

## **PUBLIC SUMMARY DOCUMENT**

**Product:** ALGLUCOSIDASE ALFA, powder for I.V. infusion, 50 mg, Myozyme®

**Sponsor:** Genzyme Australasia Pty Ltd

**Date of PBAC Consideration:** July 2011

### **1. Purpose of Application**

The re-submission sought a recommendation for inclusion on the Life Saving Drugs Program (LSDP) for the treatment of 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**

Alglucosidase alfa has been considered by the PBAC on four previous occasions for the treatment of patients with late onset Pompe disease, at its meetings in July 2008, March 2009, November 2009 and November 2010. Details of these considerations are in the relevant Public Summary Documents (PSD) available at:

<http://www.health.gov.au/internet/main/publishing.nsf/Content/public-summary-documents>

At the July 2008 meeting, the PBAC rejected a 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-glucosidase enzyme activity on the basis of unacceptably high cost effectiveness.

### **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 the PBAC that alglucosidase should be included in the LSDP for the treatment of late onset Pompe disease. The sponsor did not propose wording for a PBS listing.

*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 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. The PBAC has previously considered this appropriate.

## 7. Clinical Trials

The key study in the re-submission remained the LOTS trial, a randomised comparison of alglucosidase versus placebo in patients with late-onset Pompe disease. The details of the LOTS (AGLU002704) trial are presented in the table below.

<b>Trial ID / First author</b>	<b>Protocol title / Publication title</b>	<b>Publication citation</b>
<b>Randomised trials</b>		
AGLU002704	Late-Onset Treatment Study (LOTS)	
Van der Ploeg et al	Lysosomal storage disease II: Pompe disease.	The Lancet, 2008; 372:1342-1353.
Van der Ploeg et al	A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease;	New England Journal of Medicine, 2010; 362:1396-1406.

The re-submission also presented new survival data based on unpublished reports from the Erasmus Medical Centre (EMC) – a research organisation independent to the sponsor/International Pompe Association (IPA) Pompe survey, an 8-year prospective observational study. The main analysis was based on a non-randomised comparison of survival between treated and untreated patients (EMC research report 2011). The re-submission also presented three small case series as supportive evidence. Publication details are presented in the table below.

<b>Trial ID / First author</b>	<b>Protocol title / Publication title</b>	<b>Publication citation</b>
<b>Case series</b>		
Bembi et al	Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II.	J Inherit Metab Dis: 2010; 1-9
Papadimas et al	Adult Pompe disease: Clinical manifestations and outcome of the first Greek patients receiving enzyme replacement therapy.	Clin Neurol Neurosurg: 2011
van Capelle et al	Effect of enzyme therapy in juvenile patients with Pompe disease: A three-year open-label study	Neuromuscular Disord; 2010: 20(12):775-82.

## **8. Results of Trials**

The key results of the LOTS trial (previously reported) were a 3.4% improvement in forced vital capacity (FVC) and a 28.1 m gain in the six-minute walk test (6MWT) associated with alglucosidase treatment compared to placebo after 18 months. However, the PBAC had expressed concern about the relevance of these surrogate outcomes for patient survival.

The non-randomised comparison of survival between treated and untreated patients in the EMC research report divided the EMC/IPA survey population into two groups; those who were never treated with alglucosidase and those who received at least one dose of alglucosidase (referred to as the ever treated group).

The re-submission presented the results for deaths in the EMC/IPA survey which showed that between 2002 and February 2011, there were more deaths in the never treated group compared to the ever treated group.

The re-submission presented logistic regression analyses and an adjusted Cox Proportional Hazards regression analyses to examine the influence of various factors on patient survival.

The EMC report claimed that alglucosidase treatment has a strong positive influence on survival in patients with late-onset Pompe disease.

The PBAC considered the improvements in FVC and 6MWT values seen in the LOTS trial after 18 months of treatment (3% improvement in FVC and a 28 m gain in the 6MWT) to be relatively modest and appeared inconsistent with the substantial survival benefit claimed on the basis of the observational EMC/IPA survey population.

The EMC research report plotted unadjusted Kaplan-Meier survival curves for the ever treated and never treated patient groups.

No new safety issues were identified.

