HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

14 March 2007

ELAPRASE 2 mg/ml solution to be diluted for infusion
Box of 1 x 3 ml vials (CIP: 570 563-3)

ELAPRASE 2 mg/ml solution to be diluted for infusion
Box of 4 x 3 ml vials (CIP: 570 565-6)

ELAPRASE 2 mg/ml solution to be diluted for infusion
Box of 10 x 3 ml vials (CIP: 570 566-2)

Applicant : SHIRE

Idursulfase

List I
Medicinal product for hospital use only
Orphan drug

Date of Marketing Authorisation (MA): January 8, 2007
MA granted "under exceptional circumstances".

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
Idursulfase

1.2. Background
First therapy for enzymatic substitution in type II mucopolysaccharidosis (MPS II) or Hunter syndrome.

1.3. Indication
ELAPRASE is indicated for the long-term treatment of patients with Hunter syndrome (type II (Mucopolysaccharidosis II, MPS II).
Heterozygous females were not studied in the clinical trials.

1.4. Dosage

Elaprase is administered at a dose of 0.5 mg/kg body weight every week by intravenous infusion over a 3-hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed.

For preparation and administration instructions see section 6.6. (SPC)

Patients with renal or hepatic impairment: There is no clinical experience in patients with renal or hepatic insufficiency.

Elderly patients: There is no clinical experience in patients over 65 years of age.

Paediatric patients: The dose for children and adolescents is 0.5 mg/kg body weight weekly. There is no clinical experience in children under the age of 5.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification
A Digestive tract and metabolism
16 Other medicinal products for the digestive tract and metabolism
A Other medicinal products for the digestive tract and metabolism
B Enzymes
09 Idursulfase

2.2. Medicines in the same therapeutic category
None

2.3. Medicines with a similar therapeutic aim
None

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The laboratory has submitted two studies:

- a phase II double-blind dose-ranging study performed in a small number of patients (n=12) randomised into four arms (idursulfase 0.15, idursulfase 0.5 and idursulfase 1.5mg/kg every two weeks) and a placebo arm treated for twenty-four weeks. This study will not be described in this opinion.
- a phase III clinical trial[1] (TKT024) described below.

Study TKT-024

Objective: to assess the efficacy and tolerability of ELAPRASE in 96 patients with type II mucopolysaccharidosis (MPS II) or Hunter syndrome.

Methodology: placebo-controlled, randomised double-blind study conducted in 96 patients treated for 52 weeks.

Inclusion criteria: male patients aged 5 to 31 years with MPS II diagnosed on the basis of the following criteria:

- *clinical*: defined by the presence of at least one of the following abnormalities: hepatosplenomegaly, multiple dysostosis demonstrated by radiography, valvulopathy, obstructive respiratory syndrome,
- *biological:* defined by a deficiency in induronase 2 sulphatase (level <10% below the normal range) associated with a normal level of another sulphatase.

The patients also showed an altered respiratory function defined by a predictive forced vital capacity* (FVC) < 80%.

**The predictive forced vital capacity is expressed as a percentage calculated with respect to standard reference data as a function of the patient's age and height.*

Exclusion criteria: patients who had been subjected to tracheotomy or to grafting with bone marrow or umbilical cord blood.

Treatment:

- ELAPRASE 1: 1 injection of 0.5mg/kg per week (n=32),
- ELAPRASE 2: 1 injection of 0.5mg/kg every two weeks (n=32),
- Placebo (n=32)

Patients were stratified by age (5-11, 12-18 and 19-31) and disease severity score at baseline.

Primary efficacy endpoint: a 2-component composite variable of the sum of the variation (%) predicted FVC (measure of respiratory function) and the total distance walked in the 6-minute walk test (6MWT).

Secondary endpoints: variation (%) in absolute FVC, volumes of the liver and kidneys, urine glycosaminoglycan levels (GAG), cardiac left ventricular mass and global JROM score (Passive Joint Range of Motion, indicator of the capacity for movement).

[1] Muenzer et al. "A phase II/III clinical study of enzyme replacement therapy with idursulfate in mucopolysaccharidosis II (Hunter syndrome)", Genet Med 2006:8(8):465-473.

RESULTS: analysed on intention-to-treat (ITT) basis
Only the results relating to ELAPRASE 1, one injection per week, which corresponds to the dosage allowed in the MA, are presented below.

The mean age of the patients on inclusion was 14 years and no patients aged less than 5 years were included in the study. 45% of patients were aged between 5 and 11 years. No patients with severe disease were included.

