PUBLIC SUMMARY DOCUMENT
Product: Alglucosidase alfa-rch, powder for I.V. infusion, 50 mg, Myozyme®
Sponsor: Genzyme (A Division of Sanofi-Aventis Australia Pty Ltd)
Date of PBAC Consideration: November 2012

1. Purpose of Application

To provide the PBAC with additional data in support of the claim that alglucosidase alfa substantially prolongs life and thereby meets criterion 4 of the Life Saving Drugs Program for the treatment of patients with 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 five previous occasions (July 2008, March 2009, November 2009 , November 2010 and July 2011) for the treatment of late onset Pompe disease. Details of these considerations are in the relevant Public Summary Documents available at:

http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product

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 submission sought a recommendation from the PBAC that alglucosidase should be included in the LSDP for the treatment of late onset Pompe disease. This is unchanged from July 2011. The submission 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. This is unchanged from July 2011. The PBAC has previously considered this appropriate.

7. Clinical Trials

The key study in the July 2011 submission was the LOTS trial with additional survival data from the Erasmus Medical Centre (EMC)/International Pompe Association (IPA) Pompe survey.

See July 2011 Public Summary Document for study details.

The current submission presented updated survival data and additional analyses of the data from the EMC/IPA survey based on a draft publication (submitted for publication but not yet published at the time of PBAC consideration) by Güngör and colleagues.

8. Results of Trials

There were fewer deaths reported in the alglucosidase treated group compared to untreated patients. The majority of patient deaths were in patients who required respiratory support and/or wheelchair use at study entry. Whether these patients (i.e. those requiring respiratory support and/or wheelchair use) would qualify for treatment under the LSDP remained unclear.

Treatment with alglucosidase was associated with a statistically significant improvement in survival compared to untreated patients. However, this result was in the context of a non-randomised, observational study.

The magnitude of benefit in terms of life expectancy was uncertain as the submission presented survival results in terms of relative measures (hazard ratio) but did not provide any absolute measure of survival. The submission, through the Pre-Sub-Committee Response, provided estimates of absolute survival benefit. However, these estimates of absolute survival benefit were unable to be verified, due to insufficient information about how they were derived.

The analyses presented in the submission did not address whether the survival gain associated with alglucosidase treatment varies with disease severity. Such data could inform PBAC decision making by identifying the subgroup of patients most likely to benefit from treatment.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that the results of the updated EMC/IPA survey 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.

10. Economic Analysis

The submission did not present an economic evaluation. This was reasonable given that the PBAC had previously accepted that alglucosidase is not cost effective for PBS listing.

11. Estimated PBS Usage and Financial Implications

These were unchanged from the July 2011 submission. The July 2011 submission estimated the number of patients per year 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

The PBAC noted that the median life expectancy for late onset Pompe disease patients was estimated to be approximately 60 to 65 years in comparison with the median life expectancy in the general Australian population of about 80 years.

The submission presented an analysis of survival data from a currently unpublished study from the Erasmus Medical Centre and International Pompe Association survey (EMC/IPA survey). This is an ongoing, non-randomised observational cohort study on the clinical condition; the current analysis presented in the submission included patients with late-onset Pompe disease. Patients completed an annual questionnaire assessing disease status, functional status and quality of life. The study included several international centres including Australia, Canada, Germany, the USA, the UK and the Netherlands.

Four different statistical models (with different variables specified as time-varying) were used in the analysis of EMC/IPA data, all of which produced similar results. The PBAC noted that the main analysis of the submission obtained a hazard ratio (HR) favouring alglucosidase alfa treatment. The PBAC noted that no arithmetic measure of treatment effect (e.g. life years gained) was provided in the submission. A HR on its own is impossible to interpret because the health gain associated with a particular HR (hazard ratio) depends on the underlying hazard rate.

The sponsor, in consultation with the EMC/IPA study's authors, provided an estimate of survival gain obtained with alglucosidase alfa treatment, taking into consideration adjustments for potential confounders (i.e. prognostic variables). The PBAC noted that explicit details of the method of derivation of this estimated arithmetic survival benefit were not provided, therefore the validity of this estimate could not be established. Also, a confidence interval around the point estimate was requested prior to the meeting, but this was not provided.

While recognising the challenges (and noting the surrogate data previously considered) of generating high-quality data for rare conditions such as late onset Pompe disease, the PBAC considered that the new analysis of the observational data set did not provide a firm basis to support the submission's claims. Specifically, the PBAC considered that as a non-randomised comparison, the analysis may be subject to biases due to unmeasured or unknown

confounders. Also, the PBAC was concerned that there could be residual confounding within the broad categories of the prognostic variable "disease severity", which is a critical variable in the statistical model.

The PBAC also noted that the submission did not propose initiation and continuation criteria by which to clearly define the patient population that would be most likely to benefit from treatment with alglucosidase alfa. The PBAC noted that Australasian Society for Inborn Errors of Metabolism/ Australia New Zealand Association of Neurologists draft guidelines and indications for therapy in late-onset Pompe disease with alglucosidase alfa were submitted separately from the submission and do not represent a sufficient basis to precisely identify the population who would be treated, given the variability of the disease in its late-onset form.

The PBAC noted that the price of alglucosidase alfa in the current submission was lower than the price proposed in the July 2011 submission. The PBAC noted that the average cost included the cost of currently-treated patients with infantile-onset Pompe disease; as alglucosidase alfa is dosed according to body weight, the cost of treating patients with the late-onset form of the disease is expected to be correspondingly higher.

The PBAC noted that the price remained extremely high, with an estimated net cost in the range of $10 - 30 million in Year 5 for less than 10,000 patients, and that this represented a substantial opportunity cost of listing alglucosidase alfa. The PBAC recalled that in the sponsor's July 2011 comparison of international prices for alglucosidase alfa, it seemed that the only negotiated price quoted was with the Department of Veterans Affairs in the US (based on local regulations). The PBAC therefore had not accepted this comparison at face value. The current submission did not address this issue.

The PBAC therefore rejected the re-submission on the basis of uncertainty about whether the lifespan of a patient with late onset Pompe disease would be substantially extended as a direct consequence of using alglucosidase alfa.

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 is disappointed with the PBAC recommendation but is committed to working with the PBAC and LSDP to ensure access for patients.