HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New medicinal product
June 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

BRINEURA (cerliponase alfa), simple class

High clinical benefit for neuronal ceroid lipofuscinosis type 2 and moderate clinical added value in the management of this disease.

Main points

- BRINEURA has been granted marketing authorisation for the treatment of neuronal ceroid lipofuscinosis type 2 (NCL2) or tripeptidyl peptidase-1 (TPP1) deficiency.
- The efficacy data of a non-comparative open-label study demonstrate slowing of disease progression, based on a score evaluating 2 of its components: mobility and language, after 96 weeks of treatment, with no mortality data. These results, contrasted with those of a cohort of untreated patients, suggest a benefit of cerliponase alfa on the motor-language score.
- There are some uncertainties concerning its safety, associated with its intracerebroventricular route of administration and long-term efficacy.

Therapeutic strategy

- NCL2 is an hereditary neurodegenerative disease with autosomal recessive transmission, leading to a build-up of substrates normally metabolised by tripeptidyl peptidase in neurons, the retina and glial cells. This results in progressive brain and retinal degeneration. Initial symptoms occur between the ages of 2 and 4 years. The average age of death is of between 8 and 12 years, in a context of multiple major disabilities. Management consists of symptomatic and palliative care, with a view to maintaining functional capabilities and quality of life.
- **Role of the medicinal product in the therapeutic strategy**
  BRINEURA, administered every 2 weeks by intracerebroventricular route, is a first-line enzyme replacement therapy that slows disease progression in terms of its mobility and language components.
  In light of the speed and predictability of untreated disease progression, replacement therapy should be implemented at the earliest stages of disease progression, hence the importance of the earliest possible diagnosis for this disease. BRINEURA treatment can be initiated at an early to moderate stage of disease progression, i.e. a score of 3 to 6 on the mobility and language (ML) scale, with a score of at least 1 point for each of the two domains. Thus, BRINEURA treatment should not be initiated in a patient who has lost all walking ability.
  Current perspective concerning BRINEURA safety data is limited to 96 weeks of treatment. Optimum treatment duration is thus unknown.

Clinical data

- A non-comparative dose escalation study evaluated the safety and efficacy of cerliponase alfa, at a stable dose of 300 mg/2 weeks (MA dosage) over a period of 48 weeks in 24 children aged between 3 and 8 years, suffering from neuronal ceroid lipofuscinosis. The efficacy results cover 23 patients. The average ML score at inclusion was 3.6. Most patients (20/24) had a score falling within the lower part of the inclusion range (ML of 3 or 4), 2 patients were at an early stage of the disease (ML = 6) and 2 patients had a score of 5 points. After 48 weeks of treatment, the response rate (absence of irreversible reduction of 2 points, or achievement of a score of 0 relative to the last ML score determination) was significantly higher (87%; 20/23 patients) with cerliponase alfa than that expected in untreated patients, estimated, from an historical cohort, at 50% (p=0.0002) (primary endpoint). Two patients showed a 2-point improvement in ML score. The score remained stable for 13 patients (57%). The ML

score deteriorated by 2 points during treatment for 3 patients (13%). The score deteriorated by 1 point under treatment for 5 patients (22%) and improved by 1 point for 2 patients (9%).

- The 96-week results of the extension study of the 23 patients treated during the first phase suggest maintenance of efficacy, more in terms of language than of mobility. At 96 weeks, the results of a paired analysis of the data from the clinical study and from the retrospective analysis of a cohort of patients not treated with cerliponase alfa, demonstrated a 100% response rate (21/21) in patients treated with cerliponase alfa, compared to 48% (10/21) in the historical control group (estimated response rate difference: 52%, p=0.0002). Unfortunately, 2 patients from the study could not be paired.
- The purely exploratory quality-of-life results suggest stabilisation of quality-of-life in patients treated with cerliponase alfa compared to the deterioration in quality of life observed during the natural course of NCL2.
- The most frequently observed adverse events (AEs) associated with the treatment were: fever (46%), hypersensitivity (38%), convulsions (38%), vomiting (21%) and epilepsy (17%). Most of these events were mild to moderate. Three patients (13%) presented with grade 3 hypersensitivity considered to be related to the treatment. No deaths were reported. 79% and 33% of patients treated with cerliponase alfa for up to 157 weeks developed anti-drug antibodies in their serum and CSF respectively. No association with reduced treatment efficacy or with increased incidence or severity of hypersensitivity reactions was observed.
- Intracerebroventricular administration may be associated with potentially severe AEs and with device-related problems. Perspective concerning the efficacy and safety of BRINEURA in NCL2 is currently limited to 96 weeks of administration.

Special prescription requirements

- Medicinal product for hospital use only

Benefit of the medicinal product

- The actual clinical benefit* of BRINEURA is high.
- BRINEURA provides a clinical added value** (CAV III, moderate) in the management of neuronal ceroid lipofuscinosis type 2.
- Approved for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 20 June 2018 (CT-16359) available at **www.has-sante.fr**

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