PUBLIC SUMMARY DOCUMENT
Product: Myozyme Alglucosidase alfa alfa, powder for I.V. infusion, 50 mg, Myozyme®
Sponsor: Genzyme Australasia Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought a Section 100 Highly Specialised Drug PBS listing or inclusion on the Life Saving Drugs Program for the treatment of Pompe disease in patients with a documented deficiency of acid alfa-glucosidase (GAA) enzyme activity.

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 they do not 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

This drug has not previously been considered by the PBAC.

3. Registration Status

Alglucosidase alfa was granted Orphan drug status on 8 September 2003.

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 Drugs
Authority Required
Patients with a confirmed clinical diagnosis of Pompe disease who have had their diagnosis confirmed by a documented deficiency of 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 acid maltase or GAA). This results in an accumulation of

glycogen impairing the function of certain 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 can present 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 on-set) present later in life with less rapid but steadily progressive disease.

Life expectancy may vary in Pompe disease but many will experience premature death as a result of this chronic disease.

There is no cure for Pompe 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. The PBAC considered this was appropriate.

7. Clinical Trials

The basis of the submission was:
A randomised trial comparing alglucosidase alfa 20 mg/day with alglucosidase alfa 40 mg/day in infantile-onset Pompe disease (Study 1602/2403), and a non-randomised trial of alglucosidase alfa 20 mg/day in infantile-onset Pompe disease (unpublished interim report) (Study 1702). The results of these two studies were compared with an historical control group (Study 00400).

The PBAC was unable to form a view on the clinical efficacy of alglucosidase alfa in late onset Pompe disease as there was insufficient data at the time of submission.

The randomised comparative trial (Study 1602/2403) and the historical retrospective study (Study 00400) had been published at the time of the submission. Their details are as follows:

Trial	Protocol title/Publication title	Publication citation
Single arm of randomised trial		
Study 1602/2403 Kishnani et al (2007)	Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease.	Neurology, Vol 68, 99-109
Historical control		
Study 00400 Kishnani et al (2006)	A retrospective, multinational, multicentre study on the natural history of infantile-onset Pompe disease	J Pediatr. 2006 May; 148(5): 671-676.

8. Results of Trials

In studies 1602/2403 the primary efficacy endpoint presented was overall survival. Invasive ventilator-free survival was analysed as an additional primary endpoint.

The results compared invasive ventilator-free survival, survival, and any ventilator-free survival between alglucosidase alfa-treated infants and historical controls.

Invasive ventilation was defined as ventilatory support applied with the use of an endotracheal tube or tracheostomy, and non-invasive ventilation was defined as any form of ventilatory support applied without the use of an endotracheal tube or tracheostomy (i.e., no invasion of the airway).

All patients (100%) were alive at 12 months of age compared to 16.8% of patients in the untreated control group. After 36 months, 72% of alglucosidase alfa treated patients were alive compared to 1.9% of untreated controls. The invasive ventilator-free survival at 36 months was 49.4% with the 95% CI ranging between 26.0% and 72.8%. At present there is insufficient data available to support extension of lifespan beyond early childhood.

Outcome	**Proportion of treated patients (95% CI)**	**Portion of patients alive in historical reference group (95% CI)**
Study 1602/2403		
Patients alive at: 12 months of age 36 months of age	100 (100, 100) 72 (47.9, 96)	16.8 (6.8, 26.8) 1.9 (0.0, 5.5)
Patients alive and free of invasive ventilation at: 12 months of age 36 months of age	88.9 (74.4, 100) 49.4 (26, 72.8)	

The use of ventilator support at first infusion did not appear to adversely affect patient survival compared with patients who were ventilator-free at baseline. However all five patients in Study 1702 who were receiving invasive ventilation at baseline continued to require ventilation throughout the study.

In relation to cardiac outcomes and developmental outcomes reported in Study 1602/2403, 39% of patients (7/18) were classified as “walkers” and could ambulate independently; 22% of patients (4/18) were classified as “functional sitters” and were sitting independently; the remaining 7 (39%) were classified as “motor non-responders” and had minimal or no significant gross motor function.

All patients in Study 1602/2403 reported adverse events, attributed mostly to the underlying disease. The most common infusion related adverse events were urticaria (33%) and pyrexia (33%). Sixteen alglucosidase alfa-treated patients (88.9%) developed anti-alglucosidase alfa IgG antibodies; six had sustained high antibody-titres (range 51,200 to 1,638,400). The higher-titre patients had more infusion associated reactions and serious adverse events and accounted for 5 of the 6 patient deaths.

9. Clinical Claim

The submission claimed alglucosidase alfa is superior to supportive care in terms of comparative effectiveness.

For PBAC's views, see Recommendations and Reasons.

10. Economic Analysis

The submission presented a trial based economic evaluation in the form of a cost-effectiveness analysis, which was considered valid. The analysis only included Pompe disease in patients less than 26 weeks of age and no economic data for late-onset Pompe disease were presented. Quality of life was not considered.

The analysis used a time horizon of 52 weeks (date of birth to 52 weeks) i.e 52 weeks of treatment from the first infusion.

