HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New medicinal product
May 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

RAVICTI (glycerol phenylbutyrate), digestive tract and metabolism medicinal product

High clinical benefit in urea cycle disorders, but no demonstrated clinical value over AMMONAPS

Main points

- RAVICTI oral solution has been granted marketing authorisation for the treatment of urea cycle disorders involving deficiency in carbamyl-phosphate synthase I, ornithine, carbamoyl transferase, argininosuccinate synthetase, argininosuccinate lyase, arginase I and ornithine translocase, hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome, that cannot be managed exclusively by a low-protein diet and/or by amino acid supplementation.
- RAVICTI has shown itself to be non-inferior to AMMONAPS (sodium phenylbutyrate) for controlling plasma ammonia concentration in children and adults,
- Its safety profile is characterised by gastrointestinal disorders: diarrhoea, flatulence, abdominal pain, vomiting, dyspepsia, abdominal discomfort, nausea and oral discomfort.

Therapeutic strategy

- Urea cycle disorders involving carbamyl-phosphate synthase I, ornithine, carbamoyl transferase, argininosuccinate synthetase, argininosuccinate lyase, arginase I and ornithine translocase deficiency are extremely rare metabolic diseases. Their management requires treatment of acute hyperammonaemia, along with long-term treatment once diagnosis is made.
- Basic treatment involves the following measures:
  - Very strict low-protein diet, particularly protein-free foods (dietary foods for medical purposes - DFMP)
  - Vitamin and mineral supplementation
  - Oral arginine supplementation (*de novo* synthesis no longer being ensured) or citrulline supplementation in the event of carbamyl-phosphate synthetase or ornithine transcarbamylase deficiency
  - In addition to the aforementioned measures, oral sodium phenylbutyrate is added to the long-term treatment.
- Liver transplantation may be proposed for children with a neonatal form of carbamyl phosphate synthetase or ornithine transcarbamylase deficiency.
- **Role of the medicinal product in the therapeutic strategy**
  RAVICTI is a basic treatment for children (≥2 months) and adults suffering from urea cycle disorders involving enzyme deficiencies, in conjunction with a very strict low-protein diet.
  It may be administered orally or by nasogastric or gastrostomy tube.

Clinical data

- A study of 46 adults previously treated with sodium phenylbutyrate demonstrated the non-inferiority of RAVICTI relative to sodium phenylbutyrate in controlling plasma ammonia levels.
  An exploratory safety study involving 11 children aged between 6 and 18 years demonstrated the non-inferiority of RAVICTI for controlling plasma ammonia levels compared to sodium phenylbutyrate.
  An exploratory study involving 15 children aged between 29 days and 6 years demonstrated the non-inferiority of RAVICTI *versus* sodium phenylbutyrate in controlling plasma ammonia levels.

A pooled analysis of 4 clinical studies suggested a difference in favour of RAVICTI over sodium phenylbutyrate relative to mean plasma ammonia level AUC0-24h values, though the methodological limits of this *post hoc* analysis lessened the scope of these results.

- In the study in adults, the number of patients having suffered at least one adverse event (AE) was 51.1% in the sodium phenylbutyrate group and 61.4% in the RAVICTI group, though the AEs associated with sodium phenylbutyrate were under-represented in this study. The most frequently reported AEs were gastrointestinal disorders (diarrhoea, flatulence, abdominal pain, vomiting, dyspepsia, abdominal discomfort, nausea and oral discomfort): 28.9% *versus* 36.4%, along with nervous system disorders (dizziness, headaches), with respectively: 15.6% versus 15.9%. In children aged between 6 and 18 years, 2 patients (18%) reported at least one AE with sodium phenylbutyrate treatment (lymphadenopathy and heart murmur [n=1] and treatment-related loss of appetite [n=1]) and 4 patients (36.4%) reported at least one AE with RAVICTI treatment (vomiting [n=1], upper abdominal pain [n=2], upper respiratory tract and ear infection [n=1] and contact dermatitis [n=1]). In children aged between 29 days and 6 years, the symptoms of most patients (9/11) had improved by day 10 (after RAVICTI treatment), particularly their body odour (5 patients) and recurrent vomiting (5 patients). At D10, 3 patients reported an improvement concerning the occurrence of vomiting, abdominal pains and refusal to eat.
- After 1 year of treatment, most neuropsychological criteria, particularly those relating to cognitive functions (WASI test) and behaviour (CBCL test), remained stable both in adults and children. An improvement in executive functions (BRIEF test) was observed in children aged between 6 and 18 years.
  The available data do not show any benefit of RAVICTI in terms of quality of life. No compliance data, nor sufficiently robust patient acceptability data are available.

Special prescription requirements

- Medicinal product subject to hospital prescription

Benefit of the medicinal product

- The actual clinical benefit* of RAVICTI is high.
- RAVICTI does not provide any clinical added value** (CAV V) over AMMONAPS as an adjuvant treatment, for the long-term management of adult and paediatric patients, aged 2 months and above.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 16 May 2018 (CT-16547) 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"