NCPE Technical Summary

Fenfluramine (Fintepla®)

HTA ID: 23051

16/09/2024

Applicant: UCB

The cost-effectiveness of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome as an add-on therapy to other anti-seizure medicines for patients two years of age and older.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of fenfluramine (Fintepla®). Following assessment of the Applicant's submission, the NCPE recommends that fenfluramine (Fintepla®) be considered for reimbursement if cost-effectiveness can be improved.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (UCB) Health Technology Assessment (HTA) of fenfluramine (Fintepla®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In August 2024, UCB submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome as add-on therapy to other anti-seizure medicines for patients two years of age and older. Reimbursement is sought under the High Tech Drug Arrangement.

Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy. The classic LGS triad, when the syndrome is fully developed comprises many types of seizures that include tonic seizures, mental retardation and an interictal EEG pattern of diffuse, slow spike-wave complexes. Tonic seizures are the most characteristic type of seizure in LGS and their presence is a prerequisite for the diagnosis. Atypical absences are the second most common type of seizure in LGS and sudden tonic or atonic falls (drop attacks) occur in about 56% of patients who have slow spike-waves. Approximately 50% - 75% of patients with LGS have episodes of non-convulsive status epilepticus.

Learning disability is an important component of the classic LGS triad and many patients (20% - 60%) have delayed development at the onset of LGS with neurological signs or abnormalities in neuroimaging. The proportion of patients who have cognitive impairment increases to 75% - 95% at 5 years from syndrome onset. There are few effective treatment options for the multiple seizures and comorbidities and the long-term outlook is poor for most patients. A Cochrane review of RCTs for treatment of LGS concluded that lamotrigine, topiramate and felbamate may be helpful as add-on therapies. In a European physician survey, therapy with valproate was recommended as first-line treatment for LGS with lamotrigine considered the next treatment of choice. Sustained seizure freedom is rarely achieved in LGS due to resistance to pharmacological treatments.

Fenfluramine (Fintepla) is indicated for the treatment of seizures associated with LGS as an add-on therapy to other anti-epileptic medicines for patients two years of age and older. Marketing authorisation from the European Medicines Agency (EMA) was obtained on the 18 December 2020. It is currently designated an orphan medicine by the EMA. Fenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1D, 5-HT2A, and 5-HT2C receptors, and by acting on the sigma-1 receptor. It is available as a 2.2 mg/ml oral solution in either a 120 ml or 360 ml formulation (pack size) for supply. It is administered orally with a starting dose of 0.1 mg/kg taken twice daily (0.2 mg/kg/day). The dose on day 7 is increased to 0.2 mg/kg twice daily (0.4 mg/kg/day) and increased further on day 14, as applicable, to 0.35 mg/kg twice daily (0.7 mg/kg/day). The maximum recommended dose is 26 mg daily (13 mg twice daily i.e. 6 ml twice

daily).

1. Comparative effectiveness of fenfluramine (Fintepla®)

The clinical evidence supporting the use of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome primarily comes from one phase 3 clinical trial and a long-term open-label extension (OLE) study.

The study published by Knupp et al. (2022) was a multicentre, double-blind, placebo-controlled, parallel-group randomised phase 3 clinical trial. The 263 participants were aged 2 to 35 years (median age 13 years, 56% male) with confirmed Lennox-Gastaut syndrome. At baseline 89% of patients were using 2 to 4 concomitant antiseizure medications including valproate (56%), clobazam (45%), lamotrigine (33%), levetiracetam (23%) and rufinamide (20%). The median (range) drop seizure frequency for all patients was 77 (2 – 2943) per 28 days.

Patients were randomised to fenfluramine 0.7mg/kg/day (n=87), fenfluramine 0.2mg/kg/day (n=89) and placebo (n=87) with a trial duration of 20 weeks. The primary endpoint was the percentage change from baseline in Epilepsy Study Consortium-confirmed drop seizures in the 0.7mg/kg/day fenfluramine group versus placebo. Key secondary end points by treatment group included the percentage change from baseline in frequency of drop seizures in the 0.2mg/kg/day fenfluramine group, 50% or greater responder rate, and the proportion of patients who achieved improvement (minimally, much, or very much improved) on the Clinical Global Impression-Improvement (CGI-I) scale. Additional secondary outcomes included CGI-I rated by caregivers, subgroup analyses by seizure type, change in frequency of all countable motor seizures (GTC, tonic, clonic, atonic, tonic or atonic, and clearly recognizable focal), and number of days free of drop seizures. At the end of the maintenance period patients could continue to the open-label extension (OLE) study or discontinue treatment.

