HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 September 2006

Myozyme 50 mg, powder concentrate for solution for infusion
1 x 20mL glass vial: CIP code 569 575-1
10 x 20mL glass vials: CIP code 569 576-8
25 x 20mL glass vials: CIP code 569 577-4

Applicant: Genzyme S.A.S.

alglucosidase alpha

list I
Medicine reserved for hospital use
Orphan drug status

Date of Marketing Authorisation (centralised): 29/03/2006

Reason for request: inclusion on the list of medicines approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

alglucosidase alpha

1.2. Background

Alglucosidase alpha is a recombinant form of human acid α-glucosidase and is produced by recombinant DNA technology using Chinese Hamster Ovary (CHO) cell culture. It is an enzyme replacement therapy.

1.3. Indication

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

1.4. Dosage

Myozyme treatment should be supervised by a physician experienced in the management of patients with Pompe disease or other hereditary metabolic or neuromuscular diseases.

The recommended dosage regimen of alglucosidase alpha is 20 mg/kg bodyweight administered every-other-week by intravenous infusion.

Infusions should be administered incrementally. The recommended initial infusion rate is 1 mg/kg/hr. This rate is increased by 2 mg/kg/hr every 30 minutes if there is no sign of infusion-associated reactions (IARs), until a maximum rate of 7 mg/kg/hr is reached.

- *Dosage for children, adolescents, adults and elderly patients*

  The safety and efficacy of Myozyme have been assessed mainly in children whose ages range from birth to adolescence.

  There is no need for special measureswhen Myozyme is administered to children, adolescents, adults or elderly patients.

- *Patients with renal or hepatic failure*

  The safety and efficacy of Myozyme have not been assessed in patients with renal or hepatic failure and no specific dosage regimen can be recommended.

Patient response to treatment should be regularly assessed, based on a comprehensive evaluation of all clinical manifestations of the disease.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

A : Alimentary tract and metabolism
A16 : Other alimentary tract and metabolism products
A16A : Other alimentary tract and metabolism products
A16AB : Enzymes
A16AB07 : alpha glucosidase

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

Assessment of the efficacy and safety of Myozyme is mainly based on two trials in the infantile form of Pompe disease (trial AGLU01602 and trial 1702), and on a trial (AGLU 02804) and observational data in the late-onset form.

3.1. Efficacy

3.1.1 Infantile form

- **Trial AGLU01602**

A non comparative trial to assess the efficacy and safety of Myozyme in 18 non-ventilated patients with infantile Pompe disease, aged 6 months or less at the start of treatment. Efficacy results were compared to historical data for a subgroup (n = 42) of an untreated cohort of patients (AGLU004) with similar characteristics to those in the AGLU01602 trial.

Patients were randomised to receive either 20 mg/kg or 40 mg/kg every-other-week for 52 weeks.

Main inclusion criteria

- age ≤ 6 months at treatment initiation
- clinical picture compatible with Pompe disease, and acid α-glucosidase (GAA) deficiency confirmed by peripheral blood leukocyte count
- patients with cardiomyopathy confirmed by a Left Ventricular Mass Index (LVMI) ≥ 65 g/m^2 , assessed by a cardiologist by two-dimensional echocardiography.

Main non-inclusion criteria

- symptoms of respiratory insufficiency including PaO_2 < 90% on room air
- major congenital abnormalities or serious condition not related to Pompe disease
- any type of ventilation support at time of inclusion
- patient already treated by enzyme replacement therapy.

The primary endpoint was the time from diagnosis to occurrence of an event (death and/or invasive ventilation support). Survival in patients free of invasive ventilation support was not recorded in the historical cohort. No comparison could thus be made using this end-point

Secondary endpoints
Survival free of any invasive ventilation support, survival free of any ventilation support (whether invasive or noninvasive), left ventricular mass reduction, growth, and improvement in motor function.

Results

Median age at diagnosis was 4.4 ± 2.2 (0.2–6.8) months.

After 52 weeks of treatment, all 18? patients treated by Myozyme were alive and 15/18 were free of ventilation support. In the historical subgroup, 1 of 42 patients, aged 18 months, was alive (survival was the only endpoint assessed).

A mean decrease of 57.6% in left ventricular mass compared to baseline was observed in the 12 patients for whom data was available.

Motor function score was measured by motor performance scores at equivalent age on the Alberta Infant Motor Scale (AIMS). It was improved in 13 patients (72.2%) compared to baseline. After 26 weeks of treatment by Myozyme, growth in terms of weight and height was stabilized or improved compared to baseline in 72% and 94% of patients, respectively.

Efficacy results were no different between the two dosage groups (20 mg or 40 mg/kg every-other-week). The dosage of 20 mg/kg every-other-week was chosen.

