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METABOLISM
Update
March 2017

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

MYOZYME (alglucosidase alpha), enzyme replacement therapy

Moderate clinical added value in the therapeutic strategy of infantile-onset forms of Pompe disease
Minor clinical added value in the therapeutic strategy of late-onset forms of Pompe disease

Main points

- MYOZYME has marketing authorisation in long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid alpha-glucosidase deficiency).
- In the infantile-onset forms of the disease, the new data available confirm the benefit on the overall survival of patients. On the other hand, no data document their quality of life (very deteriorated), nor the resulting neurological damage which causes major disability and a significant mortality.
- In the late-onset forms of the disease, the data available only on functional criteria are still very heterogeneous according to patient characteristics. They do not allow the assessment of MYOZYME in terms of disability progression or overall survival.

Therapeutic strategy

Treatment of Pompe disease combines an alglucosidase alpha ERT with symptomatic treatments.

- **In infantile-onset forms:**
  Once the diagnosis is confirmed by laboratory tests, the initiation should be discussed and validated by a physician from a reference centre or a speciality centre for the management of this disease. If the decision is made to initiate the treatment, this should be done as early as possible. A preventive immunomodulation may be considered in CRIM- patients; however, the benefit has not been clearly established. The ERT should be combined with symptomatic treatments that evolve according to the degree of motor and/or respiratory impairment: physiotherapy, ventilator and nutritional assistance, etc. In case of diagnostic delay associated with an already deteriorated neuromuscular status, therapeutic abstention should be considered, in agreement with the family.
- **In late-onset forms:**
  Initiation of ERT should be considered as soon as the first signs of musculoskeletal or respiratory deficit in patients whose diagnosis has been confirmed by laboratory tests. Its follow-up is based on a semi-annual assessment of motor and respiratory functions. It could be maintain as long as the annual clinical assessment shows an improvement or stabilisation of the musculoskeletal and diaphragmatic deficiencies. It is combined with symptomatic treatments that evolve according to the degree of motor or respiratory impairment: walking devices (canes, walker) then wheelchair, non-invasive assisted ventilation then invasive. The benefit of ERT with MYOZYME has not been demonstrated in asymptomatic patients.
- **In all situations** and in accordance with the national diagnosis and care protocol (PNDS), the initiation of the treatment and its continuation should be carried out as part of a comprehensive care, multidisciplinary management coordinated by specialists from reference or speciality centres. These following particular aspects should be discussed: treatment and non-treatment indications and conditions for discontinuation (wish of the patient or parents, poor tolerance, worsening of health status, lack of efficacy, etc.), taking into account the patients' quality of life. When necessary, and in accordance with the PNDS, these decisions should be made during collegial consultations within a group of experts (Pompe disease treatment evaluation committee).

Role of the proprietary medicinal product in the therapeutic strategy

MYOZYME, the only enzyme replacement therapy for acid alpha-glucosidase deficiency currently available, is a first-line treatment for symptomatic patients with a confirmed diagnosis of Pompe disease.

Clinical data

- The assessment of MYOZYME in infantile-onset forms of Pompe disease is mainly based on two non-comparative studies, the results were put in perspective with those of historical cohorts.
    - In the first study, after 52 weeks of treatment, 15/18 patients with a classic infantile-onset form of the disease, with no ventilation and under 6-months of age, were alive and free of ventilation support. The respiratory-assistance-free survival rate was 49.4% at age 36 months. As a comparison, in a historical cohort in patients with comparable characteristics, only 1 patient of the 61 studied was alive at age 36 months.
    - In the second study, after 104 weeks of treatment, 14 patients were alive out of the 21 patients included with a classic or atypical infantile-onset form. They were then from 34.7 to 80.3 months old. Half of the patients with no respiratory assistance at baseline remained free of ventilation after 104 weeks of treatment. As a comparison, in a historical cohort in patients with comparable characteristics, only 5 patients of the 47 studied were alive at age 30 months.
- The follow-up data from these studies confirm the positive effect on the overall survival of the patients. On the other hand, no data document the effect of MYOZYME on the quality of life and on the long-term evolution of disability related to neurological impairment now clearly established.
- The assessment of MYOZYME in late-onset forms of Pompe disease is mainly based on one comparative study versus placebo, conducted in 90 non-ventilated patients and able to walk at least 40 metres. After 78 weeks of treatment, MYOZYME demonstrated its superiority in the two primary endpoints: walking distance in the 6-minute walk test (+26.1 versus -4.9 m) and forced vital capacity in upright position (+1.25% of the predicted value versus -2.3%).
- The long-term data (up to 10 years) for patients with a late-onset form of the disease are from the French Pompe disease “registry” (cohort of a single Centre in Paris). These results show that the disease continues to progress in treated patients. In the absence of admissible comparative data, it is not possible to determine whether the rate of progression of the disease is altered by MYOZYME.

Special prescribing conditions

- Medicinal product reserved for hospital use.

Benefit of the medicinal product

- The actual clinical benefit* of MYOZYME is:
    - substantial in infantile-onset forms of the disease;
    - low in late-onset forms of the disease.
- MYOZYME provides a clinical added value** that is:
    - moderate (CAV III) in the therapeutic strategy of infantile-onset forms of Pompe disease;
    - minor (CAV IV) in the therapeutic strategy of late-onset forms of Pompe disease.
- Recommends continued 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 22 March 2017 (CT-15569) and is available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a 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 of the medicinal product 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 (equivalent to “no CAV”) means “no clinical added value”.