PUBLIC SUMMARY DOCUMENT
Product: Alglucosidase alfa, powder for I.V. infusion, 50 mg, Myozyme®,
Sponsor: Genzyme Australasia Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission sought a Section 100 Highly Specialised Drug PBS listing or a recommendation for inclusion on the Life Saving Drugs Program (LSDP) for the treatment of late-onset Pompe 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.

Life Saving Drugs Program
The Commonwealth Government provides funds under an appropriation item established for the specific purpose of assisting access to expensive and lifesaving drugs accepted by the PBAC as clinically effective, but not available as pharmaceutical benefits because of a failure to meet cost effectiveness criteria. Financial assistance for such drugs is approved in accordance with specified eligibility criteria and subject to certain conditions as agreed by the Ministers for Health and Finance.

2. Background

At the July 2008 meeting, the PBAC rejected the submission to list alglucosidase alfa as a Section 100 Highly Specialised Drug for the treatment of patients with Pompe disease with a documented deficiency of acid alfa-glucosidase (GAA) enzyme activity on the basis of unacceptably high cost effectiveness. However, the Committee concluded that alglucosidase alfa met the criteria for the Life Saving Drugs Program (LSDP) for infantile-onset Pompe disease only.

A copy of the Public Summary Document from that meeting is available from http://www.health.gov.au/internet/main/publishing.nsf/Content/104DDB6DAE2F4AEECA2574EE008351FE/$File/Alglucosidase%20Final%20PSD%20Genzyme.pdf

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

Section 100 Highly Specialised Drug
Authority Required
Patients with a confirmed clinical diagnosis of Pompe disease who have had their diagnosis confirmed by a documented deficiency of acid alfa-glucosidase enzyme activity in either skin fibroblasts, muscle tissue, lymphocytes, mixed leukocytes or dried blood spots (< 40% of normal levels) or through identification of a mutation in the GAA gene.

The prescription should allow for sufficient vials for the patients to obtain 20 mg/kg (i.e., one treatment) every two weeks. The original prescription and one repeat may be authorised per

authority, providing 4 weeks of treatment. Treatment would be ongoing, requiring an intravenous infusion once every two weeks.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Pompe disease is an inherited disorder caused by a lack of the enzyme called acid alpha-glucosidase (commonly called GAA or acid maltase). 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 phenotypes 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 as it provides a source of GAA.

6. Comparator

The submission nominated standard (palliative) therapy including intensive respiratory support, cardiac care, dietary therapy and rehabilitative services, as the main comparator, which the PBAC considered appropriate.

7. Clinical Trials

The submission presented one randomised trial (LOTS trial) comparing alglucosidase alfa 20 mg/kg with placebo (supportive care) in 90 patients with late-onset Pompe disease over a treatment period of 18 months. Trial details are shown below.

Trial	Protocol title
AGLU02704 Late-Onset Treatment Study (LOTS)	A Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled Study of the Safety, Efficacy, and Pharmacokinetics of Myozyme, Recombinant Human Acid alpha-Glucosidase (rhGAA), Treatment in Patients with Late-Onset Pompe disease.

8. Results of Trials

Alglucosidase alfa met both co-primary endpoints. The results showed that, at 18 months, patients treated with alglucosidase alfa increased their distance walked in six minutes by an average of approximately 30 meters as compared with the placebo group (P=0.0283; Wilcoxon test). The placebo group did not show any improvement from baseline. The average baseline distance walked in six minutes in both groups was approximately 325 metres.

Percent predicted forced vital capacity in the group of patients treated with alglucosidase alfa increased by 1 percent at 18 months. In contrast, it declined by approximately 3 percent in the placebo group (P=0.0026; Wilcoxon test). The average baseline percent predicted forced

vital capacity in both groups was approximately 53 percent. The results for both efficacy endpoints were consistent across various prospectively defined subgroups.

The safety of alglucosidase alfa was similar to placebo in the LOTS study. The number of patients with serious and treatment-emergent non-serious adverse events was similar in the alglucosidase alfa and placebo groups. Approximately 25 percent of patients in each group experienced infusion-associated reactions. There was one death in the alglucosidase alfa group unrelated to treatment.

