NCPE Technical Summary

Fenfluramine (Fintepla®)

HTA ID: 23048

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Applicant: UCB

The cost-effectiveness of fenfluramine for the treatment of seizures associated with Dravet 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 relative to existing treatments*.

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 May 2024, UCB submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of fenfluramine for the treatment of seizures associated with Dravet 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.

Dravet syndrome is a severe developmental and epileptic encephalopathy with onset in the first year of life in previously healthy infants. It is characterised by drug-resistant, lifelong seizures and is associated with comorbidities such as intellectual disability, behavioural disturbances, sleep disorders and gait problems that adversely impact on the quality of life of patients and their families. Mortality rates are increased in patients with Dravet syndrome primarily due to status epilepticus and sudden unexpected death in epilepsy. Pathogenic variants in the SCN1A gene that encodes the α-1 subunit of voltage-gated sodium channel Nav 1.1 may lead to loss of channel function and are identified in over 80% - 90% of patients with Dravet syndrome. Genetic testing is recommended for certain cohorts including infants 2–15 months old, presenting with either a first prolonged hemiclonic seizure or first convulsive status epilepticus with fever or following vaccination, in the absence of another cause. Sustained seizure freedom is rarely achieved in Dravet syndrome due to resistance to pharmacological treatments.

Fenfluramine (Fintepla) is indicated for the treatment of seizures associated with Dravet syndrome 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 18/12/2020. 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. If it is being administered without stiripentol the dose on day 7 is increased to 0.2 mg/kg twice daily and increased further on day 14, as applicable, to 0.35 mg/kg twice daily. The maximum recommended dose is 26 mg daily. If fenfluramine is being used in combination with stiripentol it is titrated to 0.2 mg/kg twice daily on day 7 and the maximum recommended dose is 17 mg daily. The lower dose of fenfluramine in combination with stiripentol is due to the ability of stiripentol to inhibit hepatic cytochrome P450 isoenzymes thereby increasing fenfluramine concentrations.

1. Comparative effectiveness of fenfluramine (Fintepla®)

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

One of the phase 3 trials (Lagae et al. 2019) represents a planned merged analysis of the first cohort of 119 patients from two identical studies, one conducted in the USA and Canada and the second study conducted in Western Europe, Japan and Australia. This randomised, double-blind, placebo-controlled clinical trial of children and young adults with Dravet syndrome commenced with a 6-week observation period to establish baseline monthly convulsive seizure frequency (MCSF). Patients were randomly assigned in a 1:1:1 ratio to placebo (n=40), fenfluramine 0·2 mg/kg per day (n=39), or fenfluramine 0·7 mg/kg per day (n=40), added to existing antiepileptic agents for 14 weeks. The primary outcome was the change in mean monthly frequency of convulsive seizures during the treatment period compared with baseline in the 0·7 mg/kg per day group versus placebo; 0·2 mg/kg per day versus placebo was assessed as a key secondary outcome. Genetic testing was done for all patients where permitted, but a positive SCN1A mutation was not required for enrolment.

The mean age of the 119 participants was 9 years, 64 (54%) were male and they received a mean of 2.4 antiepileptic drugs at baseline. The median baseline convulsive seizure frequency per month ranged from 17.5 – 27.3 among the three treatment groups. During treatment, the median reduction in seizure frequency was 74·9% in the fenfluramine 0·7 mg/kg group (from median 20·7 seizures per 28 days to 4·7 seizures per 28 days), 42·3% in the fenfluramine 0·2 mg/kg group (from median 17·5 seizures per 28 days to 12·6 per 28 days) and 19·2% in the placebo group (from median 27·3 per 28 days to 22·0 per 28 days). The study met its primary efficacy endpoint, with fenfluramine 0·7 mg/kg per day showing a 62·3% greater reduction in mean MCSF compared with placebo (95% CI 47·7%-72·8%, p<0·0001). Fenfluramine 0·2 mg/kg per day showed a 32·4% reduction in mean MCSF compared with placebo (95% CI 6·2%-52·3%, p=0·0209). During the treatment period 27 (68%) of the 40 patients in the fenfluramine 0.7 mg/kg/day group and 15 (38%) of the 39 patients in the fenfluramine 0.2 mg/kg/day group had a reduction in convulsive seizure frequency of at least 50% as compared with five (12%) of the 40 patients in the placebo group. In terms of quality of life, no significant differences were observed between the groups in the overall composite score from the Quality of Life in Childhood Epilepsy instrument. However, total scores on the parent-reported Pediatric Quality of Life Inventory improved by a mean of 5.9 points in the fenfluramine 0.7 mg/kg/day group and 6.8 points in the fenfluramine 0.2 mg/kg/day group as compared with a

decrease in the placebo group.

