Aug 2010	VPRIV is indicated for long term ERT in patients with GaD1.
Canada	1 Oct 2010	VPRIV (velaglucerase alfa) is indicated for long term ERT for paediatric and adult patients GaD1.

There are currently two other therapies already registered for the treatment of GaD:

1. Cerezyme® (imiglucerase) by IV infusion is approved for the following indication:
 “Cerezyme is indicated for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Type 1 Gaucher’s disease that results in one or more of the following conditions: (a) anaemia; (b) thrombocytopenia; (c) bone disease; (d) hepatomegaly or splenomegaly”.

- Zavesca® (miglustat), available as a capsule, acts as a competitive and reversible inhibitor of glucosylceramide synthase, the enzyme responsible for the first and committed step in the synthesis of most glycosphingo lipids. Its approved indication is as follows:

“Zavesca® is indicated for the oral treatment of patients with mild to moderate Type 1 Gaucher’s disease for whom enzyme replacement treatment is not a therapeutic option”.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

The drug substance has the following structure shown in Figure 1.

Figure 1: Amino acid sequence of secreted velaglycerase alfa using three letter code.

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1 Ala Arg Pro Cys Ile Pro Lys Ser Phe Gly Tyr Ser Ser Val Val Cys Val Cys Asn Ala 70
21 Thr Tyr Cys Asp Ser Phe Asp Pro Pro Thr Phe Pro Ala Leu Gly Thr Phe Ser Arg Tyr 80
41 Glu Ser Thr Arg Ser Gly Arg Arg Met Glu Leu Ser Met Gly Phe Ile Glu Ala Asn His 90
61 Thr Gly Thr Gly Leu Leu Leu Thr Leu Glu Pro Glu Glu Lys Phe Glu Lys Val Lys Gly 90
81 Phe Gly Gly Ala Met Thr Asp Ala His Ala Leu Asn Ile Leu Ala Leu Ser Pro Pro Ala 100
101 Glu Asn Leu Leu Leu Lys Ser Tyr Phe Ser Glu Glu Gly Ile Gly Tyr Asn Ile Ile Arg 110
121 Val Pro Met Ala Ser Cys Asp Phe Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro Asp 140
141 Asp Phe Glu Leu His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys Leu Lys Ile Pro Leu 160
161 Ile His Arg Ala Leu Glu Leu Ala Glu Arg Pro Val Ser Leu Leu Ala Ser Pro Trp Thr 180
181 Ser Pro Thr Trp Leu Lys Thr Asn Gly His Val Asn Gly Lys Gly Ser Leu Lys Gly Glu 200
201 Phe Gly Asp Ile Tyr His Glu Thr Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala Tyr 220
221 Ala Glu His Lys Leu Glu Phe Trp Ala Val Thr Ala Glu Asn Glu Pro Ser Ala Gly Leu 240
241 Leu Ser Gly Tyr Pro Phe Glu Cys Ser Gly Phe Thr Pro Glu His Glu Arg Asp Phe Ile 260
261 Ala Arg Asp Leu Gly Pro Thr Leu Ala Asn Ser Thr His His Asn Val Arg Leu Leu Met 280
281 Leu Asp Asp Glu Arg Leu Leu Leu Pro His Trp Ala Lys Val Val Leu Thr Asp Pro Glu 300
301 Ala Ala Lys Tyr Val His Gly Ile Ala Val His Trp Tyr Leu Asp Phe Leu Ala Pro Ala 320
321 Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe Pro Asn Thr Met Leu Phe Ala Ser Glu 340
341 Ala Cys Val Gly Ser Lys Phe Trp Glu Glu Ser Val Arg Leu Gly Ser Trp Asp Arg Gly 360
361 Met Glu Tyr Ser His Ser Ile Ile Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr Asp 380
381 Trp Asn Leu Ala Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg Asn Phe Val Asp Ser 400
401 Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe Tyr Lys Glu Pro Met Phe Tyr His Leu 420
421 Gly His Phe Ser Lys Phe Ile Pro Glu Gly Ser Glu Arg Val Gly Leu Val Ala Ser Glu 440
441 Lys Asn Asp Leu Asp Ala Val Ala Leu Met His Pro Asp Gly Ser Ala Val Val Val Val 460
461 Leu Asn Arg Ser Ser Lys Asp Val Ser Leu Thr Ile Lys Asp Pro Ala Val Gly Phe Leu 480
481 Glu Thr Ile Ser Pro Gly Tyr Ser Ile His Thr Tyr Leu Trp Asn Arg Glu 497
    
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Asn (asparagine) denotes potential N-linked glycosylation site; Cys (cysteine) residues are highlighted.

Velaglycerase alfa is a highly purified recombinant form of the naturally occurring human lysosomal enzyme glucocerebrosidase and is similar to alglucerase also used in the treatment of Type I GaD.

Drug product

The formulation of the drug substance is shown in Table 2.

Table 2: Formulation of drug product.

Names of Ingredients	Nominal Content per 200 U/vial ^a	Nominal Content per 400 U/vial ^b	Function	Reference to Standards
Velaglucerase alfa	5 mg (200 unit) ^c	10 mg (400 unit) ^c	Active ingredient	In-house monograph
Sucrose	100 mg	200 mg	Lyoprotectant	NF, Ph Eur
Sodium citrate, dihydrate	25.88 mg	51.76 mg	Buffer salt	USP, Ph Eur
Citric acid, monohydrate	2.52 mg	5.04 mg	Buffer salt	USP, Ph Eur
Polysorbate 20	0.22 mg	0.44 mg	Stabilizing agent	NF, Ph Eur

^a With a target fill volume of 2.3 mL, the total quantity per vial is 5.75 mg or 230 U of velaglucerase alfa. After reconstitution with 2.2 mL sterile water for injection, each vial will provide an extractable (nominal) volume of 2.0 mL containing 5 mg or 200 U velaglucerase alfa.

^b With a target fill volume of 4.4 mL, the total quantity per vial is 11 mg or 440 U of velaglucerase alfa. After reconstitution with 4.3 mL sterile water for injection, each vial will provide an extractable (nominal) volume of 4.0 mL containing 10 mg or 400 U velaglucerase alfa.

^c One mg of velaglucerase alfa is equivalent to 40 U of velaglucerase alfa.

The 200 U strength vial was withdrawn from the submission.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Velaglucerase alfa is susceptible to direct intense light. However, there were no changes by any of the test methods when drug product was photoexposed in its secondary package.

The proposed shelf life is three years when stored at 2-8°C. This is supported by adequate stability data.

In use stability data have also been submitted. The proposed shelf life and storage conditions for the reconstituted product are 48 hours when stored at 2-8°C or 24 hours under ambient conditions.

Bioavailability

The product is a simple solution for IV administration only. There are no bioavailability data.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutical data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

A number of deficiencies were identified during the evaluation and referred to the applicant. These issues were resolved satisfactorily. The Advisory Committee on Prescription Medicines (ACPM) and the Clinical Delegate were advised of a recommendation that there is no objection to the registration of this product on quality grounds.

The following condition of registration was recommended:

The first five independent batches of VPRIV velaglucerase alfa (ghu) 400 U vials imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

III. Nonclinical findings

Introduction

The nonclinical data submitted in support of the safety and efficacy of velaglucerase alfa were of high quality and were performed by reputable laboratories. The pivotal, nonclinical safety data were performed according to Good Laboratory practice (GLP) standards.

Pharmacology

Primary pharmacodynamics

A mouse model of GaD was used to compare the abilities of velaglucerase alfa and imiglucerase (another analogue of human β -glucocerebrosidase used for human enzyme replacement therapy) to lower glucocerebroside levels in liver. After 4 or 8 weeks of treatment with either of the two forms of the test article, glucocerebroside levels in liver of glucocerebrosidase deficient mice had declined to ~40% of saline control levels, but were still higher than levels found in wild type mice (~25% of saline control). Similar results were obtained when mice were dosed at 5, 15, or 60 U/kg of velaglucerase alfa (the recommended human dose is 60 U/kg). This decline in liver glucocerebroside levels was correlated with a similar decline in the frequency of lipid laden macrophages in liver tissue sections. The sponsor was asked to comment on whether this decline reflected test article induced killing of lipid laden macrophages or their conversion to a normal appearance. In their reply it was suggested that the observed decrease was likely due to a change in the activation state of the Gaucher cells due to the attenuation of the signals driving alternative macrophage stimulation.

Secondary pharmacodynamics and safety pharmacology

Neither secondary pharmacodynamics nor safety pharmacology studies were performed by the sponsor. One exception was that electrocardiograms, recorded prior to and during dosing, showed no effect of velaglucerase alfa in a rhesus monkey, six month repeat dose toxicity study. The lack of such studies appears reasonable given the history of successful use of analogues of human β -glucocerebrosidase for enzyme replacement therapy of Gaucher's disease.

Pharmacokinetics

Single dose plasma kinetics of velaglucerase alfa, given as an IV bolus dose, were studied in the rat and dog. Velaglucerase alfa concentration was determined using a validated colorimetric assay of β -glucocerebrosidase activity. In both species, velaglucerase alfa was rapidly removed from serum ($t_{1/2}$ values of ~4 minutes). The maximum (peak) plasma drug concentration (C_{max}) was dose proportional, but the area under the plasma concentration-time curve ($AUC_{0-\infty}$) increased more than dose proportionally at ≥ 3 mg/kg, indicating saturation of clearance mechanisms. Similar results were obtained in a six month rhesus monkey study with dosing every fortnight. Toxicokinetics remained comparable during the six months of dosing, with half-life ($t_{1/2}$) values of 5-11 minutes and saturation of clearance mechanisms at dose levels of ≥ 3 mg/kg. There was no evidence for accumulation of velaglucerase alfa in serum following fortnightly dosing for six months.

Distribution studies were performed using rats given an IV dose of radioactively (^{125}I)labelled velaglucerase alfa. Whilst radioactivity was being rather rapidly cleared from plasma, levels in various tissues remained relatively constant between 20 minutes and 1 h post dose before declining. The highest radioactivity concentrations were found in lungs, liver, bone marrow, spleen, kidneys, and adrenal glands, with liver the major site of tissue radioactivity (as percent of dose). By 48 h post dose, 91-106% of radioactivity had been recovered in urine, indicating that this is the main route of excretion. Similar results were obtained for both sexes.

Toxicology

Table 3 shows an overview of the repeat dose toxicity studies.

Table 3: Overview of repeat dose toxicity studies

Species	Study duration (months)	Doses (mg/kg; IV, fortnightly)	Exposure ratio ^a
Rat (SD)	3	0.85, 3.4, 17 ^b	0.1, 0.4, 1.8
	6	0.84, 3.4, 17	0.1, 0.4, 1.8
Rhesus monkey	6	0.84, 3.4, 17	0.2, 0.7, 3.7

^a Relative to human dose of 1.5 mg/kg and using conversion factors (mg/kg to mg/m²) of 6 (rat- 0.2 kg), 12 (monkey- 3.0 kg), and 37 (human- 70 kg); ^b NOAELs (bolded) were the highest dose tested in each study

An acute single dose toxicity study was performed in Sprague-Dawley (SD) rats of both sexes. A dose of up to 23 mg/kg of velaglucerase alfa was without apparent effect.

Repeat dose toxicity studies used SD rats (3 and 6 month studies) and rhesus monkeys (6 month study), of both sexes, given a fortnightly IV dose of velaglucerase alfa (Table 3). GaD patients receive a fortnightly IV infusion at 1.5 mg/kg.

The high dose (HD) administered in the rat and monkey studies is expected to produce exposure ratios of ~1.8 and 3.7 times, respectively, as compared with the human dosing protocol. The only clinical sign of dosing was seen in the rat studies where HD animals showed an adverse reaction after the first dose of velaglucerase alfa. This reaction involved various combinations of reddening/swelling of the muzzle and/or limbs and, at lower incidence, reduced activity, laboured breathing, and/or lateral recumbency. The reddening/swelling was the most persistent response, but resolved within ~24 h of dosing. This reaction continued in most/all HD animals after all subsequent doses. The same response was seen in animals receiving vehicle or the low dose (LD) or the middle dose (MD) of the test article; although in these groups, the reaction was seen after the third or fourth dose and the initial incidence of animals showing the reaction was low but increased with further dosing such that nearly all animals showed the reaction after the final dose. The occurrence of this reaction in the control group suggested that the vehicle was at least partly involved. (The vehicle contained Tween 20 (also known as Polysorbate 20), which is chemically related to Tween 80, a known inducer of severe, nonimmunologic anaphylactoid reactions.¹) Some of the observed clinical signs (that is, reddening/swelling) appeared consistent with a histamine type response (see section below: 'Antigenicity'). This response was seen in rats but not in monkeys. (According to

¹ Coors EA, et al. Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions. *Annals of Allergy, Asthma & Immunology* 2005; 95:593-599.

the sponsor's Nonclinical Overview, the response was also not seen in rabbits or dogs dosed with velaglucerase alfa.) Because the reddening/swelling response seen in rats was transient and not associated with other changes (for example, food consumption, body weight), it was not considered an adverse effect of velaglucerase alfa dosing.

Studies in normal versus diseased animals

β -Glucocerebrosidase catalyses the hydrolytic cleavage of glucocerebroside to produce glucose and ceramide. Following enzyme replacement therapy of GaD patients with velaglucerase alfa, a considerable increase in ceramide levels in macrophages might be anticipated. Any such increase in macrophages containing normal levels of glucocerebroside would likely be much smaller. Ceramide is capable of modulating various critical cellular functions, including an ability to induce apoptosis.² Accordingly, the sponsor was asked why no toxicity studies had been performed with a mouse model of GaD. The reasons given included:

1. the timing of availability of the mouse model (2003) did not fit the development timeline for velaglucerase alfa and did not allow the collection of a historical range of normal clinical pathology values;
2. testing of enzyme replacement therapy has usually been performed with normal animals;
3. The lack of background information on animal models of disease confounds the interpretation of toxicity studies, and
4. velaglucerase alfa is only active in lysosomes, a site assumed not to contribute to toxicity.

The sponsor was also asked to comment on the toxicological relevance of treating normal animals (with fully functional glucocerebrosidase activity) with velaglucerase alfa. Justifications provided included: (1) the targets for uptake of velaglucerase alfa, mannose receptors, are present on macrophages (and other cell types) in normal animals; and (2) mice that lack β -glucocerebrosidase might show a stronger immune response to velaglucerase alfa.

In addition to macrophages, other cell types, such as rodent hepatic and lymphatic endothelial cells, are known to express mannose receptors³ and the former have been shown to endocytose mannose-terminal β -glucocerebrosidase.⁴ The sponsor was asked whether effects of velaglucerase alfa on such cell types had been described. The reply was that while the literature regarding the impact of recombinant glucocerebrosidase on endothelial cells is not expansive, twenty years of collective experience with glucocerebrosidase enzyme replacement therapy has thus far shown no off target effects on endothelial cells.

Genotoxicity and carcinogenicity

Possible genotoxic or carcinogenic action by velaglucerase alfa was not examined by the sponsor. Given velaglucerase alfa's mode of action (that is, breakdown of lysosomal glucocerebroside) and the products of its enzymic action (that is, glucose and ceramide), it appears unlikely that it would have direct genotoxic or carcinogenic activity.

² Taha TA, et al. A house divided: ceramide, sphingosine, and sphingosine-1-phosphate in programmed cell death. *Biochimica et Biophysica Acta* 2006; 1758:2027-2036

³ Takahashi K, et al. Distribution of murine mannose receptor expression from early embryogenesis through to adulthood. *Cell and Tissue Research* 1998; 292:311-323

⁴ Murray GJ, Jin FS. Immunoelectron microscopic localization of mannose-terminal glucocerebrosidase in lysosomes of rat liver Kupffer cells. *Journal of Histochemistry and Cytochemistry* 1995; 43:149-158

Reproductive toxicity

Table 4 shows an overview of the reproductive and developmental toxicity studies.

Table 4: Overview of reproductive and developmental toxicity studies.

Species	Study type	Time of dosing	Doses (mg/kg; IV)	Exposure ratio ^a
Rat (SD)	Male fertility	twice per week	1.5, 5.0, 17 ^b	0.2, 0.5, 1.8
	Female fertility	twice per week	1.5, 5.0, 17	0.2, 0.5, 1.8
	Embryofoetal dev. (dose range finding)	GD 6, 9, 12, 15, and 17	1.5, 3.0, 5.0, 17	0.2, 0.3, 0.5, 1.8
	Embryofoetal dev. (main study)	GD 6, 9, 12, 15, and 17	1.5, 5.0, 17	0.2, 0.5, 1.8
	Pre and postnatal development	GD 6, 9, 13, 16, and 20 and LD 1, 5, 8, 12, 15, and 19	1.5, 5.0, 17	0.2, 0.5, 1.8
Rabbit (NZW)	Embryofoetal dev. (dose range finding)	GD 6, 9, 12, 15, and 18	0.5, 1.5, 5, 10, 20	0.1, 0.4, 1.4, 2.7, 5.4
	Embryofoetal dev. (main study)	GD 6, 9, 12, 15, and 18	1.5, 10, 20	0.4, 2.7, 5.4

^aRelative to human dose of 1.5 mg/kg and using conversion factors (mg/kg to mg/m²) of 6 (rat- 0.2 kg), 15 (rabbit- 3.0 kg), and 37 (human- 70 kg); ^bNOAELs (bolded) were the highest dose tested in each study

Repeat dosing of rats or rabbits with velaglucerase alfa, up to exposure ratios of ~1.8 and 5.4 times human exposure (Table 4; although dosing interval in all of these studies was considerably shorter than for human use), respectively, had no effect on fertility (both sexes), embryofoetal development, or pre and post natal development.

Pregnancy classification

The suggested pregnancy classification (B2) appears reasonable. A high molecular weight molecule such as velaglucerase alfa is unlikely to cross the placenta.

Use in children

Velaglucerase alfa is indicated for long term ERT of both paediatric and adult patients with GaD1. The sponsor, however, did not conduct studies using juvenile animals and this

omission was justified by the claim: “glucocerebrosidase ... would not be expected to exert effects in juvenile animals that would not be observed in adult animals”.

Antigenicity

The development of antibodies to velaglucerase alfa was monitored using an ELISA based method and was shown to occur in a significant fraction of both rats and monkeys after several doses of test article. The development of anti velaglucerase alfa antibodies appeared to have no adverse toxicological effects. The sponsor indicated that only a low percentage of human patients develop anti velaglucerase alfa antibodies.

