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RARE DISEASE
New medicinal product
October 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

CERDELGA (eliglustat), metabolism medicinal product

No clinical benefit demonstrated in the long-term treatment of adults with type 1 Gaucher's disease when compared with CEREZYME and VPRIV

Main points

- CERDELGA, administered orally, has Marketing Authorisation in the long-term treatment of adult patients with type 1 Gaucher's disease (GD1) who are poor metabolisers (PMs), intermediate metabolisers (IMs) or rapid metabolisers (RMs) of cytochrome 2D6 (CYP2D6).
- Its efficacy is non-inferior to that of CEREZYME for a short period of 1 year in patients stabilised on enzyme therapy.

Therapeutic use

- Gaucher's disease is a rare autosomal recessive genetic disorder due to a mutation in the GBA1 gene that leads to a deficiency in the activity of the lysosomal enzyme glucocerebrosidase. The type 1, chronic, non-neurological form makes up more than 90% of cases. Its clinical presentation is very heterogeneous. The principal manifestations are hepatosplenomegaly, bone lesions (bone pain, bone infarction, osteonecrosis) and thrombocytopaenia. Asthenia is common. There may be growth retardation or a delay in puberty. The diagnosis is often confirmed by a myelogram, which reveals Gaucher's cells. The definitive diagnosis is provided by demonstration of a deficiency (< 20-25%) in the activity of the enzyme glucocerebrosidase in leukocytes as a whole or in mononuclear cells.
  All patients require regular monitoring, but treatment is not routinely initiated. In adults, specific treatment is indicated for symptomatic forms of the disease. Once started, treatment is generally administered for life.
- The reference first-line medicinal treatment is enzyme replacement therapy with the recombinant enzyme imiglucerase (CEREZYME) administered intravenously every 15 days. Velaglucerase alfa (VPRIV) is an alternative. Miglustat (ZAVESCA), an oral treatment that acts by reduction of the level of the substrate (glucosylceramide, GL-1), is an alternative limited to mild to moderate forms of MG1 for the rare patients in whom enzyme replacement therapy cannot be continued.
- **Role of the medicinal product in the therapeutic strategy**
  CERDELGA is an orally administered alternative to enzyme replacement therapy. Before the initiation of CERDELGA treatment, patients must undergo CYP2D6 genotyping to determine their CYP2D6 metaboliser status. The decision to prescribe CERDELGA must be taken in the light of its adverse effects, the question of treatment compliance and the lack of experience relating to its long-term efficacy. The consumption of grapefruit or of grapefruit juice must be avoided.

Clinical data

- A placebo-controlled, randomised, double-blind study in adults with symptomatic, untreated MG1 included 40 patients (20 per group). At 9 months, 75% of the patients in the CERDELGA group displayed a reduction in the volume of the spleen of more than 20% relative to the baseline value, compared with 5% in the placebo group (primary endpoint). The difference in the effect on spleen volume between the two groups was 30% ($p < 0.0001$). In the CERDELGA group, the haemoglobin and platelet levels increased, whereas the liver volume decreased (secondary endpoints).
  On the other hand, these three parameters deteriorated in the placebo group. The clinical parameters were maintained over the course of the 18-month extension phase.
- An open, randomised, non-inferiority study versus CEREZYME included adults with MG1 who were stable on the reference enzyme replacement therapy. The patients randomised to the CEREZYME group continued their treatment at an unchanged dose, those randomised to the CERDELGA group started treatment with 50 mg twice

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daily with a possible increase in the dose up to 100 or 150 mg twice daily, depending on the plasma concentration. The intention-to-treat population comprised 106 patients in the CERDELGA group and 53 in the CEREZYME group. At 1 year, the percentage of patients who met the requirements of the composite primary efficacy endpoint of haematological and visceral stability (change in haemoglobin, platelets, spleen volume, and liver volume) was 84.8% in the CERDELGA group and 93.6% in the CEREZYME group, which represents a 8.8% difference of effect. CERDELGA was shown to be non-inferior to CEREZYME in the maintenance of the haematological and visceral stability of the patients (lower limit of the 95% confidence interval of a difference in the effect (-17,6%) higher than the pre-defined limit of non-inferiority of -25% of the per-protocol population).

- The principal adverse events under CERDELGA were headaches, arthralgia, upper respiratory tract infections, diarrhoea and dizziness. The great majority were mild and transient. A total of 1% of the patients (5/393) presented a serious adverse effect: three syncopes (two of them probably of vasovagal origin), a second-degree atrioventricular block (Mobitz I) and one case of asymptomatic nonsustained ventricular tachycardia.
- The numerous drug interactions linked to its metabolism make it more difficult to use than enzyme therapy.

Special prescribing conditions

- Medicine for hospital prescription

Benefit of the medicinal product

- The actual benefit* of CERDELGA is substantial.
- CERDELGA does not provide clinical added value** (CAV V) by comparison with the reference enzyme replacement therapy (CEREZYME, VPRIV).
- 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 21 October 2015 (CT-14208) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) 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 AB, 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".

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