PUBLIC SUMMARY DOCUMENT

Product: Alglucosidase alfa-rch, powder for I.V. infusion, 50 mg, Myozyme®
Sponsor: Genzyme (Sanofi-Aventis Australia Pty Ltd)
Date of PBAC Consideration: March 2013

1. Purpose of Application

To provide the PBAC with additional data to demonstrate that alglucosidase alfa meets criterion 4 of the Life Saving Drugs Program (LSDP) for the treatment of patients with late-onset Pompe disease.

Life Saving Drugs Program:
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 was the seventh time the PBAC has considered alglucosidase for the treatment of late onset Pompe disease. Alglucosidase alfa had previously been considered in July 2008, March 2009, November 2009, November 2010, July 2011 and November 2012. Details of these considerations are in the relevant Public Summary Documents available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product

Treatment with alglucosidase alfa for the infantile-onset variant of Pompe disease was recommended by the PBAC in July 2008 and has been subsidised through the LSDP since February 2010.

3. Registration Status

Alglucosidase alfa was TGA registered on 14 March 2008 for the long-term treatment of patients with a confirmed diagnosis of Pompe disease (acid alfa-glucosidase deficiency).

4. Listing Requested and PBAC's View

The re-submission sought a recommendation from PBAC that alglucosidase alfa be included in the LSDP for the treatment of late onset Pompe disease. The sponsor did not propose wording for a PBS listing.

The draft guidelines for the treatment of patients with late-onset Pompe disease, developed by the Australasian Society for Inborn Errors of Metabolism (ASIEM) and the Australia New Zealand Association of Neurologists (ANZAN) were presented by the sponsor as follows:

Initial Treatment Criteria

Patients with a diagnosis of Pompe based on enzymology OR mutational analysis AND clinical features of juvenile or late- onset.

Pompe disease fulfilling the following criteria will be recommended to start treatment with enzyme replacement therapy (Myozyme).

1) Impaired respiratory function as indicated by any one of:
   a. <80% predicted supine forced vital capacity (FVC) (the most sensitive noninvasive measure of diaphragmatic weakness),
   b. <80% predicted maximal inspiratory pressure (MIP) or maximal expiratory pressure (MEP), or
   c. Significant nocturnal respiratory compromise as demonstrated by a sleep study. Patients with an apnoea/hypopnea index of > 5 events/hour of total sleep time or more than 2 severe episodes of desaturation (oxygen saturation <80%) in an overnight sleep study.
   OR
2) Significant muscular weakness as evidenced by manual muscle testing (MMT) (employing the MRC score) of 4 or less in either limb girdle AND a significant change in functional tests from baseline (depending on age and applicability – 6MWT, NSAA, Timed "up and go" and "stair climb"). Timed tests will be videoed for review.

Treatment will be authorised initially for 12 months in the first instance until review to ascertain stabilisation in disease (see continuation and discontinuation of therapy).

Exclusion Criteria

1. Patients who are invasive ventilator dependent at the time of the application
2. Patients who become unresponsive to therapy despite all reasonable support therapy including patients who develop irreversible or untreatable complications of the disease may be withdrawn from therapy. This includes patients who become invasive ventilator dependent during therapy.
3. Patients will be withdrawn or not be given authorisation for treatment if they fail to comply with the requirements of the LSDP
4. Patients may be withdrawn from therapy if there are severe adverse events to treatment and those events are unresponsive to standard therapies for immune or other reactions
5. Patients who have another life threatening or severe disease or develop such a disorder while on therapy
6. Current smoker

Continuation Criteria

1. The Patient will be examined at 6 months after the start of treatment and at 12 months after the start of treatment, and then yearly thereafter.
2. At the 12-month examination the baseline evaluations including MRI scans will be repeated and continuation of treatment will be recommended if the patient shows an improvement, stabilisation of their respiratory function or muscle function, or a substantial reduction in the slope of deterioration as ascertained by timed testing

3. Should the test not show improvement or stabilisation or a substantial reduction in the slope of deterioration as ascertained by timed testing in either respiratory or muscle function then it is recommended that the testing be undertaken again after one month to ensure consistency of testing. If after review, there is again no evidence of efficacy, treatment will be discontinued.

Discontinuation Criteria
In general terms, the reasons for consideration of cessation of specific treatment will include:

1. Intolerable and unavoidable adverse effects.
2. Failure to observe improvement or stabilisation or a substantial reduction in the slope of deterioration as ascertained by timed testing after 12 months of monitoring
3. Intercurrent illness, especially where long-term quality of life or expected survival is such that the patient is likely to gain no significant benefit from the specific treatment for acid-maltase deficiency.
4. Lack of responsiveness to treatment having taken all appropriate measures to improve effectiveness. It is expected that the treatment will result in improvement and/or stabilization or a substantial reduction in the slope of deterioration of the condition.
5. At the request of the patient certified to be of sound mind, or of a properly allocated guardian acting in the patient's best interests, if the patient is deemed not to be competent.
6. If the circumstances of the patient's lifestyle is such that sufficient compliance with treatment and the schedule of monitoring assessment is not possible.
7. If the health and well-being of medical or nursing staff is placed under significant threat as a result of the actions or lifestyle of the patient.
8. Emigration of the patient outside the jurisdiction of the Life Saving Drugs Program.

