HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

21 June 2006

Naglazyme 1 mg/mL, concentrate for solution for infusion
1 glass vial of 5 mL: CIP code 567 218-7

Applicant: BioMarin Europe Ltd

galsulfase (mammalian/hamster/CHO cells)

list I
Medicine reserved for hospital use
Orphan drug status

Date of Marketing Authorisation: 24/01/2006

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

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

galsulfase (mammalian/hamster/CHO cells)

1.2. Background

Galsulfase is a recombinant form of human N-acetylgalactosamine 4-sulfatase (rhASB). It is an enzyme replacement therapy.

Naglazyme is the first medicinal product granted an indication in the treatment of mucopolysaccharidosis VI (MPS VI) or Maroteaux-Lamy syndrome.

1.3. Indications

Naglazyme is indicated as long-term enzyme replacement therapy in patients with a confirmed diagnosis of mucopolysaccharidosis VI (MPS VI; N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux-Lamy syndrome) (see SPC section 5.1).

As with all lysosomal genetic disorders, it is of primary importance, especially in severe forms, to start treatment as early as possible, before irreversible clinical manifestations of the disease appear.

It is very important to treat young patients under 5 with a severe form of the disease, even though patients under 5 were not included in the pivotal phase III study.

1.4. Dosage

Naglazyme therapy should be supervised by a doctor experienced in managing patients with MPS VI or other inherited metabolic diseases.

Naglazyme should be given in an appropriate clinical setting with access to resuscitation equipment to deal with medical emergencies.

The recommended dosage schedule for galsulfase is 1 mg/kg bodyweight once a week, by intravenous infusion over 4 hours. The initial infusion rate should be adjusted so that approximately 2.5% of the total volume of solution is infused during the first hour, and the remaining volume (approximately 97.5%) over the next 3 hours.

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
A16AB08 : Galsulfase

2.2. Medicines in the same therapeutic category

None.

2.3. Medicines with a similar therapeutic aim

Haematopoietic stem cell transplant or bone marrow transplant.

3 ANALYSIS OF AVAILABLE DATA

The dossier contains 3 trials: ASB-00-01, ASB-01-04, and ASB-03-05.

ASB-00-01: a double-blind phase I/II dose-comparison trial. This will not be described below.

3.1. Efficacy

ASB-01-04: a 48-week phase II noncomparative single-dose study to assess the efficacy, safety and pharmacokinetics of rhASB in 10 patients aged 5 and over with MPS VI.

Primary endpoint (composite): range of shoulder movement, 3-minute stair climb test, 12-minute walk test and urinary glycosaminoglycan (GAG) levels.
Patients were given rhASB 1 mg/kg/week for 48 weeks.

Results
In the 12-minute walk test, a mean increase of 155 ± 146 metres was seen at 24 weeks for the 10 patients compared to baseline.
In the 3-minute stair climb test, mean increase between baseline and value at 24 weeks for the 10 patients was 48 ± 48 stairs.
A 71% decrease in urinary GAG was seen after 24 weeks. Mean creatinine levels fell from 336 ± 116 µg/mL (baseline value) to 103 ± 50 µg/mL at 24 weeks.
There was no significant improvement in range of shoulder movement in terms of active flexion, active extension or active lateral rotation at 24 weeks compared to baseline.

Pivotal trial (ASB-03-05):
A 24-week randomised double-blind placebo-controlled phase III trial to assess the efficacy and safety of recombinant human N-acetylgalactosamine 4-sulfatase (rhASB) in 39 patients with mucopolysaccharidosis VI (MPS VI[1]).

Therapy
During the first part of the 24-week trial, patients received weekly (7 ± 3 days) IV infusions of:
- either rhASB 1.0 mg/kg/week (n = 19),
- or placebo solution (n = 20).

Patients were pretreated with antihistamines (diphenhydramine 0.5 mg/kg, or promethazine 0.15 mg/kg) to prevent anaphylactic reactions.

After 24 weeks, patients in both groups were given rhASB 1.0 mg/kg/week for 24 weeks (open-label extension).

