HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
1 DECEMBER 2021

The legally binding text is the original French opinion version

cannabidiol
EPIDYOLEX 100 mg/ml oral solution

New indication

Key points

Favourable opinion for reimbursement as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older only in the event of drug-resistant epilepsy.

Unfavourable opinion for reimbursement as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for non-drug-resistant patients 2 years of age and older.

What therapeutic improvement?

No clinical added value as adjunctive therapy in the treatment of seizures associated with tuberous sclerosis complex for patients 2 years of age and older with drug-resistant epilepsy.

Role in the care pathway?

The guidelines recommend the following in patients with TSC presenting epileptic seizures:

- As first-line therapy: vigabatrin in patients under the age of 1 year, combined with another antiepileptic which increases GABAergic inhibition in those aged at least 1 year.

- As second-line therapy: surgery, the success of which depends on the precise location of the epileptic focus and the focal nature of the seizures, is recommended in children inadequately controlled with two antiepileptic drugs and with a single and identifiable epileptogenic focus. The success rate for surgery is between 25 and 90%.

- As third-line therapy: a ketogenic diet, vagus nerve stimulation and other antiepileptics used for focal seizures.

In patients aged at least 2 years VOTUBIA (everolimus) dispersible tablets can be used in combination with conventional antiepileptics, where the epilepsy becomes drug-resistant (i.e. after failure of 2 antiepileptics). It should be noted that in patients eligible for surgery, namely patients with a single and identifiable epileptogenic focus, VOTUBIA (everolimus) is not an alternative to surgery and its use must not delay a surgical decision.

Role of EPIDYOLEX (cannabidiol) in the care pathway:

In view of:

- demonstration of the efficacy of EPIDYOLEX (cannabidiol), compared to placebo, both as adjunctive therapy, only in terms of the total frequency of TSC-associated epileptic seizures in the short term (16 weeks) with a modest size effect,
- the absence of a demonstrated statistically significant reduction compared to placebo, both as adjunctive therapy, on the ranked secondary endpoint of responder rate (at least 50% reduction in the number of seizures),
- and in the absence of available data compared to another anti-epileptic drug in a context of a high level of drug resistance (89% receiving ≥ 2 AE),

the Committee considers that EPIDYOLEX (cannabidiol) is a treatment option in seizures associated with tuberous sclerosis complex for patients 2 years of age and older with drug-resistant epilepsy.

In the absence of comparative data between EPIDYOLEX (cannabidiol) and VOTUBIA (everolimus), in a context in which they were the subject of concomitant development, the choice between these two proprietary medicinal products should be made, in particular, on the basis of the patient's characteristics, the efficacy of the medicinal products and their different safety profiles associated with contraindications.

The potential benefit of treatment with cannabidiol should be assessed taking into consideration the product's safety and the absence of long-term safety data, in particular its hepatic safety (increased hepatic enzymes).

In the other situations of the MA indication extension, i.e. non-drug-resistant patients with TSC, given the limited data in this population, the Committee considers that EPIDYOLEX (cannabidiol) has no role in the treatment strategy.

Special recommendations

The Committee points out that the multi-dose vial packaging with two dosing devices graduated in ml, whereas the dosage is expressed in mg, requires a conversion (from mg to ml), promoting the risk of medication errors and overdose. The Committee also highlights the importance of ensuring the dosage wording is clear on the medical prescription and providing adequate information to the persons responsible for dispensing and administering EPIDYOLEX (cannabidiol), including healthcare professionals and the child's family.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ TSC is a rare disease with a significant impact on the patient's quality of life and which can be life-threatening. Epilepsy, often present in these patients, contributes significantly to the morbidity of the underlying disease. It is difficult to treat and significantly increases impairment of cognitive functions of patients, particularly in infants and children who are in an important intellectual development phase.
◗ The proprietary medicinal product EPIDYOLEX (cannabidiol) is a symptomatic medicinal product for the seizures associated with tuberous sclerosis complex.
◗ Considering:

