PUBLIC SUMMARY DOCUMENT
Product: Velaglucerase alfa, powder for IV infusion, 400 units in 4 mL, VPRIV®
Sponsor: Shire Australia Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

To request inclusion on the Life Saving Drugs Program (LSDP) for the treatment of type 1 Gaucher disease in a patient who meets certain criteria.

Through the LSDP, the Australian Government provides subsidised access, for eligible patients, to expensive and potentially life saving drugs for very rare life-threatening conditions. Before a drug is made available on the LSDP, it must generally be accepted by the Pharmaceutical Benefits Advisory Committee as clinically necessary and effective, but not recommended for inclusion on the Pharmaceutical Benefits Scheme due to unacceptable cost-effectiveness.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

On 29 February 2012, velaglucerase was registered by the TGA for the following indication:

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

4. Listing Requested and PBAC's View

The submission sought a recommendation from the PBAC that velaglucerase be included in the LSDP for the treatment of type 1 Gaucher disease, under the same conditions as imiglucerase.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Gaucher disease is a rare condition caused by the inherited deficiency of an enzyme, glucocerebrosidase, which is required for the breakdown of a specialised lipid, called glucocerebroside. Glucocerebroside accumulates in the lysosomes of predominantly monocyte and macrophage cells particularly in the liver, spleen and bone marrow. This accumulation of undegraded glucocerebroside can result in a spectrum of symptoms, from mild to severe. Clinical manifestations of the disease include spleen and liver enlargement, bone marrow infiltration causing anaemia, and skeletal involvement causing bone pain and fracture.

There are three forms of Gaucher disease, characterised by the absence (Type 1) or presence (Types 2 and 3) of central nervous system (CNS) involvement. These three forms have also been labelled as adult (Type 1), infantile (Type 2) and juvenile (Type 3), based on the usual age of presentation of the disease.

The submission proposed that the place in therapy of velaglucerase was an alternative enzyme replacement therapy to imiglucerase for the treatment of paediatric and adults patients with type 1 Gaucher disease.

6. Comparator

The submission nominated imiglucerase as the comparator.

The PBAC agreed that imiglucerase was the appropriate comparator as it is the product most likely to be replaced in clinical practice.

7. Clinical Trials

The key study included in the submission was a head-to-head trial of velaglucerase 60 U vs. imiglucerase 60 U (HGT-039).

The submission also included three supportive studies: a randomised trial of velaglucerase 60 U vs. velaglucerase 45 U (TKT-032), a non-randomised study of patients switching from imiglucerase to velaglucerase (TKT-034), and a non-randomised study of the long-term safety and efficacy of velaglucerase treatment (TKT-025).

The following trials had been published at the time of submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Randomised trials		
HGT-039	A multicenter, randomized, double-blind, parallel-group study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) enzyme replacement therapy compared with Imiglucerase in patients with Type I Gaucher disease.	Shire clinical study report (October 2009)[a].
TKT-032	A multicenter, randomized, double-blind, parallel group, two-dose study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) enzyme replacement therapy in patients with Type 1 Gaucher disease.	Shire clinical study report (July 2009) [a].
Non-randomised studies		
TKT-034	A multicenter open-label study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) enzyme replacement therapy in patients with Type 1 Gaucher disease previously treated with Imiglucerase	Shire clinical study report (August 2009) [a].
TKT-025		
Zimran et al (2007)	A pharmacokinetic analysis of a novel enzyme replacement therapy with Gene-Activated® Human Glucocerebrosidase (GA-GCB) in patients with Type 1 Gaucher disease	Blood Cells, Molecules, and Diseases 39(1): 115-118
Zimran et al (2010)	Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with Type 1 Gaucher disease: 48-month experience	Blood 115(23): 4651-4656
Elstein et al (2011a)	Significant and continuous improvement in bone mineral density among type 1 Gaucher disease patients treated with velaglucerase alfa: 69-month experience, including dose reduction	Blood Cells, Molecules, and Diseases 47(1): 56-61
Elstein et al (2011b).	Early achievement and maintenance of the therapeutic goals using velaglucerase alfa in Type 1 Gaucher disease	Blood Cells, Molecules, and Diseases 46(1): 119-23.

