

PUBLIC SUMMARY DOCUMENT

Product: TALIGLUCERASE ALFA, powder for I.V. infusion, 200 units, Elelyso®

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) listing or inclusion on the Life Saving Drugs Program (LSDP) for the long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

Through the Life Saving Drugs Program (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

Taliglucerase was TGA registered on 21 May 2014 for the following indication:

“long-term enzyme replacement therapy for adult and paediatric patients with a confirmed diagnosis of Type 1 Gaucher disease associated with at least one of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopenia.”

4. Listing Requested and PBAC’s View

Section 100 (Highly Specialised Drugs Program)

Private Hospital Authority Required

Public Hospital Authority Required (STREAMLINED)

Long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease.

The PBAC did not comment on the proposed restriction.

5. Clinical Place for the Proposed Therapy

Gaucher disease is a rare and inherited condition caused by mutations in the human glucocerebrosidase gene leading to reduced activity of the lysosomal enzyme glucocerebrosidase and thereby to the accumulation of substrate glucocerebroside in the cells of the monocyte-macrophage system. This accumulation leads to the visceral manifestations

of hepatosplenomegaly, anaemia and thrombocytopenia, skeletal features and less frequently lung involvement.

There are three types of Gaucher disease, characterised by the absence (Type 1) or presence (Types 2 and 3) of central nervous system involvement.

The submission proposed that the place in therapy of taliglucerase alfa is as an alternative enzyme replacement therapy to imiglucerase for the treatment of Gaucher disease.

6. Comparator

The submission nominated imiglucerase as the main comparator.

For PBAC's view, see Recommendation and Reasons

7. Clinical Trials

The basis of the submission was ten randomised and non-randomised trials of taliglucerase (PB-06-001, PB-06-002, PB-06-003, PB-06-004 and PB-06-005) and imiglucerase (Elstein et al 2007, De Fost et al 2007, Schiffmann et al 2002, Grabowski et al 1995 and Sims et al 2008) for the treatment of Gaucher disease.

Details of the trials published at the time of the submission are in the table below.

Clinical studies included in the submission

Trial ID/First author	Protocol title/ Publication title	Publication citation
Taliglucerase randomised trials		
PB-06-001 Zimran et al (2011).	Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease.	Blood 118: 5767-5773
Imiglucerase randomised trials		
Elstein et al (2007)	Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement.	Blood 110: 2296-2301
De Fost et al (2007)	Low frequency maintenance therapy with imiglucerase in adult type I Gaucher disease: a prospective randomized controlled trial.	Haematologica 92: 215-221
Schiffmann et al (2002)	Decreased bone density in splenectomized Gaucher patients receiving enzyme replacement therapy.	Blood Cells, Molecules, and Diseases 28: 288-296.
Grabowski et al (1995)	Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. Genzyme Corporation (2005). Protocol RC 91-0110: An Evaluation of the Safety and Effectiveness of Recombinant, Human, Macrophage-Targeted β -Glucocerebrosidase.	Annals of Internal Medicine 122: 33-39 Genzyme clinical research website

	Genzyme Corporation (2005). Protocol RC 92-0501: An Extended Evaluation of the Safety and Effectiveness of Recombinant, Human-derived, Macrophage-Targeted β Glucocerebrosidase in Patients with Gaucher disease.	Genzyme clinical research website
Imiglucerase non-randomised studies		
Sims et al (2008)	Improvement of bone disease by imiglucerase (Cerezyme) therapy in patients with skeletal manifestations of type 1 Gaucher disease: results of a 48-month longitudinal cohort trial.	Clinical Genetics 73: 430-440
Systematic review		
Connock (2006)	Connock et al (2006). The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review	Health Technology Assessment 10: No. 24

Note: the publication by Zimran et al (2011) was identified during the evaluation

The PBAC noted that the submission excluded Trial NCT00553631 – (A Multicentre, Randomised, Double-Blind, Parallel Group Study of Gene Activated Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy Compared with Imiglucerase in Patients with Type 1 Gaucher Disease – www.clinicaltrials.gov (also known as HGT-039)) from the analysis based on the data being unpublished, however the results were available during the evaluation and as this was considered a key study for the comparison of taliglucerase alfa to imiglucerase, the results were included in the evaluation.

