HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
19 MAY 2021

The legally binding text is the original French opinion version

Fenfluramine
FINTEPLA 2.2 mg/ml oral solution

First assessment

Key points

Favourable opinion for reimbursement in the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.

What therapeutic improvement?

Therapeutic improvement in the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older, like EPIDYOLEX (cannabidiol).

Role in the care pathway?

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, duration and intensity of seizures, taking into consideration the context of significant drug resistance observed in this disease. In particular, the choice of treatment takes into account the patient's clinical profile, the type of seizures, pharmacokinetic interactions between anti-epileptic medicines (in a context in which the majority of patients are polymedicated) and the safety profile.

Sodium valproate in conjunction with benzodiazepines (clobazam or lorazepam) is recommended as 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.

In addition, the Committee recently assessed, on 13 May 2020, the proprietary medicinal product EPIDYOLEX (cannabidiol) indicated for use 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. It considered that this treatment is a therapeutic option in drug-resistant patients.

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 FINTEPLA (fenfluramine) in the care pathway:

In view of:

- demonstration of the efficacy of FINTEPLA (fenfluramine) as add-on therapy (including in conjunction with stiripentol plus clobazam and/or sodium valproate) compared to placebo, in the short term (14 and 15 weeks) in two randomised clinical studies,
- and in the absence of available data compared to another anti-epileptic medicinal products in a drug resistance context,

FINTEPLA (fenfluramine) is a therapeutic option in the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older who are drug-resistant (defined as patients who have failed to respond to at least two well-managed and well-tolerated anti-epileptic treatments, either as monotherapy or in combination).

Taking into account abnormal echocardiographic events (all trace mitral and/or aortic valve regurgitations and one case of mild mitral valve regurgitation) reported during short-term studies (16.4% in the fenfluramine groups versus 6.0% in the placebo groups) in a context of previous market withdrawal of fenfluramine following cases of valvular heart disease and pulmonary hypertension reported in the indication of obesity in adults and uncertainties regarding the pathophysiology of valve damage in children, as well as the dose-effect relationship of fenfluramine, the Committee reiterates the need, as recommended in the SPC, to:

- perform an initial echocardiogram before initiating treatment in order to determine the baseline situation and exclude any valvular heart disease or pulmonary hypertension,
- perform regular ECG monitoring in the event of treatment with FINTEPLA (fenfluramine) every 6 months for the first two years, then once yearly.

Since the efficacy and safety data for FINTEPLA (fenfluramine) are limited, with maximum follow-up of 3 years and this treatment is intended for long-term administration, the Committee highlights the need to regularly reassess the benefit of treatment.

In the absence of robust indirect comparative data between FINTEPLA (fenfluramine) and EPIDYOLEX (cannabidiol), 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 safety profile of the drugs and the resulting contraindications.

The Summary of Product Characteristics (SPC) and the Risk Management Plan (RMP) must be complied with.

Special recommendations

The Committee reminds prescribers and pharmacists dispensing FINTEPLA (fenfluramine) that this proprietary medicinal product is the subject of a controlled access programme associated with prescribing and dispensing specificities, aimed at:

- 1) preventing the off-label use of FINTEPLA (fenfluramine) for weight reduction purposes in obese patients insofar as the benefit/risk ratio in this population is deemed to be unfavourable
- 2) confirming that prescribing physicians have been informed of the need for regular cardiac monitoring in patients taking FINTEPLA (fenfluramine) due to the potential risk of valvular heart disease and pulmonary hypertension.

In the context of this controlled access programme, prescribing physicians must be registered in the mechanism in advance (with a controlled access program ID number allocated). During this registration, the prescriber will be informed of the need for periodic cardiac monitoring in patients taking FINTEPLA (fenfluramine) due to the potential risk of valvular heart disease and pulmonary hypertension and will have access to product information documents (SPC, healthcare professionals guide) listing these various risks, including off-label use for weight control purposes.

Prescribing and dispensing will thereafter be checked on the basis of the controlled access program ID number, which must be indicated on the prescription for FINTEPLA (fenfluramine) for pharmacies to be able to dispense the medicinal product.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Dravet syndrome is a severe form of drug-resistant epileptic encephalopathy resulting in delayed neurocognitive development and a significant impairment of quality of life for patients and their carers.
◗ The proprietary medicinal product FINTEPLA (fenfluramine) is a symptomatic medicinal product for the seizures associated with Dravet syndrome.
◗ The efficacy/adverse effects ratio of FINTEPLA (fenfluramine) is high.
◗ There are a limited number of medicinal alternatives.
◗ FINTEPLA (fenfluramine) is a therapeutic option in the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older who are drug-resistant.

Public health impact

Considering:
- the seriousness of Dravet syndrome,
- its prevalence,
- the partially met medical need in view of the limited number of available alternatives,
- the partial response to the identified need:
    - with an additional impact expected on morbidity and mortality, but only demonstrated in the short term (14 and 15 weeks) at this stage,
    - the lack of demonstrated impact on quality of life,
    - the lack of demonstrated impact on the organisation of care and the patient's life pathway,

FINTEPLA (fenfluramine) is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of FINTEPLA (fenfluramine) is substantial in the MA indication.

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 marketing authorisation indication and dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- **demonstration of the superiority of fenfluramine compared to placebo, as add-on therapy, evaluated in two double-blind, randomised studies (including one study in combination with stiripentol plus clobazam and/or sodium valproate), in children and adolescents with Dravet syndrome,**
    - **with respect to the mean change in total seizure frequency in the short term over 14 and 15 weeks (primary endpoint), with a 54 to 62% reduction, for a mean number of seizures at baseline ranging from 22 to 45 seizures per month, respectively,**
    - **with respect to the percentage of patients responding to treatment (i.e. ≥ 50% reduction in seizures) and the seizure-free interval over 14 and 15 weeks, ranked secondary endpoints**
- **the medical need that remains substantial, due to the limited alternatives in this rare disease, despite the recent availability of cannabidiol (EPIDYOLEX)**
- **the absence of robust indirect comparative data versus cannabidiol (EPIDYOLEX) in a concomitant development context**

and despite:

- **the absence of robust data on quality of life,**
- **abnormal echocardiographic events (all trace mitral and/or aortic valve regurgitations and one mild mitral valve regurgitation) reported during short-term studies: 16.4% in the fenfluramine group versus 6.0% in the placebo groups,**
- **the absence of long-term efficacy and safety data for fenfluramine, 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 FINTEPLA (fenfluramine) provides a minor clinical added value (CAV IV), like EPIDYOLEX (cannabidiol), in the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.