SMC2569

fenfluramine oral solution (Fintepla®)

UCB Pharma Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicines process

fenfluramine (Fintepla®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of seizures associated with Dravet syndrome as an add-on to other anti-epileptic medicines for patients 2 years of age and older.

SMC restriction: as add-on therapy for treating seizures associated with Dravet syndrome where seizures have not been controlled in people aged 2 years and older after trying two or more antiseizure medicines.

In three phase III studies compared with placebo, the addition of fenfluramine significantly reduced convulsive seizure frequency in children aged 2 to 18 years with Dravet syndrome that was inadequately controlled by current anti-epileptic medicines.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Fenfluramine is a serotonin releasing agent, which stimulates multiple 5-HT receptor subtypes. The precise mode of action of fenfluramine in Dravet syndrome is not known but it may reduce seizure frequency by acting on certain serotonin receptors in the brain and also by acting on the sigma-1 receptor. Fenfluramine is administered as an oral solution at doses ranging between 0.2 to 0.7mg/kg/day (0.2 to 0.4 mg/kg/day when used with stiripentol) in two divided doses; further details on maximum dosing are in the SPC.[1]

1.2. Disease background

Dravet syndrome is a severe, genetic form of epilepsy affecting approximately 1 in 20,000 births. It is characterised by various seizures that present in the first year of life including febrile, afebrile, generalised, unilateral, clonic or tonic-clonic seizures. Other seizure types including myoclonic and focal seizures and atypical absences appear when the child reaches 1 to 4 years of age. From the child's second year, significant development delays and associated neuropsychological disturbances (such as attention deficit disorder) are common. Nearly all patients have intellectual impairment. Death due to status epilepticus, drowning or accidents is common and those reaching adulthood are often dependent. Many patients (70% to 80%) carry abnormalities in the sodium channel alpha 1 subunit gene (SCN1A) which are mostly de novo, but familial SCN1A mutations can also occur.[2]

1.3. Company proposed position

The submitting company has requested that fenfluramine is restricted for use as add-on therapy for treating seizures associated with Dravet syndrome where seizures have not been controlled in people aged 2 years and older after trying two or more anti-seizure medicines.

1.4. Treatment pathway and relevant comparators

Patients are generally managed with sodium valproate in the first-line, with stiripentol and clobazam added if this is unsuccessful. If this triple therapy is unsuccessful, cannabidiol with clobazam can be considered as a second-line add-on for patients over 2 years. Further add-on treatment options include ketogenic diet, levetiracetam and topiramate. However it is difficult to achieve sufficient seizure control in patients with Dravet syndrome and new treatment are needed.[2, 3]

Stiripentol and cannabidiol are the only other medicines specifically licensed for Dravet syndrome, although sodium valproate and clobazam are licensed for use in epilepsy. SMC has accepted stiripentol for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate (SMC524). SMC has also accepted cannabidiol for use as adjunctive therapy of seizures associated with Dravet syndrome, in conjunction with clobazam for patients 2 years of age and older (SMC2262).

1.5. Category for decision-making process

Eligibility for a PACE meeting

Fenfluramine meets SMC orphan criteria

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of fenfluramine for the add-on treatment of Dravet syndrome comes from Study 1, Study 2 and Study 3. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[2, 4-6]