- the demonstrated superiority of cannabidiol versus placebo, both as adjunctive therapy, on a limited primary endpoint of reduction in the number of TSC-associated seizures in the short term (16 weeks) with a modest size effect (percent reduction of 30% in patients with a median number of 54 to 61 seizures over 28 days at baseline), in a context of a high level of drug resistance (> 89% of patients),
- the absence of a statistically significant difference for the responder rate (i.e. presenting a ≥ 50% reduction in seizures) after 16 weeks,
- the lack of robust quality of life data in a context in which this is impacted in this disease,
- limited safety data with a median follow-up of 38 weeks (3-130 weeks),

The efficacy/adverse effects ratio is:

- moderate only in patients with drug-resistant epilepsy in patients 2 years of age and older with seizures associated with tuberous sclerosis complex,
- inadequately established in the other patients within the scope of the MA indication extension, i.e. patients 2 years of age and older with non-drug-resistant epilepsy presenting seizures associated with tuberous sclerosis complex.

◗ For patients 2 years of age and older with drug-resistant epilepsy presenting seizures associated with tuberous sclerosis complex, there are a limited number of therapeutic alternatives (VOTUBIA (everolimus) dispersible tablets, as well as non-medicinal therapeutic alternatives).
For patients 2 years of age and older with non-drug-resistant epilepsy presenting seizures associated with tuberous sclerosis complex, vigabatrin (SABRIL and KIGABEQ) is a therapeutic alternative.
◗ EPIDYOLEX (cannabidiol) is a treatment option in the treatment of seizures associated with tuberous sclerosis complex for patients 2 years of age and older with drug-resistant epilepsy.
EPIDYOLEX (cannabidiol) has no role in the care pathway for non-drug-resistant epilepsy in patients with TSC given the limited data in this population.

Public health impact

Considering:

- the seriousness of tuberous sclerosis complex, which can be life-threatening,
- its prevalence,
- the substantial medical need in view of the limited number of available alternatives,
- the lack of additional response to the identified need, with:
    - the absence of an additional impact on morbidity and mortality, with demonstration only on a limited endpoint of reduction in the frequency of TSC-associated seizures in the short term versus placebo, in the absence of a difference for responder rate (non-significant endpoint) and quality of life (exploratory data),
    - the lack of demonstration of an impact on the organisation of care in the absence of data,

EPIDYOLEX (cannabidiol) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of EPIDYOLEX (cannabidiol) is:

- **MODERATE in the adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) in patients 2 years of age and older with drug-resistant epilepsy.**
- **INSUFFICIENT to justify public funding cover in the other patients within the scope of the MA indication extension, corresponding to patients 2 years of age and older with non-drug-resistant epilepsy with seizures associated with tuberous sclerosis complex (TSC).**

The Committee issues:

- **a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) in drug-resistant patients 2 years of age and older and at the MA dosages,**
- **an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the other patients within the scope of the MA indication extension, corresponding to patients 2 years of age and older with non-drug-resistant epilepsy with seizures associated with tuberous sclerosis complex.**

◗ **Recommended reimbursement rate: 30%**

Clinical Added Value

Considering:

- demonstration of the superiority of cannabidiol compared to placebo, as adjunctive therapy, in a randomised, double-blind study, on a limited primary endpoint of variation in the total frequency of TSC-associated epileptic seizures in the short term (16 weeks), the primary endpoint, with a modest size effect (median difference of -30.1% in patients with a median number of 54 to 61 seizures per month at baseline), in a context of a high level of drug resistance,
- the substantial medical need, due to the limited alternatives in this rare disease,

but in view of:

- the absence of a demonstrated statistically significant difference compared to placebo for the percentage of patients presenting an at least 50% reduction in the number of seizures, a relevant ranked secondary endpoint,
- the absence of robust data on quality of life data, which is particularly impacted in this disease,
- the absence of long-term efficacy and safety data for cannabidiol, particularly in terms of the impact on the neurocognitive deterioration and psychomotor development of patients, in the context of a chronic disease,

the Committee considers that EPIDYOLEX (cannabidiol) provides no clinical added value (CAV V) in the treatment of drug-resistant seizures associated with tuberous sclerosis complex in patients 2 years of age and older.