The transient reddening/swelling of extremities seen in rats shortly after velaglucerase alfa dosing (see above) was shown to correlate with an increase (relative to pre dose) in serum histamine concentration of ~10-fold at 15 minutes after dosing. It was also shown that the incidence of reddening/swelling of extremities was reduced by dosing with the histamine receptor antagonist diphenhydramine prior to velaglucerase alfa exposure. Complement activation can lead to mast cell degranulation; however, velaglucerase alfa dosing was shown to have no effect on total complement activity in rat serum. Alternatively, the triggering of mast cell degranulation may have been initiated by secreted products of activated macrophages.⁵

Nonclinical summary and conclusions

- Shire Australia Pty Ltd proposes to register the new biological entity, velaglucerase alfa (a form of human β -glucocerebrosidase, the enzyme responsible for converting glucocerebroside to ceramide), for the ERT of GaD1.
- The pivotal, nonclinical safety data presented in support of velaglucerase alfa's use were performed according to GLP standards.
- Velaglucerase alfa had comparable efficacy to imiglucerase in lowering liver glucocerebroside levels in a mouse model of GaD.
- Velaglucerase alfa was cleared rapidly ($t_{1/2}$ values ~4 minutes) from the serum of rats, dogs, and monkeys following an IV bolus dose. There was no evidence for accumulation of velaglucerase alfa in serum following fortnightly dosing of monkeys for 6 months. Distribution studies in rats using IV bolus dosing with radioactively labelled velaglucerase alfa revealed highest concentrations in lungs, liver, bone marrow, spleen, kidneys, and adrenal glands.
- No adverse effects of fortnightly velaglucerase alfa dosing were observed in repeat dose toxicity studies of rats and monkeys for up to six months at exposure ratios (relative to GaD patients) of up to 1.8 and 3.7, respectively. While high doses of velaglucerase alfa produced reddening/swelling of the muzzle and/or limbs in rats, this effect was transient and was not seen in other species (including monkeys).
- Possible genotoxic or carcinogenic action by velaglucerase alfa was not examined. Given velaglucerase alfa's mode of action, its target cells (terminally differentiated), and the assumed lack of genotoxicity of the products of its enzymic action, it would seem most unlikely that velaglucerase alfa would have direct carcinogenic activity.
- Velaglucerase alfa dosing had no effect on fertility (both sexes), embryo foetal development, or pre and post natal development in rats and rabbits with normal β -glucocerebrosidase activity.

⁵ Triggiani M, et al. Activation of human inflammatory cells by secreted phospholipases A2. *Biochim Biophys Acta*. 2006; 1761:1289-1300.

- A significant number of rats and monkeys developed anti velaglucerase alfa antibodies after several doses. These antibodies appeared to have no adverse toxicological effects. Rats also showed an innate immune system response to velaglucerase alfa with the occurrence of high histamine levels in serum soon after dosing.

Velaglucerase alfa showed comparable efficacy with imiglucerase in lowering liver glucocerebroside levels in a mouse model of GaD.

The toxicology studies in rats and monkeys raised no direct issues of clinical concern.

Based on assessment of the Sponsor's non-clinical studies, there are no objections to the Risk Management Plan (RMP) dated 23 June 2010 (version 6.0).

There are no nonclinical objections to registration.

IV. Clinical findings

Introduction

The clinical data included two pharmacokinetic studies and five clinical studies. There was some overlap of patients in the clinical studies as some of these were extension studies. All of the studies were stated to comply with GCP.

Pharmacokinetics

Introduction

The current Australian submission included three pharmacokinetic (PK) studies in support of the application. All of the studies were performed on a subset of patients who were enrolled in one of the efficacy and safety studies. The PK of VPRIV was investigated at doses of 15, 30, 45 and 60 U/kg in a total of 45 patients with GaD1 receiving 60 minute intravenous infusions every other week.

Study TKT032

This report described the PK component of study TKT032; a multi centre, randomised, double blind, parallel group, two dose study of gene activated human glucocerebrosidase (GA-GCB) enzyme replacement therapy (VPRIV) in patients with GaD1. Of the 25 patients enrolled in Study TKT032, all were included in the pharmacokinetic component. The study was conducted in five centres in Europe. PK were evaluated at Weeks 1 and 37 of the clinical study. Patients received one of two doses of VPRIV; either 45 U/kg/dose or 60 U/kg/dose, infused over 1 hour every other (second) week by intravenous infusion. Of the 25 patients; 13 patients were enrolled in the 45 U/kg arm and 12 patients were enrolled in the 60 U/kg arm. In patients greater than 18 years old, blood samples were collected pre dose and at 5, 10, 15, 20, 40, 60 (end of infusion) 65, 70, 80, 90, 105 and 120 minutes after the start of the infusion. In patients 2 to 17 years old, blood samples were collected pre dose and at 10, 20, 40, 60 (end of infusion), 70, 80 and 90 minutes after the start of the infusion. All samples were obtained from the non infusion arm. Additional blood samples for determination of anti velaglucerase alfa antibodies were collected at Weeks 7, 13, 19, 25, 31, 37, 43, 49, and 53.

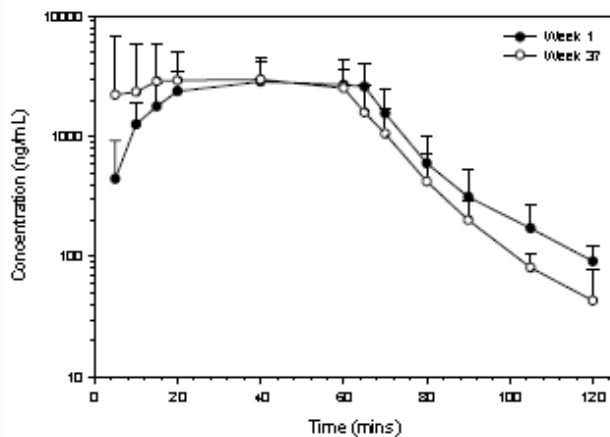
The bioanalytical analyses were performed at Shire HGT's bioanalytical laboratory. Serum samples for pharmacokinetic analysis were analysed for velaglucerase alfa protein content with a validated, GLP bioanalytical method, using an enzyme linked immunosorbent assay (ELISA).

The pharmacokinetic analysis was performed by the Clinical Pharmacology and Pharmacokinetics Department of Shire, using WinNonlin Professional Version 5.1 (Pharsight). The primary analysis was using a non compartmental approach. Statistical analysis and programming of the tables, figures and listings based on the pharmacokinetic data was also conducted by Shire, using SAS version 9.1 (SAS Institute Inc.).

VPRIV 45 U/kg dose

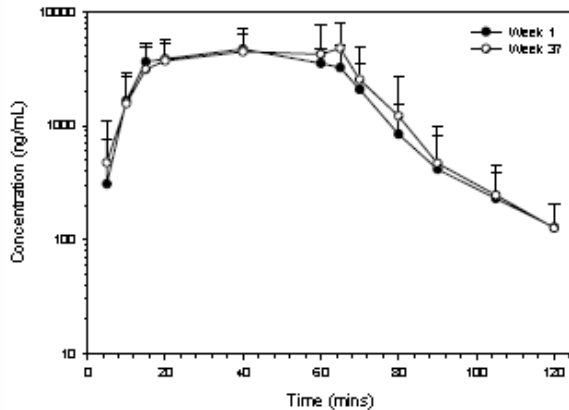
During the infusion, the serum concentration increased during the first 20 minutes before plateauing for the remainder of the infusion. The time to reach maximum (peak) plasma concentration following drug administration (T_{max}) was typically attained at ~40 minutes after the commencement of the infusion. After the end of the infusion, serum concentrations fell rapidly (Figure 2). The mean velaglucerase alfa apparent volume of distribution at steady state (V_{ss}) was 104 mL/kg at Week 1 and 108 mL/kg at Week 37. There was no evidence of accumulation over the study period and there was a short half life of approximately 12 minutes at both study time points.

Figure 2: Pharmacokinetic profile for VPRIV 45 U/kg at Week 1 and 37 (Study TKT032).



VPRIV 60 U/kg dose

The 60 U/kg dose produced a similar pharmacokinetic profile to that of the 45 U/kg dose; the serum concentration increased during the first 20 minutes after administration before plateauing for the remainder of the infusion. T_{max} was typically attained at ~40 minutes after the commencement of the infusion. After the end of the infusion, serum concentrations fell rapidly (Figure 3). The mean velaglucerase alfa V_{ss} was 106 mL/kg at Week 1 and 82 mL/kg at Week 37. There was no evidence of accumulation over the study period and there was a short half life of approximately 12 minutes at both study time points (Table 5).

Figure 3: Pharmacokinetic profile for VPRIV 60 U/kg at Week 1 and 37 (Study TKT032).

As stated in the sponsor's submission, the mean velaglucerase alfa C_{max} and AUC were approximately 40% to 50% higher in the subjects receiving 60 U/kg than in the subjects receiving 45 U/kg, which is greater than the expected 33% increase assuming linear dose proportionality. The main pharmacokinetic parameters are shown below in Table 5.

Table 5: Pharmacokinetic parameters (Study TKT032).

Treatment	C_{max} (ng/mL)	T_{max} (h)	AUC _{inf} (ng•min/mL)	$T_{1/2}$ (min)	CL (mL/min/kg)	V_{ss} (mL/kg)
45 U/kg, Week 1 (n=13) ^a	3437 ± 1283	40 ± 19	178318 ± 62162	12.4 ± 3.1	7.02 ± 2.59	104 ± 66
45 U/kg, Week 37 (n=12) ^b	4033 ± 2939	37 ± 20	181056 ± 91591	11.9 ± 5.5	7.56 ± 3.56	108 ± 59
60 U/kg, Week 1 (n=12)	5256 ± 2323	45 ± 16	254148 ± 111749	11.5 ± 3.5	7.16 ± 3.54	106 ± 60
60 U/kg, Week 37 (n=12)	5721 ± 2795	44 ± 15	268085 ± 125438	11.4 ± 3.2	6.72 ± 2.91	82 ± 39

Values are mean ± SD.

a: n=13 for C_{max} , n=10 for AUC_{inf}, $T_{1/2}$, CL and V_{ss} .

b: n=12 for C_{max} , n=10 for AUC_{inf}, $T_{1/2}$ and CL, n=9 for V_{ss} .

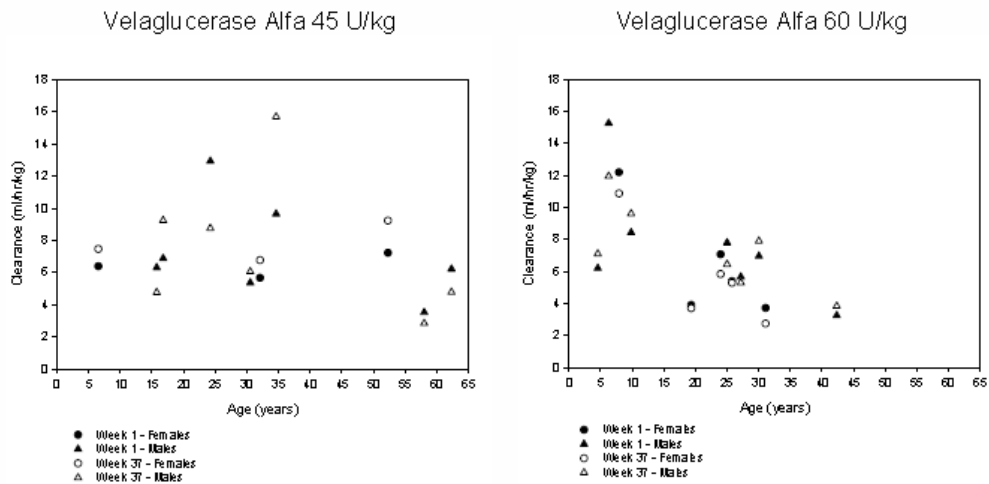
Neutralising antibodies

There was only one positive antibody response observed in this study. Subject 191-0002 was positive for anti velaglucerase alfa immunoglobulin G (IgG) type antibodies at Week 53 (end of study), but was negative for immunoglobulin E (IgE) antibodies at this time. The neutralising antibody assay result was reported as 42% inhibition. None of the subjects were positive for anti velaglucerase alfa antibodies on the days of pharmacokinetic evaluation.

Age

In the 45 U/kg group, there was no apparent trend for C_{max} , AUC or apparent total body clearance of the drug from plasma (CL) to change with increasing age. However, in the 60 U/kg group, there was an apparent trend for lower C_{max} and AUC values and higher CL values in subjects below 10 years of age compared to the adult subjects (19 to 42 years old). There are no apparent differences between male and female patients (Figure 4).

Figure 4: Relationship between VPRIV CL and subject's age and gender (Study TKT032).



Not all subjects were evaluated at all pharmacokinetic time points and therefore some of the parameter estimates were based on less than a full data set. Three subjects, with PK scheduled for Week 37, had their PK evaluation at a later visit (in Weeks 39 51 (n=2)). The sponsor compared the PK data with the Week 37 data from the other subjects. Finally, the details of the model development and validation were not included in the submission and could not be verified.

Summary

In summary, the PK of VPRIV were not quite dose proportional but there was no evidence of accumulation over the 37 weeks of the study. VPRIV was rapidly cleared from plasma, and coupled with its small volume of distribution, had a short half life of ~12 minutes. There were some discrepancies in the PK data but these were unlikely to significantly alter the interpretation of the data.

Study TKT025EXT

This report described the pharmacokinetic component of Study TKT025EX; an open label safety study of glucocerebrosidase replacement therapy in patients with GaD1. The PK study was performed at Week 65 in patients enrolled in Study TKT025EX. Of the twelve patients enrolled, nine were included in the pharmacokinetic component of the study. The study was conducted at three centres in Israel, Serbia and Romania. Patients received a dose of 30 U/kg of VPRIV, infused over 1 h by intravenous infusion. Blood samples were collected pre dose and at 5, 10, 15, 20, 40, 60, 65, 70, 80, 90, 105, and 120 minutes following the start of infusion. The actual dose administered on Week 65 is shown in Table 6.

Table 6: Dose per patient during Week 65 (Study TKT025EXT).

Body Weight (kg)	GA-GCB Dose volume of drug (mL)	Total Dose (mg per patient)
53.0	15.9	39.75
72.0	20.4	51.0
55.0	15.6	39.0
63.0	20.1	50.25
58.0	17.4	43.5
82.0	24.3	60.75
58.0	17.4	43.5
47.0	15.0	37.5
79.5	23.1	57.75

Pharmacokinetic results

VPRIV was rapidly cleared from the circulation and could be modelled using a first order elimination kinetics (Figure 5). T_{max} was near the end of the infusion time at approximately 60 min (Figure 5). C_{max} values ranged from 1.2 to 3.2 microgram/mL. The mean C_{max} value was 2.3 microgram/mL with a standard deviation of 0.74 microgram/mL (CV of 32%). The half life ranged from approximately 5 to 12 min. The mean half life was approximately 9 min with a standard deviation of 2.2 minutes. The mean VPRIV serum clearance was 6.5 mU.min/kg, and individual values ranged from 4.3 to 10.2 mU.min/kg. Mean V_{ss} (% BW) was 8.3% with individual values ranging from 6.0 to 12.3 V_{ss} % BW (Table 7).

Figure 5: Mean VPRIV serum concentration (microgram/mL) at Week 65 (Study TKT025EX).

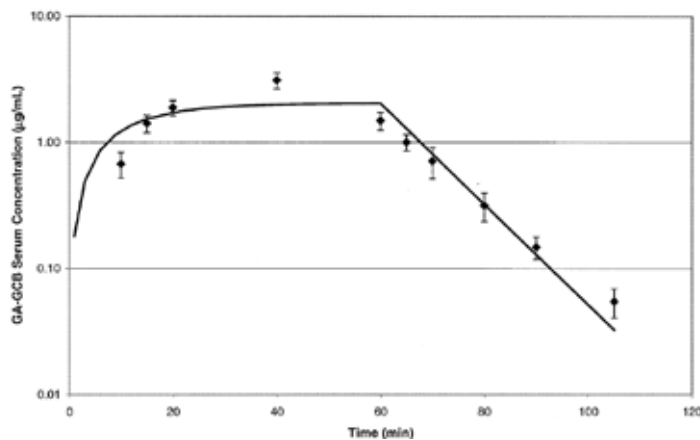


Table 7: VPRIV pharmacokinetic parameters (30 U/kg) (Study TKT025EX).

Body Weight (kg)	Nominal infusion Time (min)	T_{max} (min)	C_{max} (µg/mL)	AUC (min·µg/mL)	Cl (mL/min)	Cl (mL/min/kg)	MRT (min)	$T_{1/2}$ (elim) (min)	V_{ss} (L)	V_{ss} (% BW)	
56.9	60	60	1.3	75.3	528	9.3	9.5	6.6	5.02	8.8%	
64.0	60	45	2.6	121.9	418	6.5	15.0	10.4	6.30	9.8%	
53.0	60	60	1.2	72.3	539	10.2	7.7	5.4	4.18	7.9%	
63.5	60	55	2.6	144.0	349	5.5	12.7	8.8	4.42	7.0%	
59.5	60	60	1.7	102.6	424	7.1	17.2	11.9	7.29	12.3%	
82.0	60	60	2.3	130.5	466	5.7	16.5	7.7	7.70	9.4%	
60.5	60	50	3.2	163.3	266	4.4	13.5	9.4	3.61	6.0%	
50.0	60	55	2.4	132.7	283	5.7	12.2	8.4	3.44	6.9%	
79.5	60	60	3.2	169.3	341	4.3	16.4	11.4	5.59	7.0%	
Mean	63.2	60.0	55.0	2.3	123.5	402	6.5	13.4	8.9	5.28	8.3%
SD	10.9	0.0	5.6	0.74	34.7	99	2.0	3.3	2.2	1.55	1.95%
N	9	9	9	9	9	9	9	9	9	9	

Note: individual patient numbers have been deleted from this table.

Neutralising antibodies

No neutralising antibodies were detected in Study TKT025EX so the effects of antibodies could not be explored.

Age

The relationship between age and pharmacokinetics was not explored in this analysis.

Deficiencies

The details of the model development and validation were not included in the current submission and could not be verified.

Summary

In summary, the pharmacokinetics of VPRIV in this small single dose study at steady state again demonstrated that VPRIV was rapidly cleared from plasma, resulting in a short half life of ~9 minutes. The results are comparable to the PK parameters described in PK Study TKT032.

Study TKT025

This report was included as an appendix to Study TKT025 and not as a separate report in the pharmacokinetic component of the current submission. This study utilised an enzyme activity assay rather than the ELISA method used in the above two studies.

Study TKT025 was an open label safety study of glucocerebrosidase replacement therapy in patients with GaD1 at one centre in Israel. Three patients received 15 U/kg, 30 U/kg, and then 60 U/kg using an intra patient dose escalation. After dose escalation was completed, patients in this cohort as well as an additional 9 patients were treated at a dose level of 60 U/kg every two weeks for a total of 20 infusions. The PK results are from the dose escalation cohort (15, 30 and 60 U/kg) and from the additional nine patients, who received an initial infusion of VPRIV at 60 U/kg (Table 8). VPRIV was infused over 1 h by intravenous infusion. Blood samples were collected pre dose, 15, 30, 60, 65, 70, 80, 90, 105, 120, 150 and 180 minutes following the initiation of infusion. PK studies were performed at Weeks 1-5 and Week 39.

Table 8: Pharmacokinetic parameters following IV Infusion of VPRIV in Gaucher patients (Study TKT025).

Body Weight (kg)	Nominal Infusion Time (min)	T _{max} (min)	C _{max} (mU/mL)	AUC (min*mU/mL)	Cl (mL/min)	Cl (mL/min/kg)	MRT (min)	T _{1/2} (elim) (min)	V _d (L)	V _d (% BW)
53.1	60	60	19.6	1177	675	12.7	6	4.0	3.9	7.3%
52.7	60	60	29.8	1830	869	16.5	16	11.0	13.7	26.0%
51.5	60	65	56.9	3712	857	16.6	11	7.9	9.8	19.0%
72.0	60	60	29.5	1770	610	8.5	8	5.5	4.9	6.8%
69.0	60	60	53.4	3246	665	9.6	14	9.6	9.2	13.4%
70.0	60	60	113	6949	622	8.9	16	11.2	10.0	14.3%
74.0	60	60	27.1	1629	672	9.1	9	6.5	6.3	8.5%

Blood samples were processed to serum and evaluated for GA-GCB serum levels using an enzyme activity assay. Individual serum PK profiles were determined using an infusion model with 1-compartment. Serum samples for PK analysis were analysed by an enzyme activity assay. The assay measured β -glucocerebrosidase activity using the synthetic substrate p-nitrophenyl- β -D-glucopyranoside (PNPG). In this assay, VPRIV hydrolyses PNPG to release p-nitrophenol (PNP), which has a characteristic absorbance at 405 nm.