The median percentage reduction in frequency of drop seizures was 26.5 percentage points in the 0.7mg/kg/day fenfluramine group, 14.2 percentage points in the 0.2mg/kg/day fenfluramine group, and 7.6 percentage points in the placebo group. Therefore, the trial met its primary efficacy end point i.e. patients in the 0.7mg/kg/day fenfluramine group achieved a −19.9 percentage points (95% CI, −31.0 to −8.7 percentage points; P = .001) estimated median difference in drop seizures from baseline vs placebo. More patients in the 0.7mg/kg/day fenfluramine group achieved a 50% or greater response (22 of 87 [25%]; P = .02) vs placebo (9 of 87 [10%]). Site investigators and caregivers

gave a much improved or very much improved rating on the Clinical Global Impression of Improvement scale to more patients in the 0.7mg/kg/day fenfluramine group than patients in the placebo group (21 [26%] vs 5 [6%]; P = .001). The seizure subtype that appeared most responsive to fenfluramine was generalized tonic-clonic seizure (120 of 263 [46%]), with a decrease in frequency of 45.7% in the 0.7mg/kg/day fenfluramine group and 58.2% in the 0.2mg/kg/day fenfluramine group compared with an increase of 3.7% in the placebo group. Most common treatment-emergent adverse events included decreased appetite (59 [22%]), somnolence (33 [13%]), and fatigue (33 [13%]). No cases of valvular heart disease or pulmonary arterial hypertension were observed.

Eligible patients with LGS who completed the phase 3 randomized clinical trial (n=247) enrolled in an open-label extension (OLE) study. All patients were initially started on 0.2mg/kg/day fenfluramine (regardless of their randomised treatment arm) and after 1 month were titrated up to a maximum of 0.7mg/kg/day. Effectiveness and safety was assessed at 3-month intervals. The mean age of participants was 14.3 ± 7.6 years (79 [32%] adults) the median duration of fenfluramine treatment was 364 days and 88.3% of patients received 2–4 concomitant antiseizure medications. The median percentage change in monthly drop seizure frequency was −28.6% over the entire OLE study period and −50.5% at Month 15 (n = 142, p < .0001). Seventy five of 241 patients (31.1%) experienced ≥ 50% reduction in drop seizure frequency. Median percentage change in nondrop seizure frequency was −45.9% (n = 192, p = .0038). Generalized tonic–clonic seizures (GTCS) and tonic seizures were most responsive to treatment, with median reductions over the entire OLE period of 48.8% (p < .0001, n = 106) and 35.8% (p < .0001, n = 186), respectively. A total of 37.6% (95% confidence interval [CI] = 31.4%–44.1%, n = 237) of investigators and 35.2% of caregivers (95% CI = 29.1%–41.8%, n = 230) rated patients as Much Improved/Very Much Improved on the Clinical Global Impression of Improvement scale. The most frequent treatment-emergent adverse events were decreased appetite (16.2%) and fatigue (13.4%). No cases of valvular heart disease (VHD) or pulmonary arterial hypertension (PAH) were observed. Patients with LGS experienced sustained reductions in drop seizure frequency and a reduction in the frequency of generalised tonic-clonic seizures, the key risk factor for sudden unexpected death in epilepsy.

2. Safety of fenfluramine (Fintepla®)

Side effects of fenfluramine may be subdivided into cardiovascular and non-cardiovascular adverse events. The most common non-cardiovascular adverse event associated with fenfluramine was decreased appetite which may be expected as fenfluramine was first approved in Europe in the 1960s at a dose of 60 – 120 mg per day as an appetite suppressant for the treatment of obesity. In