Criteria	Study 1, 2 and 3	
Study design	Double-blind, randomised, placebo-controlled phase III studies comprising a 6-week baseline observation period, before randomisation followed by a 2-week (3-week in Study 2) titration period and a 12-week maintenance treatment period.	
Eligible patients	• Patients aged 2 to 18 years with clinical diagnosis of Dravet syndrome. • Seizures not completely controlled by current regimen of antiepileptic medicines or other therapies. • Experienced ≥4 convulsive seizures in a 4-week period during previous 12 weeks and ≥6 convulsive seizures during the 6-week baseline period. • Stable medications or interventions for epilepsy for ≥4 weeks before screening and during the study period. In study 1 and 3, patients were not receiving or had not received stiripentol in the previous 21 days. In study 2, patients were receiving stable doses of stiripentol (plus clobazam or valproate) for ≥4 weeks before screening and to remain stable during the study period.	
Treatments	Study 1 and 3 • Fenfluramine 0.7mg/kg/day • Fenfluramine 0.2mg/kg/day • Placebo	Study 2 (with stiripentol) • Fenfluramine 0.4mg/kg/day Placebo
Randomisation	Eligible patients were randomised equally to treatment groups. Randomisation was stratified according to age (<6 years and ≥6 years).	
Primary outcome	Change in mean CSF per 28 days between baseline and the treatment periods (titration and maintenance) for fenfluramine 0.7 mg/kg/day (Study 1 and Study 3) or fenfluramine 0.4mg/kg/day (Study 2) compared with placebo.	
Key secondary outcomes	Study 1 and 3 • Patients with ≥50% reduction from baseline in CSF between fenfluramine 0.7mg/kg/day and placebo groups. • Longest interval between convulsive seizures between fenfluramine 0.7mg/kg/day and placebo groups. • Change in mean MCSF from baseline to treatment period between fenfluramine 0.2mg/kg/day and placebo groups. • Patients with ≥50% reduction from	Study 2 • Patients with ≥50% reduction from baseline in convulsive seizure frequency between fenfluramine and placebo groups. • Longest interval between convulsive seizures between the fenfluramine and placebo groups.

	baseline in CSF between fenfluramine 0.2mg/kg/day and placebo groups. • Longest interval between convulsive seizures between fenfluramine 0.2mg/kg/day and placebo groups.	
Statistical analysis	A hierarchical testing procedure was applied to the primary and key secondary outcomes in all studies with no formal testing after the first non-significant outcome in the hierarchy. Additional secondary outcomes were not controlled for multiplicity.	
Abbreviations: MCSF=monthly convulsive seizure frequency; CSF= convulsive seizure frequency		

In the three clinical studies, fenfluramine, at all doses, was significantly more effective than placebo for the primary and key secondary outcomes; p<0.001 unless otherwise stated. In Study 1 and Study 3, the fenfluramine 0.2mg/kg/day dose was included to assess dose-response and is the recommended starting dose for fenfluramine. Details of results are presented in Table 2.2.

Table 2.2. Results for primary and key secondary outcomes in Study 1 and Study 3 (without stiripentol) and Study 2 (with stiripentol)[2, 4-7]

	Study 1			**Study 3**			**Study 2 (with stiripentol)**	
	Fenfluramine		**Placebo (n=40)**	**Fenfluramine**		**Placebo (n=48)**	**Fenfluramine 0.4mg/kg/d (n=43)**	**Placebo (n=44)**
	0.7mg/kg/d (n=40)	**0.2mg/kg/d (n=39)**		**0.7mg/kg/d (n=49)[A]**	**0.2mg/kg/d (n=46)**			
Primary outcome: mean change in MCSF from baseline to treatment period								
Median MCSF at baseline	20.7	17.5	27.3	13.0	18.0	12.7	14.0	10.7
Median % reduction in MCSF from baseline	-75%	-42%	-19%	-74%	-47%	-7.6%	-63%	-1.1%
Mean difference versus placebo (95% CI)	-62% (-48 to -73)[B]	-32% (-6.2 to -51)[C] p=0.021	-	-65%[B]	-50%[BC]	-	-54% (-36 to -67)[B]	
Key secondary outcomes:								
Patients with ≥50% reduction from baseline in CSF	68% (27/40)	38% (15/39)	12% (5/40)	73%	46%	6.3%	54% (23/43)	4.6% (2/44)

Odds ratio versus placebo (95% CI)	15.0 (4.5 to 50.0)[B]	4.8 (1.5 to 15.0)	-	53.3[B]	13.4[B]	-	26.0 (5.5 to 123)[B]	
Median longest interval between convulsive seizures, days	25.0	15.0	9.5	30.0	18.5	10.0	22.0	13.0
Median difference versus placebo (95% CI)	15.5 (6 to 25)[B]	4.5 (0 to 9) p=0.035	-	*	*	-	15.5 (6 to 25) p=0.004	

[A] in Study 3, one patient randomised to fenfluramine 0.7mg/kg/day was not treated; [B] p-value <0.001 unless otherwise stated; [C] mean change in MCSF from baseline to treatment period between fenfluramine 0.2mg/kg/day and placebo was a key secondary outcome in Study 1 and Study 3, MCSF=monthly convulsive seizure frequency; CI=confidence interval; CSF= convulsive seizure frequency;