[a] Study results are publicly available on the ClinicalTrials.gov website

8. Results of Trials

The HGT-039 trial was designed to demonstrate that velaglucerase alfa is non-inferior to imiglucerase in terms of maintaining haemoglobin concentration.

The key results for the primary outcome of the HGT-039 trial are summarised in the table below.

Primary outcome (change in haemoglobin concentration) of the HGT-039 trial

Outcome	Velaglucerase (N = 17)	Imiglucerase (N = 17)
Mean change in Hb concentration from baseline		
Baseline Hb concentration (g/dL) [mean, SE]	11.51 (0.30)	10.46 (0.33)
Final Hb concentration (g/dL) [mean, SE]	13.14 (0.36)	11.95 (0.28)
Change for baseline (g/dL) [mean, SE]	1.62 (0.22)	1.49 (0.28)
Treatment difference (g/dL) [mean, 97.5% CI]	0.135 (-0.596, inf)	

Abbreviations: Hb, haemoglobin; inf, infinity; SE, standard error
Note: Difference in Hb concentration treatment effect > 0 favours velaglucerase

There was no statistically significant difference between treatment arms in the mean change in haemoglobin concentration from baseline. The lower bound of the treatment effect confidence interval (-0.596 g/dL) met the pre-defined non-inferiority criterion (lower 97.5% CI should not exceed -1g/dL).

Key secondary outcomes of the HGT-039 trial included a responder analysis based on the minimum clinically meaningful change in haemoglobin concentration, platelet count, liver volume, and spleen volume.

Velaglucerase and imiglucerase appear to be associated with similar improvements in measures of disease burden.

Study TKT-032 was a randomised, controlled trial evaluating the efficacy and safety of two different doses of velaglucerase (45 U/kg and 60 U/kg) in Type 1 Gaucher disease. Both doses were associated with improvements in disease burden measures (particularly haemoglobin concentration and spleen volume) with the results generally favouring the 60 U/kg dose. However, the lack of statistical comparisons between treatment groups limited any formal assessment of a dose response relationship.

Study TKT-034 was a non-randomised study evaluating the efficacy and safety of patients switching from imiglucerase to velaglucerase. All patients were required to have received consistent treatment with imiglucerase for a minimum of 30 consecutive months. Patients were switched to a velaglucerase maintenance dose that was the same as previous imiglucerase maintenance dose.

Patients switching from imiglucerase to velaglucerase appeared to maintain constant haemoglobin concentrations over time. Similar results were also observed in terms of platelet counts, liver volumes and spleen volumes. Maintenance of treatment effect was observed in all dose cohorts (15, 30, 45 and 60 U/kg).

Study TKT-025 was a non-randomised study evaluating the long-term efficacy and safety of velaglucerase alfa treatment. Patients treated in the TKT-025 study (and extension) received up to five years of therapy. The majority of patients enrolled in the TKT-025 extension study had their velaglucerase dose titrated down from 60 U/kg to 30 U/kg every two weeks after successfully meeting therapeutic goals. Results from the study show that patients were able to maintain initial improvements in disease burden measures for up to five years.

Velaglucerase and imiglucerase appear to have similar safety profiles when used at a dose of 60 U/kg every two weeks. The most frequently reported adverse events in the HGT-039 trial were influenza, arthralgia, pyrexia, nasopharyngitis, headache, rhinitis, diarrhoea, peripheral oedema, bone pain and upper abdominal pain.

