SUMMARY

fenfluramine

FINTEPLA 2,2 mg/mL

oral solution

Reassessment at the request of the TC

Adopted by the Transparency Committee on 23 October 2024

Summary of opinion

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

Unfavourable opinion for reimbursement in the other situations covered by the MA indication.

Transparency Committee's conclusions

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.
- This is a symptomatic medicinal product for the seizures associated with Dravet syndrome.
- Considering:
  - initial data having demonstrated the superiority of fenfluramine compared to placebo, as add-on therapy, 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,
  - new comparative efficacy data versus placebo issues from a study with a similar methodology having reported similar results for these endpoints,
  - the absence of robust data on quality of life,
  - the safety profile with 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) reported at the time of initial inclusion,

- the risk of pulmonary arterial hypertension now classed as an important identified risk following a post-marketing case, along with the potential risks of valvular heart disease, suicidal behaviour or ideation and growth retardation,
- 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 efficacy/adverse effects ratio is high in the short term only; the long-term efficacy/adverse effects ratio is not known.

➔ 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 drug-resistant patients 2 years of age and older, only in last-resort situations.

➔ Public health benefit

Considering:

- the seriousness of the disease and its prevalence,
- the substantial medical need in view of the limited number of available alternatives,
- the partial response to the identified need given:
  - the additional impact expected on morbidity and mortality, but only demonstrated in the short term versus placebo at this stage (14 and 15 weeks),
  - the lack of evidence of an additional impact on quality of life,
  - the lack of evidence of an additional impact on the organisation of care,

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

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

- **substantial in the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for drug-resistant patients 2 years of age and older, only in last-resort situations;**
- **insufficient to justify public funding in view of the available alternatives in the other MA situations.**

The Committee issues the following opinions:

- **a favourable opinion for maintenance of inclusion of FINTEPLA (fenfluramine) in both the list of covered drugs for outpatients and the list of covered drugs for inpatients approved for use in the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for drug-resistant patients 2 years of age and older, only in last-resort situations;**
- **an unfavourable opinion for maintenance of inclusion of FINTEPLA (fenfluramine) in both the list of covered drugs for outpatients and the list of covered drugs for inpatients approved for use in the other MA situations.**

Clinical Added Value

Considering:

- initial data having demonstrated the superiority of fenfluramine compared to placebo, as add-on therapy, 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,
- new comparative efficacy data versus placebo issues from a study with a similar methodology having reported similar results for these endpoints,
- the medical need that remains substantial, due to the limited alternatives in this rare disease,
- the absence of robust indirect comparative data versus cannabidiol (EPIDYOLEX) in a concomitant development context,

but:

- the absence of robust data on quality of life,
- the safety profile with 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) at the time of initial inclusion,
- the risk of pulmonary arterial hypertension now classed as an important identified risk following a post-marketing case, justifying the maintenance of supervision along with the need for echocardiogram monitoring, taking into account the history of the drug in the obesity indication in adults,
- 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 deems that FINTEPLA (fenfluramine) provides a minor clinical added value (CAV IV) in the current last-resort care pathway for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for drug-resistant patients 2 years of age and older.