HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
Update
June 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

VOTUBIA (everolimus), tyrosine kinase inhibitor

High clinical benefit in subependymal giant cell astrocytoma and in renal angiomyolipoma both associated with Bournville tuberous sclerosis and moderate clinical improvement in the management of these diseases.

Main points

- VOTUBIA has been granted a marketing authorisation for patients with subependymal giant cell astrocytoma (SEGA) and for patients with renal angiomyolipoma, both associated with Bourneville tuberous sclerosis (BTS).
- The follow-up data from 2 studies suggest maintenance of the reduction in SEGA or AML volume according to the final analysis after 4 years of median follow-up.
- The findings of 2 registry-based observational studies do not offer any precise indications in terms of the proportion of patients becoming secondarily operable, or on the optimal therapeutic strategy in respect of BTS-related tumours including VOTUBIA and surgery.
- The known safety profile of VOTUBIA is unchanged.

Pre-existing indications*

- VOTUBIA has also been granted a marketing authorisation in combination for patients (>2 years) in whom drug-resistant partial epileptic seizures, with or without secondary generalisation, are associated with BTS.

Therapeutic strategy

- Curative surgical resection is the treatment of choice for SEGA, in the event of complications or a risk of complications due to the size or location of the lesion.
- Embolisation is proposed as a first-line treatment in the event of a decision to administer preventive asymptomatic AML treatment. Surgery may be proposed if embolisation fails or in certain specific cases. Haemorrhagic AML represents a clinical emergency for which arterial embolisation is proposed as the first-line treatment. If this is not possible or the size of the angiomyolipoma is greater than 5 cm, partial nephrectomy may be proposed and must be as conservative as possible. Systematic treatment is not justified for asymptomatic renal angiomyolipoma < 4 cm in diameter, unless symptoms occur. These cases are subject to annual ultrasonographic monitoring.
- **Role of the medicinal product in the therapeutic strategy**
  VOTUBIA is a palliative treatment in the therapeutic arsenal for SEGA and AML. In these 2 indications, VOTUBIA is not an alternative to surgery.
  For SEGA, it may be proposed:
  - to prepare for surgery in some advanced cases for which immediate surgery would be difficult (particularly multiple or invasive SEGA for which complete surgical resection is not possible). VOTUBIA should be reserved for preparing the surgical approach, in order to simplify and ensure more complete surgery for some advanced cases of SEGA,
  - if surgery is not possible (existence of a contraindication to a surgical procedure) or involves a risk (multiple SEGA, location in at-risk zones).

* This summary does not cover this indication.

For AML, it may be proposed:
- as a preventive treatment for cases of extensive angiomyolipoma involving risks of complications, in a non-haemorrhagic context, not suitable for immediate intervention (embolisation or nephrectomy),
- for patients with multiple AML of increasing size and for patients previously having undergone nephrectomy or embolisation. Cases of large and multiple AML frequently require repeated embolisations and/or iterative surgical procedures, which are risk factors for kidney failure,
- if surgery is not possible (existence of a contraindication to a surgical procedure) or involves a risk.

Clinical data

- The final findings of the 2 follow-up studies on SEGA and the follow-up study on AML suggest long-term maintenance (maximum 5 years) of the benefit of everolimus on SEGA or AML volume reduction. However, besides the findings in respect of the efficacy of everolimus on tumour volume, no further information is available on other relevant clinical criteria associated with this disease with multiple clinical impacts, or on the progression of complications of the disease, and very little information is available on the causes of treatment failure. The data from the TOSCA registry do not appear to provide any information on the optimal therapeutic strategy in respect of BTS-related tumours including everolimus and surgery, which remains the conventional treatment for these tumours, when it can be envisaged
- The safety data based on the follow-up from the phase II and III clinical trials for a maximum period of 5 years and the findings of the registry-based observational studies do not provide any new indications with respect to the known safety profile of everolimus characterised by stomatitis, diarrhoea, headaches, and rhinopharyngitis.

Specific prescribing conditions

- Medicinal product subject to hospital prescription

Benefit of the medicinal product

- The actual clinical benefit* of VOTUBIA is high.
- VOTUBIA provides clinical added value (CAV III) for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with Bourneville tuberous sclerosis who are not immediately eligible for surgical SEGA resection.
- VOTUBIA provides moderate clinical added value (CAV III) for the treatment of adult patients with angiomyolipoma (AML) associated with Bourneville tuberous sclerosis involving a risk of complications and who are unsuitable for immediate surgery (nephrectomy or embolisation).
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

HAS
HAUTE AUTORITÉ DE SANTÉ
This document was drafted on the basis of the Transparency Committee opinion dated 26 June 2019 (CT-17636) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a 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 ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

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