the study by Knupp et al. (2022) the most common treatment – emergent adverse events (TEAE) included decreased appetite (59 of 263 [22%]), somnolence (33 of 263 [13%]), and fatigue (33 of 263 [13%]). More patients in the fenfluramine treatment groups than in the placebo group experienced decreased appetite (31 of 87 [36%] in the 0.7mg/kg/day fenfluramine group; 18 of 89 [20%] in the 0.2mg/kg/day fenfluramine group; 10 of 87 [11%] in the placebo group). Weight loss of 7% or more from baseline was reported in 7 of 87 patients (8%) in the 0.7mg/kg/day fenfluramine group, 2 of 89 (2%) in the 0.2mg/kg/day fenfluramine group, and 2 of 87 (2%) in the placebo group. The most frequent TEAEs leading to study withdrawal were seizures (3 patients in the 0.2mg/kg/day fenfluramine group) and somnolence (3 patients in the 0.7mg/kg/day fenfluramine group). Status epilepticus was observed in 3 of 87 patients (3%) in the 0.7mg/kg/day fenfluramine group, 0 patients in the 0.2mg/kg/day fenfluramine group, and 1 of 87 (1%) in the placebo group.

In the late 1990s fenfluramine was withdrawn worldwide because of the risks of valvular heart disease and pulmonary arterial hypertension which were fatal in some cases. The dose and the duration of treatment may be a factor in the development of cardiovascular adverse events associated with fenfluramine. No cases of valvular heart disease or pulmonary arterial hypertension were reported in the phase 3 clinical trial or the open-label extension study. This may be expected due to the relatively small patient numbers participating in the clinical trial programme, the short duration of study and the key exclusion criteria including a history of pulmonary hypertension and cardiovascular disease in addition to aortic or mitral valve regurgitation as established by echocardiography. However, post-marketing data suggests that pulmonary arterial hypertension may occur with doses used to treat epilepsy.

The cardiovascular risk associated with fenfluramine is acknowledged in the European Public Assessment Report recommending the implementation of a form of controlled access programme in European Member States. Discussions are currently underway between the Applicant and the Health Products Regulatory Authority (HPRA) as to the exact nature of the required controlled access programme in the Irish healthcare setting. The current advice is that prior to starting fenfluramine for the treatment of Lennox-Gastaut syndrome or Dravet syndrome all patients should undergo an echocardiogram to establish a baseline prior to treatment and to exclude any pre-existing valvular heart disease or pulmonary arterial hypertension. Fenfluramine is contraindicated in patients with pulmonary arterial hypertension and in patients with aortic or mitral valvular heart disease. Echocardiogram monitoring should be conducted every 6 months for the first 2 years and annually thereafter during fenfluramine treatment.

3. Cost effectiveness of fenfluramine (Fintepla®)

Methods

A Markov model was developed in Microsoft Excel to represent the natural history of the disease, clinical pathway and clinical outcomes reported for people with Lennox-Gastaut syndrome. The clinical evidence supporting this economic evaluation comes from the pivotal phase 3 clinical trial and the open-label extension study outlined above. The relevant comparator for fenfluramine + standard of care (SoC) anticonvulsant therapy was cannabidiol + clobazam + SoC anticonvulsant therapy. As there are no direct comparative data between fenfluramine and cannabidiol + clobazam a network meta-analysis (NMA) was performed to provide the relevant comparative data. This network included fenfluramine 0.7mg/kg, cannabidiol 10mg/kg and cannabidiol 20mg/kg and placebo.

In the model health states were defined as four mutually exclusive and clinically established categories of percent change in drop seizure frequency since baseline and included state 0: no response (< 25% reduction in drop seizure frequency), state 1: low response (25% to < 50% reduction), state 2: medium response (50% to < 75% reduction) and state 3: best response (> 75% reduction). The model included two additional states, one for discontinued patients and the death state. Discontinuation could occur at titration and at any cycle after that throughout the time horizon due to adverse events, lack of efficacy and a stopping rule.

The base case used a lifetime horizon and a 3-month cycle length in keeping with reporting rates in the fenfluramine and cannabidiol trials. A standard half-cycle correction was applied as events and transitions could occur at any point during the cycle. The model started with the titration phase with a duration of 2 weeks and the initial distribution of patients across the health states were calculated using quartiles of drop seizure distribution at baseline from the phase III clinical trial outlined above. The main efficacy parameter was the drop seizure frequency and at the end of cycle 1 (3.5 months) patients would move to health states according to efficacy data from the indirect treatment comparison (ITC) of the pivotal trials. Movement between health states up to cycle 5 (or up to 15 months) were estimated from the ITC based on the open-label extension (OLE) studies for fenfluramine and cannabidiol. In the post-OLE period from cycles 6 to 9 (15 – 27 months) the average of cycles 2 to 5 were calculated and applied to estimate the transitions among health states and after cycle 9 (27 months onwards) the model assumed that the patients would stay in their corresponding state with potential competing occurrences of discontinuation or death. Treatment waning was applied after cycle 9 as a proportion of patients assumed to undergo waning calculated from the OLE