*Other data were also assessed but remain confidential.**

Additional secondary outcomes included convulsive seizure freedom (defined as no convulsive seizures during the treatment period) which was achieved by 7.5% and 12% of fenfluramine 0.7mg/kg/day patients in Study 1 and Study 3, 7.7% and 0 of fenfluramine 0.2mg/kg/day patients in Study 1 and Study 3 and by 2.3% of fenfluramine 0.4mg/kg/day plus stiripentol patients in Study 2; compared with no placebo treated patients in any of the studies. During the treatment period, the median number of days of rescue medication per 28 days was reported as 0.9 days for fenfluramine 0.7mg/kg/day in Study 1, as 1.7 days for fenfluramine 0.2mg/kg/day patients in Study 1 and 0.3 days for fenfluramine 0.4mg/kg/day in Study 2 and as 1.7 days and 0.3 days for placebo in Study 1 and Study 2 respectively.[2, 4-9]

Clinical Global Impression of Improvement (CGI-I) was an additional secondary outcome assessed by parent or caregiver. Patients considered to be “very much” or “much improved”, were 55%, 41% and 10% in the fenfluramine 0.7mg/kg/day, 0.2mg/kg/day and placebo groups respectively in Study 1, 62%, 37% and 8.3% respectively in Study 3 and 33% in the fenfluramine 0.4mg/kg/day group and 21% in the placebo group in Study 2.[4-6]

Patients who completed treatment in Study 1, Study 2 or Study 3 were able to enrol in an open-label extension study to assess the long-term efficacy and safety of fenfluramine. All patients started treatment with fenfluramine 0.2mg/kg/day that could be titrated according to efficacy and tolerability to a maximum dose of 0.7mg/kg/day (or 0.4mg/kg/day in patients also receiving stiripentol) after 4 weeks. Efficacy was assessed by the change from baseline in MCSF for the open-label extension period. Results have been published at cut-off at 13 March 2018, when 232 patients had been treated for a median of 256 days (range 58 to 634) at a mean dose of 0.44 ± 0.12mg/kg/day for patients not receiving stiripentol and 0.32 ± 0.12mg/kg/day for patients receiving stiripentol. At this analysis, there was a median 71% reduction in MCSF from a median

baseline of 19.7 (range 0 to 1464). A ≥25% reduction in MCSF was achieved by 78% of patients, ≥50% reduction by 64% and ≥75% reduction by 41%.[10]

Results of an updated analysis (cut-off at 14 October 2019) have been published as a poster when 330 patients had been treated for a median of 631 days (range 7 to 1,086); the mean dose of fenfluramine was not reported. At this analysis, there had been a median 64% reduction in MCSF from a median baseline of 15.3 (range 2.7 to 2719). A ≥25% reduction in MCSF was achieved by 75% of patients, ≥50% reduction by 63% and ≥75% reduction by 38%.[11]

2.2. Evidence to support the positioning proposed by the submitting company

The submitting company advised that full study populations reflected the proposed positioning since the majority of study patients had or were receiving at least two concomitant anti-epileptic medicines.

2.3. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the Quality of Life in Childhood Epilepsy Scale and the Paediatric Quality of Life Inventory. The Quality of Life in Childhood Epilepsy Scale was completed by the parent or caregiver and assessed day-to-day functioning and general health (total score ranges from 0 to 100, with higher scores indicating better quality of life). The Paediatric Quality of Life Inventory is an age-appropriate assessment of physical, emotional, social, and school functioning which can be completed by the child or parent (total score ranges from 0 to 100, with higher scores indicating better quality of life). Across the three studies, HRQoL results were generally similar or indicated small improvements with fenfluramine compared with placebo.

2.4. Supportive studies

The submitting company also presented real world data from a small number of patients treated with fenfluramine in Belgium and available data from the US and European Expanded Access Programs.