For PBAC's view, see Recommendation and Reasons

8. Results of Trials

For four key outcomes of percentage reduction in spleen and liver volumes, increases (g/dL) in haemoglobin concentration and improvements in platelet counts ($\times 10^9/L$), the results for mean change from baseline to 9 months suggested comparable improvements in spleen volume, haemoglobin concentration and platelet counts between taliglucerase and imiglucerase. Reductions in liver volume were larger for imiglucerase than taliglucerase alfa. The results from the HGT-039 trial showed reductions in spleen volume of around 55% for imiglucerase and reductions of liver volume around 25-30%.

While the PB-06-001 trial demonstrated that both taliglucerase alfa treatment arms were associated with improvements in disease burden measures, the results were generally better with 60 U/kg dose compared to 30 U/kg dose.

Responder analyses were conducted during the evaluation. The results suggested similar levels of response between taliglucerase alfa and imiglucerase in spleen volume, haemoglobin concentration and platelet counts. Comparability of response rates was hampered by the substantially different estimates of treatment effect in the two imiglucerase studies.

The results of study PB-06-002 suggested that for most patients, following switching to taliglucerase alfa, mean spleen volume, mean haemoglobin concentration, mean liver volume and mean platelet counts all remained stable over the course of 9 months.

The results of the extension study PB-06-003, suggested that mean spleen volume, mean haemoglobin concentration, mean liver volume and mean platelet counts remain stable or continue to improve with ongoing taliglucerase alfa treatment over two years.

For PBAC's view, see Recommendation and Reasons

The most frequently reported adverse events in the included taliglucerase studies were headache, pruritis, hypersensitivity, throat irritation, infusion-related reaction, erythema and flushing. Approximately 5% of patients (5/121) discontinued treatment due to an adverse event (primarily hypersensitivity/allergic reactions).

The PBAC noted that enzyme replacement therapy for Gaucher disease may be associated with the development of IgG antibodies, although the clinical importance of this outcome is unclear. Results from trial HGT-039 suggested that there may be cross-reactivity between imiglucerase and velaglucerase antibodies. This may mean that some patients who have sensitivity issues to imiglucerase could also have sensitivity issues with velaglucerase alfa and vice versa. It is unclear whether there is any cross-reactivity between imiglucerase and taliglucerase alfa antibodies.

No Periodic Safety Update Report (PSUR) for taliglucerase alfa was available, as the treatment is yet to be approved for use in any country.

For PBAC's view, see Recommendation and Reasons

9. Clinical Claim

The submission described taliglucerase alfa as similar to imiglucerase in terms of comparative efficacy. The submission did not make a specific claim related to the comparative safety of treatments due to the limited body of evidence available.

For PBAC's view, see Recommendation and Reasons

10. Economic Analysis

The submission presented a simple non-comparative cost-per-outcome analysis of taliglucerase alfa.

The cost per unit gained varied considerably across outcomes and patient populations. The results of the sensitivity analyses indicated that the economic evaluation was sensitive to uncertainty regarding dose, patient weight, magnitude of outcome change and the requested price of taliglucerase alfa.

Given the high cost of taliglucerase, the PBAC considered it unlikely that taliglucerase alfa would be considered cost-effective.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net cost saving to the PBS in year 5 of listing.

For PBAC's view, see Recommendation and Reasons

12. Recommendation and Reasons

The PBAC noted that this submission is being considered under the TGA/PBAC parallel process and that neither the TGA Clinical Evaluator's Report nor the Delegate's Summary had been received. The PBAC considered that these documents would have informed the discussion regarding uncertainties about the clinical place of taliglucerase alfa, in terms of treatment of patients outside of Type 1 Gaucher disease, and the clinical effectiveness and safety of taliglucerase alfa.