The details of the PK analysis were not included in the report. The sponsor's study report stated that, in the Week 1-5 study time, two sets of serum data could not be modelled; VPRIV serum activity results from one patient at Week 3 (30 U/kg) and Week 5 (60 U/kg) were inconsistent and could not be modelled. The sponsor was unable to offer an adequate explanation for this.

Pharmacokinetic results

VPRIV was rapidly cleared from the circulation and the sponsor's study report stated that it was modelled using first order elimination kinetics. T_{max} was near the nominal infusion time of 60 minute. The sponsor's study report stated that both C_{max} and AUC were linearly proportional to dose from 15 U/kg to 60 U/kg. It should be noted that this part of the study was only performed in three patients (Table 8).

Eleven patients were evaluated for PK parameters at 60 U/kg. Mean half life was ~10 minutes; mean clearance was ~13 mL/min/kg, and the mean V_{ss} was ~18% of body weight (Table 9 and Table 10).

Table 9: Pharmacokinetic parameters following IV infusion of VPRIV in Gaucher patients (first dose at 60 U/kg) (Study TKT025).

Body Weight (kg)	Nominal Infusion Time (min)	T_{max} (min)	C_{max} (mU/mL)	AUC (min*mU/mL)	Cl (mL/min)	Cl (mL/min/kg)	MRT (min)	$T_{1/2}$ (elim) (min)	V_{ss} (L)	V_{ss} (% BW)
51.5	60	65	56.9	3712	857	16.6	11	7.9	13.7	26.6%
70.0	60	60	113	6949	622	8.9	16	11.2	10.0	14.3%
50.0	60	60	61.4	3754	799	16.0	15	10.5	12.1	24.1%
52.5	60	60	30.3	3017	1034	19.7	6	4.3	6.4	12.2%
57.0	60	65	97.6	6393	472	8.3	13	9.2	6.2	10.9%
63.0	60	60	75.8	4555	830	13.2	10	6.6	7.9	12.6%
55.0	60	60	92.3	5689	580	10.5	16	11.4	9.6	17.4%
68.0	60	60	95.2	6090	670	9.9	22	14.9	14.4	21.2%
53.5	60	65	95.6	6292	544	10.2	15	10.2	8.0	15.0%
50.0	60	65	63.0	4140	725	14.5	14	10.0	10.4	20.9%
71.0	60	65	85.9	5684	750	10.6	16	11.2	12.1	17.1%
Mean	58.3		80.6	5116	717	12.6	14	9.8	10.1	17.5%
SD	8.2		20.3	1322	161	3.7	4	2.8	2.8	5.1%
N	11		11	11	11	11	11	11	11	11
All patients received 60 U/kg										

Note: individual patient numbers have been deleted from this table.

Table 10: Pharmacokinetic parameters following IV infusion of VPRIV in Gaucher patients (Week 39, Study TKT025).

Body Weight (kg)	Nominal Infusion Time (min)	T_{max} (min)	C_{max} (mU/mL)	AUC (min*mU/mL)	Cl (mL/min)	Cl (mL/min/kg)	MRT (min)	$T_{1/2}$ (elim) (min)	V_{ss} (L)	V_{ss} (% BW)
55.0	60	60	68.6	4120	801	14.6	9	6.2	7.2	13.0%
63.0	60	65	161	10537	359	5.7	13	8.9	4.6	7.3%
58.0	60	60	211	12671	275	4.7	7	5.1	2.0	3.5%
82.0	60	60	256	15456	318	3.9	12	8.4	3.9	4.7%
58.0	60	65	257	16728	208	3.6	8	5.6	1.7	2.9%
47.0	60	70	196	13706	206	4.4	8	5.3	1.6	3.3%
71.0	60	65	345	22499	189	2.7	12	8.4	2.3	3.2%
73.0	60	60	360	22643	192	2.6	10	7.0	1.9	2.7%
Mean	63.4		234	13674	318	5.6	10	6.8	3.1	5.4%
SD	11.3		99.4	5664	205	4.0	2	1.5	2.0	3.7%
N	8		8	8	8	8	8	8	8.0	8

Note: individual patient numbers have been deleted from this table.

Neutralising antibodies

No antibodies were detected in Study TKT025 so the effects of antibodies could not be explored.

Age

The relationship between age and pharmacokinetics was not explored in this analysis.

Deficiencies

The details of the model development and validation were not included in the sponsor's study report and could not be verified. The enzyme activity assay is different to the ELISA

assay used in the other two pivotal PK studies. It is unclear whether the inability to model two of the patients was a result of a problem with the assay.

Summary

In summary, the PK results of VPRIV in this study are not comparable to the two pivotal PK studies as the assay used was of a different type, and limits its applicability. However, the general PK profile and half life (T_{max} at ~60 minutes and a half life of ~10 minutes) did appear to be comparable with the other two pivotal studies.

Addendum to the pharmacokinetic study reports

The sponsor produced an addendum in response to regulatory questions regarding the PK studies presented in this current submission. The sponsor detailed the assays and their validation. The sponsor confirmed that a different method (an activity assay) was used to analyse Study TKT025 compared to the two pivotal PK studies; TKT025EXT and TKT032 (an ELISA) (Table 11). The method validations were supplied.

Table 11: Summary of analytical methods used for pharmacokinetic analysis.

Test Method	Assay Type	Study	Report #
SOP 7371-BA0	Two-site Sandwich ELISA	TKT025EXT, TKT032	Report 500-1U0-07-833 Pharmacokinetic report TKT032
SOP 7364-BA0	Colorimetric activity assay	TKT025	Report 500-1U0-05-722 Report 500-1U0-05-714

The assays did appear to be appropriately validated.

Methods

Analytical methods

The pivotal Studies TKT032 and TKT025EX used the validated ELISA. Study TKT025 used an enzyme activity assay and the results were not directly comparable to the two pivotal PK studies.

Pharmacokinetic data analysis

The pivotal Studies TKT032 and TKT025EX were analysed using WinNonlin; a valid pharmacokinetic modelling program produced by Pharsight. Study TKT025 did not state the details of the program used for pharmacokinetic analysis. None of the reports provided details of the modelling process.

Statistical analysis

The pivotal Studies TKT032 and TKT025EX were analysed using SAS; a valid statistical program produced by Pharsight. Study TKT025 did not state the details of the program used for statistical analysis. None of the reports provided details of the statistical analysis.

Absorption

VPRIV was administered by a one hour intravenous infusion. T_{max} is reached near the end of the infusion at ~60 minutes.

Distribution

The clinical data did not present any data on distribution. As stated below, the sponsor proposed that VPRIV is primarily distributed to macrophages.

Elimination

The elimination of VPRIV was not directly addressed in the clinical studies. No mass balance studies were performed. VPRIV was rapidly cleared from the plasma after the infusion and the current submission stated that this was probably due to uptake by macrophages. The clinical evaluator could not confirm that this was the case.

Dose proportionality and time dependency

There are data presented related to dose proportionality. For the three patients in Study TKT025, there was some evidence that there were linear increases in the concentration dependent pharmacokinetic parameters between doses of 15 U/kg and 60 U/kg. However, Study TKT032 found that there was a disproportionate increase in the concentration dependent pharmacokinetic parameters between 45 U/kg and 60 U/kg doses. The clinical significance of this is unclear.

Both Study TKT025 and TKT032 investigated whether there were any time dependent changes in concentration. Both supported the sponsor's conclusion that there is no evidence of accumulation after up to 53 weeks of dosing. Given the extremely short serum half life of 10 minutes and that the dosing interval is two weeks, accumulation after longer periods would appear to be unlikely.

Intra and inter individual variability

The sponsor did not present data on intra and inter-individual parameter variability. In the two pivotal studies, which were analysed using WinNonlin, it is likely that estimates of variability would be available.

Special populations

Children

A total of 20 children (Table 12) were studied, the youngest studied being four years of age. While the number is small, these limited data suggested that children had slightly greater clearance of VPRIV but in other respects demonstrated a similar kinetic profile to the adult population. There is no suggestion that there needs to be a dose adjustment for children.

Table 12: Exposure by age group and gender, all clinical trials population (TKT025, TKT025EXT, TKT032, TKT034, and HGT-GCB-039).

Age Group	Persons (N)		Person Years	
	Male	Female	Male	Female
2 to 5 years	1	0	1.0	0.0
6 to 11 years	3	5	2.6	4.2
12 to 17 years	6	5	5.3	4.8
18 to 65 years	34	36	47.7	50.3
>65 years	2	2	1.7	1.6

Drug Interactions

No data on interactions were presented in the clinical dossier.

Pharmacodynamics

No pharmacodynamic studies were submitted in this dossier.

Efficacy

Introduction

The current Australian submission included five clinical studies in support of the application.

Dose response studies and main clinical studies

Study TKT032

Study TKT032, a pivotal study, was a multicentre, randomised, double blind, parallel group, two dose study of VPRIV, as enzyme replacement therapy in patients with GaD1. It was conducted in 5 centres in Israel, Tunisia, Paraguay, Argentina and Russia over 51 weeks. Patients received VPRIV at a dose of either 45 U/kg/dose or 60 U/kg/dose, administered as a single infusion every other (second) week. Patients were randomly allocated to either group. A total of 25 patients were enrolled in the study and all were included in the intention to treat (ITT) analysis. Of these, 13 were enrolled in the 45 U/kg group and 12 in the 60 U/kg group. There were 15 males and 10 females with 7 patients (28%) aged between 4 years and 17 years of age. The patients had an average age of 26 years (range: 4-62 years of age).

Outcome measures

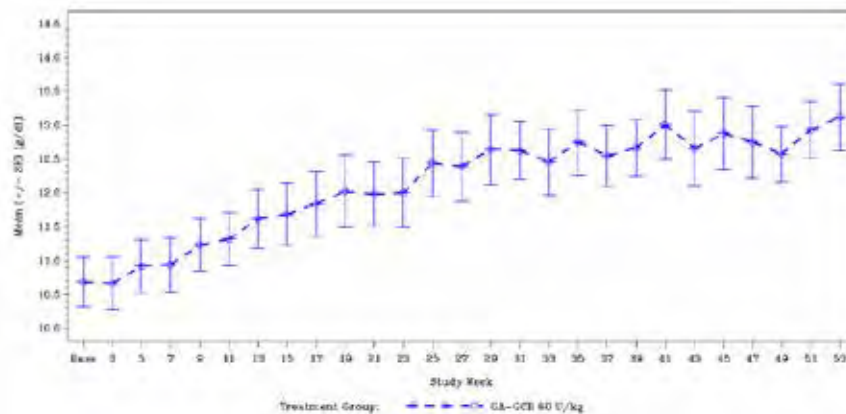
The primary outcomes measure was an increase in haemoglobin concentration at a dose of 60 U/kg over the period of the study. The secondary outcome measures included haemoglobin concentration in the 45 U/kg group, increases in platelet counts, decreases in spleen and liver volumes, decreases in levels of plasma chitotriosidase and chemokine ligand 18 (CCL18), and quality of life measures. Quality of life for patients ≥ 18 years old was assessed by the SF-36 multi purpose, short form health survey; this survey yields an eight scale profile of functional health and wellbeing scores. Quality of life for patients 5 to 17 years old was assessed by the Child Health Questionnaire CHQ-PF50. There were also some tertiary outcomes assessed including the time to haemoglobin response, pulmonary function tests (in ≥ 18 year olds), growth velocity, Tanner staging (in 2-17 yo) and changes in skeletal age (in 2-17 year olds). Further outcome measures were added, as a response to questions from the European Medicines Agency (EMA), including the inclusion of response categories for haemoglobin, platelet count, liver and spleen volumes.

Results

1. Haemoglobin concentration

In the 60 U/kg group, the mean haemoglobin increase was +2.429 g/dL (+23.25%) from a baseline of 10.825 g/dL to 12.550 g/dL at Week 53 (Figure 6). In the 45 U/kg group, the mean haemoglobin increase was +2.438 g/dL (+23.81%) from a baseline of 10.723 g/dL to 13.162 g/dL at Week 53 (Figure 7).

Figure 6: Mean haemoglobin concentration (g/dL) (+/- SE) at scheduled visits VPRIV (GA-GCB) 60 U/kg Treatment Group - ITT population (Study TKT032).



The time to haemoglobin response is shown in Figure 7 with 100% response reached at Week 27 in the 60 U/kg group and at Week 37 in the 45 U/kg group. The response categories for haemoglobin, platelet count, liver, and spleen volumes were documented. Table 13 shows the response categories for haemoglobin concentration.

Figure 7: Mean haemoglobin concentration (g/dL) (+/- SE) at scheduled visits VPRIV (GA-GCB) 45 U/kg Treatment Group - ITT population (Study TKT032).

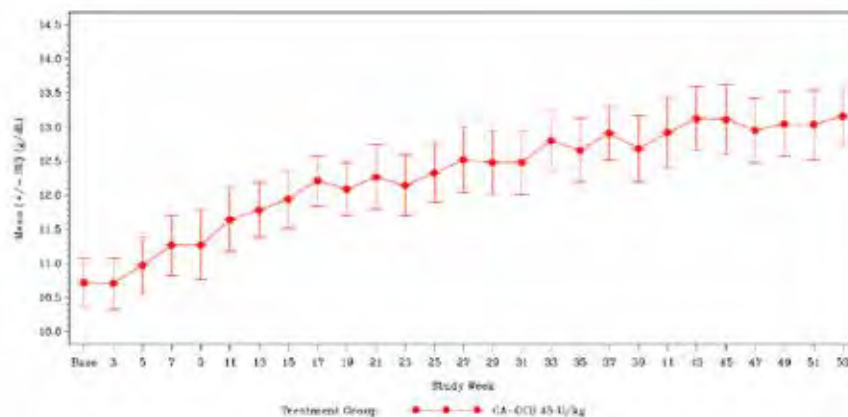


Table 13: Haemoglobin concentration (g/dL) response category at scheduled visits by randomised VPRIV treatment group - ITT population.

	Week 13		Week 25		Week 37		Week 49	
	Velaglucease alfa		Velaglucease alfa		Velaglucease alfa		Velaglucease alfa	
Haemoglobin Concentration Endpoint	45 U/kg	60 U/kg	45 U/kg	60 U/kg	45 U/kg	60 U/kg	45 U/kg	60 U/kg
Response category ^a (n[%])								
Good response	3 (23.1)	1 (8.3)	7 (53.8)	7 (58.3)	10 (76.9)	7 (58.3)	8 (61.5)	10 (83.3)
Moderate response	6 (46.2)	9 (75.0)	3 (23.1)	5 (41.7)	3 (23.1)	5 (41.7)	5 (38.5)	2 (16.7)
No response	4 (30.8)	2 (16.7)	3 (23.1)	0	0	0	0	0

Note: Imputation was applied to missing data.

^a A good response is defined as an increase from baseline of ≥ 1.5 g/dL; a moderate response is defined as an increase of ≥ 0.5 g/dL, but < 1.5 g/dL; no response is defined as an increase from baseline of < 0.5 g/dL.

Data source: Table 10.2.1.4

2. Platelet count

The platelet counts increased by $50.88 \times 10^9/L$ (+65.93%) in the 60 U/kg group and by $40.92 \times 10^9/L$ (+66.38%) in the 45 U/kg group.

3. Liver and spleen volume

In the 60 U/kg group, the spleen volume decreased by 1.92% body weight while there was not a significant decrease in liver volume.

In the 45 U/kg group, the spleen volume decreased by 1.87% body weight while there was not a significant decrease in liver volume.

4. Chitotriosidase and CCL18 levels

In the 60 U/kg group, chitotriosidase levels decreased by 27413.0 nmol/mL/h in two patients but this was not statistically significant while in the 45 U/kg group chitotriosidase levels decreased by 24499.3 nmol/mL/h which was statistically significant (unadjusted for multiple comparisons). CCL18 levels decreased in both groups.

5. Quality of life measures

The study was unable to demonstrate any significant improvement in the quality of life scores over the study.

6. Pulmonary function

No definitive conclusions can be drawn from the pulmonary function test results in this study as only 1 centre had the spirometry equipment to evaluate PFTs.

7. Annualised growth velocity

Seven patients aged from 2 to 17 years old (4 in the 60 U/kg group and 3 in the 45 U/kg group) were evaluated for annualised growth velocity. After 1 year the mean growth velocity was 8.30 ± 0.850 in the 60 U/kg group and 7.83 ± 0.726 in the 45 U/kg group.

8. Tanner staging

None of the 4 patients in the 60 U/kg group had a change in Tanner stage after 1 year. In the 45 U/kg group, 1 patient changed from Stage 2 to Stage 4, 1 patient changed from Stage 3 to Stage 4 and 1 patient had no change from Stage 1.

9. Skeletal age

Seven patients 2 to 17 years old (3 in the 45 U/kg group and 4 in the 60 U/kg group) were evaluated. Four patients the 60 U/kg group had mean skeletal ages of -2.15 ± 0.922 years (compared to chronological age) at baseline and -1.68 ± 1.055 at 1 year (compared to chronological age); a difference of 0.48 ± 0.250 years. No change from baseline was observed (-1.37 ± 0.977 at baseline, -1.97 ± 0.933 at 1 year) in the 45 U/kg group.

Study HGT-GCB-039

Study HGT-GCB-039, a pivotal, multicentre, Phase III, randomised, double blind, parallel group study designed to compare the safety and efficacy of the enzyme replacement therapy VPRIV with imiglucerase in the treatment of patients with GaD1. It was conducted in 11 centres in 9 countries over 41 weeks. Patients received a 60 U/kg dose of either VPRIV or imiglucerase, administered as a single infusion every other (second) week. Patients were randomly allocated to either group. A total of 34 patients were enrolled in the study with 17 patients allocated to each group. All were included in the ITT analysis. There were 15 males, 18 females with 9 children included. The patients had a mean age of 29.7 years (range 7-73 years of age).

Outcome measures

The primary outcomes measure was the difference in the change in haemoglobin concentration at 41 weeks (between the two groups). The secondary outcome measures included platelet counts, spleen and liver volumes, plasma chitotriosidase and CCL18, and the difference in time to response for haemoglobin concentration (increase by 1 g/dL).

There were also some tertiary outcomes assessed including quality of life measures, growth velocity, Tanner staging changes in skeletal age and bone biomarkers.

Results

1. Haemoglobin concentration

The mean haemoglobin increase was 1.624 g/dL in the velaglucerase group and 1.488 g/dL in the imiglucerase arm (Figure 8) with a mean difference between the groups of 0.135 g/dL (Figure 9).

Figure 8: Mean haemoglobin concentration (g/dL)(+/-SE) at scheduled visits and by randomised treatment group - ITT population (Study HGT-GCB-039).

