HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New medicinal product
December 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

LAMZEDE (velmanase alpha), enzyme

Moderate clinical benefit in non-neurological manifestations of mild to moderate alpha-mannosidosis and minor clinical added value in terms of stabilisation of the disease.

Main points

- LAMZEDE has been granted a marketing authorisation for the enzyme replacement therapy of non-neurological manifestations in patients suffering from mild to moderate alpha-mannosidosis.
- Its efficacy is superior to that of the placebo in terms of a biological endpoint, i.e. the reduction of serum oligosaccharide concentration after one year of treatment.
- The results for various clinical endpoints suggest a stabilisation in disease progression with LAMZEDE compared to a deterioration observed with the placebo.
- Uncertainties remain concerning the long-term efficacy and safety of this medicinal product administered by weekly intravenous infusion.

Therapeutic strategy

- Alpha-mannosidosis is a rare genetic disease with autosomal recessive transmission, linked to a reduction in the activity of alpha-mannosidase, a lysosomal enzyme, leading to the toxic intracellular accumulation of mannose-rich oligosaccharides, causing cellular dysfunction and impairing the immune system. The treatment objectives of patients suffering from mild to moderate alpha-mannosidosis are to improve their state of health and quality of life by reducing the incapacitating symptoms and preventing complications particularly infectious ones. Therapeutic management relies on symptomatic treatments such as ENT treatment, physiotherapy, orthopaedic surgery, hearing aids, or early learning assistance.
- **Role of the medicinal product in the therapeutic strategy**
  LAMZEDE, administered once weekly by intravenous infusion, is a first-line enzyme replacement treatment that appears to stabilise disease progression and should be initiated during the most initial stages of the disease, hence the importance of the earliest possible diagnosis. Current perspective is limited to 2.5 years of LAMZEDE treatment. Optimum treatment duration is thus unknown.
  LAMZEDE treatment must not be initiated in patients suffering from severe alpha-mannosidosis, which would correspond to off-label use.

Clinical data

- One study randomised 25 patients aged between 6 and 35 years, suffering from mild to moderate alpha-mannosidosis: 15 in the LAMZEDE and 10 in the placebo group. These patients were not severely affected as all were capable of walking autonomously upon inclusion.
  At 52 weeks, during the primary analysis, the mean serum oligosaccharide concentration had decreased on average by -5.11 µmol/l in the LAMZEDE group and by -1.61 µmol/l in the placebo group, i.e. a significant difference of -3.50 µmol/l (CI95% [-4.37; -2.62]; p<0.001) between the two groups. The number of steps climbed in the 3-minute step-climbing test increased on average by +0.46 steps in the LAMZEDE group and decreased by -2.16 steps in the placebo group, though without revealing any significant difference between the two groups. The results of the unranked secondary endpoints, comprising in particular a 6-minute step-climbing test, along with respiratory, cognitive and auditory function tests, failed to show any significant difference between the LAMZEDE group and the placebo group.

The descriptive results of the two quality of life questionnaires filled out by the patients, at 26 weeks then at 52 weeks, failed to demonstrate any impact of LAMZEDE on the patients' quality of life, particularly in terms of the level of disability, pain and general health.

- A non-comparative study grouped the data of 18 patients treated in the context of a compassionate treatment programme, and of 15 patients included in 2 observational studies, with an average exposure to LAMZEDE of 2.5 years. The mean absolute variation in serum oligosaccharide concentration, between inclusion and the last observation, was significantly reduced (difference of -4.59 µmol/l, CI95% [-5.74; -3.45], p<0.001). A statistically significant increase in the number of steps climbed in 3 minutes was observed between inclusion and the last observation (difference of +6.4 steps/minute; CI95% [2.66, 10.12], p=0.001).
- The adverse events most frequently reported during the phase III clinical studies were rhinopharyngitis, fever and headaches. Two serious adverse events considered to be linked to the study treatment were: one case of acute kidney failure and one case of loss of consciousness. After resolution, the patients were both able to continue the study treatment. 9% of patients experienced infusion-related reactions during the clinical trials, all were of mild to moderate severity. These reactions were sometimes associated with the presence of anti-velmanase-alfa antibodies, though no correlation between antibody levels and adverse reactions was established. Hypersensitivity reactions were reported in approximately 12.5% of patients receiving LAMZEDE during the two phase III clinical studies.

Special prescription requirements

- Medicinal product subject to hospital prescription

Benefit of the medicinal product

- The actual clinical benefit* of LAMZEDE is moderate.
- LAMZEDE provides a minor improvement in actual clinical benefit** (IACB IV) in the management of alpha-mannosidosis.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 12 December 2018 (CT-16972) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"