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing fenfluramine with cannabidiol plus clobazam, the submitting company presented an indirect treatment comparison, a pre-print of which has been published.[12] This has been used to inform the economic base case.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian network meta-analysis (NMA) using fixed effects.
Population	Patients with a clinical diagnosis of Dravet syndrome.
Comparators	Cannabidiol plus clobazam.
Studies included	Evidence for fenfluramine from published Study 1 and Study 2 (described in Table 2.1).[4-6] Evidence for cannabidiol plus clobazam is based on subgroups of patients from two randomised, placebo-controlled studies (GWPCARE1B and GWPCARE2).[13, 14]
Outcomes	Primary: percentage change from baseline in MCSF compared to placebo. Secondary: ≥50% reduction from baseline in MCSF (not used in the economic evaluation).

Results

The submitting company presented results of the NMA for both fenfluramine and cannabidiol plus clobazam versus placebo.

Table A: NMA results for fenfluramine and cannabidiol plus clobazam versus placebo[12]

	Fen 0.7mg	Fen 0.4mg	Cann 10mg	Cann 20mg
Mean % reduction in MCSF: mean difference (95% CrI)				
versus placebo	62% (48 to 73)	54% (35 to 67)	40% (19 to 56)	36% (19 to 50)
≥50% reduction in CSF: odds ratio (95% CrI)				
versus placebo	15.8 (5.3 to 57.2)	29.0 (7.1 to 222)	2.1 (1.0 to 4.1)	2.4 (1.4 to 4.1)
Abbreviations: Fen=fenfluramine; Cann=cannabidiol; MCSF=monthly convulsive seizure frequency; CSF= convulsive seizure frequency; CrI=credible interval				

On request, the company also provided results for fenfluramine versus cannabidiol plus clobazam.[12]

Table B: NMA results for fenfluramine versus cannabidiol plus clobazam[12]

	Fenfluramine 0.7mg/kg/day	Fenfluramine 0.4mg/kg/day (+ stiripentol)
Mean % reduction in MCSF: mean difference (95% CrI)		
Cannabidiol 10mg plus clobazam	37% (2.0 to 60)	24% (-20 to 51)
Cannabidiol 20mg plus clobazam	40% (10 to 60)	27% (-9.4 to 53)
≥50% reduction in CSF: odds ratio (95% CrI)		
Cannabidiol 10mg plus clobazam	7.2 (1.8 to 32.1)	13.2 (2.5 to 115.0)
Cannabidiol 20mg plus clobazam	5.4 (1.5 to 22.4)	9.8 (2.0 to 81.7)
Abbreviations: MCSF=monthly convulsive seizure frequency; CSF= convulsive seizure frequency; CrI=credible interval		

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In Study 1, any treatment-emergent adverse event (AE) was reported by 95% (38/40) of patients in the fenfluramine 0.7mg/kg/day group, 95% (37/39) of patients in the fenfluramine 0.2mg/kg/day group and 65% (26/40) in the placebo group. Patients discontinuing therapy due to an AE was 12%, 0 and 0, respectively. During Study 1, the most frequently reported treatment-emergent AEs of any grade in the fenfluramine 0.7mg/kg/day group, fenfluramine 0.2mg/kg/day group and placebo group respectively were: decreased appetite (38%, 20% and 5.0%), diarrhoea (18%, 31% and 7.5%), fall (0, 10% and 5.0%), fatigue (10%, 10% and 2.0%), lethargy (18%, 10% and 5.0%), nasopharyngitis (18%, 10% and 12%), pyrexia (5.0%, 18% and 20%), seizure (7.5%, 10% and 12%),

somnolence (10%, 15% and 7.5%), upper respiratory tract infection (0, 21% and 12%), vomiting (7.5%, 10% and 10%) and weight decrease (5.0%, 13% and 0).[4, 8]

In Study 3, any treatment-emergent AE was reported by 92% (44/48) of patients in the fenfluramine 0.7mg/kg/day group, 91% (42/46) of patients in the fenfluramine 0.2mg/kg/day group and 83% (40/48) in the placebo group and these were serious in 6.2%, 6.5% and 4.2%, respectively. The proportion of AEs that led to patients discontinuing therapy due to an AE was 4.2%, 2.2% and 2.1%.[6, 7]