*For PBAC's comments on these results, see Recommendation and Reasons.*

## **9. Clinical Claim**

The submission claimed that the results of the EMC research report show 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.*

The PBAC considered that, in spite of the new Erasmus data, and the multiple analyses thereof, significant uncertainty remains as to whether alglucosidase therapy as proposed substantially prolongs life.

## **10. Economic Analysis**

The re-submission did not present an economic evaluation. The PBAC has previously accepted that alglucosidase alfa is not cost-effective.

## **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 in Year 5, at an estimated net cost per year to the Government of between \$10-30 million in Year 5.

## **12. Recommendation and Reasons**

As previously, the key study in the re-submission remained the LOTS trial, a randomised comparison of alglucosidase versus placebo in patients with late-onset Pompe disease. The key results were a 3% improvement in FVC and a 28m gain in the 6MWT associated with alglucosidase treatment compared to placebo after 18 months. However, the PBAC had expressed concern about the relevance of these surrogate outcomes for patient survival.

The resubmission presented new survival data based on unpublished reports from the Erasmus Medical Centre (EMC)/International Pompe Association (IPA) Pompe survey, an 8-year prospective observational study. The PBAC agreed that the Erasmus study was probably more relevant to the Australian population than the trial population but acknowledged that the information was typical of that seen with rare diseases – low quality, uncontrolled data with major inherent and unknown biases. Varying analytical choices have been performed to try and overcome the resulting confounders.

Between 2002 and February 2011 there were statistically significantly more deaths in the in the never treated group than in the ever treated group in the EMC/IPA survey population. These results were based on a non-randomised comparison and the PBAC considered that any differences in death between treatment groups cannot necessarily simply be attributed to alglucosidase treatment due to potential confounding factors that may mean that there are systematic differences between the ever-treated and the never-treated groups. No deaths were recorded in either arm over 18 months in the LOTS trial.

The re-submission extrapolated the results of the EMC research report using various survival models and claimed that alglucosidase treatment may be associated with a mean survival benefit of between 4.58 years and 12 years compared to no treatment. The PBAC considered that this estimate was highly uncertain due to the limitations of the EMC research report. Additionally, there was sufficient uncertainty associated with the long-term survival of patients with late-onset Pompe disease to make it difficult to reliably extrapolate the results.

The PBAC noted that the proposed price of alglucosidase per vial had been reduced in the re-submission and was now claimed to be comparable to other LSDP drugs. The PBAC considered that, while the revised Australian price was comparable to idursulfase (for the treatment of MPS Type 2); it was still substantially more expensive than other drugs listed on the LSDP and the international prices quoted were not accepted at face value as it seemed that the only negotiated price was with the Department of Veterans Affairs in the US (based on local regulations).

The PBAC considered that decision making around the type of patient in whom to initiate therapy and when this should start in Australia was critical, particularly as it involved starting a patient on long term therapy at a very high cost per annum. Better definition around what level of functional incapacity and the discontinuation rules were also needed before the PBAC could identify which patients would be treated with alglucosidase under the LSDP. The possibility of dose titration based on residual activity instead of using a fixed dose of

regimen was raised, but the sponsor's clinical expert at the Hearing stated that it was not possible to do so at this stage.

The PBAC considered that, in spite of the new Erasmus data, and the multiple analyses thereof, significant uncertainty remains as to whether alglucosidase therapy as proposed substantially prolongs life. It was accepted that the dataset was the best that is likely to be obtained and that the study provided some new information that contributed to the discussion. However, the paucity of the data and the difficulty in interpreting it did not allow committee to have confidence that it was prolonging life.

PBAC therefore deferred its decision on the submission for alglucosidase to seek further analysis of observational data provided to see if it will allow PBAC to have confidence that criterion 4 of LSDP guidelines has been met.

The PBAC also acknowledged and noted the consumer comments received in its consideration of alglucosidase.

***Recommendation***  
**Defer**

**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 disappointed at the PBAC deferring its recommendation on Myozyme for late-onset Pompe disease, given the new evidence provided in the submission. Genzyme Australasia continues to be committed to working with the PBAC and the LSDP to demonstrate the life-saving benefit of Myozyme experienced by 1500 patients worldwide and ensure that people with late-onset Pompe disease have funded access to treatment.