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

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) listing or 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 alfa-glycosidase 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.

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 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 did 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.

A copy of the Public Summary Document from that meeting is available from http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-alglucosidase-march09

3. Registration Status

Alglucosidase alfa was granted orphan drug status by the TGA 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 Drug)

Private hospital 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 and who meet the criteria below:

- Inclusion criteria:
  - Patients with significant deterioration in either:
    - Lung function: FVC in upright position of < 80% predicted;

    or
    - Muscle function: clinically significant muscle weakness.
- Exclusion criteria:
  - Patients with chronic invasive ventilation of >12 months duration.

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 key study in the re-submission remained the LOTS trial (ALGLU02704), a randomised trial comparing alglucosidase 20 mg/kg with supportive care in late-onset Pompe disease.

The main clinical outcome in the re-submission was ventilator use in the LOTS study, rather than forced vital capacity (FVC) and 6 minute walk test (6MWT) as in previous submissions. This was in order to address the PBAC's concern in the previous submission regarding the uncertainty in assuming FVC and 6MWT outcomes can be extrapolated to improvements in patient morbidity and mortality.

Three additional non-randomised studies (AGLU02804, Hartung 2007 and Angelini 2009) were included as supportive evidence.

The key trials presented in the submission are shown in the table below:

Trial ID/First author	Protocol title / Publication title	Publication citation
Randomised trials		
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.	
Non-randomised studies		
AGLU02804	A Single Center, Open-Label, Bridging Study of the Safety, Pharmacokinetics and Efficacy of Recombinant Human Acid Alpha-Glucosidase (rhGAA) Treatment in Patients with Late-Onset Pompe disease (Glycogen Storage Disease Type II).	
Hartung et al (2007)	Initial therapy response of 6 months of enzyme replacement therapy in 11 juvenile/adult M. Pompe patients.	Clinical Therapeutics, Vol 29 p S86
Supportive non-randomised trial		
Angelini et al (2009)	Progress in enzyme replacement therapy in glycogen storage disease type II.	Therapeutic Advances in Neurological Disorders 2009; 2; 143

To support the correlation between FVC and ventilator use, the resubmission presented two published studies as shown below:

Trial ID/First author	Protocol title / Publication title	Publication citation
Pellegrini et al (2005)	Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease	Eur Respir J 2005; 26: 1024–1031
Van der Beek (2009)	Rate of disease progression during long-term follow-up of patients with late-onset Pompe disease	Neuromuscular Disorders 19 (2009) 113–117

8. Results of Trials

The re-submission aimed to address the PBAC's previous uncertainty from the March 2009 submission around the survival benefits of alglucosidase alfa treatment in late-onset Pompe disease patients by demonstrating a link between forced vital capacity (FVC) and survival, via another surrogate outcome: ventilator use.

Two patients in the alglucosidase alfa treatment group did not require ventilatory support at the time of treatment initiation, despite having indicated in the Pompe Disease Questionnaire that they used ventilatory support. The re-submission included these patients as not utilising ventilatory support at baseline, resulting in 3 patients initiating ventilator use in the duration of the study in the alglucosidase arm, and 4 in the placebo arm: a risk difference of 8.3%. If these patients were classified as ventilator users at baseline, then only one patient in the alglucosidase alfa treatment arm would have initiated ventilator use during the trial, for a risk difference of 11.6%.

An updated Periodic Safety Update Report (PSUR) for alglucosidase was presented in the re-submission for the period of December 2008 – March 2009. This report included patients with both infantile-onset and late-onset Pompe disease. The PSUR stated that the majority of adverse reactions observed during the current reporting period were consistent with the manifestation of the underlying disease, and notes that reports of significant allergic and

anaphylactic reactions, immune mediated reactions and clinical decline, as well as reports of cardiac, respiratory and muscular nature will be closely monitored by the Sponsor, and followed for further evaluation.

For PBAC's comments see Recommendation and Reasons.

9. Clinical Claim

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

The PBAC recalled that at the March 2009 meeting it accepted that alglucosidase alfa therapy was associated with an improvement in the 6-minute walk test (6MWT) and a stabilisation of forced vital capacity (upright) compared with placebo.