- **Trial 1702**

A non comparative trial assessing the efficacy and safety of Myozyme in 21 patients with non typical infantile Pompe disease, aged 6 months to 3.5 years at treatment initiation. Efficacy results were compared to historical data from a subgroup (n = 48) of an untreated cohort of patients (AGLU004) with similar characteristics to those of patients in the AGLU01702 trial.

Patients received Myozyme 20 mg/kg every-other-week for 52 weeks.

Main inclusion criteria
- age ≥ 6 months and ≤ 36 months at treatment initiation,
- clinical picture compatible with Pompe disease confirmed before the age of 12 months and documented GAA deficiency
- patients with cardiomyopathy confirmed by a Left Ventricular Mass Index (LVMI) ≥ 65 g/m^2 in patients of ≤ 12 months, and a LVMI > 79 g/m^2 in patients over 12 months, assessed by a cardiologist by two-dimensional echocardiography.

Main non-inclusion criteria
- symptoms and signs of heart failure with ejection fraction < 40%
- major congenital abnormality or serious condition not related to Pompe disease
- patient already treated by enzyme replacement therapy.

Primary endpoint
Time from diagnosis to occurrence of an event (death and/or invasive ventilator support).

Secondary endpoints
Survival free of invasive ventilator support, survival free of ventilator support (whether invasive or noninvasive), reduction of left ventricular mass, growth, and improvement in motor function.

Results

Median age at diagnosis was 6.7 ± 5.8 (1.9–22.6) months.

Interim analysis

In the first 15 patients included and treated for 52 weeks, the survival rate was 73% (CI 95%: 44.9–92.2) in the Myozyme group versus 37% (CI 95%: 13.8–61.2) in an untreated group drawn from the historical data.

The protocol included an analysis of survival rates by subgroup according to age (< 1 year and > 1 year), which showed:

- survival rates of 50% (3/6) in patients treated by Myozyme and 16.2%[1] in the historical subgroup, in patients < 1 year,
- survival rates of 88.9% (8/9) in patients treated by Myozyme and 45.5% in the historical subgroup, in patients > 1 year.

Of the 10 patients free of invasive ventilation support at baseline:

- 3 died
- 2 required invasive ventilation support
- 5 did not require ventilation support.

Thirteen out of the 15 patients (86.6%) with follow-up data showed a 33% improvement in ventricular ejection fraction as compared to baseline.

Stabilization or improvement of growth parameters was seen in 80% 93.3% of patients for weight and height, respectively.

Six out of the 15 patients assessed (40%) had improvement of motor function score as compared to baseline, measured by motor performance on the Alberta Infant Motor Scale (AIMS).

3.1.2 Late-onset form

A non-comparative trial (AGLU 02804) was carried out to assess the safety and efficacy of Myozyme in 5 patients with late-onset Pompe disease, aged 5–15 years at treatment initiation.

Patients received Myozyme 20 mg/kg every-other-week for 26 weeks.

All patients were ambulatory and 4 did not require any form of ventilation support (1 patient required nocturnal non-invasive ventilation).

Ofthe 3 patients with substantial respiratory involvement at inclusion (predicted percentage of forced vital capacity (FVC) in the sitting position ranging from 58–67%), 2 showed improvement in FVC in the sitting position (between +11.5 and +16%) by week 26.

Results for motor function were not concordant; no conclusion could be drawn.

As part of an expanded access programme (EAP), observational data were gathered after 8 months to 2.8 years of Myozyme treatment in 18 patients with late-onset form, aged 9–42 years. Eight patients needed invasive ventilation support. All 18 treated patients were wheelchair-bound.

One patient showed an improvement of 35% in FVC and 5 patients a reduction in number of hours of ventilation support. Results for motor function were not concordant; no conclusion could be drawn.

Assessment of respiratory function and motor function showed variable results. Patients with a higher degree of residual muscle function showed better results.

[1] Estimated survival rate (Kaplan Meyer analysis).

3.2. Undesirable effects

Assessment of the safety of Myozyme in clinical trials of the infantile form of Pompe disease showed that 51.9% of patients had a treatment-related adverse event. In most cases, it was an infusion-associated reaction such as skin rash, urticaria or pyrexia.

There were fewer safety data for the late-onset forms. In most cases, they involved - as in the infantile form - infusion-associated reactions such as intolerance. In all these trials, reactions were considered to be mild and resolved satisfactorily. None of the adverse events required treatment discontinuation. However, the applicant mentioned 4 major infusion-associated reactions that were notified to Genzyme in March - April 2006. These were life-threatening anaphylactic reactions.

Most patients developed anti-rhGAA antibodies during the first 3 months of treatment. No relationship was established between infusion-associated reactions and seroconversion.

3.3. Conclusion

In trial 1602, Myozyme treatment increased survival in Pompe disease patients aged under 6 months. The 18 patients treated with Myozyme were alive at the age of 18 months, while in the untreated historic subgroup, one out of the 42 patients was alive.