In Study 2 with concomitant stiripentol, any treatment-emergent AE was reported by 98% (42/43) of patients in the fenfluramine 0.4mg/kg/day group and 96% (42/44) in the placebo group and these were serious in 14% and 16% respectively. Patients discontinuing therapy due to an AE was 4.7% and 2.3%, respectively. The most frequently reported treatment-emergent AEs of any grade in the fenfluramine 0.4mg/kg/day group and placebo group respectively were: decreased appetite (44% and 11%), diarrhoea (23% and 6.8%), fatigue (26% and 4.5%), lethargy (14% and 4.5%), nasopharyngitis (16% and 34%), pyrexia (26% and 9.1%), decreased blood glucose (14% and 4.5%), seizure (4.7% and 16%) and upper respiratory tract infection/bronchitis (12% and 4.5%).[5]

During the open-label extension study, the most frequently reported AE included pyrexia (22%), nasopharyngitis (19%) and decreased appetite (16%). No cases of valvular heart disease or pulmonary hypertension were reported. One patient died due to sudden unexpected death in epilepsy (SUDEP) which was considered unrelated to treatment.[10]

Fenfluramine at higher doses of 60mg to 120mg daily was previously approved as an appetite suppressant for the treatment of adult obesity but was withdrawn due to associated cardiac valve abnormalities. No cases of valvular heart disease or pulmonary arterial hypertension have been reported during the clinical studies for Dravet syndrome, but the studies included small numbers of patients and the duration of controlled treatment was limited to 14 to 15 weeks. A controlled access programme has been established to prevent off-label use in weight management and to confirm that prescribers are aware of the need for periodic cardiac monitoring. The SPC recommends that cardiac monitoring is performed using echocardiogram before starting fenfluramine, then every 6 months for the first 2 years and then annually during treatment. A patients and caregivers alert card is also available.[1, 2]

*Other data were also assessed but remain confidential**

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the three clinical studies (Study 1, Study 2 and Study 3), fenfluramine significantly reduced the frequency of convulsive seizures when compared with placebo (primary outcome); percentage reductions from baseline over placebo ranged from 62% to 65% for fenfluramine 0.7mg/kg/day and 54% for fenfluramine 0.4mg/kg/day when used with stiripentol. When assessed as a secondary outcome in Study 1 and Study 3, the percentage reductions from baseline over placebo was also significant for fenfluramine 0.2mg/kg/day (32% and 50%).[2, 4-6]
- Results for the primary outcomes were considered clinically relevant and were supported by key secondary outcomes, which also significantly favoured fenfluramine over placebo,

including the proportions of patients achieving ≥50% reduction in MCSF and longest seizure-free interval.[2, 4-6]

- The efficacy of fenfluramine appeared to be maintained when assessed in the open-label extension of these studies; however these longer-term data are uncontrolled.[10, 11]

4.2. Key uncertainties

- There is some uncertainty about the analysis of patients in Study 1 and Study 3. Both studies are merged analyses of two identical clinical studies; NCT02682927, performed in North America and NCT02826863, in Europe and Australia. Due to incomplete enrolment and to meet regulatory requirements, the datasets were merged before the results were unblinded and analysed. Study 1 included the first 119 patients from the merged dataset and Study 3, the second set of 143 patients.[4 6]
- The primary outcome was reported as a percentage change relative to baseline and not as an absolute treatment difference. In addition, there was substantial variability in the convulsive seizure frequency at baseline.
- Results from Study 1 and Study 3 for fenfluramine 0.2mg/kg/day were significantly better than placebo for the key secondary outcomes. However, sensitivity analysis performed on Study 1 suggested that the efficacy of this dose was not supported by robust clinical data. This is the recommended starting dose for fenfluramine and patients will be titrated according to efficacy, tolerability and concomitant treatment.[1, 2]
- The fenfluramine treatment period was limited to 14 or 15 weeks in the clinical studies, which is short to determine the effect of chronic treatment on clinically relevant outcomes such as status epilepticus and SUDEP. In addition there is a lack of long-term controlled safety data.
- The key studies used fixed doses of fenfluramine and did not allow titration according to response and tolerability, which may affect the generalisability of study results to clinical practice. In study 1 and study 3, patients were not receiving stiripentol which is recommended as a first-line add-on treatment to sodium valproate in clinical guidelines. Although some patients had previously received treatment with stiripentol, it is unclear if the concomitant treatment of these study patients had been optimised before study entry.[2]
- The submitting company has requested that fenfluramine is positioned as add-on therapy for patients with Dravet syndrome whose seizures have not been controlled after trying at least two anti-seizure medicines. No additional data were presented to support the proposed positioning and the company clarified that the full study populations represented this positioning since the majority of patients were receiving two or more concomitant treatments. In patients uncontrolled on current therapy, unless there is a tolerability issue, medicines are often added-on rather than replaced so treatment is often concomitant instead of previous.
- Fenfluramine is licensed for use in patients with Dravet syndrome aged 2 years and older. The clinical studies enrolled patients aged 2 to 18 years and there are limited, uncontrolled data to support the use of fenfluramine in patients over 18 years. However, given the similarity of seizure burden and seizure types in adolescents and adults and the limited evidence of efficacy in adults, the regulator considered it acceptable to extrapolate the efficacy results to adults.[2]