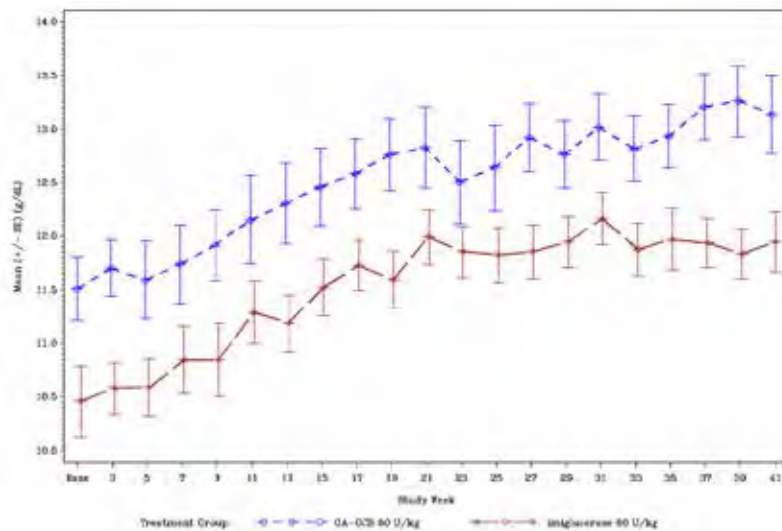
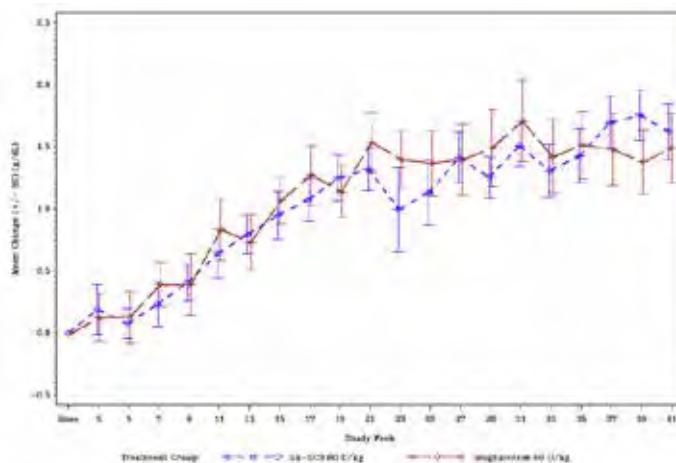
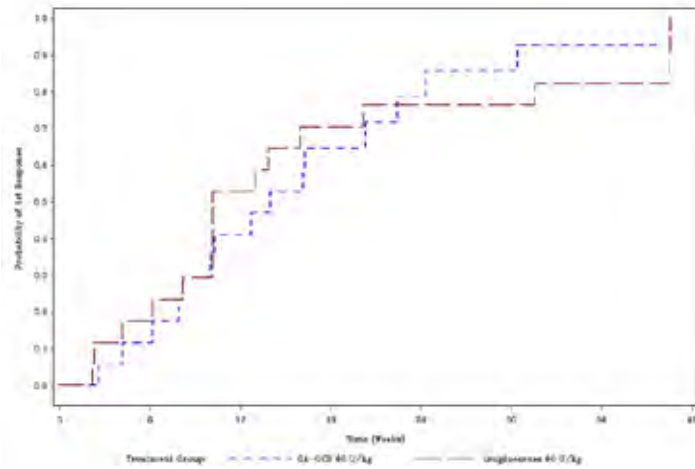


Figure 9: Mean haemoglobin concentration (g/dL)(+/-SE) at scheduled visits by randomised treatment group - change from baseline - ITT population (Study HGT-GCB-039).



The time to first haemoglobin response was similar between the 2 treatment groups (log rank p-value = 0.8965) (Figure 10). Two patients, one per treatment group, were excluded (due to study discontinuation) prior to reaching a first haemoglobin response and one patient in the VPRIV group completed 41 weeks of treatment without achieving a ≥ 1 g/dL change from baseline haemoglobin.

Figure 10: Time to first haemoglobin response by randomised treatment group - Kaplan-Meier Curves - ITT population (Study HGT-GCB-039).



2. Platelet count

The platelet counts at Week 41 were $110.4 \times 10^9/L$ in the velaglucerase group and $144.4 \times 10^9/L$ in the imiglucerase group (Figure 11).

The sponsor recognised that there appeared to be a trend of a greater platelet response with imiglucerase compared to velaglucerase. They subsequently performed post hoc analyses in which they suggest that the three patients in the 2 to 4 years age group have skewed the data. The analysis found that these patients had large spleens and low platelet counts at baseline and appeared to have worse disease at the start of the study (Figure 12).

Figure 11: Mean platelet count ($\times 10^9/L$)(\pm SE) at scheduled visits and by randomised treatment group - ITT patient population (Study HGT-GCB-039).

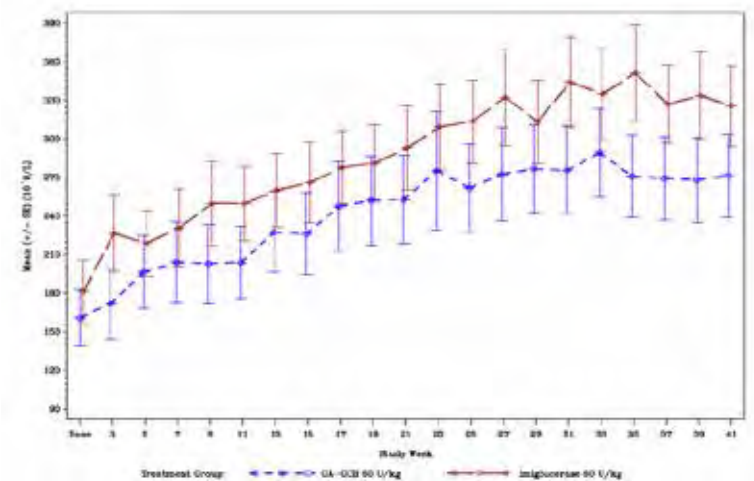
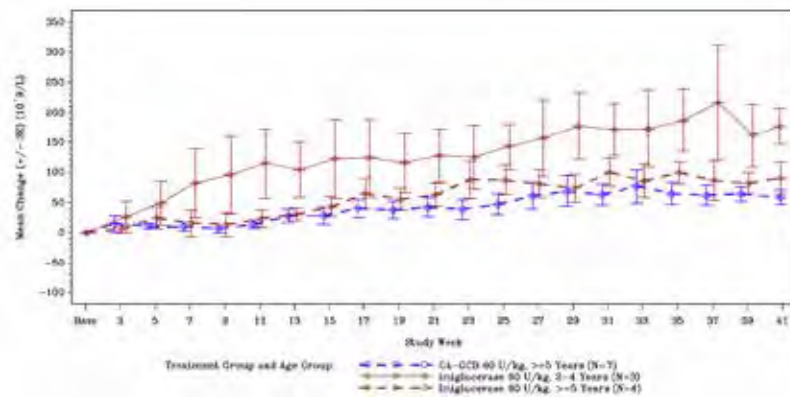


Figure 12: Mean platelet count ($\times 10^9/L$) (\pm SE) at scheduled visits and by randomised treatment group and age group (2 to 4 years; ≥ 5 years) – change from baseline – ITT Patient Population – in patients without a spleen (Study HGT-GCB-039).



3. Liver and spleen volume

In the velaglucerase group, the spleen volume decreased from 1.92% of body weight at baseline to 1.0% at 41 weeks. This compared to the imiglucerase group with a decrease from 1.40% of body weight at baseline to 0.9% at 41 weeks.

In the velaglucerase group, the liver volume decrease from 3.9% of body weight at baseline to 2.6% at 41 weeks. In the imiglucerase group the liver volume decreased from 4.0% of body weight at baseline to 3.0% at 41 weeks.

4. Chitotriosidase and CCL18 levels

In the velaglucerase group, chitotriosidase levels decreased from 45534.2 nmol/mL/h at baseline to 34711.9 nmol/mL/h at 41 weeks; a change of 77.59%. This compared to the imiglucerase group in which chitotriosidase levels decreased from 50076.9 nmol/mL/h at baseline to 35109.5 nmol/mL/h at 41 weeks; a change of 69.5%.

In the velaglucerase group, CCL18 levels decreased from 1637.0 ng/mL at baseline to 926.2 ng/mL at 41 weeks; a change of 55.12%. This compared to the imiglucerase group in which CCL18 levels decreased from 1849.0 ng/mL at baseline to 1153.4 ng/mL at 41 weeks; a change of 48.82%.

5. Quality of life measures

For those older than 18 years, at Week 41, 6 of 10 (60%) patients in the VPRIV group and 7 of 9 (78%) patients in the imiglucerase group reported their health was either “much better now than one year ago” or “somewhat better now than one year ago”.

For children aged 5 to 17 years, one patient in each group reported their health was “somewhat better now than one year ago”.

6. Annualised growth velocity

The median observed value for the annualised growth velocity (rate at which a child grows in a one year period) at Week 41 was 7.70 cm/year for the VPRIV group (n = 3) and 8.30 cm/year for the imiglucerase group (n = 5).

7. Tanner staging

Of the four paediatric patients in the VPRIV group, two patients were Tanner Stage 1 at baseline, one of whom was Stage 1 at Week 41 and the other had missing data; one patient was Stage 3 at baseline and Stage 4 at Week 41; one patient was at Stage 4 at baseline and Week 41. All five paediatric patients in the imiglucerase group were Tanner Stage 1 at both baseline and Week 41.

9. Skeletal age

The median observed value for the difference in skeletal age and chronological age at baseline was -2.00 for the VPRIV group (n = 4) and -1.15 for the imiglucerase group (n = 4). The median observed value at Week 41 was -0.90 for the VPRIV group (n = 3) and -2.10 for the imiglucerase group (n = 5).

Clinical studies in special populations

No specific studies in special populations were submitted.

Analysis performed across trials (pooled analyses and meta analysis)

No pooled analyses were presented.

Supportive studies

Study TKT025

Study TKT025, a supportive study and primarily a safety study of VPRIV enzyme replacement therapy in patients with GaD1. It was conducted in one centre in Israel over 37 weeks. Patients received VPRIV at a dose of 60 U/kg/dose, administered as a single infusion every other (second) week. Of the 12 enrolled patients, 11 completed the study. The study included patients over 18 years of age with GaD1 who had anaemia and thrombocytopenia. There were 5 males and 7 females who were aged between 18 to 70 years.

Outcome measures

While the primary aim of the study was safety, there were several efficacy measures included in the study; haemoglobin concentration, platelet counts, spleen and liver volumes, plasma chitotriosidase, and chemokine ligand 18 (CCL18).

Results

Over the study period, the mean haemoglobin increase was 2.24 g/dL (19.22%) and the mean platelet increase was $40.6 \times 10^3/\text{mm}^3$ (67.6%). Spleen volume decreased by 49.47% and liver volume decreased by 18.20%. There were also decreases in both plasma chitotriosidase (74.2%), and CCL18 (57.1%). The study also measured pulmonary function, bone density, bone marrow (MRI) and cardiac function but found no significant changes in any of these parameters.

Study TKT025EXT

Study TKT025EXT, a supportive study, was the extension study to TKT025 described above. It was conducted in three centres in Israel, Serbia and Romania with follow up to 59 months. Ten enrolled patients received VPRIV at a dose of 60 U/kg/dose, administered as a single infusion every other (second) week. No efficacy outcomes were included in the interim report which focused on safety.

Study TKT034A

Study TKT034A, a supportive study, was a multicentre, open label study of VPRIV in patients with GaD1 previously treated with imiglucerase. It was conducted at 15 sites across five countries (Israel, Poland, Spain, and the United Kingdom [UK] with one site each, and USA with 11 sites). Five additional sites (two sites in Italy, three sites in USA) were initiated but did not enrol patients. The previous imiglucerase dose ranged between 15 and 60 U/kg, administered as a single infusion every other (second) week. Each patient received a dose of VPRIV identical to the imiglucerase dose that they received for at least 6 months prior to enrolment. The study lasted for a total of 51 weeks. A total of 40 patients

were enrolled. Nine patients (22.5%) were under 18 years of age (between 5 and 17 years of age). There were 18 males and 22 females who were aged between 9 to 71 years. Of note, 3 patients (7.5%) tested positive for anti imiglucerase alfa antibodies prior to receiving treatment.

Outcome measures

While the primary aim of the study was safety, there were several efficacy measures included in the study; haemoglobin concentration, platelet counts, spleen and liver volumes, plasma chitotriosidase, and chemokine ligand 18 (CCL18). There were additional measurements performed in the children aged 5 to 17 years including skeletal age, growth velocity and Tanner staging.

Results

Over the study period, there was a decrease in the mean haemoglobin by 0.10 g/dL and a mean increase platelet of $9.5 \times 10^3/\text{mm}^3$ (7.04%). Spleen volume decreased by 5.56% and liver volume decreased by 0.03%. There were also decreases in both plasma chitotriosidase (28.14%), and CCL18 (16.44%). In those aged 5 to 17 years skeletal age was similar to chronological age, and Tanner staging was available in six patients and two of these advanced with 1 or 2 stages.

Safety

Introduction

The current Australian submission included five clinical studies which were assessable for safety data. Patients from the three pharmacokinetic studies were included within the five clinical studies. While two of the studies included several arms, all patients received an active treatment at varying doses and there were no placebo arms. The primary studies (TKT025, HGT-GCB-039, TKT032 and TKT034) included data up to 12 months while their extension arms (TKT025EXT and HGT-GCB-044) included data up to 60 months. Adverse Events (AE) were coded using the Medical Dictionary for Regulatory Activities (MEDRA), version 9 and were also summarised by subgroups of gender (male; female) and age 4 to 17 years old and ³ 18 years old for the 0 to 9 month, and 0 to 12 month exposure groups.

Summaries of 0 to 9 months dose exposure are presented by four treatment groups: VPRIV Overall (45 or 60 U/kg), VPRIV 45 U/kg, VPRIV 60 U/kg, and imiglucerase 60 U/kg. Summaries of 0 to 12 months dose exposure were presented by treatment groups: VPRIV Overall, VPRIV 45 U/kg, and VPRIV 60 U/kg.

Patient exposure

A total of 94 patients with GaD1, treated with VPRIV were included for safety in the current submission. The dose of VPRIV ranged from 15 to 60 U/kg and are the subject of this safety summary. There were 54 treatment naïve patients and the remaining 40 were transitioned from imiglucerase. Of the treatment naïve patients, a total of 41 patients have been treated with a VPRIV at a dose of 60 U/kg.

Adverse events (AE)

AE were recorded for all patients enrolled in the clinical studies and recorded up to 30 days after the last infusion (except for patients enrolled in Study TKT032 prior to Protocol Amendment 1, AE for these patients were collected from time of first dose). Infusion related AE included those AE which occurred within 12 hours after the start of the infusion. The sponsor's submission presented the occurrence of AE by exposure time (0-9

months, 0-12 months and > 12 months). The number of AE are shown in Table 14 while the most common AE (>10%) are shown in Table 15 and Table 16.

Table 14: Summary of treatment emergent AE for patients with 0-12 months exposure safety population.

Description	Patients n (%)		
	Velaglucerase alfa		
	Overall N = 35	45 U/kg N = 13	60 U/kg N = 22
Experienced No Adverse Events	2 (5.7)	2 (15.4)	0
Experienced At Least 1 Adverse Event	33 (94.3)	11 (84.6)	22 (100.0)
Experienced At Least 1 Drug-Related Adverse Event	23 (65.7)	9 (69.2)	14 (63.6)
Experienced At Least 1 Infusion-Related Adverse Event	22 (62.9)	8 (61.5)	14 (63.6)
Experienced At Least 1 Severe Or Life-Threatening Adverse Event	2 (5.7)	2 (15.4)	0
Experienced At Least 1 Serious Adverse Event	3 (8.6)	0	3 (13.6)
Discontinued Due To An Adverse Event	0	0	0
Deaths	0	0	0

Studies: TKT032, TKT025 and TKT025EXT (first 3 months)

Table 15: Most common ($\geq 10\%$ of patients) treatment emergent AE in patients with 0-9 months exposure safety population.

System Organ Class Preferred Term ^a	Patients n(%)			
	Overall N = 54	Velaglucerase alfa		Imiglucerase
		45 U/kg N = 13	60 U/kg N = 41	60 U/kg N = 17
Any Adverse Event	51 (94.4)	11 (84.6)	40 (97.6)	16 (94.1)
Infections and infestations				
Nasopharyngitis	13 (24.1)	2 (15.4)	11 (26.8)	3 (17.6)
Influenza	11 (20.4)	3 (23.1)	8 (19.5)	4 (23.5)
Rhinitis	6 (11.1)	1 (7.7)	5 (12.2)	1 (5.9)
Bronchitis	1 (1.9)	0	1 (2.4)	2 (11.8)
Blood and lymphatic system disorders				
Thrombocytopenia	4 (7.4)	2 (15.4)	2 (4.9)	1 (5.9)
Nervous system disorders				
Headache	19 (35.2)	6 (46.2)	13 (31.7)	3 (17.6)
Dizziness	12 (22.2)	4 (30.8)	8 (19.5)	2 (11.8)
Vascular disorders				
Hypertension	4 (7.4)	2 (15.4)	2 (4.9)	0
Respiratory, thoracic and mediastinal disorders				
Cough	7 (13.0)	3 (23.1)	4 (9.8)	2 (11.8)
Epistaxis	4 (7.4)	0	4 (9.8)	2 (11.8)
Pharyngolaryngeal pain	5 (9.3)	2 (15.4)	3 (7.3)	1 (5.9)
Nasal congestion	5 (9.3)	3 (23.1)	2 (4.9)	0
Rhinorrhoea	4 (7.4)	2 (15.4)	2 (4.9)	1 (5.9)
Productive cough	4 (7.4)	3 (23.1)	1 (2.4)	0
Gastrointestinal disorders				
Abdominal pain upper	6 (11.1)	0	6 (14.6)	3 (17.6)
Diarrhoea	8 (14.8)	2 (15.4)	6 (14.6)	1 (5.9)
Vomiting	5 (9.3)	3 (23.1)	2 (4.9)	2 (11.8)
Abdominal pain	4 (7.4)	1 (7.7)	3 (7.3)	2 (11.8)
Skin and subcutaneous tissue disorders				
Ecchymosis	3 (5.6)	2 (15.4)	1 (2.4)	0
Petechiae	3 (5.6)	2 (15.4)	1 (2.4)	0
Purpura	2 (3.7)	2 (15.4)	0	0
Musculoskeletal and connective tissue disorders				
Bone pain	13 (24.1)	1 (7.7)	12 (29.3)	3 (17.6)
Arthralgia	12 (22.2)	5 (38.5)	7 (17.1)	3 (17.6)
Back pain	9 (16.7)	3 (23.1)	6 (14.6)	2 (11.8)
Myalgia	5 (9.3)	3 (23.1)	2 (4.9)	1 (5.9)
Muscle spasms	3 (5.6)	2 (15.4)	1 (2.4)	2 (11.8)
Musculoskeletal pain	5 (9.3)	2 (15.4)	3 (7.3)	0
General disorders and administration site conditions				
Pyrexia	12 (22.2)	3 (23.1)	9 (22.0)	2 (11.8)
Asthenia	7 (13.0)	2 (15.4)	5 (12.2)	0
Influenza like illness	1 (1.9)	0	1 (2.4)	2 (11.8)

Table 16: Most common ($\geq 10\%$ of patients) treatment emergent AE in patients with 0-12 months exposure safety population.