Drug-related adverse events were reported by eight (47.1%) patients in the velaglucerase treatment group. Two of these events were classified as severe (allergic skin reaction, prolonged activated partial thromboplastin time (aPTT)). Drug-related adverse events experienced by more than one patient in the velaglucerase treatment arm included headache and urticaria.

Drug-related adverse events were also reported by 6 (35.3%) patients in the imiglucerase treatment group. One of these events was classified as severe (chills/rigours). Headache was the only drug-related adverse events experienced by more than one patient in the imiglucerase treatment arm.

Drug-related adverse events associated with velaglucerase treatment in the supportive TKT-032, TKT-034 and TKT-025 studies included: arthralgia, back pain, dizziness, fatigue, headache, hypertension, hypotension, malaise, nausea, pain in the extremity, petechiae and tremor.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described velaglucerase (60 U/kg every two weeks) as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety to imiglucerase (60 U/kg every two weeks).

Based on the surrogate measure of disease burden outcomes presented in the submission, the PBAC concluded that velaglucerase may be non-inferior to imiglucerase in terms of comparative effectiveness and equivalent in terms of comparative safety, pending a final decision from the TGA.

10. Economic Analysis

The submission presented a cost-minimisation analysis of velaglucerase compared to imiglucerase.

The submission claimed that the dose relativity of velaglucerase to imiglucerase is 1 U/kg to 1 U/kg.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated by the submission to be less than 100 patients in Year 5. The estimate is uncertain.

The financial cost/year to the PBS was estimated by the submission to be nil. The submission claimed that the listing of velaglucerase is not expected to increase the cost of treating Type 1 Gaucher disease under the LSDP based on the assumption that all patients who will be treated with velaglucerase would have otherwise received imiglucerase. The submission therefore assumed that the costs of listing velaglucerase are completely offset by the reduced usage of imiglucerase.

12. Recommendation and Reasons

The PBAC agreed that imiglucerase was the appropriate comparator as it is the product most likely to be replaced in clinical practice.

The PBAC noted that the key study (HGT-039 trial) presented in the submission was designed to demonstrate that velaglucerase alfa is non-inferior to imiglucerase in terms of maintaining haemoglobin concentration. The PBAC noted that there was no statistically significant difference between treatment arms in the mean change in haemoglobin concentration from baseline, the primary outcome. The lower bound of the treatment effect confidence interval (-0.596g/dL) met the pre-defined non-inferiority criterion (lower 97.5% CI should not exceed -1g/dL). The PBAC agreed that the chosen non-inferiority margin is reasonable.

The PBAC noted that the key secondary outcomes of the HGT-039 trial included a responder analysis based on the minimum clinically meaningful change in haemoglobin concentration, platelet count, liver volume, and spleen volume. The PBAC considered that velaglucerase and imiglucerase appear to be associated with similar improvements in measures of disease burden.

The PBAC noted that velaglucerase had not yet been approved by the TGA and therefore could not make a decision on its place in therapy.

Based on the surrogate measure of disease burden outcomes presented in the submission, the PBAC concluded that velaglucerase may be non-inferior to imiglucerase in terms of comparative effectiveness and equivalent in terms of comparative safety, pending a final decision from the TGA. The Committee considered that velaglucerase and imiglucerase appear clinically equi-effective at a 1:1 dose ratio, although data investigating the comparative effectiveness of velaglucerase and imiglucerase at other relative doses in this patient population are not available.

The PBAC noted that due to the probable high cost of velaglucerase (even if at a significant discount to imiglucerase), it would not be considered cost effective for listing on the PBS and hence proceeded to consider the possible inclusion of velaglucerase on the LSDP. The PBAC noted that this was a necessary prerequisite under the LSDP criterion 5.

The PBAC considered that if the TGA recommends velaglucerase as an alternative first line ERT, and non-inferiority versus imiglucerase is accepted, there is an inherent acceptance, based on equivalence with imiglucerase, that velaglucerase meets the criteria for the funding of a drug through the LSDP, in particular criterion 4: “There is evidence acceptable to the

PBAC to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug." This would not be the case if velaglucerase was approved for second line therapy.