- There is no direct evidence comparing fenfluramine with other treatment options. The submitting company presented an NMA of fenfluramine with cannabidiol plus clobazam, which it considered the most relevant comparator. There are no indirect data comparing with other potential add-on treatments. The company concluded that fenfluramine (with or without stiripentol) was clearly superior to cannabidiol plus clobazam. However, there is insufficient evidence to determine a difference in efficacy for the mean percentage difference in MCSF between fenfluramine 0.4mg/kg/day (plus stiripentol) versus cannabidiol plus clobazam with a probability of at least 95% (results for the 95% CrIs include 0). There are a number of limitations which affect the company's conclusion. The evidence network consists of only four studies with small patient numbers and the use of results of subgroup data from the cannabidiol studies which may explain the high levels of uncertainty around the estimated treatment effects. There was heterogeneity across the study populations in terms of baseline seizure frequency and concomitant anti-epileptic medicines and this was illustrated in the difference in placebo responses across the studies.[12] Due to these limitations, the company's conclusion that fenfluramine is clearly superior to cannabidiol plus clobazam is uncertain.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that fenfluramine is a therapeutic advancement as it offers a treatment option to reduce seizure frequency when other existing treatments are ineffective or not tolerated. They indicated that it would be used as per the company's positioning.

4.4. Service implications

Fenfluramine is administered as an oral solution but the need for regular cardiac monitoring using echocardiogram may have service implications.

5. Patient and carer engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of fenfluramine, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Dravet Syndrome is a rare, life-long and life-limiting neurological condition, which is characterised by refractory seizures and associated with cognitive, behavioural and motor impairment leading to significant disability throughout life. Patients often require 24-hour supervision and additional family support or home care is likely to be required throughout life. This condition has a catastrophic impact on health and quality of life for patients, their parents/carers and the entire family.
- Dravet syndrome is associated with treatment-resistant seizures and there are limited treatment options licensed specifically for Dravet syndrome with many clinicians trialling and adapting different treatment combinations for their patients based on efficacy and tolerability. Fenfluramine adds an additional, effective treatment option.

- For patients who achieve improved control of seizures, fenfluramine may reduce the risk of complications, injury and mortality, including SUDEP. Experience from PACE participants noted that there may also be improvements in comorbidities. This may reduce the burden of care with less concomitant anti-seizure medication, emergency medication, hospital visits and hospitalisation. PACE participants with experience of fenfluramine noted that some patients experience more consecutive seizure-free days or seizure-freedom, which can provide the confidence to arrange normal family activities, even holidays abroad. However even a small improvement in seizure control can have a big impact on the patient's life. Such improvements may allow the patient to participate more fully in family and social life and in education, leading to improved development.
- The impact of providing 24-hour care and coping with the frequent and prolonged seizures of Dravet syndrome is enormous on family and carers. Through better seizure control, fenfluramine may reduce this burden, reducing the anxiety surrounding the risks of frequent seizures and the fear of injury, SUDEP and mortality, as well as the exhaustion particularly associated with nocturnal seizures. It may make it easier to facilitate care and even arrange suitable respite care. Dravet syndrome also has a significant impact on the well-being of patient's siblings who are affected by frequent hospital visits, disruptions to nights and to schooling. An improvement in seizure control may ease the adverse effects of the condition on the whole family and carers and improve their quality of life.
- The use of fenfluramine requires additional cardiac monitoring with baseline and subsequent echocardiograms recommended every 6 months for the first 2 years and annually thereafter. There may be associated service implications.
- Fenfluramine would offer an additional, anti-seizure medicine which would have a positive impact for patients, who have tried at least two other medicines, and for their families and carers.