The PBAC noted that the draft guidelines by ASIEM and ANZAN did not provide definitions for "improvement" or "stabilisation" of respiratory function or muscle function, or "substantial reduction" in the slope of deterioration as ascertained by timed testing, to enable an objective, independent assessment of whether treatment had been effective.

The draft guidelines did not provide information on the dose of alglucosidase alfa to be used for treatment. The PBAC noted that the only dose approved by the Therapeutic Goods Administration (TGA) is for 20mg/kg/fortnight by intravenous infusion. The sponsor stated that the 40mg/kg/fortnight is not an approved dose for the treatment of Pompe disease and is currently not supported by a significant evidence base. The sponsor also stated that no Australian patients are expected to receive this higher dose either now or in the future.

5. Clinical Place for the Proposed Therapy

Pompe disease is an inherited disorder caused by a lack of the enzyme acid alfa-glucosidase. This results in an accumulation of glycogen, impairing the function of muscle tissues. Clinically, Pompe patients experience progressive muscle weakness and often death from respiratory and/or cardiac failure secondary to glycogen accumulation in cardiac, respiratory and skeletal muscle tissue.

Pompe disease encompasses a single disease continuum and presents in a spectrum of patients characterised by the amount of enzyme activity present. On one end, patients with low or absent enzyme activity (Infantile-onset) present within a few months of birth with rapidly progressive disease. On the other end, patients with some residual enzyme activity (Late-onset) present later in life with less rapid but steadily progressive disease.

Alglucosidase alfa is an enzyme-replacement therapy for patients with Pompe disease.

6. Comparator

The submission nominated standard (palliative) therapy including intensive respiratory support, cardiac care, dietary therapy and rehabilitative services, as the main comparator. This is unchanged from November 2012. The PBAC has previously considered this appropriate.

7. Clinical Trials

No new data were presented in the re-submission.

The re-submission again presented updated survival data and additional analyses of the data from the Erasmus Medical Centre (EMC)/International Pompe Association (IPA) Pompe survey, based on a draft publication (submitted for publication but not yet published at the time of PBAC consideration) by Güngör and colleagues. The analysis presented in the re-submission has subsequently been published as follows:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Güngör D, et al	Impact of enzyme replacement therapy (ERT) on survival in adults with Pompe disease: results from a prospective international observational study.	*Orphanet J Rare Dis.* 2013 Mar 27;8(1):49.

8. Results of Trials

In paragraph 2 of the discussion of the Güngor article the authors' state: "Because of the time-dependent nature of the analysis it was not possible to estimate the additional years of life gained under enzyme replacement therapy (ERT). However, we have made 'ad hoc' calculations assuming the adjusted HR can be interpreted as a relative risk over approximately 4 years median and 8 years maximum follow-up (from start of treatment). Using the overall raw death rate as an estimate of the raw death rate of the treated population (16%, 46/283), eight years of ERT would result in 1 year of life gained."

Based on the EMC/IPA survey the sponsor, in consultation with the EMC/IPA study's authors, estimated that one life year is gained for every four years of treatment with alglucosidase alfa, taking into consideration adjustments for potential confounders (i.e. prognostic variables). The PBAC noted that the main analysis of the sponsor's previous submission obtained a hazard ratio (HR) of 0.41 (95% CI 0.19 to 0.87, p=0.02).

The PBAC accepted the sponsor's statement that "quantification of survival gain after only short-term follow-up (average of 4 years of treatment) is extremely challenging" and noted the description of the methods for quantification of the survival gain. However, the PBAC noted a lack of transparency around the statistical derivation of the sponsor's claims of 1 life year gained for 4 years of treatment. The PBAC noted that the confidence interval provided

in this submission for the arithmetic measure of the treatment effect (0.5 years to 1.5 years) seemed implausibly narrow and symmetrical. The PBAC calculated that when the 95% limits of the HR (0.19, 0.87) were applied to the method used by the sponsor to obtain the point estimate of the survival gain, a 95% confidence interval (CI) of 1.1 months to 32.7 months was obtained – a much wider CI than calculated by the sponsor.

The PBAC also recalled the LOTS trial, a randomised comparison of alglucosidase alfa versus placebo in patients with late-onset Pompe disease. The key results of the LOTS trial were a 3% improvement in FVC and a 28m gain in the six minute walk test (6MWT) associated with alglucosidase alfa treatment compared to placebo after 18 months. The PBAC remained concerned about uncertainty associated with assuming that these short term surrogate markers can be extrapolated to improvements in patient morbidity.

No new data regarding the safety or toxicity of alglucosidase alfa were presented in this submission.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The November 2012 re-submission claimed that the results of the updated EMC/IPA survey showed a strong and statistically significant relationship between alglucosidase use and survival in patients with late-onset Pompe disease.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The re-submission did not present an economic evaluation. This was reasonable given that the PBAC had previously accepted that alglucosidase is not cost effective for PBS listing.