9. Clinical Claim

The submission claimed that alglucosidase alfa was associated with greater efficacy than placebo (supportive care) and would be expected to stop disease progression but was associated with greater toxicity. *(For details of toxicity/safety see "Results of Trials").*

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a trial-based economic evaluation (cost-effectiveness analysis) using data from the LOTS trial. The analysis used a time horizon of 52 weeks (based on the first 52-weeks of the 78-week LOTS trial).

The PBAC noted that the incremental cost per additional metre walked at 52 weeks was with in the range $15,000-$45,000.

The results of the sensitivity analyses indicated that the economic evaluation was sensitive to assumptions regarding: patients' weight, the size of the treatment effect, the time horizon chosen and the outcome measure used.

11. Estimated PBS Usage and Financial Implications

The submission advised an estimate of Australian birth prevalence (i.e. annual incidence) of 1:70,000 has been calculated and estimated the financial cost per year to the PBS to be $10-18 million in Year 4 of listing.

The PBAC considered this estimate to be uncertain due to the high drug cost per patient per year and sensitivity to assumptions regarding the number of treated patients and the weight of patients.

12. Recommendation and Reasons

The pivotal clinical evidence presented was the LOTS trial, a randomised trial of 90 patients with late-onset Pompe disease (aged 8 years or older) comparing alglucosidase alfa with placebo over 18 months. The PBAC also noted the clinical study reports of the two non-randomised trials, provided in the sponsor's Pre-Sub-Committee Response, which provided data on patients with more severe Pompe disease. The PBAC accepted that alglucosidase alfa therapy is associated with an improvement in the 6-minute walk test (6MWT) and a stabilisation of forced vital capacity (upright) compared with placebo. However, the PBAC remained concerned about the uncertainty associated with assuming that these short-term surrogate outcomes can be extrapolated to improvements in patient morbidity and mortality in a chronic disorder and that this uncertainty remained unaddressed. The PBAC agreed that there was still considerable uncertainty remaining around the magnitude of benefit gained

through treatment with this product, and the extent to which alglucosidase alfa can be reasonably expected to prolong life in late-onset Pompe patients. The PBAC therefore did not consider that it was appropriate to include alglucosidase alfa in the LSDP as criterion 2 was not satisfied – ie a patient's lifespan will be extended as a direct consequence of the use of the drug.

The PBAC also expressed concern that Australian patients currently on the alglucosidase alfa compassionate access programme have more advanced disease when compared with the patients in the LOTS trial, as they seem to require higher ventilator support and have less ability to walk 10 metres. Therefore, the results of the LOTS trial may not be applicable to the requested population as the LOTS trial excluded patients with advanced disease (ie patients requiring invasive ventilation, patients requiring non-invasive ventilation while awake or patients with severe ambulatory impairment) and also may have excluded patients with asymptomatic/mildly symptomatic disease (ie patients with forced vital capacity (FVC) > 80%).

A trial-based economic analysis using a time horizon of 52 weeks (based on the first 52 weeks of the 78 week LOTS trial) was presented in the submission. The PBAC noted that the incremental cost per additional metre walked at 52 weeks was in the range $15,000-$45,000.

The PBAC rejected the submission to list alglucosidase alfa as a Section 100 Highly Specialised Drug for the treatment of patients with late-onset Pompe disease with a documented deficiency of alfa-glycosidase enzyme activity on the basis of unacceptably high cost effectiveness.

The PBAC concluded that alglucosidase alfa for treatment of late-onset Pompe disease does not fulfil criterion 2 of the LSDP criteria as there is no evidence to expect that a patient's lifespan will be extended as a direct consequence of the use of alglucosidase alfa and therefore did not recommend inclusion of alglucosidase alfa on the LSDP for late-onset Pompe disease.

The PBAC reaffirmed its previous recommendation for inclusion of alglucosidase alfa on the LSDP for infantile-onset Pompe disease only with the formation of a reference group to establish treatment initiation and continuation guidelines and to develop specific criteria for the cessation of alglucosidase alfa treatment.

The PBAC noted that the submission meets the criteria for an Independent Review.

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 Australia continues to work with the PBAC and LSDP to ensure that all appropriate Pompe disease patients have funded access to Myozyme by addressing the uncertainties raised by the PBAC.