System Organ Class Preferred Term	Patients n(%)		
	Overall N = 35	45 U/kg N = 13	60 U/kg N = 22
Nervous system disorders			
Headache	16 (45.7)	7 (53.8)	9 (40.9)
Dizziness	12 (34.3)	4 (30.8)	8 (36.4)
Eye disorders			
Eye pain	2 (5.7)	2 (15.4)	0
Ocular hyperaemia	2 (5.7)	2 (15.4)	0
Vascular disorders			
Hypertension	3 (8.6)	2 (15.4)	1 (4.5)
Respiratory, thoracic and mediastinal disorders			
Cough	7 (20.0)	4 (30.8)	3 (13.6)
Nasal congestion	5 (14.3)	3 (23.1)	2 (9.1)
Pharyngolaryngeal pain	4 (11.4)	2 (15.4)	2 (9.1)
Productive cough	4 (11.4)	3 (23.1)	1 (4.5)
Rhinorrhoea	4 (11.4)	2 (15.4)	2 (9.1)
Gastrointestinal disorders			
Vomiting	7 (20.0)	3 (23.1)	4 (18.2)
Abdominal pain upper	5 (14.3)	0	5 (22.7)
Diarrhoea	5 (14.3)	2 (15.4)	3 (13.6)
Abdominal pain	4 (11.4)	2 (15.4)	2 (9.1)
Cheilitis	4 (11.4)	0	4 (18.2)
Nausea	4 (11.4)	1 (7.7)	3 (13.6)
Toothache	4 (11.4)	1 (7.7)	3 (13.6)
Dyspepsia	3 (8.6)	2 (15.4)	1 (4.5)
Skin and subcutaneous tissue disorders			
Erythema	4 (11.4)	1 (7.7)	3 (13.6)
Petechiae	4 (11.4)	3 (23.1)	1 (4.5)
Rash	4 (11.4)	1 (7.7)	3 (13.6)
Ecchymosis	3 (8.6)	2 (15.4)	1 (4.5)
Purpura	2 (5.7)	2 (15.4)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	9 (25.7)	6 (46.2)	3 (13.6)
Bone pain	9 (25.7)	1 (7.7)	8 (36.4)
Back pain	8 (22.9)	3 (23.1)	5 (22.7)
Pain in extremity	6 (17.1)	2 (15.4)	4 (18.2)
Musculoskeletal pain	4 (11.4)	2 (15.4)	2 (9.1)
Myalgia	4 (11.4)	3 (23.1)	1 (4.5)
Muscle spasms	2 (5.7)	2 (15.4)	0
General disorders and administration site conditions			
Pyrexia	9 (25.7)	4 (30.8)	5 (22.7)
Asthenia	6 (17.1)	2 (15.4)	4 (18.2)
Investigations			
Activated partial thromboplastin time prolonged	5 (14.3)	2 (15.4)	3 (13.6)
Injury, poisoning and procedural complications			
Injury	8 (22.9)	6 (46.2)	2 (9.1)

Infusion related reactions*0 to 9 months exposure*

Infusion related AE were commonly reported in the clinical studies. In TKT025, 9 (75%) patients had infusion related adverse events. In the Phase III studies (Studies TKT032 and HGT-GCB-039) 19 patients (45.2%) had infusion related AE. In the imiglucerase treated group, four patients (23.5%) had infusion related AE. Most events were assessed as mild; however two events were moderate and one event (rigors) was severe and resulted in discontinuation in that patient (Table 17).

Table 17: Infusion related AE for patients with 0-9 months exposure safety population.

System Organ Class Preferred Term ^a	Phase I/II Patients n(%)		Phase III Patients n(%)		
	Velaglugerase alfa		Velaglugerase alfa		Imiglucerase
	60 U/kg N = 12	Overall N = 42	45 U/kg N = 13	60 U/kg N = 29	60 U/kg N = 17
Any Infusion-Related Adverse Event	9 (75.0)	19 (45.2)	8 (61.5)	11 (37.9)	4 (23.5)
Nervous system disorders	4 (33.3)	9 (21.4)	3 (23.1)	6 (20.7)	2 (11.8)
Headache	2 (16.7)	5 (11.9)	2 (15.4)	3 (10.3)	2 (11.8)
Dizziness	2 (16.7)	2 (4.8)	1 (7.7)	1 (3.4)	0
Somnolence	0	2 (4.8)	1 (7.7)	1 (3.4)	0
Migraine	1 (8.3)	0	0	0	0
Paraesthesia	0	1 (2.4)	0	1 (3.4)	0
Tremor	1 (8.3)	0	0	0	0
Cardiac disorders	0	2 (4.8)	1 (7.7)	1 (3.4)	0
Tachycardia	0	2 (4.8)	1 (7.7)	1 (3.4)	0
Vascular disorders	0	6 (14.3)	2 (15.4)	4 (13.8)	2 (11.8)
Hypotension	0	4 (9.5)	1 (7.7)	3 (10.3)	1 (5.9)
Hypertension	0	2 (4.8)	1 (7.7)	1 (3.4)	0
Flushing	0	0	0	0	1 (5.9)
Respiratory, thoracic and mediastinal disorders	0	1 (2.4)	1 (7.7)	0	0
Productive cough	0	1 (2.4)	1 (7.7)	0	0
Rhinorrhoea	0	1 (2.4)	1 (7.7)	0	0
Gastrointestinal disorders	2 (16.7)	2 (4.8)	0	2 (6.9)	0
Nausea	1 (8.3)	1 (2.4)	0	1 (3.4)	0
Abdominal pain	1 (8.3)	0	0	0	0
Diarrhoea	0	1 (2.4)	0	1 (3.4)	0
Skin and subcutaneous tissue disorders	0	2 (4.8)	0	2 (6.9)	0
Pruritus	0	1 (2.4)	0	1 (3.4)	0
Rash	0	1 (2.4)	0	1 (3.4)	0
Urticaria	0	1 (2.4)	0	1 (3.4)	0
Musculoskeletal and connective tissue disorders	4 (33.3)	5 (11.9)	3 (23.1)	2 (6.9)	0
Back pain	2 (16.7)	2 (4.8)	2 (15.4)	0	0
Arthralgia	0	3 (7.1)	2 (15.4)	1 (3.4)	0
Bone pain	2 (16.7)	1 (2.4)	0	1 (3.4)	0
Pain in extremity	1 (8.3)	1 (2.4)	0	1 (3.4)	0
Muscle spasms	0	1 (2.4)	1 (7.7)	0	0
Reproductive system and breast disorders	0	1 (2.4)	0	1 (3.4)	0
Pelvic pain	0	1 (2.4)	0	1 (3.4)	0
General disorders and administration site conditions	1 (8.3)	4 (9.5)	2 (15.4)	2 (6.9)	2 (11.8)
Feeling cold	0	2 (4.8)	1 (7.7)	1 (3.4)	1 (5.9)
Asthenia	1 (8.3)	1 (2.4)	1 (7.7)	0	0
Chills	0	1 (2.4)	0	1 (3.4)	1 (5.9)
Feeling abnormal	0	0	0	0	1 (5.9)
Feeling hot	0	0	0	0	1 (5.9)
Oedema peripheral	0	1 (2.4)	0	1 (3.4)	0
Pyrexia	0	0	0	0	1 (5.9)
Investigations	2 (16.7)	0	0	0	1 (5.9)
Body temperature increased	2 (16.7)	0	0	0	0
Blood pressure systolic increased	0	0	0	0	1 (5.9)
Oxygen saturation decreased	0	0	0	0	1 (5.9)

0 to 12 Months Exposure

In the TKT025 study and first three months of the TKT025EXT study, 8 patients (80%) had infusion related AE. Infusion related adverse events occurring in more than one patient were headache, hypotension (three patients each, 12.0%), dizziness, somnolence,

tachycardia, hypertension, back pain, arthralgia, and feeling cold (two patients each, 8.0%). Infusion related adverse events were more likely to be reported in the first six months of the study than later in the treatment.

>9 months exposure

Two patients in Studies TKT025 and TKT025EXT experienced treatment emergent adverse events that were infusion related; the events were tremor and pain in extremity.

Serious adverse events (SAE) and deaths

No deaths occurred during the studies. Of the 54 treatment naïve patients who received VPRIV, eight patients experienced a total of 12 SAE. In patients who transitioned from imiglucerase, four of the 40 patients (10.0%) experienced at least one SAE (Table 18).

Table 18: Serious adverse events - treatment naïve patients who received VPRIV.

Treatment Period	Patient ID	Age (years) Gender	Treatment	Preferred Term	Severity	Relationship to Study Drug	Action Taken with Study Drug	Outcome
> 9 months	025-071-0001	36/M	60 U/kg	Osteonecrosis	Grade 2	Not related	Dose unchanged	Resolved without sequelae
			60 U/kg	Osteonecrosis	Grade 3	Not related	Dose unchanged	Resolved without sequelae
	025-071-0011	19/F	60 U/kg	Scar	Grade 1	Not related	Dose unchanged	Resolved without sequelae
	025-071-0002	63/M	60 U/kg	Inguinal hernia repair	Grade 2	Not related	Dose unchanged	Resolved without sequelae
	025-071-0001	25/F	60 U/kg	Abdominal pain lower	Grade 1	Not related	Dose Unchanged	Resolved without sequelae
				Headache	Grade 1	Not related	Dose Unchanged	Resolved without sequelae
Pyrexia				Grade 2	Not related	Dose Unchanged	Resolved without sequelae	
0 to 9 months	002-152-0006	25/F	60 U/kg	Grand mal convulsions	Grade 2	Not related	Dose Unchanged	Resolved without sequelae
	009-165-0001	49/F	60 U/kg	Dermatitis allergic	Grade 3	Probably related	Dose Temporarily Withheld	Resolved without sequelae
	009-180-0001	7/M	60 U/kg	Thrombocytopenia	Grade 2	Not related	Dose unchanged	Resolved without sequelae
				Thrombocytopenia	Grade 3	Not related	Dose unchanged	Resolved without sequelae
009-185-0001	9/F	60 U/kg	Convulsion	Grade 4	Not related	Dose unchanged	Resolved without sequelae	

Laboratory findings

Changes in haemoglobin and platelet counts were considered under efficacy. Overall most other laboratory investigations did not show clinically significant changes over the course of the study. However, six treatment naïve patients (11.1%) who were treated with VPRIV developed a prolonged activated partial thromboplastin time. The sponsor's study report did not present a more detailed analysis of laboratory AE but included them in the general analysis of AE.

Safety in special populations

Patients with 0 to 9 months exposure

Eleven paediatric patients were treated with VPRIV and five paediatric patients were treated with imiglucerase. All 16 paediatric patients experienced at least one AE. The most frequently reported adverse events in the overall VPRIV paediatric group were pyrexia (six patients [54.5%]), nasopharyngitis, headache, cough, nasal congestion, productive cough, activated partial thromboplastin time prolonged, and injury (three patients [27.3%], each).

Patients who transitioned from imiglucerase

Nine paediatric patients reported at least one AE. The most common (reported by >1 paediatric patient) AE were nasopharyngitis, pharyngolaryngeal pain (four patients each, 44.4%), headache, cough (three patients each, 33.3%), nasal congestion, nausea, myalgia,

and pain in extremity (two patients each, 22.2%). One paediatric patient reported two drug related AE (proteinuria and nausea). No infusion related AE or SAE were reported among the paediatric patients.

Immunological events

Of the 94 patients who were treated with VPRIV, one patient (1.1%) developed anti velaglycerase antibodies. Of the 17 patients treated with imiglucerase, four patients (23.5%) have tested positive for anti imiglucerase antibodies.

Safety related to drug-drug interactions and other interactions

No significant drug-drug interactions were identified during the clinical trials.

Discontinuation due to adverse events

No treatment naïve patients, treated with VPRIV, withdrew due to an adverse event. One patient, previously treated with imiglucerase, withdrew due to an infusion related adverse event. The patient withdrew after developing an anaphylactoid reaction during their first infusion of VPRIV (50 U/kg group). This patient had tested positive for neutralising antibodies to imiglucerase.

Post marketing experience

The current Australian submission included one post marketing periodic safety update report (PSUR; 26 February 2010 to 25 August 2010). As part of the sponsor's signal detection and medical surveillance program, the following risks were being monitored for:

- Infusion related reactions including allergic type hypersensitivity reactions
- Potential for reduced efficacy due to the development of neutralising antibodies
- Increased activated partial thromboplastin time (aPTT) and bleeding disorders
- Off label use; specifically GaD2 and GaD3
- AE experienced in patients who transition to velaglycerase from prior imiglucerase treatment

The sponsor estimated that there was a minimum worldwide exposure to velaglycerase, for the period of February 2010 to August 2010 of 291 person years treatment. There was one death reported in a three month old Caucasian male patient who received VPRIV on compassionate grounds. The child received four doses of VPRIV but continued to deteriorate rapidly and probably had GaD2. The death was thought to be unrelated to VPRIV.

List of questions

Many of the outstanding issues were addressed by the sponsor's responses to the EMEA questions. The questions below should be considered in addition to those responses.

Pharmacokinetics

1. Could the sponsor please provide a detailed report of the pharmacokinetic analyses for each of the submitted pharmacokinetic studies? This should include details of the models used, the modelling process and the program outputs. The sponsor should adequately justify the choice of model and why compartmental analyses rather than non compartmental analyses were chosen in some studies and not others.

2. Could the sponsor please provide a detailed report of the statistical analyses for each of the submitted pharmacokinetic studies? This should include details of analysis process and the program outputs.
3. Could the sponsor please provide details of the intra and inter subject variability for each of the pharmacokinetic studies?
4. Could the sponsor please provide a details of those patients whose data could not be modelled, an explanation of why this was so and how this was addressed in each case?
5. Could the sponsor please provide details of modelling in children and what approaches to scaling (for example, allometric modelling) were employed?

Pharmacodynamics

No further questions.

Efficacy

No further questions.

Safety

1. Could the sponsor please provide a report on the current status of the ongoing safety studies?
2. Could the sponsor please provide a separate analysis of abnormal laboratory results (they are currently included within the general AE analysis)?

Product information/ consumer medicine information

Could the sponsor please provide any available clinical data on the management of allergic infusion reactions (including premedication) to support the management guideline outlined in the Product Information?

Clinical summary and conclusions

Clinical aspects

The sponsor has presented a relatively small submission in support of their application. This is primarily because GaD is rare and it would be almost impossible to conduct large randomised controlled trials in this population.

Pharmacokinetics

Three pharmacokinetic studies of VPRIV were performed. In all of the studies, VPRIV was infused over 60 minutes. T_{max} was typically attained between 40 and 60 minutes after the commencement of the infusion. After the end of the infusion, serum concentrations fell rapidly, with a short half life of ~12 minutes (Figure 2). In Study TKT032, the mean VPRIV volume at steady state was 106 mL/kg at Week 1 and 82 mL/kg at Week 37.

While there are some deficiencies in the presentation of the methodology, the pharmacokinetic data supports the use of a dose of VPRIV dose of 60 U/kg dose every other week.

Pharmacodynamics

No pharmacodynamic data were presented in the sponsor's clinical submission.

Clinical efficacy

A total of 94 patients who received VPRIV were assessed for efficacy. Of these, 46 patients were males and 48 females. A total of 54 patients were treatment naïve (that is, the patient had not received treatment for GaD period prior to study entry) and 40 patients had transitioned from stable treatment with imiglucerase. There were 20 paediatric patients (≤17 years of age) of whom 13 were treatment naïve and seven had received imiglucerase prior to VPRIV.

The primary outcome measures included changes in haemoglobin concentration, changes in platelet count, changes in liver and spleen volume (measured by magnetic resonance imaging), changes in plasma chitotriosidase level and changes in plasma CCL18 level.

The secondary or tertiary efficacy measures used in one or more of the four studies and included pulmonary function, bone abnormalities, bone density, bone marrow, growth velocity, skeletal growth, Tanner staging, bone disease and overall quality of life. The results concentrated on the 60 U/kg dose as this is the proposed dose.

Treatment naïve patients in the pivotal studies

Over the study period, haemoglobin concentrations increased by 2.43 g/dL (23%) in Study TKT032 and by 1.62 g/dL (14%) in Study HGT-GCB-039. This was a significant increase in both studies.

The platelet count increased by 50.88 x10⁹/L (65.9%) in Study TKT032 and by 110.411 x10⁹/L (68%) in Study HGT-GCB-039. These changes were also significant.

The size of the spleen decreased by 1.92% of body weight in Study TKT032 and by 0.9% of body weight in Study HGT-GCB-039. These were significant changes.

Liver size did not show a significant decrease in volume in Study TKT032 but did decrease by 1.3% of body weight in Study HGT-GCB-039.

The sponsor included response categories for the primary endpoints (haemoglobin concentration, changes in platelet count, changes in liver and spleen volume) as requested by the EMEA. Study HGT-GCB-039 was a comparator control study comparing VPRIV with imiglucerase. The study numbers were too small to demonstrate a difference between the two treatments or that the treatments were equivalent. However, the magnitude of the change in the primary endpoints were comparable between the two groups.

Both plasma chitotriosidase and CCL18 levels decreased over time in both studies, consistent with the action of VPRIV.

None of the secondary or tertiary endpoints were altered after treatment. Significantly, the sponsor was unable to demonstrate a significant improvement in quality of life measures in the two pivotal studies.

Previously treated patients in the pivotal studies

Study TKT034 enrolled patients who had previously been treated with imiglucerase. There were only small changes in the primary outcome measures which is to be expected as patients had been previously stabilised on an alternative enzyme replacement therapy. There were no clinically significant changes in any of the secondary or tertiary outcome measures.

Dose response studies and main clinical studies

Study TKT032 investigated two doses of VPRIV; 45 U/kg and 60 U/kg. Both doses showed similar changes in the primary endpoints and the study did not demonstrate a dose dependent response for any of the clinical parameters.

Clinical studies in special populations***Paediatric patients***

The current submission included 20 patients between the ages of 4 and 17 years of age. Of these, 12 patients received VPRIV and 8 received imiglucerase. The children received the same doses as the adults in the respective studies. The numbers were too small to reach any conclusion about differences between children and adults treated with VPRIV, suffice to say that the clinical response profile in terms of the primary outcome measures was similar.

Analysis performed across trials (pooled analyses and meta analysis)

There was no true pooled analysis performed combining studies. The sponsor stated that the studies varied too much in design to allow for a meta-analysis.

Supportive studies

The sponsor's submission included two extra safety studies which were supportive of the pivotal study conclusions.

Clinical safety

The sponsor's submission included four clinical studies (TKT025, TKT032, TKT034, and HGT-GCB-039) for safety analysis. Treatment naïve patients were the study population in the Phase I/II study (TKT025) and the Phase III studies (TKT032 and HGT-GCB-039), while the Phase II/III study (TKT034) enrolled patients who transitioned from treatment with imiglucerase, an approved ERT for GaD1.

An extension study, TKT025EXT (patients rolled over from TKT025), is ongoing and included 10 of the 12 patients from TKT025.

A second extension study, HGT-GCB-044, was reported to be ongoing and was open to patients who completed study TKT032, TKT034, or HGT-GCB-039. This study was reported to include up to 102 patients. This study was not included in the current Australian submission.

There was also mention of a third study, HGTGCB-058. This was an open label follow up study in up to 500 patients previously treated with imiglucerase. This study was also reported to be ongoing and was not included with the current submission.