Primary efficacy endpoint: walking capacity measured by the 12-minute walk test at 24 weeks.

Secondary endpoints: 3-minute stair-climb test (nonstandardised test) and urinary glycosaminoglycan (GAG) levels.

[1] Diagnosis confirmed by leukocyte arylsulfatase enzyme activity of less than 10% compared with normal. Distance walked in 6 minutes had to be 5–270 metres and distance walked in 12 minutes under 400 metres.

Results

Patients were aged 7 and over for the rhASB group, and 5 and over for the placebo group.

Patients who had undergone haematopoietic stem cell transplantation were excluded; one patient had undergone bone marrow transplantation 11 years previously.

36 of the 39 patients had already participated in the open-label phase II trial and had taken rhASB 1 mg/kg/week.

Walking capacity in the 12-minute test at 24 weeks (in metres)

	rhASB			Placebo			rhASB vs. placebo
	Baseline value	Week 24	Difference	Baseline value	Week 24	Difference	
n	19	19	19	20	19	19	
mean ± standard deviation	227 ± 170	336 ± 227	109 ± 154	381 ± 202	399 ± 217	26 ± 122	83 ± 45[a] 92 ± 40[b] p = 0.025

[a] mean observed difference; [b] mean adjusted difference

A mean walk test improvement of 92 ± 40 metres in favour of the rhASB group (p = 0.025) compared with placebo was seen at 24 weeks.

Despite the statistically significant difference on the primary endpoint, the substantial imbalance between the groups makes interpreting the data difficult. At enrolment, patients in the placebo group were able to walk further than those in the rhASB group. Distances walked at 24 weeks were similar in the 2 groups.

At the request of the CHMP (Committee for Human Medicinal Products), an analysis was carried out by patient subgroup with similar baseline values. This analysis suggested that the advantage of rhASB therapy was not dependent on the imbalance at enrolment.

Secondary endpoints

A significant reduction in urinary GAG excretion was seen in the rhASB group compared with the placebo group (mean difference at week 24: -227 ± 18 µg GAG/mg of creatinine, p < 0.001).

No significant difference was seen between the two groups in the 3-minute stair climb test (mean difference at week 24: 5.7 ± 2.9 stairs/minute, p = 0.053).

Results at 48 weeks (open-label extension phase)

rhASB/rhASB: patients given rhASB 1.0 mg/kg/week for 24 weeks followed by rhASB for a further 24 weeks

placebo/rhASB: patients given placebo for 24 weeks followed by rhASB 1.0 mg/kg/week for the next 24 weeks.

Walking capacity in the 12-minute walk test (in metres)

	Week 48	Week 24 – baseline value	Week 48 – baseline value	Week 48 – week 24
rhASB/rhASB				
n	19	19	19	19
mean	372 ± 240	109 ± 154	145 ± 25	36 ± 25
p	-	< 0.001	< 0.001	0.15
placebo/rhASB				
n	18	19	18	18
mean	482 ± 206	26 ± 122	91 ± 92	66 ± 133
p	-	0.28	0.001	0.007

In the rhASB/rhASB group, no difference was seen in the 12-minute walk test between week 24 and week 48 (36 ± 25 metres, p = 0.15).

In the placebo/rhASB group, a significant improvement was seen in the 12-minute walk test between week 24 and week 48 (66 ± 133 metres, p = 0.007), i.e. after the change to rhASB therapy.

Secondary endpoints

In the 3-minute stair climb test, a mean difference of 5.9 ± 7.9 stairs/minute was seen between week 24 and week 48 in the placebo/rhASB group.

A reduction in GAG was seen at 48 weeks in the placebo/rhASB group, of the same order of magnitude as that seen at 24 weeks in the rhASB group (figures not submitted).