The analysis of patients from the remaining cohort of the two identical studies outlined above (Sullivan et al. 2023) was a multicentre, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial which enrolled patients with Dravet syndrome, aged 2-18 years with poorly controlled convulsive seizures, provided they were not also receiving stiripentol. Eligible patients who had ≥6 convulsive seizures during the 6-week baseline period were randomized to placebo, fenfluramine 0.2 mg/kg/day, or fenfluramine 0.7 mg/kg/day (1:1:1 ratio) administered orally (maximum dose = 26 mg/day). Doses were titrated over 2 weeks and maintained for an additional 12 weeks. The primary endpoint was a comparison of the monthly convulsive seizure frequency (MCSF) during baseline and during the combined titration-maintenance period in patients treated with fenfluramine 0.7 mg/kg/day versus placebo.

A total of 169 patients were screened, and 143 were randomized to treatment. Mean age was 9.3 ± 4.7 years (±SD), 51% were male, and median baseline MCSF in the three groups ranged 12.7-18.0 per 28 days. Patients treated with fenfluramine 0.7 mg/kg/day demonstrated a 64.8% (95% confidence interval = 51.8% - 74.2%) greater reduction in MCSF as compared with placebo ($p < .0001$). Following fenfluramine 0.7 mg/kg/day, 72.9% of patients had a ≥50% reduction in MCSF compared with 6.3% in the placebo group ($p < .0001$). The median longest seizure-free interval was 30 days in the fenfluramine 0.7 mg/kg/day group compared with 10 days in the placebo group ($p < .0001$). In this study change from baseline on the Quality of Life in Childhood Epilepsy Scale was significantly greater than placebo for the fenfluramine 0.7 mg/kg/day group ($p = 0.0445$). In contrast, there was no significant change on the Pediatric Quality of Life Inventory score between the treatment groups.

The third study was a double-blind, placebo-controlled, parallel-group randomized clinical trial of patients aged 2 to 18 years with a confirmed clinical diagnosis of Dravet syndrome who were receiving stable, stiripentol-inclusive antiepileptic drug regimens. Patients with 6 or more convulsive seizures during the 6-week baseline period were randomly assigned to receive fenfluramine 0.4 mg/kg/day (maximum, 17 mg/day) or placebo. After a titration period of three weeks patients' assigned dosages were maintained for an additional twelve weeks. The primary efficacy end point was the change in mean monthly convulsive seizure frequency (MCSF) between fenfluramine and placebo during the combined titration and maintenance periods relative to baseline.

From the 115 eligible patients 87 were enrolled in the study. The mean age was 9.1 years, 50 were male patients (57%) and the mean baseline seizure frequency was approximately 25 seizures per month. Patients were randomized to fenfluramine 0.4 mg/kg/day (n = 43) or placebo (n = 44).

Patients treated with fenfluramine achieved a 54.0% (95% CI, 35.6%-67.2%; p < .001) greater reduction in mean monthly seizure frequency as compared with those receiving placebo. With fenfluramine, 54% of patients demonstrated a clinically meaningful (≥50%) reduction in monthly convulsive seizure frequency vs 5% with placebo (p < .001). The median (range) longest seizure-free interval was 22 (3.0-105.0) days with fenfluramine and 13 (1.0-40.0) days with placebo (p = 0.004).