The submission estimated that the incremental cost per additional patient alive at 52 weeks was in the range of $45,000 - $75,000 based on alglucosidase alfa treatment costs with supportive care cost offset (base case), which increased to between $75,000 – $105,000 for alglucosidase alfa treatment costs without the supportive care cost offset.

11. Estimated PBS Usage and Financial Implications

Based on the most conservative (highest) estimate of birth prevalence in the published literature, which is 1:100,000 (Martiniuk et al, 1998), the likely number of patients per year for infantile-onset Pompe disease was estimated to be up to 10.6 patients in Year 5. The submission's estimates did not include the currently known 20 late-onset patients in Australia.

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5 for infantile-onset Pompe disease. For Late-onset Pompe patients, the average cost of treatment per year, based on 20 known Australian Pompe patients, was estimated to be an additional cost of between $10 - $30 million per year.

12. Recommendation and Reasons

The submission nominated standard (palliative) care as the comparator, which the PBAC considered was appropriate. Clinical evidence presented included two open-label observational studies (study 1602 and 2403) where treatment with alglucosidase alfa in infantile-onset Pompe disease was compared to a historical control group. The trials investigated survival, invasive ventilator-free survival and ventilator free survival. The results of these studies suggest that alglucosidase alfa prolongs survival in infants, but does not appear to extend the lifespan beyond early childhood. In addition, some patients experienced disease progression whilst on alglucosidase alfa, indicating that in those patients treatment with alglucosidase alfa delays the need for supportive care, rather than reducing the need for supportive care, as claimed in the submission. The Committee was unable to form a view on the clinical efficacy of alglucosidase alfa in late onset Pompe disease as there was insufficient data available at the time of submission. Any future data for late-onset Pompe disease would require evaluation in the form of a major submission.

The PBAC noted that treatment with alglucosidase alfa is associated with significant toxicities. All patients in studies 1602 and 2403 reported adverse events, attributed mostly to the underlying Pompe disease. However, infusion related adverse events including urticaria (hives) and pyrexia (fever) were experienced by 33% of patients. Sixteen alglucosidase alfa treated patients (88%) developed anti-alglucosidase alfa antibodies; six with sustained high antibody titres. The higher titre patients had more infusion related adverse events and constituted five of the six patient deaths. Severe or significant hypersensitivity reactions, including one case of anaphylactic shock, were noted to have been reported in post-marketing surveillance.

A trial-based economic analysis was presented in the submission. The Committee noted that the economic evaluation included patients less than 26 weeks of age and no economic data were presented for late-onset Pompe disease. The analysis used a time horizon of 52 weeks (date of birth to 52 weeks), however the model used 52 weeks of treatment from the first infusion. However, the major limitation with the model is the short time horizon which does not capture the costs of ongoing treatment with alglucosidase alfa. As patients are not cured by treatment with alglucosidase alfa, ongoing treatment beyond 52 weeks is likely to be needed, resulting in escalating treatment costs. In addition, drug costs per year of treatment are also likely to escalate as the child grows. As alglucosidase alfa dosing is based on weight, the quantity of alglucosidase alfa required to treat an adult would be much higher than for an infant, resulting in a much higher treatment cost for late-onset Pompe disease.

The incremental cost per additional patient alive at 52 weeks is between $45,000 and $75,000 based on alglucosidase alfa treatment costs with supportive care cost offset (base case). This increases to between $75,000 – $105,000 for alglucosidase alfa treatment costs without the supportive care cost offset.

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 alfa-glycosidase enzyme activity on the basis of unacceptably high cost effectiveness as discussed in Section 10 of the Public Summary Document (PSD).

The Committee concluded that alglucosidase alfa meets the criteria for the Life Saving Drugs Program (LSDP) for infantile - onset Pompe disease. Insufficient data were presented on the clinical efficacy of alglucosidase alfa in the treatment of late-onset Pompe disease and it was therefore excluded from the clinical evaluation. Evidence in the submission supported the claim that infantile-onset Pompe disease patients typically die within the first year of life due to respiratory or cardiac failure and that treatment with alglucosidase alfa increases the life expectancy, fulfilling criterion 2 of the LSDP (that the disease has been associated with a significant shortening of expected age matched lifespan for those suffering from the disease and that there is evidence to expect that a patient's lifespan will be extended as a direct consequence of the use of the drug). The PBAC did however note that although alglucosidase alfa prolongs survival in infants it does not appear to extend the lifespan beyond early childhood. Alglucosidase alfa also meets criterion 1 and 3 of the LSDP as infantile-onset Pompe disease is a rare clinically definable disease able to be diagnosed by measurement of acid alfa-glucosidase enzyme activity.

The PBAC therefore recommended consideration by the Government of inclusion of alglucosidase alfa in the LSDP for infantile onset Pompe disease. The formation of a

reference group was recommended to establish treatment initiation and continuation guidelines and to develop specific criteria for the cessation of alglucosidase alfa treatment.

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 Australasia welcomes the PBAC's decision to recommend Myozyme (alglucosidase alfa) for inclusion in the LSDP for infantile Pompe disease. Genzyme Australasia will continue to work with the PBAC and the LSDP to ensure all appropriate Pompe disease patients have funded access to Myozyme and will support the listing of Myozyme in patients with late onset Pompe disease with new data recently made available.