Table 1: Baseline values:

	ELAPRASE 1		Placebo	
	Mean	Standard deviation	Mean	Standard deviation
6MWT (m)	392	19	392	19
Predictive FVC %	55.3	2.8	55.6	2.2

Table 2: Development of the principal composite endpoint after one year of treatment (ITT analysis): Mean (standard deviation)

	ELAPRASE 1 0.5mg/kg/wk n=32	Placebo n=32	Mean difference versus placebo (standard deviation)	p
Primary composite endpoint (6MWT and FVC in %)	74.5 (4.5)	55.5 (4.5)	19.0 (6.5)	p=0.0049

Table 3: Development of secondary endpoints after 1 year of treatment

Endpoint	Mean (standard deviation)		Mean difference versus placebo (standard deviation)	p (compared to placebo)
	ELAPRASE 1	Placebo		
6MWT (m)	43.3 (9.6)	8.2 (9.6)	35.1 (13.7)	0.0131
Predicted FVC (%)	4.2 (1.6)	-0.04 (1.6)	4.3 (2.3)	NS
Absolute FVC volume	230.0 (40.0)	50.0 (40.0)	180.0 (60.0)	0.0011
Urine GAG (µg GAG/mg creatinine)	-223.3 (20.7)	52.23 (20.7)	-275.5 (30.1)	<0.0001
Variation in hepatic volume (%)	-25.7 (1.5)	-0.5 (1.6)	-25.2 (2.2)	<0.0001
Variation in splenic volume (%)	-25.5 (3.3)	7.7 (3.4)	-33.2 (4.8)	<0.0001

After one year of treatment, a significant improvement in the primary endpoint combining variation (%) predicted FVC and the 6-minute walk test (6MWT) was observed in the ELAPRASE group, 1 injection per day, compared to the placebo group (difference of 19 $\pm$ 6.5, p=0.0049).

Despite the statistically significant difference for the primary endpoint, a substantial imbalance between the groups makes interpretation of these data difficult. At inclusion, the baseline severity scores of the patients showed that patients in the placebo group were slightly more affected:

- disease severity score (scale of 2 to 6): 94% of the ELAPRASE group *versus* 100% of patients in the placebo group with a score $\geq$ 3,
- score for predicted FVC (scale of 1 to 3): 80% *versus* 88% with a score $\geq$ 2,
- score for 6MWT walk test (scale of 1 to 3): 81% *versus* 87% with a score $\geq$ 2.

Secondary endpoints:
The improvement in combined endpoint (primary endpoint) is based exclusively on the significant efficacy of the ELAPRASE group on the 6MWT endpoint in comparison to the placebo group (difference of 35.1 $\pm$ 13.7, p=0.0131). The effect of ELAPRASE on pulmonary function could not be clearly established: no difference was observed for predicted FVC in comparison to placebo (difference of 4.3$\pm$ 2.3, NS).

The efficacy of ELAPRASE was superior to that of placebo for all other secondary endpoints.

There are no clinical data demonstrating a benefit on neurological manifestations of the disease.

97.9% of patients completed the study after 1 year. Two patients died; one in the placebo group and one in the ELAPRASE group, 1 injection per week.

3.2. Adverse events

The treatments were well tolerated on the whole. The most common adverse events noted were:

- respiratory tract infections: 84.4% in the ELAPRASE group *versus* 78.1% in the placebo group,
- respiratory disorders, namely: cough (50% *versus* 59.4%), nasal congestion (37.5% *versus* 37.5%), pharyngitis (40.6% *versus* 31.3%),
- central nervous system disorders, namely: headache (59.4% *versus* 43.8%), dizziness (12.5% *versus* 25%),
- gastrointestinal disorders, namely: nausea (21.9% *versus* 28.1%), vomiting (25% *versus* 50%), abdominal pain (34.4% *versus* 34.4%), diarrhoea (34.4% *versus* 46.9%),
- skin disorders, namely: rash and pruritus (71.9% *versus* 36%), urticaria (15.6% *versus* 0%).

Two deaths due to respiratory complications were observed: 1 in the ELAPRASE 1 injection per week group and 1 in the placebo group.

3.3. Conclusion

The efficacy and tolerability of ELAPRASE were assessed in an open-label phase III trial (TKT024).
After one year of treatment, the efficacy of ELAPRASE, 1 injection per day on the composite endpoint (primary endpoint) combining FVC and the 6-minute walk test (6MWT) was significantly superior to that of placebo (difference of 19 $\pm$ 6.5, p=0.0049). This improvement was based exclusively on the significant efficacy of the ELAPRASE group on the endpoint of improvement in walking (6MWT).