The evaluator found that there are 94 patients included in the safety analysis with the potential for up to 500 more to be available. The safety profile of VPRIV was similar to that reported in imiglucerase, although infusion related reactions were more common with VPRIV compared to imiglucerase. The range and types of AE were consistent across studies. All groups that received VPRIV had a significant incidence of infusion related reactions. Most of these were mild in nature and did not result in discontinuation of the treatment. However, there were two patients who experienced moderate to severe reactions and one of these patients was discontinued because of this.

Evaluator's overall conclusions on clinical safety

The safety data is consistent with that of an enzyme replacement. There does appear to have been a large number of drug related AE. The overall number of subjects in the studies was small and the duration of the studies in most patients was limited. Finally there are safety data available that have not been fully reported in the current submission. The sponsor should report on their current status and ensure that any important safety warnings are included in the product information and CMI.

Adverse events

There was a relatively high rate of reported AE in the clinical studies.

In the 0-9 month exposure, 51/54 patients (94%) experienced one or more AE and 33/54 (61.1%) were thought to be drug related. Infusion related events occurred in 28/54 patients (51.9%).

In the 0-12 month exposure, 33/35 patients (94%) experienced one or more AE and 23/35 (65.7%) were thought to be drug related. Infusion related events occurred in 22/35 patients (62.9%).

This is a much higher rate of AE than reported in the imiglucerase group in Study HGT-GCB-039; 6/17 (35.3%) reporting one or more drug related AE and 4/17 (23%) reporting one or more infusion reactions, although the total number of patients who received imiglucerase was small.

Serious adverse events and deaths

No deaths were reported in the clinical studies. One death, in a three month old baby who received VPRIV on compassionate grounds, was reported in the postmarketing data. The death was thought to be unrelated to VPRIV.

In the 0-9 month exposure, 4/54 patients (7.4%) experienced one or more SAE and 1 was thought to be drug related.

In the 0-12 month exposure, 3/35 patients (8.6%) experienced one or more SAE and none of these were thought to be drug related.

Laboratory findings

Changes in haemoglobin and platelet counts were reported as efficacy outcomes. Overall the remaining laboratory investigations did not demonstrate any clinical significant trends. The exception was that 6/54 patients (11%) developed a prolonged activated partial prothrombin time. A detailed analysis of the laboratory data was not presented.

Safety in special populations

Paediatric population

All 20 paediatric patients reported one or more AE. The range of events was similar to those seen in adults. No SAE were reported in the paediatric population. There are no clinical data available for patients under 4 years of age. Patients 2 years of age or older were permitted to be enrolled in three of the clinical studies (TKT032, TKT034, and HGT-GCB-039); however the youngest patients exposed to VPRIV were: a four year old in Study TKT032, a nine year old in Study TKT034 and a seven year old in Study HGT-GCB-039. There were too few paediatric patients enrolled to be able to draw firm conclusions with statistical power.

Immunological events

Of the 94 patients who received VPRIV, only one developed antibodies. It may be that over time and with increasing exposure, a higher rate of antibody development occurs. The clinical effect of positive anti velaglucerase antibodies cannot be determined from the current data submission.

Safety related to drug-drug interactions and other interactions

No drug-drug interactions were observed during the clinical studies. No specific studies were performed.

Discontinuation due to AE

Only one patient, who was transitioned from imiglucerase, withdrew from the study after developing an anaphylactoid reaction during the first infusion.

Benefit risk assessment***Benefits***

Patients treated with VPRIV demonstrate an improvement in haemoglobin concentrations and platelet counts. There is also data to support that spleen volume, and perhaps liver volume, decrease with treatment. The data did not demonstrate an improvement in quality of life or any of the other secondary or tertiary outcome measures. The studies included patients with low haemoglobin concentrations, low platelet counts and hepatosplenomegaly. The use of VPRIV should be limited to patients with one or more of these clinical problems. Whether the use of VPRIV will influence the long term prognosis of GaD is yet to be determined.

Risks

The main risks associated with the use of VPRIV are the high rate of adverse events, especially the associated infusion reactions. There was an indication that the rate of adverse events may be higher than with imiglucerase, the alternative enzyme replacement therapy for GaD. There are limited long term safety data, although some patients have been followed for up to 60 months.

Balance

There is a significant risk of an infusion reaction with the use of VPRIV in GaD. However, the risk can be managed and the benefits of the treatment of the GaD outweigh the risk. It may be, however, that imiglucerase is preferred to VPRIV due to a more favourable side effect profile.

Conditions of registration

The clinical evaluator recommends that the provision of the final study reports of each of the ongoing studies TKT025EXT, HGT-GCB-044 and HGT-GCB-058, as evaluable data within the context of category 1 applications, be made a specific condition of registration.

Conclusions

There are adequate data to support the registration of VPRIV for the treatment of GaD1.

The clinical evaluator recommends approval of the application for the registration of VPRIV as a second line choice for enzyme replacement after imiglucerase due to its less favourable adverse event profile and no demonstrable advantage for efficacy.

V. Pharmacovigilance findings**Risk management plan**

The sponsor submitted a Risk Management Plan (RMP) that was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 19.

Table 19: Important identified and potential risks and missing information for VPRIV.

Important identified risks	Infusion-related reactions
Important potential risks	Potential for reduced efficacy due to development of neutralizing antibodies to velaglucerase alfa Increased activated partial thromboplastin time (aPTT)
	Off label use
Important missing information	Lack of safety data for patients who transition to velaglucerase alfa and have a prior history of significant adverse drug reactions to other ERT, and insufficient safety data for patients who transition to velaglucerase alfa and who developed antibodies to previous ERT

OPR reviewer comment:

The above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance plan***Proposed pharmacovigilance activities***

The sponsor has proposed to undertake pharmacovigilance activities for all of the Ongoing Safety Concerns. In addition to routine pharmacovigilance, the sponsor has proposed to undertake a Gaucher Outcome Survey (GOS) as an additional pharmacovigilance activity for all of the Ongoing Safety Concerns.

In addition to the GOS, the following additional pharmacovigilance activities have been proposed for the following safety concerns:

Important identified risk: Infusion related reactions

- As a part of safety data collection, the sponsor proposes to recommend that IgE antibody testing (as per specific guidelines provided by the sponsor and as part of routine follow up queries) is requested in all SAE cases of severe infusion related reactions (that is, suspected anaphylactic/anaphylactoid reactions).

The sponsor states that the objective and rationale for the proposed activity is to continue to categorise severe infusion related reactions from the point of the associated symptomatology and frequency and to further categorise risks in an expanded, post approval patient population, and scrutinise the new information against the existing information in the product reference safety information RSI and labelling.

Important potential risk: Potential for reduced efficacy due to development of neutralising antibodies to velaglucerase alfa

- As a part of safety data collection, the sponsor proposes to recommend antibody testing is considered in AE cases involving patients who have a lack or loss of effect.

The sponsor states that the objective and rationale for the proposed activity is to continue to categorise determinants of long term efficacy and that additional information is required to further characterise the potential relationship between loss or lack of effect and development of antibodies to velaglucerase alfa. The evidence collected from clinical trials, which indicates that those immunological phenomena are likely to be clinically inconsequential, should be confirmed in an expanded patient population with focus on relevant patient subgroups.

Important potential risk: Off label use

- Experience with velaglucerase alfa in GaD3 patients will be obtained from Study HGT-GCB-068 as part of the Paediatric Investigational Plan (PIP).

The sponsor states that the objective for the proposed activity is to monitor extent of off label use and associated safety findings. The sponsor further states that as it is unlikely

that velaglucerase alfa crosses the blood brain barrier, it is not expected to improve the central nervous system (CNS) manifestations of GaD2 and GaD3. It is thought that velaglucerase alfa may improve the somatic manifestations of GaD3, but no effect is expected on the CNS manifestations. Hence, the benefit risk profile of velaglucerase alfa in GaD2 is expected to be negative. It will be further investigated in GaD3 disease based on the PIP. The sponsor proposes to provide interim study reports in the Periodic Safety Update Report (PSUR). The planned date for the submission of the final study data is 2017.

Important missing information: Lack of safety data for patients who transition to velaglucerase alfa

- Assess safety of transitioning from other ERTs to velaglucerase alfa based on post-marketing reporting and possible evidence from treatment Protocol HGT-GCB-058. Study HGT-GCB-058 is a US treatment protocol implemented at the request of the FDA to provide open label velaglucerase alfa treatment to patients with GaD1 who may not have access to approved ERT treatment due to an imiglucerase shortage. Safety evaluation is a primary endpoint of this study and it is expected that some safety data with regards to transitioning from other ERTs may be obtained as the study enrolment criteria allows participation of patients who have had previous significant adverse drug reactions or antibodies to other ERT. However, patients who previously experienced anaphylactic reactions are excluded from this study. Up to 500 patients may be involved in the study. The study will end after one year of treatment or when VPRIV becomes commercially available in the US, whichever comes first. The sponsor proposes reporting of interim findings in the PSUR and that relevant data from this study will be included in the subsequent updates of the RMP.
- As a part of safety data collection, the sponsor proposes to recommend that antibody testing is requested for all SAE cases from all reporting sources involving patients who after transitioning to velaglucerase alfa and developed severe (that is, suspected anaphylactic/anaphylactoid reactions) infusion related reactions.

The sponsor states that the objective of the proposed activities is to further characterise patient subpopulations in which transitioning to velaglucerase alfa is safe and offers improved benefit/risk profile to other ERT. The sponsor's rationale for the proposed activities is that as ERT is currently the most effective therapy for GaD1. The durable benefit can only be achieved with lifelong treatment hence offering the best tolerated ERT is of paramount importance.

OPR reviewer's comments:

The GOS has been proposed as an additional pharmacovigilance activity for all of the Ongoing Safety Concerns. As the GOS has already commenced (the first patient enrolled on 29 December 2010 and as of 11 August 2011 a total of 35 patients at 9 sites in the US were participating), this protocol has not been formally evaluated.

In summary the GOS is a long term observational survey open to patients with GaD who are naïve to therapy or who have received or are receiving VPRIV for injection. The entry of patients into GOS is at the discretion of the participating physician and the patient; participation is not a prerequisite for prescribing VPRIV. Accordingly, there is no predefined sample size and the sponsor states that all data entered will be used for analysis purposes. There are no geographic restrictions to participation and the sponsor anticipates that GOS will be open to prescribers/patients from Australia post approval of VPRIV in Australia. All patient care and management is determined by the participating physician. Effectiveness of VPRIV will be monitored through collection of data entered by the participating physicians to the survey's database obtained through routine clinical and laboratory testing that constitute standard medical care for patients with GaD.

Collection of safety data are expected to be entered in real time. Specifically, all SAE, regardless of causality, and all non serious AE considered related to the use of VPRIV occurring in patients participating in GOS will be reported to the survey database. Three to six monthly adverse reaction assessments and laboratory testing (haematology and disease biomarker) are listed among others in the Schedule of Recommended Survey Assessments.

Statistical reporting of adverse events will be descriptive. Patients with missing data will not be excluded from the all patient analysis population but will be included to the extent that evaluable data are present. However, some patients with missing values might be excluded from survey specific analyses. Outlying values will be investigated. The sponsor states that if any outliers are determined to be legitimate values, statistical tests may be run, with and without them, to determine their influence on the conclusions. The duration of the registry is a minimum of seven years. Given the rare incidence of the indication, the GOS is likely to provide adequate enhanced surveillance of the safety of VPRIV in the post approval setting and as such the sponsor should provide a commitment to the TGA to submit regular interim reports of the analyses of the registry data and the final study report.

Having regard to the evaluation and recommendations provided by the clinical evaluator, it is also recommended that the sponsor commits to ensuring that there are adequate processes in place to support the enrolment of Australian patients into the GOS or, if Australian patients are not able to participate in the GOS, that additional active safety monitoring be implemented in Australia. Such active monitoring could, for example, consist of active surveillance at sentinel sites or an Australian treatment registry.

The sponsor has proposed to recommend to physicians that antibody testing is requested as part of the routine follow up of all serious adverse events as an additional pharmacovigilance activity. The RMP provides a summary of the specific guidelines for antibody testing. The RMP further states that each prescriber is informed about the antibody testing by either a local medical or sales representative. In addition a written document entitled "Guidelines for Collection, Preparation, and Shipment of Lab Specimens" has been prepared.

The sponsor anticipates that the proposed antibody testing will be implemented in Australia when VPRIV is launched in the Australian market. It is stated that the availability of antibody testing will be communicated to prescribers through Shire personnel and that for additional awareness, the proposed Product Information for VPRIV contains information on when to conduct antibody testing.

The draft PI of 2 August 2011 has the following text in the *Precautions* section: "Antibodies may play a role in treatment related reactions found with the use of veleglucerase alfa. 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." The sponsor states that the 'Instructions for Collection, Preparation, and Shipment of Lab Specimens' is a global document and will apply to the Australian market and that at present, the testing of specimens will be conducted centrally at a US laboratory. The sponsor should ensure this document is readily available to prescribers. Samples collected from patients will be analysed and results summarised and presented in the PSUR.

While not specifically identified by the sponsor in the Pharmacovigilance Plan, Annex III of the RMP lists veleglucerase alfa clinical Studies TKT025EXT and HGT-GCB-044 as having long term safety as a primary endpoint. Study TKT025EXT is a multicentre open label extension study to evaluate the long term safety of veleglucerase alfa in patients (n = 10) who completed study TKT025. Study HGT-GCB-044 is a multicentre open label study to evaluate the long term safety of veleglucerase alfa in patients who completed Study

TKT032, TKT034, or HGT-GCB-039. The reported number of patients is up to 102 and the study duration is until of veleglucerase alfa is commercially available or to study termination. It was recommended that interim and final study reports for these two studies are submitted when available.

Risk minimisation activities

The sponsor concluded that routine risk minimisation activities were sufficient for each of the identified Ongoing Safety Concerns. In justifying the use of routine risk minimisation with respect to infusion related reactions, the sponsor states that “home infusions should only be provided by currently registered health care professionals who are adequately trained. These health care professionals should be experienced in the field of home infusions and are able to recognise and medically manage serious infusion related reactions under the direction of practicing physician, as also described in the product label.”

OPR reviewer comments:

As stated in the safety specification of the RMP, infusion related reactions occurred in 51.9% of treatment naïve patients and 22.5% of patients who transitioned from imiglucerase. Most infusion related reactions were mild or moderate in severity. Furthermore, the risk of infusion related tends to decline with increased duration of exposure; in treatment naïve patients the majority of infusion related reactions occurred during the first six months of treatment of VPRIV. The sponsor asserts that in the post marketing surveillance experience with VPRIV for over 18 months, infusion related reactions were mild to moderate in severity, non serious, with no cases of anaphylactic/anaphylactoid reactions reported.

There is potential for home administration to patients who are tolerating VPRIV infusions well. The decision to transition a patient to home infusions is based on clinical grounds. The proposed PI has the following statement in the dosage and administration section: “VPRIV should be administered under the supervision of a healthcare professional. Home administration may be considered for patients who are tolerating their infusions well.”

There is information provided in the draft PI on suggested management of infusion-related reactions. With regard to hypersensitivity reactions, the following advice is provided in the precautions section of the draft PI: “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.” However these PI statements do not convey all the advice provided by the sponsor in the justification for the use of routine risk minimisation. The draft PI (2 August 2011) does not contain reference to home infusions only being provided by currently registered health care professionals who are adequately trained. Nor does it emphasise that health care professionals should be experienced in the field of home infusions and be able to recognise and medically manage serious infusion related reactions under the direction of practicing physician. Therefore it is recommended that the draft PI be updated to include the following suggested wording (underlined) in the *Dosage and Administration* section and repeated, or cross referenced, in the *Precautions* section:

VPRIV should be administered under the supervision of a healthcare professional. Home administration may be considered for patients who 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.

Provided the sponsor agrees to this additional advisory information in the draft PI, there is no objection to the implementation of routine risk minimisation activities.

Potential for medication errors

The sponsor has provided the following discussion on the potential for medication errors:

“Velaglucerase is supplied in a 400 U/vial, which upon reconstitution with sterile water for injection contains approximately 2.5 mg/mL (100 U/mL) of velaglucerase alfa. Each vial contains an extractable volume of 4.0 mL for the 400 U/vial. Based on a maximum dosage of 60 U/kg, a typical patient will require multiple vials of velaglucerase alfa.

There is potential for dilution and calculation errors resulting in the administration of an incorrect dose. Vials will be clearly labelled to distinguish the contents and the required volume of sterile water for reconstitution.

Velaglucerase alfa is not a vesicant, and therefore the risk of extravasation is minimal.

There is no experience with overdose of velaglucerase alfa.”

OPR reviewer comments:

The sponsor's discussion on the potential for medication errors is acceptable.

Furthermore, as the sponsor is not seeking to register the 200 U/vial in Australia, the potential for medication errors associated with incorrect dosing will be reduced.

Summary of recommendations

The OPR provides the following recommendations in the context that the submitted RMP is supportive to the application:

- The implementation of RMP version 6.0 (date 23 June 2010), and any subsequent updated versions, be implemented as a condition of registration in Australia with the following considerations:
 - a. While the sponsor *anticipates* that the GOS will be open to prescribers/patients from Australia post approval of VPRIV in Australia, it is recommended that the Sponsor provide the following commitment:
 - § That if the GOS is open to prescribers/patients from Australia post approval of VPRIV in Australia, that there are adequate processes implemented to support patient enrolment.
 - OR
 - § If the GOS is not open to prescribers/patients from Australia post approval of VPRIV in Australia, that the sponsor will design and implement, in consultation with the TGA, active safety monitoring of VPRIV in Australia. For example, active surveillance at selected sentinel sites or the formation of an Australian treatment registry.
 - b. The sponsor should provide timely interim and final study reports for the following studies identified as additional pharmacovigilance activities:
 - § The GOS
 - § Study HGT-GCB-058
 - § Study HGT-GCB-068
 - c. The sponsor should provide timely interim and final study reports with regard to the outstanding safety data for the following studies:
 - § Study TKT025EXT
 - § Study HGT-GCB-044

- d. The global document entitled '*Instructions for Collection, Preparation, and Shipment of Lab Specimens*' should be provided to prescribers who enquire about antibody testing.
- e. It is recommended that the product information contain strengthened advice about adequately trained health care professionals with regard to home infusions.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator had no objections to the registration of VPRIV, velaglucerase alfa, powder for solution for infusion 200 & 400 units. The evaluator has recommended the standard condition of registration relating to batch release testing by OLSS and the Delegate intends to impose this as a specific condition of registration.

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

Velaglucerase alfa showed comparable efficacy with imiglucerase in lowering liver glucocerebroside levels in a mouse model of GaD.

The nonclinical studies in rats and monkeys raised no direct issues of clinical concern. While high doses of velaglucerase alfa produced reddening/swelling of the muzzle and/or limbs in rats, this effect was transient and was not seen in other species (including monkeys). A significant number of both rats and monkeys developed anti velaglucerase alfa antibodies after several doses of velaglucerase alfa. These antibodies appeared to have no adverse toxicological effects. Rats also showed an innate immune system response to velaglucerase alfa with the occurrence of high histamine levels in serum soon after dosing.

Based on an assessment of the sponsor's nonclinical studies, there were no nonclinical objections to registration. The nonclinical evaluator made a number of recommendations for amendments to the PI and the Delegate endorses these recommendations.

Clinical

The clinical evaluator has provided a report on the submitted data. Each of the PK studies was performed on a subset of patients from one of the efficacy and safety studies.

