HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New medicinal product
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

MEPSEVII (vestronidase alfa), enzyme

Insufficient clinical benefit to justify reimbursement in mucopolysaccharidosis VII or Sly syndrome.

Main points

- MEPSEVII has an MA for the treatment of non-neurological manifestations of Mucopolysaccharidosis VII (MPS VII; Sly syndrome).
- Its efficacy is based solely on the reduction in urinary dermatan sulfate excretion compared to placebo, after 24 weeks of treatment, i.e. a biological endpoint with no established correlation with a clinical benefit and without any other benefit demonstrated on a clinically relevant endpoint.
- It can cause reactions related to infusion if the infusion rate is too rapid, including hypersensitivity reactions, and adverse reactions such as diarrhoea, ataxia, confusion, abdominal pain, vomiting, febrile convulsion.

Therapeutic strategy

- MPS VII requires multidisciplinary, global management tailored to each patient, the primary objectives of which are:
  - to improve or slow down the multi-systemic progression of the disease;
  - to improve the patient's quality of life and social, school or professional integration.

  No studies have demonstrated the effect of haematopoietic stem cell transplant therapy (HSCT). Only a few clinical cases have been published in the literature, with no robust demonstration and with heterogeneous results from one patient to another. According to expert opinion, this can sometimes be performed in the absence of any alternative, in certain situations only, since it is a complex and restrictive therapy, requiring chemotherapy and a compatible donor.
- **Role of the medicinal product in the therapeutic strategy**

  MEPSEVII has no role in the management of MPS VII.

Clinical data

- A randomised, placebo-controlled phase III trial evaluated the reduction in urinary glycosaminoglycan (GAG) excretion (dermatan sulfate) after 24 weeks of treatment with vestronidase alfa compared to inclusion. The patients, randomised into 4 groups, started their treatment with vestronidase alfa at different pre-defined dates, thanks to a double-blind crossover design. A total of 12 patients were included and completed the 48 weeks of the study. Nine patients were under the age of 18 [mean age 14.0 years, min.-max.: 8 – 25 years]. Patients were included in the study regardless of the severity of their physical and cognitive impairments, leading to heterogeneous clinical profiles, with severely affected patients, reflecting advanced disease (in particular, severe bone deformities were present in almost all the patients, 3 patients were unable to walk at inclusion). The mean duration of vestronidase alfa treatment was 36.0 weeks versus a mean duration of placebo administration of 15.8 weeks. The primary endpoint demonstrated a mean reduction of 64.82% ± 2.47% in urinary GAG excretion after 24 weeks of treatment with vestronidase alfa compared to inclusion. This reduction, significant from 2 weeks of treatment, was maintained up to 24 weeks of treatment (IC95% [-69.66; - 59.98], $p < 0.0001$). At inclusion, the mean urinary GAG level was 27 times (± 7.74) higher than the upper limit of normal. After 24 weeks of treatment with vestronidase alfa, this mean level was around 10 times (± 1.69) higher than the upper limit of normal.

Among the secondary endpoints, of the 12 patients included in the study, half had an improvement compared to inclusion of at least 1 point in their Multi-Domain clinical Responder Index (MDRI, including 6 domains: six-minute walk test (6MWT), forced vital capacity (FVC), shoulder flexion, Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) (which includes fine motor and gross motor function) and visual acuity) after 24 weeks of treatment (5 patients improved by one point and one patient improved by 2 points), 5 patients saw their scores unchanged and 1 patient demonstrated a 1-point reduction in MDRI score. The 6-minute walk test result was below the minimum clinically relevant difference expected. The results of the other 5 endpoints are difficult to interpret, due to the small number of patients evaluated and/or the impossibility of performing the test.

- A non-comparative paediatric study included 8 patients, 5 of whom completed the 48-week treatment period and were included in an extension phase. The other 3 patients had completed at least one visit at week 24. The mean age of the patients at inclusion in the study was 3.25 ± 1.20 years. The patients had been diagnosed with their MPS VII at birth at the earliest and at the age of 3.5 years at the latest. The mean age of the patients at the time of diagnosis was 1.41 ± 1.20 years. Urinary GAG at inclusion was 11 times higher than the upper limit of normal. Under treatment with vestronidase alfa, a rapid and marked reduction in urinary GAG was observed. The mean reduction in urinary GAG was 63.52% ± 4.90% between inclusion and week 4. The mean reduction at week 48 compared to inclusion was 50.61% ± 5.996% for the 5 patients evaluated over this period.
- The safety profile for MEPSEVII is characterised by: anaphylactoid reaction, urticaria, infusion site swelling or extravasation, pruritus, diarrhoea and rash. Most of these adverse reactions were mild to moderate. Infusion reactions (including hypersensitivity reactions) are important identified risks in the risk management plan.

Special prescription requirements

- Medicinal product for hospital use only

Benefit of the medicinal product

The actual clinical benefit* of MEPSEVII is insufficient to justify its reimbursement by public funding in its indication.

- Not approved for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 27 February 2019 (CT-17339) 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 may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.