3.2. Undesirable effects

The most common undesirable effects reported in the rhASB group during the phase III and phase I/II trials were:

- infection: pharyngitis (16%), gastroenteritis (11%)
- areflexia (11%)
- eye disorders: conjunctivitis (21%), corneal opacity (11%)
- ear pain (42%)
- hypertension (11%)
- respiratory disorders: dyspnoea (21%), apnoea (5%), nasal congestion (11%)
- abdominal pain (42%)
- facial oedema (11%)
- general disorders and administration site conditions: pain (26%), chest pain (16%), tremor (21%), feeling unwell (11%).

Most of the undesirable effects were considered to be related to progression of the disease.

Reactions associated with infusion (fever, tremor, rash and urticaria) were seen in 56% of patients treated with rhASB across the 3 trials.

In patients treated with rhASB, the most common undesirable effect was myalgia.

In all, 39 severe undesirable effects were reported during the 3 trials. Three were considered to be therapy-related: one case of apnoea and one case of urticaria occurring during infusion in patients treated with rhASB; one case of asthma occurring several hours after infusion.

One patient treated with rhASB in the phase I/II trial died, having left the trial after 3 weeks of treatment.

Formation of immunoglobulin antibodies against galsulfase was seen after 24 weeks in all the pivotal trial patients except one.

The effect of antibody formation on the safety and efficacy of the medicinal product is not yet known.

3.3. Conclusion

In a comparative phase III trial in patients aged 5 and over, a significant improvement in the walk test (primary endpoint) of 92 ± 40 metres was seen at 24 weeks, in favour of the rhASB group compared with the placebo group (p = 0.025).

A significant reduction in urinary GAG excretion levels was noted in patients taking rhASB. However, no significant difference was seen between the two groups for the 3-minute stair climb test.

Results at 48 weeks confirmed those seen at 24 weeks.

Most of the undesirable effects were considered to be connected to progression of the disease.

Three severe undesirable effects were considered to be therapy-related (one case of apnoea, one of urticaria and one of asthma).

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

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Mucopolysaccharidosis VI or Maroteaux-Lamy syndrome is a rare, serious, life-threatening disease that impairs quality of life.

This medicinal product is replacement therapy.

This medicinal product is first-line therapy.

The only alternative treatment is nonmedical, consisting in bone marrow transplantation.

Public health benefit

Mucopolysaccharidosis VI (MPS VI) is a serious disease which is a low public health burden because it is rare (orphan disease).

Improving the management of orphan diseases is a stated priority (GTNDO[2], *Plan Maladies Rares*) and treating this condition is therefore a public health requirement.

The impact of this medicine in terms of morbidity and quality of life compared with the only existing treatment (allogenic bone marrow transplantation), especially on bone and joint disorders, cannot be quantified on the basis of the data available.

It is not possible to conclude that Naglazyme offers a partial response to the identified public health requirement.

This medicinal product is not therefore expected to benefit public health.

The efficacy/safety ratio is moderate.
The actual benefit is substantial.

4.2. Improvement in actual benefit

In view of the seriousness of mucopolysaccharidosis VI and the lack of any alternative medical treatment, Naglazyme offers a moderate improvement in actual clinical benefit (level III) in managing mucopolysaccharidosis VI.

4.3. Therapeutic use

Apart from symptomatic therapy, the only treatment for MPS VI is allogenic bone marrow transplantation. This should be carried out at an early stage of the disease.

It should be noted that allogenic transplantation does not treat all clinical manifestations of the disease. In particular it has no effect on bone and joint disorders.

Intravenous Naglazyme is a long term enzyme replacement therapy in patients with a confirmed diagnosis of MPS VI, including young patients under 5.

[2] *Groupe Technique National de Définition des Objectifs* (DGS)

4.4. Target population

Mucopolysaccharidosis VI is a rare disease with a prevalence of 1/248 000–1/667 000 in the general population. The number of patients with this disease in France is around 26.

All patients with MPS VI are likely to be given enzyme replacement therapy.
On this basis, the target population for Naglazyme in MPS VI is around 20 patients in France.

4.5. Transparency Committee recommendations

The Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services.

The Committee asked for complementary data on patient follow-up over 12 months, and requested a reassessment of this product in 3 years' time.