Scottish Medicines Consortium

alglucosidase alfa 50mg powder for concentrate for solution for infusion (Myozyme) No. (352/07)

Genzyme

9 February 2007

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

alglucosidase alfa (Myozyme®) is not recommended for use within NHS Scotland for the treatment of Pompe disease (acid α-glucosidase deficiency).

Treatment in patients with the infantile-form of Pompe disease significantly improved survival compared with historical controls. The evidence is less clear for patients who are already receiving ventilatory support or who have the late-onset form of the disease. The economic case has not been demonstrated.

The SMC orphan drug policy requires manufacturers to make complete submissions to allow a comprehensive product assessment similar to all other drug submissions. However, in addition to the usual assessment of clinical and cost-effectiveness, SMC may consider additional factors specific to orphan products. Within this context the particular features of the condition and population receiving the technology and whether a drug can reverse (rather than stabilise) the condition or bridge a gap to a definitive therapy may also be considered.

SMC considered the submission in the context of its orphan drug policy.

Overleaf is the detailed advice on this product.

Vice-Chairman
Scottish Medicines Consortium

Indication

For long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). The benefits in patients with late-onset Pompe disease have not been established.

Dosing information

20mg/kg of body weight administered once every two weeks as an intravenous infusion.

Product availability date

May 2006

Summary of evidence on comparative efficacy

Pompe disease is a rare autosomal recessive disorder caused by a deficiency of the lysosomal enzyme responsible for degrading glycogen (acid α-glucosidase). This results in the lysosomal accumulation of glycogen leading to high levels in various tissues, particularly cardiac and skeletal muscle, as well as respiratory muscle, which causes myopathy, cardiomyopathy and respiratory failure. Pompe disease ranges in severity from a rapidly progressing infantile-onset form (onset of symptoms typically within the first year of life and a very short expected lifespan) to a less rapidly progressing late-onset form. Infantile-onset disease may be subclassified as infantile-classic or non-classic (a more slowly progressive form of infantile-onset disease). Treatment has been of palliative and supportive nature. Alglucosidase alfa is a recombinant human acid α-glucosidase which due to the rarity of the condition (estimated to be 0.137 per 10,000 population in the European Union) has been designated an orphan drug.

Two key clinical studies have assessed the efficacy of alglucosidase alfa in patients with infantile-onset Pompe disease. The first study enrolled 18 patients aged ≤ 6 months with a diagnosis of infantile-onset Pompe disease and cardiomyopathy (measured by left ventricular mass index (LVMI) ≥ 65g/m^2). The study excluded patients who had symptoms of respiratory insufficiency or required any ventilatory support. Patients were randomised to receive alglucosidase alfa 20mg/kg or 40mg/kg every two weeks. The primary endpoint was the proportion of patients alive and free of invasive ventilation at 18 months of age. At this time, after 52 weeks of treatment, the Kaplan-Meier proportional estimate of survival based on time to invasive ventilation or death was 83% (95% CI: 66,100) in the combined dose alglucosidase alfa group (n=18); 89% (95% CI: 68,100) in the 20mg/kg group (n=9) and 78% (95% CI: 51,100) in the 40mg/kg group (n=9). These results were compared to data from a matched subgroup of patients from an untreated historical cohort. Since the historical data contained no information on invasive ventilator survival, comparison of this endpoint was not possible. At 18 months of age, one of 61 untreated patients was alive corresponding to a Kaplan-Meier proportional estimate of survival based on time to death of 1.9% (95%; 0.0, 5.5). Further Cox proportional hazards regression against a subgroup (n=42) of the 61 untreated patients born in or later than 1993 included treatment, age of diagnosis and age at symptom onset as time-varying covariates. This demonstrated that alglucosidase alfa reduced the risk of death by 99% (hazard ratio: 0.01; 95% CI: 0.00, 0.10; p<0.0001). In addition, alglucosidase alfa-treated patients experienced improvements in cardiomyopathy, growth, motor development and functional status.

The second study assessed the efficacy of alglucosidase alfa (at an initial dose of 20mg/kg every two weeks) in patients with a diagnosis of infantile-onset Pompe disease aged > 6 months and ≤ 36 months. Patients were older than in the first study and had more advanced disease. Eligible patients had LVMI ≥ 65g/m^2 in patients aged ≤ 12 months or >79g/m^2 in those > 12 months. Patients were excluded if they had signs or symptoms of cardiac failure and ejection fraction < 40%. The primary endpoint was survival based on all cause mortality. Results of interim analysis are available for the first 15 patients who have been treated for 52 weeks at which time 11 were still alive (73%; 95% CI 45, 92). This compared to a survival rate of 37% (95% CI: 14, 61) in a matched subgroup of untreated patients (n=16). Further Cox proportional hazards regression against a subgroup (n=48) of untreated patients born in or later than 1995 included treatment, age of diagnosis and age at symptom onset as time-varying covariates. This demonstrated that alglucosidase alfa reduced the risk of death by 71% (hazard ratio: 0.29; 95% CI: 0.11, 0.81; p<0.018). Ten of these patients were free of invasive ventilator support at baseline and five (50%) remained so after 52 weeks. The five patients who were receiving invasive ventilatory support at baseline continued to need this with the exception of one patient who died. The majority of treated patients also demonstrated improvements in cardiomyopathy and growth.