The nominated comparator of imiglucerase was considered appropriate by the PBAC. However, the PBAC also noted the potential of velaglucerase alfa as a comparator, as an alternative enzyme replacement therapy in the treatment of Type 1 Gaucher disease.

The PBAC noted that no direct trials comparing taliglucerase alfa and imiglucerase in Gaucher disease were identified. Instead, the basis of the submission was a comparison of results from single arms of several randomised and non-randomised studies, of which study PB-06-001 was considered the pivotal taliglucerase alfa study and Grabowski (1995) the pivotal imiglucerase study. The PBAC noted that the submission excluded Study HGT-039 from the analysis based on the data being unpublished, however the results were available during the evaluation and as this was considered a key study for the comparison of taliglucerase alfa to imiglucerase the results were included in the evaluation. The main outcomes examined by these studies were reductions in spleen volume, liver volume and improvements in haemoglobin concentration and platelet counts. The PBAC noted that none of the studies included a placebo arm.

The PBAC considered it difficult to make any meaningful assessment of the data presented due to the lack of head-to-head data and the inability to perform a formal indirect comparison as there was no common reference. The PBAC acknowledged the difficulty in performing a head-to-head study in a rare disease such as Gaucher but noted that it is possible, as evidenced by the availability of trial HGT-039, and that head-to-head data would be preferable for decision making.

The PBAC noted that despite study PB-06-001 demonstrating that taliglucerase alfa is associated with improvements in disease burden measures such as spleen volume, haemoglobin concentration, liver volume and platelet counts, no data were available assessing benefits of treatment with taliglucerase alfa in terms of survival or quality of life in Gaucher disease patients. The PBAC further noted that HGT-039 and the single arm result comparisons of studies PB-06-001 and Grabowski (1995) suggest that improvements in spleen volume, haemoglobin concentration and platelet counts may be broadly similar between taliglucerase alfa and imiglucerase. However, reported results for liver volume appear to favour imiglucerase. In regards to patients switching from imiglucerase to taliglucerase alfa, the PBAC noted that individual patient data, from the PB-06-002 switching study, suggests that a small percentage of patients showed some signs of clinical deterioration at 9 months after being switched from imiglucerase to taliglucerase alfa.

Based on the data presented, the PBAC did not accept the submission's clinical claim that taliglucerase alfa is similar to imiglucerase in terms of comparative effectiveness. With regards to whether taliglucerase alfa and imiglucerase are similar in terms of safety, the PBAC considered this also remains uncertain, given the limited body of evidence available.

The PBAC noted that the submission presented a simple non-comparative cost-per-outcome analysis with taliglucerase alfa treatment and given the high cost of taliglucerase, considered it unlikely that taliglucerase alfa would be considered cost-effective. The submission assumed that most patients on the Life Savings Drugs Program (LSDP) are treated with imiglucerase 60 U/kg however the PBAC noted that a review of the LSDP (Goldblatt 2005) indicated that the majority of patients (98%) are treated with doses lower than 60 U/kg per fortnight. The PBAC considered that these lower doses would need to be accounted for in determining equivalent treatment costs.

The PBAC therefore rejected the submission on the basis of uncertain clinical effectiveness, unknown equi-effective doses and unknown interchangeability. The PBAC indicated that any future consideration of taliglucerase alfa should include relevant TGA documentation.

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

The PBAC noted that the submission meets the criteria for an Independent Review in relation to the decision to not recommend listing on the PBS. The PBAC noted that its decision not to recommend inclusion on the LSDP is not subject to Independent Review.

The PBAC noted the advice of the Highly Specialised Drugs Working Party.

Recommendation:

Reject

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

Pfizer Australia remains committed to working with the PBAC and LSDP to resolve the issues and ensure that Australia Gaucher disease patients have access to this medication.