HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New indication
June 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

VOTUBIA (everolimus), tyrosine kinase protein inhibitor

High clinical benefit and minor clinical improvement in the treatment of drug-resistant, partial epileptic seizures, with or without secondary generalisation, associated with Bourneville tuberous sclerosis.

Main points

- VOTUBIA has MA in combination in patients (≥2 years) with drug-resistant partial epileptic seizures, with or without secondary generalisation, associated with Bourneville tuberous sclerosis (BTS).
- VOTUBIA was superior to the placebo on the reduction in the frequency of epileptic seizures at 3 months in patients with BTS and partial epilepsy resistant to a combination of 2 or 3 antiepileptic drugs. The effect appeared to be sustained after 1 year's treatment.
- The most common adverse effects include stomatitis, mouth ulcers, diarrhoea, with uncertainty as to the long-term safety in a young population.

Pre-existing indication*

VOTUBIA also has MA in patients with subependymal giant cell astrocytoma (SEGA) and BTS.

Therapeutic strategy

- BTS is an autosomal dominant genetic disease characterised by the appearance, in various organs, of benign tumours, caused by embryo cell anomalies. The neurological signs such as epileptic seizures, mental disorders and mental retardation, dominate the clinical picture. 85% of patients present with early onset epilepsy (infantile spasms and/or focal convulsions).
- The following are recommended in patients with BTS and focal seizures:
  - first-line: vigabatrin in patients under the age of 1 year, combined with another antiepileptic which increases GABAergic inhibition in those age at least 1 year,
  - second-line: surgery, the success of which depends on the precise location of the epileptic focus and the focal nature of the seizures. Surgery is recommended in children insufficiently managed with 2 antiepileptic drugs and a unique and identifiable epileptogenic focus. The rate of success of surgery is between 25 and 90%.
  - third-line: a ketogenic diet, vagus nerve stimulation and other antiepileptics used for focal seizures.
- **Role of the medicinal product in the therapeutic strategy**
  In patients age at least 2 years, with BTS, VOTUBIA can be used in combination with conventional antiepileptics, where the epilepsy becomes drug-resistant (i.e. After failure of ≥ 2 antiepileptics).
  In patients eligible for surgery, namely patients with a unique and identifiable epileptogenic focus, VOTUBIA is not an alternative to surgery and its use must not delay a surgical decision.

Clinical data

- A phase 3, randomised, double-blind study compared the reduction in the frequency of epileptic seizures in 2 everolimus dose groups (residual plasm concentrations 3 to 7 ng/ml and 9 to 15 ng/ml) compared to a placebo

* This summary does not cover this indication

group, in patients with BTS and partial epilepsy resistant to 2 (41.3% of patients) or 3 (47.3% of patients) combined antiepileptics. A total of 366 patients was randomised, of which 117 patients in the everolimus "3 to 7 ng/ml" group, 130 patients in the everolimus "9 to 15 ng/ml" group and 119 patients in the placebo group. The MA provides for a residual plasma concentration of 5 to 15 ng/ml. Patients' average age was 12.6 years. Almost 20% of patients had previously undergone surgery to treat the epilepsy. During the 12-week maintenance phase, the everolimus + antiepileptics combination was significantly more effective than the placebo + antiepileptics combination on the proportion of responder patients (primary endpoint): everolimus 3-7 ng/ml group (28.2%) and everolimus 9-15 ng/ml group (40.0%), placebo group (15.1%, p=0.008 and p<0.001 respectively). The reduction in the weekly frequency of seizures was higher in the everolimus 3-7 ng/ml (18.0%) and everolimus 9-15 ng/ml (34.2%) groups than in the placebo group (4.7%, p=0.003 and p<0.001 respectively). The results of the extension study up to 54 weeks suggest maintenance of efficacy. The results on quality of life, which cannot be interpreted, do not make it possible to conclude on an improvement with everolimus treatment.

- The adverse events the most frequently reported with everolimus in the clinical study were stomatitis, mouth ulcers and diarrhoea.

Special prescription requirements

- Medicinal product subject to hospital prescription.

Benefit of the medicinal product

- The actual clinical benefit* of VOTUBIA is high.
- VOTUBIA provides a minor improvement in actual clinical benefit** (IACB IV) in the strategy for the treatment of partial epileptic seizures resistant to more than 2 antiepileptic drugs, with or without secondary generalisation, associated with Bourneville tuberous sclerosis.
- Approved for non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 13 June 2018 (CT-16027) available at **www.has-sante.fr**

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