HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
Update
March 2017

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

ALDURAZYME (laronidase), enzyme replacement

Substantial clinical added value in mucopolysaccharidosis type I

Main points

- ALDURAZYME has marketing authorisation for long-term enzyme replacement therapy in patients with mucopolysaccharidosis type I (MPS I), to treat the non-neurological manifestations of the disease.
- It is the only enzyme replacement therapy and the only treatment option for patients who are not eligible for haematopoietic stem cell transplant.
- The results of clinical trials imply stabilisation of respiratory function, endurance, sleep quality and quality of life in patients with an intermediate or attenuated form of MPS I.
- ALDURAZYME has no effect on the neurological signs of MPS I and little efficacy on osteoarticular signs, ophthalmic signs and valve disease.

Therapeutic use

Two specific therapies for MPS I are available:

- haematopoietic stem cell transplantation (HSCT), mainly indicated in patients aged under 2.5 years with a severe form of MPS I (clinical signs and symptoms compatible with the Hurler phenotype and/or genetic mutations exclusively associated with a severe phenotype);
- enzyme replacement therapy with ALDURAZYME.

Multiple factors are involved in the choice of treatment. This decision should be made in consultation with families by a multidisciplinary team within the expert centres or reference centres dedicated to inherited metabolic or lysosomal diseases, possibly after obtaining an opinion from the Centre for Evaluating Mucopolysaccharidosis Treatment.

Role of the medicinal product in the therapeutic strategy

ALDURAZYME is recommended from diagnosis in all patients with MPS I, whether or not they are eligible for HSCT. In patients who are eligible for HSCT, there is no consensus on whether to continue laronidase after the transplant.

Clinical data

- In 2004, the assessment of ALDURAZYME in the treatment of MPS I was based on two studies: a phase I/II study of 10 patients aged between 5 and 22 years, followed up for 152 weeks, and a phase III placebo-controlled trial of 45 patients aged between 6 and 43 years, which lasted 26 weeks followed by a 24-week open-label extension phase. The majority of patients had a moderate form (Hurler-Scheie, n=45) or attenuated form (Scheie, n=8) of MPS I. The main results observed in comparison with placebo were an improvement in lung function, a reduction in urinary glycosaminoglycans and normalisation of liver volume. During the extension phase, the group initially treated with laronidase maintained superior lung function and endurance to the group who initially received placebo.
- The new available data are primarily as follows:
  - A 52-week phase II study of 20 patients aged under 5 years, most of whom ~~(16/20)~~ had a severe form of MPS I, found a reduction in urinary glycosaminoglycans, normalisation of hepatomegaly in 9/18 patients (50%), improvement or stabilisation of sleep quality in 10/15 patients (66%), and an improvement in height Z-score. Based on the investigators' overall evaluation, 17/18 patients (94%) who completed the study had a clinical improvement, which was moderate in 6 patients and mild in 11 patients, and one patient showed no change.
  - The 3.5-year open-label extension phase of the phase III study included 45 patients who had taken part in the double-blind phase. Overall, the responses observed during the double-blind phase were maintained, with stabilisation of lung function, improvement or stabilisation of endurance and obstructive sleep apnoea, and maintenance of range of motion in the shoulder and knee joints. An MPS I international cohort study included 1,087 patients with MPS I (60% Hurler, 22% Hurler-Scheie, 12% Scheie and 6% unknown phenotype) followed

up for a median period of 4 years. The majority of patients (n=766, 70%) received laronidase with or without HSCT; 205 patients (19%) had a transplant only and 116 patients (11%) did not receive any specific treatment. Given the very heterogeneous nature of patients treated and not treated, and the missing data, the descriptive efficacy results from this cohort of patients cannot identify the inherent effect of laronidase.

- The main risks identified during the clinical development of laronidase were infusion-related reactions and the development of IgG antibodies to laronidase. No new safety signals have been identified since ALDURAZYME became available.

Special prescribing conditions

- Medicinal product reserved for hospital use

Benefit of the medicinal product

- The actual benefit* of ALDURAZYME is substantial.
- Taking into account:
  - the results of the extension phase of the phase III study and the results of observational studies implying stabilisation of respiratory function, endurance, sleep quality and quality of life in patients with an intermediate or attenuated form of MPS I;
  - the recommendation to use ALDURAZYME from diagnosis in all patients with MPS I, whether or not they are eligible for haematopoietic stem cell transplant;
  - the lack of any other treatment option for patients who are not eligible for haematopoietic stem cell transplant;
  - and despite the limitations of treatment:
    - the absence of neurological and cognitive effects because the drug does not cross the blood-brain barrier;
    - little efficacy on the osteoarticular signs, valve disease and ophthalmic signs of the condition (corneal opacity and retinopathy);
    - practical constraints related to administration, requiring a ½ day of hospitalisation every week;
  - and the fact that the data have a low methodological level of evidence,

  ALDURAZYME continues to provide substantial clinical added value** (CAV II) in the therapeutic management of MPS I.
- Recommends inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 08 March 2017 (CT-15423) and is available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.