In both the Round 1 and Round 2 clinical assessments, the clinical evaluator was of the opinion that there were adequate data to support the registration of VPRIV for the treatment of GaD1. In making this recommendation, the clinical evaluator also recommended that VPRIV should be registered as a second line choice for enzyme replacement after imiglucerase due to its less favourable adverse event profile and no demonstrable advantage with regard to efficacy.

Pharmacology

PK component of TKT032

TKT032 was a randomised, double blind, parallel group, two dose study of VPRIV in patients with GaD1. There were 25 patients in the study, 13 enrolled in the 45 U/kg arm and 12 in the 60 U/kg arm, the doses infused over one hour every two weeks. For each dose, serum concentration increased during the first 20 minutes before plateauing for the remainder of the infusion. T_{max} was typically attained about 40 minutes after the commencement of the infusion. After infusion, serum concentrations fell rapidly. There was no evidence of accumulation and the half life was approximately 12 minutes. The pharmacokinetics were not quite dose proportional. There was only one positive antibody response with one subject testing positive for anti velaglucerase alfa IgG type antibodies at Week 53 (end of study) but negative for IgE antibodies. In the 45 U/kg group, there was no apparent trend for C_{max} , AUC or CL versus age. However, in the 60 U/kg group, there was a trend for lower C_{max} and AUC and higher CL in subjects below ten years of age compared to adults. There were no obvious gender differences. This was the only study which analysed the data.

PK component of TKT025EXT

TKT025EXT was an open label safety study and the PK component was performed at Week 65. Of the 12 patients enrolled in TKT025EXT, 9 were included in the PK component. The dose was 30 U/kg, infused over one hour. Again VPRIV was rapidly cleared from plasma with a half life of ~9 minutes. No neutralising antibodies were detected. These results are comparable to those from the PK component of TKT032.

PK component of TKT025

This report was included as an appendix to TKT025 and not as a separate report in the PK component of the sponsor's submission. The PK study was of a three patient dose escalation cohort (15, 30 and 60 U/kg) and of the remaining nine patients who received an initial infusion of VPRIV at 60 U/kg. Details of the PK analysis were not included in the report. Again VPRIV was rapidly cleared from plasma with T_{max} equal to 60 minutes. There was linear proportionality for both C_{max} and AUC from 15 U/kg to 60 U/kg. No neutralising antibodies were detected.

The PK data showed that VPRIV was rapidly cleared from the plasma. Distribution and elimination of VPRIV was not directly addressed in the clinical studies. Uptake is assumed to be by macrophages. There were some limited data on dose proportionality. Only a small number of children, 20 in all, were studied and the limited data suggest that children had a slightly greater clearance of VPRIV but in other respects demonstrated a similar PK profile to that in the adult population. The evaluator asked the sponsor a number of questions about the PK assessments. The sponsor acknowledged that different modelling approaches were used in the PK studies. Study TKT025 and its extension TKT025EXT used a compartmental model while TKT032 used a non compartmental model. No justification for the use of different models was offered. The evaluator accepts that this has probably not affected interpretation of the results. No further analyses, beyond those already presented as part of Study TKT032 were able to be provided. The evaluator believed that a more detailed analysis of the paediatric data would be desirable but also that the descriptive analysis could be considered adequate for registration.

Efficacy

Pivotal studies

TKT032

This was a multicentre, randomised, double blind, parallel group, two dose study conducted in 5 centres in Europe over 51 weeks. There were altogether 25 patients enrolled, 13 in the 45 U/kg group and 12 in 60 U/kg group, and treatment was administered as an IV infusion every 2 weeks. There were 15 males and 10 females with 7 patients (28%) aged between 4 years and 17 years.

The primary outcome measure was an increase in haemoglobin concentration at a dose of 60 U/kg over the period of the study. Secondary outcome measures included haemoglobin concentration in the 45 U/kg group, increases in platelet counts, decreases in liver and spleen volumes, decreases in levels of plasma chitotriosidase and chemokine ligand 18 (CCL 18) and quality of life measures. There were also some tertiary outcomes, including annualised growth velocity, Tanner staging and changes in skeletal age (all the latter in 2 to 17 year olds).

In the 60 U/kg group, the mean haemoglobin increase was +2.429 g/dL (+23.25%) from a baseline of 10.825 g/dL to 12.550 g/dL at Week 53. The corresponding result in the 45 U/kg group was +2.438 g/dL (+23.81%) from a baseline of 10.723 g/dL to 13.162 g/dL.

Platelet counts increased by about 66% in each group. Spleen volumes decreased by about 1.9% (adjusted for body weight) in each group. The liver volumes decreased in each group but not to a significant level. Chitotriosidase and CCL 18 levels decreased in each group. No significant improvement in Quality of Life (QoL) scores was reported. After one year, the mean growth velocity was much the same in each group (at around 8 cm/year).

The study did not demonstrate a dose dependent response for any of the clinical parameters.

HGT-GCB-039

This was a pivotal, multicentre, Phase III, randomised, double blind, parallel group study designed to compare the safety and efficacy of velaglucerase alfa with that of imiglucerase in the treatment of patients with GaD1. There were altogether 34 patients, 17 receiving a 60 U/kg dose of velaglucerase alfa and the other 17 receiving a 60 U/kg dose of imiglucerase, each dose administered as a single IV infusion every two weeks. There were 16 males, 18 females and of the 34, there were 9 children.

The primary outcome measure was the difference in the change in haemoglobin concentration at 41 weeks between the two groups. The secondary outcome measures included platelet counts, spleen and liver volumes, plasma chitotriosidase and CCL 18 levels and the difference in the time to response for haemoglobin concentration. Again there were some tertiary endpoints.

The mean haemoglobin increase was 1.624 g/dL in the velaglucerase group and 1.488 g/dL in the imiglucerase arm with a mean difference between the groups of 0.135 g/dL. The time to first haemoglobin response was similar between the two treatment groups. The clinical evaluation report (CER) states that the mean platelet counts at Week 41 were $110.4 \times 10^9/L$ in the velaglucerase group and $144.4 \times 10^9/L$ in the imiglucerase group and refers the reader to Figure 11 (in this AusPAR). However, Figure 11 appears to show baseline mean platelet counts/L at baseline of about 160×10^9 and 180×10^9 in the velaglucerase and imiglucerase groups, respectively, and at Week 41 of about 270×10^9 and 330×10^9 in the velaglucerase and imiglucerase groups, respectively. The Delegate suspects that what the clinical evaluator meant to say was that the increases in mean platelet counts at Week 41 were $110.4 \times 10^9/L$ in the velaglucerase group and $144.4 \times 10^9/L$ in the imiglucerase group. The sponsor is requested to clarify this point. While it

may appear that there is a trend of a greater platelet response with imiglucerase compared to velaglucerase, the latter group commenced with a lower baseline value, both groups displayed steady increases in platelet count over the study period and a post hoc analysis suggested that the data from 3 patients in the 2 to 4 years age group had skewed the data. Decreases in both liver and spleen volumes were comparable between groups as were the decreases in the levels of both chitotriosidase and CCL 18. There were some positive QoL outcomes, essentially comparable in each group. Median annualised growth velocities were around about 8 cm/year in each group but this was based on very small numbers of children (3 in the VPRIV group and 5 in the imiglucerase group).

Supportive studies

TKT025

This was primarily a safety study, conducted in one centre in Israel over 37 weeks. Twelve patients (5 male and 7 female) over 18 years of age with GaD1 who had anaemia and thrombocytopenia were enrolled. Eleven completed the study. Over the study period, the mean haemoglobin increase was 2.24 g/dL (19.22%) and the mean platelet increase was of the order of 67.6%. Spleen volume decreased by 49.47% and liver volume by 18.2% (these percentages relative to the organ volumes themselves, not adjusted for body weight). There were also decreases in both plasma chitotriosidase (74.25) and CCL 18 (57.1%).

TKT025EXT

Extension to TKT025; no efficacy outcomes were reported as the focus was on safety.

TKT034

This was a multicentre, open label study of VPRIV in patients with GaD1 previously treated with imiglucerase, at doses ranging between 15 U/kg and 60 U/kg. Each patient received a dose of velaglucerase alfa identical to the imiglucerase dose which they had received for at least six months prior to enrolment. The study lasted for 51 weeks. There were altogether 40 patients (18 male and 22 female) with 9 patients (22.5%) between 5 and 17 years of age. While the primary aim of the study was safety, there were several efficacy measures assessed. There was a decrease in mean haemoglobin but only by 0.10 g/dL. There was a slight increase in platelet counts (by 7.04%), slight decreases in spleen (5.56%) and liver volumes (0.03%) as well as moderate decreases in plasma chitotriosidase (28.14%) and CCL 18 (16.44%) noted. Thus, there were only small changes in the outcome measures which were to be expected as patients had been previously stabilised on an alternative ERT.

Safety

There were five clinical studies assessable for safety data. A total of 94 patients with GaD1 and treated with VPRIV were evaluable for safety. The doses ranged from 15 U/kg to 60 U/kg. There were 54 treatment naive patients and the remaining 40 were transitioned from imiglucerase. Of the 54 treatment naive patients, 41 were treated with VPRIV at a dose of 60 U/kg. There were 10 patients, all from TKT025EXT who were exposed to velaglucerase for greater than 9 months at doses from 30 to 60 U/kg.

Table 16 of this AusPAR lists the most common ($\geq 10\%$) treatment emergent AE in patients with up to 12 months' exposure to velaglucerase alfa with the results overall and by dose (45 U/kg or 60 U/kg). The most common AE overall were headache in 16/35 (45.7%) patients, dizziness in 12/35 (34.3%) patients, arthralgia and bone pain in 9/35 patients each (25.7%), back pain and injury in 8/35 (22.9%) patients each, cough and vomiting in 7/35 (20.0%) patients each, pain in extremity in 6/35 (17.1%) patients each, nasal congestion, abdominal pain upper, diarrhoea and aPTT prolonged in 5/35 (14.3%) patients each and pharyngolaryngeal pain, productive cough, rhinorrhoea, abdominal

pain, cheilitis, nausea, toothache, erythema, petechiae, rash, musculoskeletal pain and myalgia in 4/35 (11.4%) patients each. The higher dose of 60 U/kg, somewhat paradoxically, appeared less prone to causing AE than the lower dose of 45 U/kg. The AEs for which there appeared to be a dose response (increased frequency with the higher dose) were abdominal pain upper [0% versus 22.7%], cheilitis [0% versus 18%] and bone pain [7.7% versus 36.4%].

Table 15 of this AusPAR compares the most common ($\geq 10\%$) treatment emergent AEs in patients with up to 9 months of exposure to either velaglucerase alfa or imiglucerase. Comparing AE rates at a dosage level of 60 U/kg, that is, head to head rather than pooled velaglucerase versus one dose imiglucerase as done by the clinical evaluator, there are somewhat notably increased rates for velaglucerase alfa compared with imiglucerase (in that order) for the following AEs: headache 13/41 (31.7%) versus 3/17 (17.6%); dizziness 8/41 (19.5%) versus 2/17 (11.8%); hypertension 2/41 (4.9%) versus 0/17 (0%); nasal congestion 2/41 (4.9%) versus 0/17 (0%); diarrhoea 6/41 (14.6%) versus 1/17 (5.9%); bone pain 12/41 (29.3%) versus 3/17 (17.6%); musculoskeletal pain 3/41 (7.3%) versus 0/17 (0%); pyrexia 9/41 (22.0%) versus 2/17 (11.8%) and asthenia 5/41 (12.2%) versus 0/17 (0%). However, there were some AE for which somewhat notably higher AE rates were observable with imiglucerase. These AE were (with the same order as above, namely velaglucerase alfa versus imiglucerase): bronchitis 1/41 (2.4%) versus 2/17 (11.8%); vomiting 2/41 (4.9%) versus 2/17 (11.8%); muscle spasms 1/41 (2.4%) versus 2/17 (11.8%) and influenza like illness 1/41 (2.4%) versus 2/17 (11.8%). On balance, it would appear from all these results that velaglucerase alfa is somewhat less well tolerated than imiglucerase.

Table 17 of this AusPAR compares infusion related AE for patients with up to 9 months exposure. The table offers a comparison of the rates of such infusion related AE in Phase III patients on velaglucerase alfa 60 U/kg versus imiglucerase 60 U/kg. Such a head to head comparison appears not to have been done by the clinical evaluator. In that order, velaglucerase alfa versus imiglucerase, some rates were: any infusion related AE 11/29 (37.9%) versus 4/17 (23.5%); headache 6/29 (20.7%) versus 2/17 (11.8%); hypotension 3/29 (10.3%) versus 1/17 (5.9%). There were a number of AE which were reported by one person in one treatment arm and by none in the other, most such AE occurring in the velaglucerase arm as opposed to the imiglucerase. Again, on balance, velaglucerase appears to be somewhat less well tolerated than imiglucerase.

No deaths occurred during the studies. Of the 54 treatment naive patients who received VPRIV, 8 patients experienced a total of 12 SAEs, including two events of osteonecrosis, two of convulsions and two of thrombocytopenia, all of the latter being judged as not related to the study treatment. In fact, out of the 12 SAE, only one was judged as related (probably related) and that was an AE of allergic dermatitis. All 12 SAE occurring in the treatment-naive patients resolved without sequelae. The sponsor was asked for a brief comment on the events of osteonecrosis, convulsions and thrombocytopenia, including whether or not these were judged to be due to the underlying disorder, namely GaD. In patients who transitioned from imiglucerase, 4 of the 40 patients experienced at least one SAE. The only one of these which was judged to be related (probably related) was an AE of anaphylactoid infusion reaction for which the treatment was permanently discontinued. All of the other SAE were judged as not treatment related including two severe events in the one person (facial swelling and hives) but for all of these events the dose was unchanged.

Overall most laboratory findings did not show clinically significant changes over the course of the study. However, six treatment naive patients (11.1%) who were treated with VPRIV developed a prolonged aPTT. The sponsor's submission did not present a more detailed analysis of laboratory AE but included them in the general analysis of AE. The clinical evaluator requested the sponsor to provide a separate and detailed analysis of the

abnormal laboratory results. In the Round 2 assessment, the clinical evaluator has not presented these data in any detailed fashion. Instead, the evaluator has commented that a summary of those reactions thought possibly related to VPRIV should be included in the Adverse Effects section of the PI, in particular parameters of coagulation, liver function, blood count and iron status. The Delegate requested the sponsor to undertake this revision of the PI. Furthermore, the Delegate requested the sponsor, in the pre ACPM response, to include brief summaries of any clinically significant shifts in laboratory values which occurred in any of the eight categories analysed, namely coagulation, liver function, CRP, complete blood count, biochemistry/chemistry, iron status, bone disease and kidney function.

All 20 paediatric patients reported one or more AE. The range of AEs was similar to that in adults. The most frequently reported AE in the overall VPRIV paediatric group were pyrexia, nasopharyngitis, headache, cough, nasal congestion, productive cough, aPTT prolonged and injury. No SAE were reported in the paediatric population. There are no clinical data available for patients under 4 years of age (although patients 2 years of age or older were permitted to be enrolled in three of the clinical studies).

Of the 94 patients treated with VPRIV, one patient (1.1%) developed anti velaglucerase antibodies. Of the 17 patients treated with imiglucerase, four patients (23.5%) tested positive for anti imiglucerase antibodies.

No treatment naive patients treated with VPRIV withdrew due to an AE. One patient, previously treated with imiglucerase, withdrew due to an infusion related AE: an anaphylactoid reaction during the first infusion of VPRIV. This patient had previously tested positive for neutralising antibodies to imiglucerase.

The sponsor estimated a minimum worldwide exposure to velaglucerase, for the period Feb 2010 to Aug 2010, of 291 person years of treatment. There was one death reported in a three month old infant who probably had GaD2.

The clinical evaluator was of the opinion that the AE profile identified in the Safety Specifications of the RMP was consistent with the clinical trial data submitted for evaluation.

Risk management plan

The final summary of recommendations to the Delegate from the Office of Product Review evaluator, that is, the evaluator of the RMP, is outlined in the RMP section above. It was recommended that the implementation of the RMP version 6.0, dated 23 June 2010 and any subsequent updated versions be a specific condition of registration. The latter will be a specific condition of registration imposed by the Delegate.

The RMP noted a number of considerations related to the RMP including commitments asked of the sponsor in relation to the GOS, the provision of a number of final study reports of studies yet to be completed, the supply of the document entitled '*Instructions for Collection, Preparation and Shipment of Specimens*' to any prescriber who enquires about antibody testing and the strengthening of advice in the PI concerning home infusions. The issue of home infusions was one for which the Delegate requested further information from the sponsor and for which specific advice of the ACPM was sought. The Delegate strongly endorsed all of these requests of the sponsor by the OPR and also all other requests for amendments to the PI made in the RMP evaluation. Some of them, particularly those relating to the provision of final study reports of studies still ongoing, lend themselves to being made into specific conditions of registration. The Delegate outlines later in this overview the proposed specific conditions of registration. The sponsor was requested to provide the latest information available concerning the GOS. In particular,

the Delegate wished to know whether or not participation in this survey will be open to prescribers/patients in Australia post approval.

Risk-benefit analysis

Delegate considerations

The Delegate agreed with the clinical evaluator that patients treated with VPRIV demonstrate an improvement in haemoglobin concentrations and platelet counts. There are also data showing decreases in spleen volume and to a lesser degree in liver volume. No firm conclusions can be drawn from either the QoL results or tertiary outcomes. Velaglucerase alfa and imiglucerase appeared to have similar efficacy. Whether the use of VPRIV will influence the long term prognosis of GaD is yet to be determined.

The sponsor's submission included results from 20 patients between the ages of 4 years and 17 years. Of these, 12 received VPRIV and 8 received imiglucerase. The children received the same doses as the adults in the respective studies. As noted by the evaluator, the numbers were too small to reach any conclusion about differences between children and adults treated with VPRIV. However, the Delegate would agree with the clinical evaluator that the clinical response as evidenced by the primary outcome measures was similar in both children and adults. The ACPM was asked for advice as to whether the indication should reflect the fact that there were no children below the age of 4 years in the clinical trials.

As noted by the clinical evaluator, the studies included patients with low haemoglobin concentrations, low platelet counts and hepatosplenomegaly. The Delegate agreed with the clinical evaluator that the use of VPRIV should be restricted to patients with GaD1 with at least one of these three clinical problems.

As noted by the clinical evaluator the main risk associated with the use of VPRIV is the high rate of AEs, in particular infusion reactions. The most common AE were headache, dizziness, arthralgia, bone pain, nasal congestion, hypertension, hypotension, cough, vomiting, abdominal pain and diarrhoea. One patient, previously treated with imiglucerase, withdrew due to an infusion related AE: an anaphylactoid reaction during the first infusion of VPRIV. On balance, velaglucerase was slightly less well tolerated than imiglucerase, both with regard to infusion related AE and other AE. It is important to note that the clinical evaluator did not undertake a head to head comparison of the safety data for velaglucerase versus imiglucerase. This was undertaken by the Delegate. There are limited long term safety data.