The PBAC noted that additional information regarding the international price comparison for alglucosidase alfa had been provided in the current re-submission, along with a revised financial proposal.

11. Estimated PBS Usage and Financial Implications

The PBAC noted that the annual treatment cost per patient proposed in the submission represented treatment of a 75 kg patient at the standard dose of 20 mg/kg/fortnight, and did not account for circumstances in which patients may require dose escalation, but considered that this could be managed through a risk-sharing arrangement.

The PBAC considered that the price requested for alglucosidase alfa remained extremely high, with an estimated net cost to Government of greater than $10 million in Year 5, for fewer than 100 patients.

At the price proposed in the submission, based on EMC/IPA survey data, the incremental cost per one life-year gained assuming one year of life extension is gained for four years of treatment was substantially greater than $500, 000. If one year of life extension is gained for eight years of treatment, the incremental cost per one life-year gained more than doubled.

12. Recommendation and Reasons

While recognising the challenges of generating high-quality data for rare conditions such as late-onset Pompe disease, the PBAC considered that the observational data set for late-onset Pompe disease did not provide a sufficient basis to support the submission's claims of substantial life extension. Specifically, the PBAC noted that the analysis may be subject to residual confounding because broad severity categories were used in the statistical model. The PBAC also considered that as a non-randomised comparison, the analysis may be further subject to biases due to unmeasured or unknown confounders.

The PBAC acknowledged that there is non-randomised evidence that alglucosidase may prolong life to some extent, but noted that the size of the prolongation is subject to much more uncertainty, than for the infantile-onset group because late-onset patients are a much more heterogeneous group than the infantile-onset group and this heterogeneity leads to concerns about confounding in non-randomised data, even with a statistical model.

The PBAC recalled that the data presented to PBAC in July 2008 to support the application for alglucosidase alfa for use in infantile-onset Pompe disease was more robust and showed a more certain, and substantial life extension in those patients, with 100% of treated patients alive at 12 months versus 17% of untreated patients, and 72% of treated patients alive at 36 months versus 2% of untreated patients.

The PBAC noted from the Kaplan Meier survival curve reported from the EMC/IPA survey in March 2011 that approximately 99% of treated late-onset Pompe disease patients were alive at 12 months versus 97% of untreated patients, while 95% of treated late-onset Pompe disease patients were alive at 36 months versus 80% of untreated patients. The PBAC did not agree that these data represent a substantial life extension in the treated population, given the heterogeneity of the population and the non-randomised nature of the analysis.

The PBAC reached the following conclusions:

- at the price proposed in the submission, alglucosidase alfa cannot be recommended for listing on the PBS in the Section 100 Highly Specialised Drugs Program for the treatment of late-onset Pompe disease due to the unacceptably high incremental cost effectiveness ratio.

- alglucosidase alfa does not meet criterion 4 of the LSDP, in that although alglucosidase alfa may have some effect on mortality and quality of life, the available data do not provide certainty to the PBAC that the drug substantially and directly extends the lifespan of patients with late-onset Pompe disease.

- even if the LSDP eligibility criteria were to be met, the large difference in the drug cost for treating infantile-onset Pompe disease previously considered by the PBAC compared with late-onset-Pompe disease is not justified in terms of differential health outcomes. On the contrary, the PBAC considered that at the price requested by the submission, alglucosidase alfa for late-onset Pompe disease appears to be less effective and more expensive (per patient per year) than alglucosidase alfa for infantile-onset Pompe disease patients.

- the PBAC advised that, in this specific circumstance, the cost per treatment should not be based on individual patient's weight, but on a determined maximum cost per patient

per year. In the case of late-onset Pompe disease, the maximum drug cost per patient per year should not be higher than the drug cost originally presented to the PBAC in July 2008 for the infantile-onset form of the disease. However, even at a fixed cost per patient per year the same as that for infantile-onset disease, the cost of alglucosidase alfa treatment per patient per year would exceed the cost of the highest priced drugs on the PBS.

- Although not requested in the submission, the PBAC considered whether a listing of alglucosidase alfa on the PBS for the treatment of late-onset Pompe disease was possible under the PBS rule of rescue criteria, on the grounds that although not suitable for inclusion in the LSDP, alglucosidase alfa may provide a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. However, a significantly lower price than that proposed by the sponsor in the current submission would be needed because the PBAC Guidelines (2008, v 4.3) state that, unlike the LSDP criteria, the rule of rescue "supplements, rather than substitutes for the evidence-based consideration of comparative cost-effectiveness."

- The PBAC considered the sponsor may wish to consider a possible application for listing of alglucosidase alfa on the PBS under the rule of rescue criteria but at a significantly lower drug cost per patient per year for treating late-onset Pompe disease than proposed in the current submission.

The PBAC also acknowledged and noted the consumer comments on this item.

Recommendation:
Rejected

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

Genzyme is very disappointed with the decision. The LSDP is the appropriate place for the funding of this therapy given the small number of patients and the published evidence base to support life extension. It is the revised LSDP criterion 4 and/or the interpretation thereof that has been shown not to offer a way forward. Genzyme is therefore currently not able to make further submissions under this system.