PUBLIC SUMMARY DOCUMENT
Product: Alglucosidase alfa, powder for I.V. infusion, 50 mg, Myozyme®
Sponsor: Genzyme Australasia Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission sought a recommendation for inclusion on the Life Saving Drugs Program for the treatment of late onset Pompe disease.

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 alpha-glucosidase 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 disease only. A copy of the Public Summary Document (PSD) from this meeting is available at: www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-alglucosidase-july08.

At the March 2009 meeting, 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 acid alpha-glucosidase enzyme activity on the basis of unacceptably high cost effectiveness. The PBAC concluded that alglucosidase alfa for treatment of late onset Pompe disease did not fulfil criterion 2 of the LSDP criteria as there was no evidence to expect that a patient's lifespan would 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. A copy of the PSD from this meeting is available at: www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-alglucosidase-march09.

At the November 2009 meeting, the PBAC rejected the re-submission to list alglucosidase on the PBS as a Section 100 Highly Specialised Drug for the treatment of patients with late onset Pompe disease on the basis of unacceptably high cost effectiveness compared to standard (palliative) therapy. Again, the PBAC did not recommend inclusion in the LSDP of alglucosidase for the treatment late onset Pompe disease considering that insufficient evidence was provided to demonstrate that a patient's lifespan would be extended as a direct consequence of treatment with alglucosidase. A copy of the PSD from this meeting is available at: www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Alglucosidase-nov09.

Revised funding criteria and conditions for the LSDP came into effect on 10 May 2010. These are available at: www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-info/$File/CCLSDP10052010.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 alpha-glucosidase deficiency).

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug Program)
Private hospital authority required
Patients with a confirmed clinical diagnosis of Pompe disease who have had their diagnosis confirmed by a documented deficiency of alpha-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 and who meet the criteria below:

Inclusion criteria:
1) Symptomatic Pompe Disease with laboratory confirmation (muscle biopsy or muscle magnetic resonance imaging (MRI) and either biochemical demonstration of enzyme deficiency or direct genetic testing)
AND
2) Impaired respiratory function as indicated by one of the following: < 80% predicted supine forced vital capacity (FVC); < 80% predicted maximal inspiratory pressure (MIP) or maximal expiratory pressure (MEP) or significant nocturnal respiratory compromise as demonstrated by a sleep study
OR
3) Significant muscular weakness

Exclusion criteria:
1) Incomplete laboratory confirmation of diagnosis
2) Invasive ventilation (ETT or tracheotomy)
3) Co-existing lethal disease
4) Unwillingness to comply with requirements for 6 monthly monitoring and data collection

The following would lead to cessation of Myozyme therapy:

Discontinuation criteria:
1) Failure to adequately benefit from ERT as evidenced by persistent decline in respiratory or motor function
2) Intolerable side effects/complications of ERT
3) Failure to comply with regular monitoring and documentation of clinical state
4) At request of patient or guardian
5) Emigration from Australia

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.

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 had previously considered this appropriate.

7. Clinical Trials

The LOTS trial (AGLU002704) remained the key study in the current re-submission. Additionally, data were presented for a new open-label extension of the LOTS trial (AGLU3206). The re-submission also presented results from six observational supportive studies: AGLU2804, Hartung et al 2007 and Angelini et al 2009 studies (which have been presented to the PBAC previously), AGLU3105 and AGLU2603 studies (excluded from the November 2009 submission due to incomplete data) and Strothotte et al 2010 study (new study identified in current submission).

The studies published at the time of the submission were as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Randomised trials		
AGLU002704 Van der Ploeg et al Van der Ploeg et al	Late-Onset Treatment Study (LOTS) Lysosomal storage disease II: Pompe disease. A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease;	 The Lancet, 2008; 372:1342-1353. New England Journal of Medicine, 2010; 362:1396-1406.
Supportive non-randomised studies		
Angelini et al	Progress in enzyme replacement therapy in glycogen storage disease type II.	Therapeutic Advances in Neurological Disorders, 2009; 2: 143-153
Hartung et al	Initial therapy response of 6 months of enzyme replacement therapy in 11 juvenile/adult M. Pompe patients.	Clinical Therapeutics, 2007; 29:S86-S87
Strothotte et al	Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial.	J Neurol, 2010; 257(1):91-97.

8. Results of Trials

The re-submission presented the main results from the LOTS trial which were the change in distance walked during the 6-minute walk test (6MWT), change in percentage predicted upright forced vital capacity (FVC) and patients commencing ventilation use.
The re-submission claimed that alglucosidase treatment led to a numerical decrease in non-invasive ventilation use compared to placebo (5% vs. 13.3%, p = 0.216) which may translate into an improvement in survival. This result was difficult to interpret as the difference was statistically non-significant and based on a very small patient population (i.e. the results of a single patient could substantially change the overall numerical results of the analysis). At the March 2009 meeting the PBAC accepted that alglucosidase alfa therapy was associated with an improvement in the 6MWT and a stabilisation of FVC (upright) compared with placebo.

The re-submission attempted to demonstrate a survival benefit of alglucosidase therapy by examining: the survival benefit of alglucosidase treatment in infantile-onset Pompe disease; the correlation between pulmonary function and mortality in the general population; the correlation between FVC and ventilation use in Pompe disease; the correlation between FVC and ventilation use in other neuromuscular diseases and; the correlation between ventilation use and survival in other neuromuscular diseases.