Improvements in cardiomyopathy, growth and motor function were also observedin most patients.

In trial 1702, interim analysis results for the first 15 patients included, treated for 52 weeks, showed a survival rate of 73% (95%CI: 44.9–92.2) in the Myozyme group versus 37% (95% CI: 13.8–61.2) in an untreated historic subgroup. Cardiomyopathyand growth improved in most patients, and growth improved in almost half of the patients.

The main adverse events were infusion-associated reactions (pyrexia, urticaria and rash).

There are no long-term efficacy and safety data available.

Since data on late-onset Pompe disease are very limited (one noncomparative trial in 5 patients and observational data, the therapeutic use of Myozyme has not been established.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

- Pompe disease is a rare, fatal metabolic myopathy. It belongs to the lysosomal storage disorders. It is caused by a deficiency of, a naturally-occurring lysosomal hydrolase, acid α-glucosidase, which degrades lysosomal glycogen into glucose. Deficiency in this enzyme results in glycogen accumulation in various tissues, especially in cardiac, respiratory and skeletal muscles, leading to hypertrophic cardiomyopathy and progressive muscle weakness, including impairment of respiratory function.
- It is a replacement therapy.
- It is a first-line therapy.
- There is no alternative therapy.
- The efficacy/safety ratio is substantial in the infantile form and not well established in the late-onset form.

- Public health benefit.
  - Pompe disease is a serious disease with a low public health burden because it is a rare (orphan) disease.
  - Improving the management of orphan diseases is one of the priorities that has been identified in France (GTNDO[2], *Plan Maladies Rares*); its treatment is therefore a public health need.
  - In view of the data available, Myozyme is expected to have a moderate impact in terms of morbidity and mortality for the infantile form of Pompe disease. However, giventhe small number of patients involved, Myozyme can have only a small impact on morbidity and mortality on a population scale.
  - Myozyme should therefore offer a partial response to the identified public health need.
  - It is therefore expected to benefit public health in infantile Pompe disease. This benefit is moderate.

The Committee considered that the actual benefit is:
- substantial in the infantile form of Pompe disease
- insufficient in the absence of current formal evidence of efficacy in late-onset Pompe disease (defined by the Committee as disease in which symptoms begin after 5 years of age according to available clinical).

4.2. Improvement in actual benefit

Myozyme offers a substantial improvement (level II) in actual benefit in the management of the infantile form of Pompe disease only.

4.3. Therapeutic use

The usual management of Pompe disease has been symptomatic and palliative depending on the degree of cardiac (mainly in the infantile form) motor or respiratory involvement.

In infantile Pompe disease, intravenous Myozyme is the first curative enzyme replacement therapy. In late-onset Pompe disease, it is not possible to specify the therapeutic use of Myozyme on the basis of the clinical data available.

4.4. Target population

Calculations based on epidemiological data from Ausems[3], Meikle[4], Martiniuk[5] and 2005 INSEE[6] data suggest that, for all forms taken together, there are currently 430–710 patients with Pompe disease in France.

Patients with the infantile form (< 1 year) have a short life expectancy and thus represent a very small percentage of the clinical forms requiring treatment.

The disease affects 1 birth per 40 000 worldwide[3], which would give an incidence of around 20 cases per year in France[7].

4.5. Transparency Committee recommendations

The Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services in the infantile form of Pompe disease.

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[2] DGS/GTNDO: The French National Health Executive's Technical Group for Defining Objectives

[3] Ausems MGEM *et al*. Frequency of glycogen storage disease type II in the Netherlands: implications for diagnosis and genetic counseling. Eur J Hum Genet 1999; 7: 713-716

[4] Meikle PJ *et al*. Prevalence of lysosomal storage disorders. JAMA 1999; 281: 249-254

[5] Martiniuk F *et al*. Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease 1998;79:69-72.

[6] INSEE: French National Institute for Statistics and Economic Studies

[7] 767 816 births in France in 2004 (INSEE data)

The Committee did not recommend inclusion on the list of medicines approved for use by hospitals and various public services in the late-onset form of Pompe disease.

The Committee drew the attention of the authorities to the situation of patients with a late-onset form of the disease currently treated with Myozyme under the ATU (authorisation for temporary use). If the authorities decide that these patients should continue to be treated, management should include periodic assessment of treatment on a case-by-case basis, to assess the clinical benefit and decide on future treatment.

The Committee also recommended that newly diagnosed patients with the late-onset form of the disease should be included in clinical trials of Myozyme.

The Committee will re-examine Myozyme in the late-onset form of Pompe disease in view of the results of the comparative trial to be submitted to the European Medicines Evaluation Agency (EMEA) and/or any new data the applicant may submit.