The PBAC noted the re-submission presented data from two retrospective reviews of the medical records of patients with late onset Pompe disease, Pellegrini et al (2005) and Van der Beek (2009), to support the proposed correlation between ventilator use and FVC. Data from these studies showed that patients requiring respiratory support tended to have worse vital capacity than patients not requiring any respiratory support, however the PBAC noted that there was no indication that one is the cause or effect of the other. The studies also showed there was considerable variation in the rate of disease progression in patients with late onset Pompe disease. The PBAC considered there was uncertainty in the assumption of correlation between FVC scores and ventilator use, and the extrapolation of the surrogate of ventilator use with survival gain, and hence the re-submission's claim that FVC is a surrogate for survival in late onset Pompe disease.

10. Economic Analysis

The submission presented a trial based economic evaluation using the data from the LOTS study with a time horizon of 52 weeks (based on the first 52 weeks of the 78 week LOTS trial). This approach was unchanged compared to the previous submission. The economic evaluation was updated to reflect updated characteristics of the overall population with a reduction in the average number of vials required per treatment however the incremental cost per additional metre walked at 52 weeks remained in the same range as previously, $15,000 – $45,000.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated to be slightly lower than the March 2009 submission but in the range of $10 – $23 million per year in Year 5. Due to the high drug cost per patient per year the estimated financial impact of alglucosidase is sensitive to any assumptions regarding the number of treated patients, and the weight of patients.

12. Recommendation and Reasons

The PBAC noted the clinical evidence presented in the re-submission of the LOTS trial (ALGLU02704) was unchanged, however the main outcome in the current re-submission was ventilator use in the LOTS trial, to address the PBAC's previous concerns, rather than forced vital capacity (FVC) and six minute walk test (6MWT) in previous submissions. The re-submission presented one open-label study with unspecified doses of alglucosidase alfa (Angelini 2009) as supportive evidence. The re-submission stated that there are currently no

studies available illustrating a statistically significant correlation between ventilator use and death in patients with late onset Pompe disease, hence no data were presented in the re-submission directly supporting the proposed correlation of survival increase and ventilator use.

The re-submission presented data from two retrospective reviews of the medical records of patients with late onset Pompe disease, Pellegrini et al (2005) and Van der Beek (2009), to support the proposed correlation between ventilator use and FVC. Data from these studies showed that patients requiring respiratory support tended to have worse vital capacity than patients not requiring any respiratory support, however the PBAC noted that there was no indication that one is the cause or effect of the other. The studies also showed there was considerable variation in the rate of disease progression in patients with late onset Pompe disease. The PBAC considered there was uncertainty in the assumption of correlation between FVC scores and ventilator use, and the extrapolation of the surrogate of ventilator use with survival gain, and hence the re-submission's claim that FVC is a surrogate for survival in late onset Pompe disease. The PBAC hence considered that criterion 2 of the LSDP was not satisfied, that is uncertainty remained as to whether a patient's lifespan would be extended as a direct consequence of treatment with alglucosidase alfa in late onset Pompe disease.

The PBAC noted the periodic safety update in the re-submission raised no new safety issues with the treatment of Pompe disease (infantile-onset and late onset) with alglucosidase alfa. The PBAC however noted that patients develop antibodies to alglucosidase alfa and that patients with sustained high anti-alglucosidase alfa IgG antibodies titres may have a poorer clinical response to alglucosidase, and that the effect of the development of antibodies on the long term efficacy of alglucosidase alfa is uncertain.

The submission presented a trial based economic evaluation using the data from the LOTS study with a time horizon of 52 weeks (based on the first 52 weeks of the 78 week LOTS trial). This approach was unchanged compared to the previous submission. The economic evaluation was updated to reflect updated characteristics of the overall population with a change to the average number of vials required per treatment.

The PBAC rejected the re-submission to list alglucosidase alfa 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. The PBAC noted that the cost of alglucosidase alfa in late onset Pompe disease, was substantially unchanged from the previous submission, was very high and the cost-effectiveness was far outside that which would be considered acceptable for listing on the PBS.

The PBAC did not recommend inclusion in the LSDP of alglucosidase alfa for the treatment late onset Pompe disease considering that insufficient evidence was provided to demonstrate that a patient's lifespan will be extended as a direct consequence of treatment with alglucosidase alfa, and hence that criterion two of the LSDP had not been met. The PBAC also 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.

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.