The re-submission included the addition of two studies that examined the association of pulmonary function and survival in the general population (Hole et al 1996, Sin et al 2005). Both studies suggested that reduced pulmonary function was associated with lower survival. This was consistent with studies presented in the previous re-submission. However, the PBAC considered that the link between improving or reducing the rate of decline of respiratory function and the increase in life expectancy was highly uncertain.

Most of the adverse events reported in the LOTS trial appeared to be related to the underlying pathology of Pompe disease. The majority of infusion-related reactions were of mild to moderate severity with all patients recovering without sequelae. Over the course of the LOTS trial, the most frequent infusion-related reactions were nausea, headache, urticaria, dizziness, chest discomfort, pruritus, hyperhidrosis, flushing, rash, increased blood pressure, papular rash and vomiting.

9. Clinical Claim

The submission described alglucosidase as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo (standard management).

For PBAC's view, see Recommendation and Reasons

10. Economic Analysis

The re-submission presented a trial-based economic evaluation (cost-effectiveness analysis) using data from the LOTS trial. The re-submission also presented an economic evaluation using the International Compassionate Access Program (ICAP) population which had been updated due to the recent death of one patient enrolled in the program. This patient death had altered some of the overall ICAP population characteristics but in general the characteristics were similar to the previous November 2009 re-submission.

The change in 6MWT from baseline to week 78 for the LOTS study participants resulted in an incremental cost per metre walked in the range of $15,000- 45,000. Both the incremental

cost per 1% predicted FVC gain from baseline to week 78 and the incremental cost per ventilation avoided at 78 weeks were more than $200,000.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the re-submission to be less than 10,000 per year in Year 5, while the predicted financial cost per year of listing alglucosidase on the PBS was expected to be in the range of $10 – 30 million.

12. Recommendation and Reasons

As in previous submissions, the LOTS trial remained the key study in the re-submission. The data presented from the LOTS study supported the submission's claim of superiority with reference to forced vital capacity (FVC) and six-minute walk test (6MWT), the co-primary efficacy outcomes of this trial, at 78 weeks. The PBAC had previously accepted that alglucosidase therapy was associated with an improvement in the 6MWT and a stabilization of upright FVC compared with placebo. However, the PBAC had expressed concern 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. The relevance of these surrogate outcomes for patient survival remained the key issue for the consideration of the PBAC. In addition, the re-submission claimed that alglucosidase treatment in the LOTS trial led to a numerical but non-significant decrease in non-invasive ventilation use, an exploratory outcome in the trial report, compared to placebo which may translate into an improvement in survival. This result was difficult to interpret as the difference was statistically non-significant and based on a very small patient population. The appropriateness of ventilation use as a surrogate for survival in late onset Pompe remained uncertain.

The re-submission presented two additional studies (Hole et al 1996, Sin et al 2005) that examined the relationship between lung function and survival in the general population. Both studies suggested that reduced pulmonary function was associated with lower survival. This was consistent with studies presented in the previous re-submission. However, the PBAC considered that the link between improving or reducing the rate of decline of respiratory function and the increase in life expectancy is highly uncertain.

The PBAC noted the revised LSDP criteria came into effect on May 10, 2010 and that all of these criteria must be met before a recommendation can be made that a product is eligible for the Life Saving Drugs Program. The PBAC considered that the alglucosidase application met seven of the first eight criteria but the evidence presented did not support criterion four as the evidence is highly uncertain and was not accepted by the PBAC as showing a substantial increase in life expectancy.

The PBAC noted the consumer comments and comments from health professionals and organisations provided for this item and acknowledged that the quality of life for patients with late-stage Pompe disease would likely be improved, however the drug was being considered under the Life Saving Drugs Program.

The re-submission presented a trial-based economic evaluation (cost-effectiveness analysis) using data from the LOTS trial. The re-submission also presented an economic evaluation using the International Compassionate Access Program (ICAP) population which had been updated due to the recent death of one patient enrolled in the program. This patient death

altered some of the overall ICAP population characteristics but in general the characteristics were similar to the previous November 2009 re-submission. The incremental cost per additional metre walked from baseline to week 78 was in the range of $15,000 - $45,000, while the incremental cost per 1% predicted FVC gain from baseline to week 78 and the incremental cost per patient avoiding ventilation at 78 weeks were more than $200,000.

At its November 2009 meeting, the PBAC noted that the cost per patient per year in the re-submission was again higher than other enzyme replacement therapies recommended for inclusion on the LSDP.

The PBAC rejected the re-submission to list alglucosidase on the PBS as a Section 100 Highly Specialised Drug for the treatment of patients with late onset Pompe disease on the basis of high and uncertain cost effectiveness.

The PBAC did not recommend inclusion of alglucosidase in the LSDP for the treatment of late onset Pompe disease as the drug fails to satisfy criterion four of the LSDP Guidelines in that no evidence satisfactory to the PBAC has been submitted to demonstrate that alglucosidase increases life expectancy in patients with late onset Pompe disease even though the drug may improve the quality of life of those patients taking the drug.

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

Genzyme Australasia remains committed to working with the PBAC and the LSDP to ensure that people with late-onset Pompe disease have funded access to Myozyme.