study. The same value was applied to patients in both treatment arms. Treatment discontinuation varied across the time horizon and all-cause mortality was applied using a background mortality rate based on Irish Life tables. All patients were at risk of sudden unexpected death in epilepsy (SUDEP) as well as death from non-SUDEP causes such as status epilepticus and accidents. Baseline characteristics were sourced from the pivotal phase III clinical trial.

Patient outcomes were quantified as quality-adjusted life years (QALYs). Health related quality of life data was not derived from the fenfluramine clinical trial rather it was obtained from the study by Verdian et al. (2008). In relation to costs the model considered intervention costs, drug monitoring costs and healthcare resource costs. Drug acquisition costs were calculated according to weight-dependent dosage considering mg/kg/day and maximum daily dose (when applicable) of each add-on treatment and basket of standard of care anticonvulsants. Costs and quality adjusted life-years (QALYs) were discounted at a rate of 4% over the lifetime horizon. Results in the base case represented the perspective of the Health Service Executive (HSE).

Results

For the treatment of seizures associated with Lennox-Gastaut syndrome in patients two years of age and older the basecase (deterministic) incremental cost-effectiveness ratio (ICER) for fenfluramine + standard of care (SoC) versus cannabidiol + clobazam + SoC was estimated at €198,407 per quality adjusted life year i.e. €198,407/QALY. An analysis of costs and QALYs is shown in table 1.

Table 1. Cost-effectiveness of fenfluramine + SoC versus cannabidiol + clobazam + SoC.

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (€/QALY)
Fenfluramine + SoC	€510,828	1.221			
Cannabidiol + clobazam + SoC	€444,222	0.886	€66,605	0.336	€198,407

ICER: Incremental cost-effectiveness ratio QALY: quality adjusted life year SoC: Standard of care anticonvulsant therapy

Sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted and the ICER was estimated at €191,381/QALY. The probability of fenfluramine + SoC being cost-effective at the €20,000/QALY and

€45,000/QALY thresholds were 7% and 10% respectively. A deterministic sensitivity analysis was also presented. The most important parameters that impacted the cost-effectiveness of fenfluramine + SoC versus cannabidiol + clobazam + SoC included the cost of fenfluramine and cannabidiol and the relative risks for the discontinuation rate of fenfluramine during the titration and maintenance period. A scenario analysis was presented and the time horizon, discount rates, utility options and cannabidiol dosage had a significant impact in the ICER. The price – ICER relationship indicates that a price reduction of at least 40% will be required to ensure cost-effectiveness.

4. Budget impact of fenfluramine (Fintepla®)

A budget impact analysis was submitted to estimate the 5 year budget impact of fenfluramine. The total cost of fenfluramine per pack (strength 2.2 mg, pack size 120) was estimated at €1,903.05. The eligible patient population was estimated at 144 patients in year 1, 279 patients in year 2, 325 patients in year 3, 392 patients in year four and 423 patients in year 5. Discontinuation rates, mortality rates and the stopping rule was taken into consideration in addition to the impact of weight change on treatment costs. A weighted annual cost of €63,385.28 was calculated for fenfluramine. The expected uptake of fenfluramine was estimated at 8% in year 1 increasing to 23% by year 5. The 5-year gross drug budget impact for fenfluramine treatment was estimated at €18,378,608. The 5-year net drug budget impact under the base case for fenfluramine was estimated at €7,658,053. The NCPE Review Group considered the budget impact figures to be an underestimate due in part to the low estimate for market share.

5. Patient Organisation Submission

Patient Organisation submissions were received from Dravet Syndrome Ireland and Epilepsy Ireland.

6. Conclusion

Having considered the cost-effectiveness of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome as add-on therapy to other anti-seizure medicines for patients two years of age and older the NCPE recommends that fenfluramine be considered for reimbursement if cost-effectiveness can be improved*

*This recommendation should be considered while also having regards to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.