



TRANSPARENCY COMMITTEE

SUMMARY

13 MAY 2020

The legally binding text is the original French opinion version

cannabidiol
EPIDYOLEX 100 mg/ml oral solution

First assessment

► Key points

Favourable opinion for reimbursement as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.

► What therapeutic improvement?

Therapeutic improvement in the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.

► Role in the care pathway?

Seizures associated with Lennox-Gastaut syndrome

The management of seizures associated with Lennox-Gastaut syndrome is based on the rapid initiation of symptomatic anti-epileptic treatment in order to reduce their frequency and intensity, taking into consideration the context of significant drug resistance observed in this disease.

Sodium valproate is recommended as a first-line treatment. Lamotrigine is added to the treatment when sodium valproate monotherapy is not sufficiently effective, or is poorly tolerated. The other

medicinal products with an MA in Lennox-Gastaut syndrome are as follows: topiramate, rufinamide, clonazepam, felbamate and clobazam, with different safety profiles.

A ketogenic diet and vagus nerve stimulation are salvage therapies in the event of failure of medicinal treatments in patients with Lennox-Gastaut syndrome. Corpus callosotomy-type palliative surgery is indicated as a last resort following the failure of drug therapy.

Role of EPIDYOLEX (cannabidiol) in the care pathway: EPIDYOLEX (cannabidiol) is a treatment option as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) in conjunction with clobazam, for patients 2 years of age and older.

Seizures associated with Dravet syndrome

The management of seizures associated with Dravet syndrome is based on the rapid initiation of symptomatic anti-epileptic treatment in order to reduce the frequency and intensity of seizures, taking into consideration the context of significant drug resistance observed in this disease.

Sodium valproate in conjunction with benzodiazepines (clobazam or lorazepam) is recommended as a first-line treatment. The combination of valproate with topiramate may also be effective, but topiramate can only be used from 2 years of age.

Stiripentol (DIACOMIT) has an MA specifically in conjunction with sodium valproate and clobazam in the treatment of generalized tonic-clonic seizures in patients with Dravet syndrome whose seizures are not adequately controlled with the clobazam/sodium valproate combination.

A ketogenic diet and vagus nerve stimulation are salvage therapies in the event of failure of medicinal treatments in patients with Dravet syndrome.

Role of EPIDYOLEX (cannabidiol) in the care pathway: EPIDYOLEX (cannabidiol) is a treatment option as adjunctive therapy of seizures associated with Dravet syndrome (DS) in conjunction with clobazam, for patients 2 years of age and older.

► Special recommendations

The Committee warns 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 health professionals and the child's family.

COMMITTEE'S CONCLUSIONS

Clinical benefit

- ▶ Lennox Gastaut syndrome and Dravet syndrome are severe forms of drug-resistant epileptic encephalopathy resulting in delayed neurocognitive development and a significant impairment of quality of life for patients and their carers.
- ▶ EPIDYOLEX (cannabidiol) is a symptomatic treatment for the seizures associated with Lennox Gastaut syndrome and Dravet syndrome.
- ▶ The efficacy/adverse effects ratio of EPIDYOLEX (cannabidiol) is high.
- ▶ There are a limited number of medicinal alternatives.
- ▶ EPIDYOLEX (cannabidiol) is a treatment option as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in conjunction with clobazam, for patients 2 years of age and older.

Public health impact

Considering:

- the seriousness of Lennox Gastaut syndrome and Dravet syndrome,
 - their prevalence,
 - the substantial medical need in view of the limited number of available alternatives,
 - an additional impact expected on morbidity and mortality but only demonstrated in the short term (14 weeks) at this stage, and hence the partial response to the identified need,
 - the lack of demonstrated impact on the organisation of care and the patient's life pathway,
 - the lack of demonstrated impact on quality of life,
- EPIDYOLEX is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of EPIDYOLEX (cannabidiol) is substantial in the MA indications.

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 in the MA indications and dosages.

Clinical Added Value

Considering:

- demonstration of the superiority of cannabidiol compared to placebo, as adjunctive therapy, primarily in conjunction with clobazam, evaluated in four double-blind, randomised studies, including two in children with Dravet syndrome and two in children and adults with Lennox-Gastaut syndrome,
 - for the change in total convulsive seizure frequency in the short term over 14 weeks (primary endpoint for Dravet syndrome) with a moderate additional size effect compared to placebo (median difference of -23% and reduction percentage of 26% to 30%), as well as the change in total drop seizure frequency in the short term over 14 weeks (primary endpoint for Lennox Gastaut syndrome) with a moderate additional size effect compared to placebo (median difference of - 17% to - 22%),
 - for the ranked secondary outcome measures, in particular the treatment responder rate (i.e. $\geq 50\%$ reduction in convulsive or drop seizures depending on the study) and the change in total seizure frequency (all seizures combined) over 14 weeks in 3 out of the 4 studies concerned,
- the substantial medical need, due to the limited alternatives in these rare diseases, and despite:
- the absence of robust data on quality of life,

- 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 deems that EPIDYOLEX (cannabidiol) provides a minor clinical added value (CAV IV) as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.