The efficacy of alglucosidase alfa has also been assessed in an open-label study in five patients (aged 5-18 years) with late-onset Pompe disease. Interim results are available after treatment with 20mg/kg every two weeks for 26 weeks. At baseline, all patients were ambulant and only one patient required ventilatory support in the form of non-invasive nocturnal ventilation. Three of the five patients had significant improvements (forced vital capacity (FVC) in the sitting position +12% and +16%). Three patients had pulmonary involvement at baseline (FVC <80% of predicted) and two of those were among the responders. There were mixed results on evaluation of motor function.

Additional data were presented on ten patients with advanced late-onset Pompe disease based on submitted physicians' narratives.

Summary of evidence on comparative safety

Treatment with alglucosidase alfa was generally well tolerated with the most common adverse events of pyrexia (probably due to the underlying disease), flushing, urticaria and rash. The majority of these were assessed as infusion-associated reactions. The majority of patients developed inhibitory antibodies to recombinant human acid α-glucosidase and one patient tested positive for in vitro inhibitory effects.

Summary of clinical effectiveness issues

The available evidence demonstrates that alglucosidase alfa significantly prolonged survival and ventilator-free survival in patients with infantile-onset Pompe disease over 52 weeks when compared to results from a historical control subgroup. The results were most marked in patients with the more severe form of the disease (infantile-classic) who began treatment before 6 months of age and had little respiratory involvement at baseline. In the majority of patients there were also significant clinical benefits in terms of improvements in cardiomyopathy, growth, motor function, and functional skills/status. However it is unclear whether these patients remain in good health in the long-term or continue to deteriorate. At present, due to limited numbers of patients, it is not possible to determine whether patients already receiving ventilatory support would benefit from alglucosidase alfa treatment in terms of pulmonary function. In addition, other clinical benefits have not been quantified in these patients.

Although some of the late-onset patients showed positive clinical responses when treated with alglucosidase alfa, the absence of clear endpoints (including quality of life assessment) and the lack of a valid control group make the data difficult to interpret. It is not clear that the results in patients with infantile-onset disease can be extrapolated to those with late-onset disease. A randomised, placebo-controlled study is planned to assess treatment in these patients. The SPC notes that the benefits in patients with late-onset disease have not been established.

Summary of comparative health economic evidence

The economic model considered three distinct subgroups of patients: infants who receive their first dose of alglucosidase alfa before the age of six months; infants who receive their first dose of alglucosidase alfa between the ages of six months and three years; and people with severe late-onset Pompe disease. Given the different levels of treatment effectiveness in these patient populations, this was a useful approach to adopt. The comparison in each case was current treatment, which was supportive care, hospitalisation and the use of ventilation where appropriate. A lifetime horizon was used in the model, which was appropriate given the continuing nature of alglucosidase alfa treatment. The model categorised patients according to their need for ventilation.

Clinical data for the two infant models came from the appropriate clinical studies and used a matched historical cohort for infants in the comparator arm. In both of these models it was necessary to estimate likely survival with alglucosidase alfa after the end of the clinical trial periods. Expert opinion was used to suggest that life expectancy would be an average of 20 years and 15 years respectively and that the survival curves in each case followed the shape for that of the general population. A survival advantage for alglucosidase alfa was incorporated into the infant models and was a key driver of the results. Utility values were estimated by asking a clinical expert but the utility scores were not assumed to vary according to whether the infant received alglucosidase alfa or current treatment or according to the need for ventilation. Costs were largely informed by existing clinical guidelines and expert opinion. In general, the analysis was well conducted and clearly presented.

The results for the two infant groups were £244,450 and £318,283 per QALY respectively compared to current treatment. The cost per QALY for the late-onset group was £819,806. Sensitivity analysis indicated that there was variation in these estimates but only when the model horizon was set at the length of the clinical trial did the ICER fall significantly and given that the treatment is ongoing, this would not be an appropriate point at which to truncate the analysis.

The analysis was clear, concise and well conducted but given the extremely high cost for health gain, the economic case has not been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Association of Glycogen Storage Disease (UK)

Additional information: comparators

There are no comparators to alglucosidase alfa. Patients have traditionally been managed with supportive and palliative care.

Additional information: costs

The dose and hence cost of alglucosidase alfa are weight dependent. The costs below illustrate doses for a 10kg infant (mean weight for a one year old) and a 60kg adult. When treating children the body weight, dose and hence cost will increase regularly.

Drug	Dose	Cost per year (£)
Alglucosidase alfa (Myozyme®)	20mg/kg by intravenous infusion every 2 weeks	10kg child: 38,333 60kg adult: 230,000

Additional information: budget impact

The manufacturer estimated the gross drug budget impact of alglucosidase alfa in infants at £167k in year 1 and £210k in year 5. The respective cost for late onset patients was £1.04M in year 1 and £2.6M in year 5. The model assumes 2 infants treated in year 1 and four in year 5 and for late onset disease 4 and 10 patients respectively. All eligible patients were assumed to receive treatment.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 31 January 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted reference was supplied with the submission.

Kishnani PS, Corzo D, Nicolino M et al. Recombinant human acid α-glucosidase: Major clinical benefits in infantile-onset Pompe disease. Neurology 2007; 68: 1 – 11.