The study population investigated in this trial included patients with a mean age of 14 years; no patients aged less than 5 years were included while the mean age at death was between 15 and 20 years and the diagnosis was made shortly after birth.
In addition, this study did not include patients in severe disease states.

There are no clinical data demonstrating a benefit on neurological manifestations of the disease (cerebral impact).
Data on the long-term efficacy and tolerability of ELAPRASE are not available.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hunter syndrome is caused by an enzyme deficiency that affects most of the tissues in the body. It is a rare and serious disease which involves deterioration in the quality of life and is life-threatening.

This medicinal product is a substitution therapy.

This medicinal product is a first-line therapy.

There is no alternative medication.

The efficacy/safety ratio for this medicinal product is high.

Public health benefit:
Hunter syndrome, a serious orphan disease, is a small burden for public health.
Its therapeutic management is an established public health priority (National Plan for rare diseases).
In view of the available results, especially the distance walked in 6 minutes, ELAPRASE is expected to have an impact in reducing morbidity associated with Hunter syndrome. This impact can at best be quantified as being weak, given the small size of the population concerned. Nevertheless, ELAPRASE enables the provision of a response to an identified public health need.
No reduction in mortality or in neurological morbidity has been demonstrated.
Overall, a benefit to public health is expected for ELAPRASE, taking into account the response provided to a public health need. This benefit may be considered to be low.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

ELAPRASE, the first enzyme substitution therapy for Hunter syndrome, provides a significant improvement in actual benefit (IAB II) in the management of this disease.

4.3. Therapeutic use [2]

Type II mucopolysaccharidosis (MPS II) or Hunter syndrome is a disease of lysosomal overload, of the mucopolysaccharidosis group. It is due to a deficiency in iduronate-2-sulphatase, which is responsible for the accumulation of two mucopolysaccharides within the lysosomes of various tissues: dermatan sulphate (DS) and heparan sulphate (HS).

It is a recessive genetic disorder associated with the X chromosome. The gene is located at Xq28 and approximately 250 genetic abnormalities have been identified.

[2] Dr I. Maire, Dr R. Froissart, « Maladie de Hunter » Orphanet – February 2005.

The child is normal at birth and the signs only appear gradually. The clinical picture, very similar to that of Hürler disease, consists of hernias, facial dysmorphia, joint abnormalities, multiple dysostosis, dwarfism, hepatosplenomegaly, cardiac disorders, deafness, respiratory abnormalities and psychomotor retardation resulting in mental retardation.
The mean lifespan is estimated to be 15 to 20 years.

Early forms of the disease (diagnosed at 2 to 4 years) are the most severe; patients with cerebral involvement have mental retardation and early death (10 years).
Later forms of the disease are more moderate; survival is prolonged and intellectual capacities are preserved. Complications are mainly osteo-articular and cardiorespiratory.

Laboratory diagnosis is based on the demonstration of increased urinary excretion of DS and HS and enzymatic deficiency (serum, leukocytes, fibroblasts, trophoblasta or amniocytes). In the case of antenatal diagnosis, knowledge of the gender is a prerequisite for the interpretation of an enzymatic deficiency. In addition to symptomatic treatments, bone marrow allografts, performed at an early stage of the disease, may be considered. However, the allografts do not enable all clinical manifestations to be treated and notably have no impact on the cerebral developments in patients.

ELAPRASE is the first enzyme substitution therapy available for the management of these patients.

4.4. Target Population

ELAPRASE has received the status of an orphan drug.
According to Orphanet, one male neonate in 80,000 births could be affected by this disease, which corresponds to 5 births per year.

Since the lifespan is estimated to be 15-20 years on average, the target population in France would be a maximum of 100 patients.

4.5. Recommendations of the Transparency Committee

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication of the MA.

Packaging:
ELAPRASE is only available as a vial of 12 g. The Committee wishes packaging to be made available that is more suited to the treated population.

Request for a study:
Following a request from the Directorate General for Health, the Transparency Committee wishes to establish a register of patients with Hunter syndrome in France.

The aim of this register will be to assess, over the long term, the impact of ELAPRASE treatment on morbidity and mortality (particularly neurological morbidity and the clinical consequences of development of anti-idursulfase antibodies), on the quality of life and on the organisation of care.

It should also have a part in improving knowledge about the disease and its management.
An independent scientific committee will be responsible for the production of this register.