In addition to the three randomised phase 3 clinical trials an open-label extension (OLE) study was conducted to assess longer-term safety and efficacy of fenfluramine in patients who completed one of the double-blind studies. Patients enrolling in the OLE study initiated fenfluramine at 0.2 mg/kg/day regardless of their treatment assignment in the double-blind study. After 4 weeks, the fenfluramine dose could be titrated based on efficacy and tolerability to maximum of 0.7 mg/kg/day (absolute maximum 27 mg/day) or maximum of 0.4 mg/kg/day (absolute maximum 17 mg/day) in patients receiving concomitant stiripentol. A total of 232 patients were treated for a median 256 days (range = 46-634 days). Over the entire OLE analysis period, the median decrease in convulsive seizure frequency compared to baseline in the double-blind studies was -66.8% (range = -100% to 234.9%; p < .001). The median reduction in seizure frequency was similar in patients <6 years (-75.7%) and ≥6 years old (-64.7%). The most commonly reported adverse events included pyrexia (21.6%), nasopharyngitis (19.4%), and decreased appetite (-15.9%). No valvular heart disease (VHD) or pulmonary arterial hypertension (PAH) was observed. Real world evidence of the long-term effectiveness of fenfluramine was also presented in the submitted economic dossier.

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 with associated weight loss in some cases. Other recognised non-cardiovascular adverse events include diarrhoea, lethargy, nasopharyngitis, fatigue, somnolence and vomiting. One of the most common serious adverse events in the clinical trial programme included hospital admission for status epilepticus. In the late 1990s fenfluramine (at higher doses i.e 60mg – 120 mg/day) 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. Cardiovascular adverse events were not observed in the clinical trial programme which may be expected due to the relatively small patient numbers, 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 show 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 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 patient-level simulation model was developed in Microsoft Excel to determine lifetime costs and quality adjusted life years (QALYs) for treatment with fenfluramine + standard of care versus cannabidiol + clobazam + standard of care. The model simulates a cohort of patients based on patient-level data from the phase 3 fenfluramine registration clinical trials. Each patient was assigned a seizure profile per 28 day cycle drawn with the following patient characteristics: age, gender, weight, comorbidities and stiripentol use. A bootstrapping method was used for the extrapolation of seizures after the first 14 or 15 weeks of treatment. The 28 day cycle length was used with two main clinical outcomes i.e the number of seizures per cycle and the number of seizure-free days per cycle. A lifetime horizon (60 years) was considered to capture all meaningful differences in costs and effects. The clinical outcomes together with patient characteristics impact on costs, mortality and quality of life (QoL) generated for each patient. Patient level data from the fenfluramine registration trials was used to inform the efficacy of the standard of care. For fenfluramine and cannabidiol the indirect treatment comparison provided efficacy inputs for the cost-effectiveness analysis. It is assumed that there is no waning of the treatment effect of fenfluramine or cannabidiol + clobazam. When a patient discontinues treatment they return to baseline seizure frequency within the respective clinical trials. Seizure-free days is a necessary component in the model as it determines patients health-related quality of life. The base case adopts a 30% stopping rule for both treatments

at 6 months. Patient outcomes were quantified as quality-adjusted life years (QALYs). Health related quality of life data was not derived from the fenfluramine clinical trial programme rather it was obtained using time trade-off weights from the study by Lo et al. (2021). 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 Dravet 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 €121,187 per quality adjusted life year (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	€298,549	5.300			
Cannabidiol + clobazam + SoC	€269,323	5.058	€29,226	0.241	€121,187

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 €95,284/QALY. The probability of fenfluramine + SoC being cost-effective at the €20,000/QALY and €45,000/QALY thresholds were 4% and 8% 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 cannabidiol and fenfluramine treatment effects, ongoing discontinuation per cycle after the fourth cycle for cannabidiol and fenfluramine and cannabidiol discontinuation at 6 months. 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. Having considered the number of patients who remain uncontrolled on current care who are being treated with cannabidiol + clobazam the eligible patient population was estimated at 21 patients in year 1, 39 patients in year 2, 45 patients in year 3, 54 patients in year four and 58 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 €57,713.48 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 €2,296,194. The NCPE Review Group consider this an underestimate and estimated that the 5 year gross budget impact could be in the region of €12.5 million. The 5-year net drug budget impact under the base case for fenfluramine was estimated at €870,934. The NCPE Review Group also considered this an underestimate.

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 Dravet 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 relative to existing treatments.*

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