Given that is unclear whether velaglucerase will be used in the first or second-line setting, pending finalisation of the TGA recommendation, the PBAC considered that it is difficult to make a recommendation whether a cost-minimisation approach might be acceptable for listing on the LSDP. If velaglucerase is approved by the TGA for use in the first-line setting then a cost-minimisation approach might be acceptable. However, given that cost-effectiveness is not a criterion for the LSDP, the PBAC noted that the implementation of a cost-minimisation approach might be different than applies for the PBS and a net cost saving as offered by the sponsor would be more appropriate. Further, the PBAC considered that, if approved for use as a second-line agent, then a different approach might be necessary.

The PBAC therefore deferred its decision on the submission for velaglucerase on the LSDP pending the finalisation of the TGA's evaluation which will determine the place in therapy of velaglucerase.

Recommendation:
Defer

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment – November 2011

Shire looks forward to working positively with the PBAC to allow patients access to this treatment in Australia.

ADDENDUM

Product: Velaglucerase alfa, powder for IV infusion, 400 units in 4 mL, VPRIV®
Sponsor: Shire Australia Pty Ltd
Date of PBAC Consideration: March 2012

Purpose of Application:

The resubmission sought inclusion on the Life Saving Drugs Program for the treatment of type 1 Gaucher disease.

Summary of Resubmission:

No changes were made to the original submission in relation to Sections A – E. This minor resubmission provided updated information from the TGA on the regulatory status of velaglucerase alfa.

The resubmission stated that the recommendation of the TGA Delegate and the Advisory Committee on Prescription Medicines (ACPM) that first line use of velaglucerase is

appropriate, was in line with the place in therapy proposed in the November 2011 submission.

Recommendation and Reasons:
In November 2011, the PBAC deferred making a recommendation pending the finalisation of the TGA's evaluation which would determine the place in therapy of velaglucerase alfa. The PBAC noted that in December 2011, the ACPM recommended approval of velaglucerase alfa for the treatment of type 1 Gaucher disease in paediatric and adult patients and recommended approval for use in the first-line setting as an alternative to imiglucerase.

In regard to the determination of equi-effective doses, at its November 2011 PBAC meeting the PBAC "considered that velaglucerase alfa and imiglucerase appear clinically equi-effective at a 1:1 dose ratio, although data investigating the comparative effectiveness of velaglucerase alfa and imiglucerase at other relative doses in this patient population are not available".

The PBAC noted that Study TKT034 investigated switching from imiglucerase to velaglucerase alfa in which 40 patients received a dose of velaglucerase alfa identical to the most recent dose of imiglucerase (ranging 15 – 60U/kg). Both the TGA Clinical Evaluator and the Delegate agreed there was no deterioration following the switch (and some measures improved). The PBAC noted the Delegate's conclusion that "there were only small changes in the outcome measures".

The PBAC noted that to be eligible for the LSDP the drug must be accepted as clinically effective, but rejected for Pharmaceutical Benefits Scheme (PBS) listing because it fails to meet the required cost effectiveness criteria (criterion 5 of the LSDP). The PBAC considered that velaglucerase alfa was clinically effective but failed to meet the required cost effectiveness criteria.

However, the PBAC considered that velaglucerase alfa meets all the criteria for inclusion on the LSDP, and recommended that it is suitable for the Government to consider for inclusion on the LSDP.

In making this recommendation the PBAC noted the consumer comments on this item.

Recommendation
Reject

15. Sponsor's comment – March 2012

Shire Australia welcomes the PBAC decision that velaglucerase alfa has met all the criteria for inclusion on the Life Saving Drugs Program (LSDP). Shire looks forward to working with the LSDP to ensure that velaglucerase alfa is made available to eligible Gaucher Disease patients in Australia as soon as possible.