HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New indication
December 2014

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

VOTUBIA (everolimus), mTOR inhibitor

Substantial improvement when a subependymal giant cell astrocytoma associated with tuberous sclerosis complex is not immediately eligible for surgical resection

Main points

- VOTUBIA, available as a tablet and dispersible tablet, now has Marketing Authorisation in children under age 3 years in subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex, in patients who require therapeutic intervention but are not eligible for SEGA surgical resection.
- This treatment is superior to placebo for reducing the SEGA volume, but has not shown any improvement in the symptoms related to the disease.
- Its therapeutic benefit is substantial only to prepare patients for surgery in certain advanced SEGA cases and for patients for whom its severity justifies a surgical procedure, but who are not amenadable to surgery.

Pre-existing indications

- VOTUBIA has Marketing Authorisation in patients aged three years and older and adult patients with renal angiomyolipoma associated with tuberous sclerosis complex.
- This summary does not cover these indications.

Therapeutic use

- Tuberous sclerosis complex is a genetic disease with autosomal dominant transmission characterised by the occurrence in various organs of benign tumours (hamartomas) due to embryonic cell abnormalities. The central nervous system, skin, kidneys, heart and lungs are preferentially affected. Neurological manifestations such as epileptic seizures, mental problems and intellectual disability dominate the clinical presentation. SEGAs are low grade glial brain tumours, exclusively localised to the interventricular foramina; they are always benign. However, these tumours can lead to hydrocephalus, a source of severe complications that can be life threatening. Surgical resection of the SEGAs is the treatment of choice in the event of complications or a risk of complications due to the size and/or localisations. Small and non-threatening SEGAs should be regularly monitored and are not to be treated with VOTUBIA, which is not an emergency treatment.
- **Role of the medicinal product in the therapeutic strategy**
  According to expert opinion, VOTUBIA could be offered as preparation for surgery in some advanced cases that are difficult to operate on immediately (multiple lesions, etc.), making the surgical approach simpler and the resection more complete. It could also be useful in patients with a SEGA for whom a surgical procedure is indicated but in whom this procedure is contraindicated. Contrary to surgery for curative purposes, VOTUBIA reduces the SEGA volume without completely destroying it. Tumour growth starts again when VOTUBIA is discontinued. The optimal treatment duration, duration of response and safety of a high cumulative dosage remain unknown. In children, especially in those below age 3 years, the effects on growth and development are unknown.

  VOTUBIA should not cause patients to lose the opportunity for a surgical cure. Given the rarity and difficulty in establishing indications, the decision to use VOTUBIA (first prescription and renewal) can only be made in a multidisciplinary consultation including a medical-surgical team involved in the management of tuberous sclerosis complex.

Clinical data

- Everolimus was evaluated in a placebo-controlled study in 117 SEGA patients in progression, associated with tuberous sclerosis complex and not eligible for a surgical procedure. The percentage of responders (reduction

≥ 50% of the SEGA volume, no worsening of lesions other than the targeted SEGA, new SEGA ≥ 1 cm long, new hydrocephalus or sign of worsening) was higher with everolimus than placebo: 34.6% versus 0 after 6 months of treatment. For information purposes, in the subgroup of children below age 3 years (n = 20), 3 out of 13 children had a response in the everolimus group and none out of 7 children in the placebo group. No data are available for children below age 1 year.

- The efficacy of everolimus has only been demonstrated in changing the SEGA volume. No data are available to show a clinical benefit on more relevant criteria, such as improvement in symptoms related to the disease, proportion of patients who became subsequently operable or overall survival. Additional data should be obtained in order to be able to document the use of VOTUBIA in current practise, especially the success rate estimate in patients subsequently eligible for surgery.
- No patient discontinued treatment due to adverse events. The frequency of grade 3-4 adverse events that could be treatment-related was 17% in the VOTUBIA group and 8% in the placebo group. The most common grade 3 adverse events were: stomatitis, hyperthermia and seizures. Clinically significant adverse events that occurred more frequently in the VOTUBIA group than in the placebo group were: mouth ulceration and stomatitis (59% vs 26%), rash (17% vs 8%), cytopenia (15% vs 3%, mainly neutropenia with 4% grades 3-4 in the VOTUBIA group vs 3%). The safety profile observed in children and adolescents was generally the same as that observed in adults, except for infections, which were more commonly reported, especially in children below age 3 years. Effects on growth and development, especially in children below age 3 years are unknown.

Prescribing conditions

Medicine for hospital prescription.
Medicinal product requiring special monitoring during treatment.

Benefit of the medicinal product

- The actual benefit* of VOTUBIA is substantial.
- Like for patients over age 3 years with SEGA associated with tuberous sclerosis complex for whom treatment is indicated but who are not candidates for SEGA surgical resection, VOTUBIA, in tablet form, provides a substantial clinical added value (CAV II) in the treatment of the paediatric population below age 3 years.
- Dispersible tablets are an addition to the range for paediatrics and for patients with difficulty swallowing. Consequently, they do not provide any clinical added value (CAV V) compared with other presentations.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 17 December 2014 (CT-13799) 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".