Given the high rate of infusion reactions with velaglucerase, the Delegate does have concerns about the infusion of the drug in a home setting. These have to be balanced against providing fair access to treatment. However, ultimately patient safety must be the prime consideration. First, the sponsor was requested to provide, in its pre ACPM response, detailed data about the types of settings which have been used so far for infusions of VPRIV. Included in these data must be details about the type of health professional supervision employed in each setting and the training provided to that health professional. Second, the sponsor was requested to give as much information it can about the settings envisaged for the infusion of VPRIV in the immediate post approval time period in Australia, for example for the first year. Third, the sponsor was requested to provide whatever detailed data it has in its safety database about the numbers of patients who have had or are having infusions at home, about the type of health professional supervision of infusions given in the home and about any emergency protocols and training in those protocols provided to health professionals supervising infusions in the home. These data should include information about the number of infusions given in whatever setting before the commencement of infusions in the home. Finally, the sponsor

was requested to give a detailed account of the serious adverse event experience encountered with home based infusions, particularly any serious infusion related AE involving hypersensitivity, anaphylaxis or any anaphylactoid reaction and the outcomes of all these events. Clearly, there are data available about home infusions during the clinical trials because there are brief references in the PI to the numbers of participants in certain clinical trials who received home therapy at least once. However, the Delegate requested the sponsor to provide a much more detailed summary in their pre ACPM response.

Delegate's proposed action

Overall, the Delegate agreed with the clinical evaluator that there were adequate data to support the registration of VPRIV for the treatment of GaD1. The Delegate agreed with the evaluator that velaglucerase does have a somewhat less favourable AE profile than imiglucerase and no demonstrable efficacy advantage over imiglucerase. However, at this stage, the Delegate was not convinced that the difference in AE profile between the two therapies should mean that velaglucerase should be approved only as second line choice for ERT after imiglucerase. The Delegate was inclined to leave the choice to the prescribers given the highly specialised nature of the treatment. The Delegate therefore sought the specific advice of the ACPM in this regard.

Response from Sponsor

Velaglucerase alfa (VPRIV®) is a highly purified recombinant form of the human lysosomal enzyme, glucocerebrosidase for use as a long term enzyme replacement therapy (ERT) for patients with a confirmed diagnosis of Type 1 Gaucher disease. The sponsor considers that the marketing application provided a body of clinical evidence which supports the safety and efficacy of VPRIV in patients with Type 1 Gaucher disease. VPRIV has received marketing approval for Type 1 Gaucher disease in more than 36 countries including the European Union, USA and Canada.

The Delegate asked the ACPM for advice on the following matters:

- Should VPRIV be restricted to second line ERT as recommended by the clinical evaluator? The Delegate supports the option for the prescriber to choose the best drug for their patient and does not support a second line indication for VPRIV.
- Should there be an age threshold included in the indication?
- Is there sufficient evidence /experience to support home infusion of VPRIV in patients who are tolerating their infusions well?

Proposed indication

The Delegate proposed to approve VPRIV as a first line treatment for patients with Type 1 Gaucher disease. The clinical evaluator concluded that velaglucerase alfa has a less favourable adverse event profile compared to imiglucerase and as a result recommended that velaglucerase alfa be used as second line ERT.

The sponsor believes that a first line indication for velaglucerase alfa is appropriate and that the data provided demonstrates a comparative adverse event profile of velaglucerase alfa and imiglucerase. Study HGTGCB-039, a rigorously designed, multi centred, randomised, Phase III, non inferiority clinical trial of velaglucerase alfa provides the most appropriate framework for making a meaningful comparison of the adverse event profile between the two ERTs.

A summary of adverse events considered related to study drug (velaglucerase alfa or imiglucerase) in study HGT-GCB-039, was provided while a presentation of infusion related adverse events was included in the proposed Product Information (PI).

In summary, sixteen of 17 (94.1%) patients in both treatment groups reported at least one adverse event. Based on the comparison of infusion related adverse events, the rate of infusion related reactions is similar between the two drugs and not statistically, significantly different. Five of 17 (29.4%) patients randomised to receive velaglucerase alfa and 4 of 17 (23.5%) patients randomised to receive imiglucerase reported at least one infusion related reaction. The observed difference in the proportions comparing velaglucerase alfa to imiglucerase is 5.9% and the corresponding 95% confidence interval is -23% to 33%. Specifically, none of the infusion related reactions at the preferred term level were different between the two balanced groups by more than one patient. Several of the reported terms that were raised as a concern by the clinical evaluator were reported at the same rate in the velaglucerase alfa and imiglucerase treatment arms. For example, the proportion of patients who reported at least one infusion related headache and at least one infusion related hypotension, was 2/17 (11.8%) and 1/17 (5.9%), respectively; these numbers were identical in both treatment groups. Furthermore, no patient in study HGT-GCB-039 on velaglucerase alfa indicated an adverse event as the cause of a discontinuation. However, one patient in the imiglucerase group withdrew consent due to multiple infusion related reactions.

In contrast, assessing adverse events from pooled velaglucerase alfa results with imiglucerase results from the single study HGT-GCB-039, as performed by the clinical evaluator, creates an unbalanced safety comparison.

Data from the head to head, well controlled double blind clinical study, demonstrate that the safety profile of imiglucerase and velaglucerase is similar and no difference in infusion related reactions was observed.

Age threshold in the indication

Early implementation of disease management with ERT in children may prevent, and in some cases reverse, the development of severe and irreversible long term complications attributable to Gaucher disease, including growth retardation, skeletal disease, and decreased quality of life.

The sponsor proposes that the indication for VPRIV does not need to specify any lower age limit. Instead, the sponsor has followed the Delegate's recommendation to include more information regarding demographics and disease characteristics in the Clinical Trials section of the PI. This information includes the age range for each of the studies in a clear tabular format. This tabular information is supplemented by a clearly stated summary in *Precautions: Paediatric Use*. Together these sections clearly delineate the experience in children and adolescents between 3 and 16 years of age (4 and 16 for velaglucerase alfa). This population comprises over 20% of the clinical trial experience and supports the conclusion that the safety and efficacy profile are similar between paediatric and adult patients.

The revised draft PI includes clear, concise and accurate information about the age range of patients treated in clinical studies. A lower age threshold in the indication is not needed.

Administration of home infusions

The ability to receive VPRIV at home every other week offers convenience for patients and care givers and may provide support for enhanced treatment compliance.

The development program for velaglucerase alfa offered optional home infusion of velaglucerase alfa in the Phase I/II, first in human, long term extension Study TKT025EXT and the Phase II/III, 12 month Study TKT034. In both these studies, home infusions were administered by a healthcare professional.

In Study TKT034, the first three velaglucerase alfa infusions were administered at the clinical site. Subsequently, 25 of the 40 (62.5%) treated patients received home administration at least once during the 12 month study. The first instance of home

administration occurred in Week 9 (5th infusion) in 17 of the 25 patients. Patients in TKT025EXT were also offered home administration and seven of 10 patients in this study received home administration at least once.

No patient discontinued due to an adverse event and no dose of velaglucerase alfa was altered as a result of home administration. No serious infusion related events involving hypersensitivity, anaphylaxis, or any anaphylactoid reaction were associated with a home infusion, including over 5 years exposure (to June 1, 2009) in Study TKT025EXT. In study TKT034, one drug related serious adverse event, an anaphylactoid reaction occurred on the first infusion which was administered in the clinic and the patient subsequently withdrew her consent.

It is important to note that patients eligible to receive home therapy in Study TKT034 may not have received home infusions for a variety of reasons unrelated to safety. For example, 13 patients (33%) in TKT034 received the first three in clinic infusions and never reported a serious or infusion related adverse event during the course of the study, yet never received a home infusion. Other factors, such as physician and patient preferences for home therapy and the local availability of home infusion services, influenced home therapy use. These factors were not captured in the case report forms.

In summary, no safety signals, and in particular no infusion related AE of hypersensitivity, anaphylaxis or any anaphylactoid reaction, have been reported following home infusion in the clinical trials. In postmarketing experience, no spontaneous reports have been received that suggest any safety signals or concerns following home therapy that would be different from those of the in-clinic experience.

Early transition to home administration may be considered for patients who have received at least three infusions in hospital and are tolerating their infusions well. Home infusion 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 sponsor considers that there is a favourable benefit/risk if physicians and patients wish to administer treatment with velaglucerase alfa in the home environment.

Response to other issues raised by the delegate

a) Update to registration status

VPRIV is approved in 37 countries, including the USA (Feb 26, 2010), EU (Aug 26, 2010), Canada (Oct 1, 2010) and Switzerland (Aug 29, 2011). A marketing application for VPRIV has not been submitted in New Zealand. In Switzerland, the sponsor submitted a request for a "Time-limit application" based on the EU approval of VPRIV which would allow for early access to VPRIV while the full marketing authorisation application was under active review. Swissmedic granted the sponsor a "Time limit application" due to the supply shortage constraints of Cerezyme to allow patients a viable treatment option allowing for an uninterrupted treatment of their Gaucher disease. This was approved on 4 June 2010, and would have expired on 06 May 2012. Shire received full approval for VPRIV in Switzerland on 29 August 2011.

In addition to the aforementioned registration status, velaglucerase alfa received Orphan drug designation in Australia, the USA and Japan. Orphan Drug Status was granted in the EU.

b) Changes in platelet counts

The sponsor confirms that the mean change in platelet counts queried by the Delegate actually increased at Week 41; $110.4 \times 10^9/L$ in the velaglucerase alfa group and $144.4 \times 10^9/L$ in the imiglucerase group. The observed mean change in platelet counts between the two treatment groups was not statistically significant.

c) Brief comment on specific adverse events (osteonecrosis, convulsions and thrombocytopaenia)

Major signs and symptoms of Type 1 Gaucher disease (also called non neuronopathic Gaucher disease because the central nervous system is not affected) include enlargement of the liver and spleen, anaemia, thrombocytopenia, and bone abnormalities such as bone pain, fractures, arthritis, and osteonecrosis. The neuropathic forms of Gaucher disease, Types 2 and 3, have similar signs and symptoms as Type 1 with the addition of central nervous system disease, including seizures.

Given the similarity in initial symptoms presented with Type 1 and Type 3 Gaucher patients, Type 3 patients may be initially misdiagnosed as having Type 1 Gaucher disease until CNS manifestations of disease appear. A total of two patients in the clinical development program for velaglucerase alfa experienced convulsions, neither of which were determined to be related to velaglucerase alfa treatment by the investigator. In addition, there was also a convulsion experienced by a patient treated with imiglucerase.

The presence of thrombocytopenia was one of the inclusion criteria for patient eligibility in the clinical studies of naïve patients that supported the marketing application for velaglucerase alfa. In the entire clinical development program a total of one patient treated with velaglucerase alfa experienced two serious adverse event of thrombocytopenia (039-180-0003) both of which were considered not to be related to velaglucerase alfa treatment by the investigator. Of note, a single patient randomised to the imiglucerase arm (in Study HGT-GCB-039 also experienced a similar event.

Osteonecrosis, one of the most common manifestations of Gaucher disease related bone disease, was reported as an unrelated serious adverse event in 3 patients in the clinical development program for velaglucerase alfa.

d) Clinical significant shifts in laboratory values

No laboratory results were notable in the clinical development program for velaglucerase alfa. Abnormal laboratory results were designated by the investigator as clinically significant or not clinically significant. A designation of clinically significant did not imply an intense severity, a need for concomitant therapy, a need for change in the administration of velaglucerase alfa, or that a confirmatory repeat test had been performed. Generally the term only indicated that the abnormal result was outside of expected normal variability of the laboratory test or day-to-day variability of an individual patient. These clinically significant laboratory results were to be reported as adverse events and the vast majority of these AE were considered by the investigators to be mild in severity and not related to velaglucerase alfa. The remaining laboratory related AE are summarized within 1 of 8 categories below.

Coagulation: A prolongation of aPTT is a frequent phenomenon observed in patients with Type 1 Gaucher disease.⁶ Enzyme replacement therapy may improve coagulation abnormalities in patients with Gaucher disease. At least four of eight subjects with prolonged aPTT had baseline aPTT levels that were prolonged. Seven of eight prolonged aPTT events occurred in studies outside of HGT-GCB-039 therefore a comparison to imiglucerase is not possible. No abnormal bleeding issues were noted in these patients. There was one adverse event of severe prolonged activated partial thromboplastin time (aPTT) that was considered probably related to velaglucerase alfa by the investigator. This was reported in a patient in Study HGT-GCB-039 who had an aPTT of 129.6 s in Week 41. No velaglucerase alfa doses were missed or adjusted. At the next assessment in Week 53, the aPTT was 40.9 s. This patient was still participating in the extension study as of 18 October 2011. Mild events of prolonged aPTT that were considered not related to

⁶ Hollak CE, et al. Coagulation abnormalities in type 1 Gaucher disease are due to low-grade activation and can be partly restored by enzyme supplementation therapy. *Br. J. Haematol.* 1997; 96:470-476.

velaglucerase alfa were reported for seven additional patients, five treatment naïve and two switched from imiglucerase.

Complete Blood Count: Changes in platelet counts are expected in patients with Gaucher disease. There were two patients with an event of moderate thrombocytopenia possibly related to velaglucerase alfa, one patient with severe thrombocytopenia, not related to velaglucerase alfa, one patient with a SAE of moderate thrombocytopenia with a subsequent AE of mild thrombocytopenia, both not related to velaglucerase alfa, one splenectomised patient with moderate thrombocytopenia, possibly related to velaglucerase alfa, one splenectomised patient with mild thrombocytopenia possibly related to velaglucerase alfa, and one patient with an event of moderate leukopenia that was not related to velaglucerase alfa.

Chemistry/Biochemistry: There was one patient with a mild AE of proteinaemia, possibly related to study drug.

Liver function, C reactive Protein, Iron Status and Bone Disease: All reported AE were considered mild and not related to velaglucerase alfa.

Kidney Function: No laboratory adverse events relating to kidney function were reported.

e) Information on Gaucher Disease Outcome Survey

The sponsor has developed a disease registry named the Gaucher Outcome Survey (GOS). The voluntary registry was launched first in the United States where velaglucerase alfa (VPRIV®) received its initial approval. The first patient consented to participate in GOS on 29 December 2010; currently more than 80 patients at 10 sites have elected to participate. The sponsor intends to expand participation subsequent to VPRIV approval in other countries globally including Australia.

f) Home based infusions

Please refer to additional information provided under the separate heading (“Administration of Home Infusions” above).

g) Management of infusion related reactions

The sponsor has performed a comprehensive literature search on the standard/routine medical management of infusion related reactions associated with ERT and the role of desensitisation.

Summary and conclusions

The overall clinical development program for velaglucerase alfa comprised 94 patients and was extensive given the rarity of Gaucher disease. The estimated prevalence of Gaucher disease in Australia is up to 400 patients. The studies presented in this submission have shown that velaglucerase alfa is highly effective and is generally well tolerated when administered to treatment naïve patients with Type 1 Gaucher disease as well as those previously treated with the ERT (imiglucerase). Study TKT034 demonstrated that patients who transitioned from imiglucerase to velaglucerase alfa treatment maintained clinical stability when administered velaglucerase alfa at the same dose and regimen. Of the 94 patients who received velaglucerase alfa, twenty (21%) were aged between 4 and 16. In this paediatric group, efficacy and safety data were consistent with the adult population. No gender related differences were observed.

Overall, therapy with velaglucerase alfa was generally well tolerated at an every other week dosage regimen. As with other ERTs, patients did experience one or more infusion related adverse events.

Overall, infusion related adverse events did not interfere with the patient's ability to continue velaglucerase alfa therapy. The current post marketing experience reflects that observed in clinical trials.

Home administration of velaglucerase alfa administered by qualified, trained, medical personnel has been shown to be safe. In the studies which permitted home therapy, seven of the ten patients (70%) in Study TKT025EXT and 25 of 40 (62.5%) patients in Study TKT034 received home infusions. Patients receiving home administration had received at least three infusions in a hospital clinic setting. None of the patients who elected to receive home therapy experienced an adverse event which prohibited future administrations in the home setting. Home infusions continue to provide convenience for patients and reduce the overall burden on hospital resources. Provided appropriate risk minimisation measures are in place, the sponsor considers that there is a favourable benefit/risk if physicians and patients wish to administer treatment with velaglucerase alfa in the home environment.

In conclusion, the sponsor supported the approval of VPRIV for the long term ERT for paediatric and adult patients with type 1 Gaucher disease. The sponsor considered that the legitimate concerns surrounding home infusions can be mitigated by including the proposed additional information in the Dosage and Administration section of the Product Information document.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy and safety:

- The ACPM agreed with the Delegate that clinically significant efficacy has been demonstrated, as measured by the improvement in haemoglobin concentration, platelet count and a reduction in spleen volume. The ACPM noted the small number of patients, particularly children aged between 4 and 17 years, involved in the study; however, the ACPM agreed with the Delegate that the clinical response was similar in both children and adults and it is therefore appropriate to include paediatric patients. The ACPM agreed that first line therapy was appropriate.
- In noting the risk of infusion related adverse events, the ACPM recommended treatment to be initiated in a hospital context, prior to consideration of home based administration.

Indication:

The ACPM considered this product to have a positive benefit-risk profile for the indication of:

VPRIV is indicated for long term ERT for paediatric and adult patients with Type 1 Gaucher disease associated with at least one of the following clinical manifestations:

- Anaemia
- Thrombocytopenia
- Hepato-splenomegaly.

PI/CMI:

The ACPM agreed with amendments proposed by the Delegate to the Product Information (PI) and Consumer Medicines Information (CMI) and that the changes should include:

- A statement in the Precautions section to highlight the incidence of infusion based adverse reactions.

- Information in the Dosage and Administration section to reflect use in children age 4 to 17 years.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for VPRIV would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of VPRIV powder for solution for infusion vials containing velaglucerase alfa ghu 400 units, indicated for:

Long-term enzyme replacement therapy for paediatric and adult patients with Type 1 Gaucher disease associated with at least one of the following clinical manifestations: anaemia, thrombocytopenia, hepato-splenomegaly.

Specific conditions of registration applying to these therapeutic goods:

1. **Batch Release Testing:** It is a condition of registration that the first five independent batches of VPRIV velaglucerase alfa (ghu) 400 U vials imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).
2. The full implementation of the Risk Management Plan version 6.0, dated 23 June 2010 and any subsequent updated & approved versions.
3. That if the Gaucher Disease Outcome Survey (GOS) is open to prescribers/patients in Australia post-approval of VPRIV in Australia, then the sponsor must ensure that there are adequate processes implemented to support patient enrolment OR if the Gaucher Disease Outcome Survey (GOS) is not open to prescribers/patients in Australia post-approval of VPRIV in Australia, then the sponsor must design and implement, in consultation with the TGA, active safety monitoring of VPRIV prescribed in Australia, such monitoring to include, for example, active surveillance at selected sentinel sites or the formation of an Australian-specific treatment registry.
4. The sponsor must, as part of its educational programme for health care professionals, make the latter aware of the existence of the document entitled '*Instructions for collection, preparation and shipment of Lab specimens*' and supply the document to any prescriber who enquires about any laboratory testing in relation to velaglucerase, including the testing for antibodies.
5. The sponsor must ensure that there are in place adequate and appropriate protocols and training for any healthcare professional involved in the home administration of velaglucerase alfa and that these protocols have been viewed by the Office of Product Review of the TGA.
6. The sponsor must provide, as evaluable data within the context of Category 1 submissions, all interim and final study reports, not already provided, for each of the following studies as soon as they become available:
 - Study TKT025EXT,
 - Study HGT-GCB-044,
 - Study HGT-GCB-058,
 - Study HGT-GCB-068 and

- The Gaucher Disease Outcome Survey

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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