Additional Patient and Carer Involvement

We received patient group submissions from Dravet Syndrome UK and Epilepsy Connections, both organisations are registered charities. Dravet Syndrome UK has received 16% pharmaceutical company funding in the past two years, including from the submitting company. Epilepsy Connections has not received any pharmaceutical company funding in the past two years. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (60 years)
Population	The population was people with Dravet syndrome aged 2 years and older where seizures have not been controlled after trying 2 or more antiseizure medicines.
Comparators	Cannabidiol plus clobazam
Model description	The model compared two treatment arms, fenfluramine plus standard of care (SoC) and cannabidiol plus clobazam plus SoC. The company utilised a patient-level simulation model with three health states: alive, on treatment; alive, treatment discontinued; and an all-absorbing dead state. Individual patients had a baseline convulsive seizure frequency (CSF) which determined seizure free days (SFD) and influenced mortality. Treatment effect was modelled as a relative reduction from baseline CSF. All patients in either arm started on treatment with the respective medicine. Each cycle patients had a chance to continue treatment, discontinue treatment or die. Patients who discontinued treatment could not restart treatment and reverted to baseline CSF for the remainder of the model. Each cycle costs and utilities were calculated for each patient that depended on patient characteristics and clinical outcomes. The model was run twice to account for the different treatment effect and dosing of fenfluramine with and without concomitant stiripentol, these results were weighted and combined.
Clinical data	Clinical data were from Study 1 and Study 2 for fenfluramine and GWPCARE1 and GWPCARE2 for cannabidiol which informed a NMA that provided the relative treatment effect (mean percentage change in CSF versus placebo) for each medicine. Patient-level data from the placebo arms of Study 1 and Study 2 were used to inform baseline CSF and individual-level patient seizure profiles. Mortality was modelled as dependent on CSF via its effect on sudden unexplained death in epilepsy (SUDEP), status epilepticus mortality and accident related mortality. The effect of CSF on these sources of mortality was modelled on relationships derived from literature on Dravet syndrome and other epilepsies. Fenfluramine discontinuation rates observed in Study 1, Study 2 and its open-label extension (OLE) study were assumed to apply to both fenfluramine and cannabidiol.
Extrapolation	Individual-level patient seizure profiles were extrapolated beyond the trial period using a bootstrapping method. Treatment effect was assumed to be constant for both medicines.
Quality of life	Health-related quality of life (HRQoL) data were collected in Study 1 and Study 2 and used in the model. Quality of life depended on the number of SFD per cycle and patient characteristics, including age, concomitant stiripentol use and comorbidities.
Costs and resource use	Costs included medicine acquisition, concomitant anti-epilepsy medications, monitoring costs, ongoing health care utilisation and emergency care costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. A PAS discount is in place for cannabidiol and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The company-provided base case results and sensitivity analysis. The QALY gain estimated by the model is primarily driven by increases in seizure-free days which were assumed to be a function of the relative efficacy of each medicine to reduce convulsive seizure frequency from baseline. The main driver of costs is the acquisition cost of the intervention and comparator medicine and average dose in practice.

The results used for decision-making included the PAS for fenfluramine and the PAS for cannabidiol. SMC is unable to present the results provided by the company which used an estimate of the PAS price for cannabidiol or using the list prices for both medicines due to commercial confidentiality and competition law issues. As such, no results can be reported.

6.3. Sensitivity analyses

A number of sensitivity analyses were provided by the company with further scenarios requested by SMC. Key scenarios are summarised in table 6.3. The results were sensitive to dosing assumptions for both medicines and the largest changes were observed when using alternative evidence for discontinuation rates.

Table 6.3: Scenario analysis (list prices)

	Scenario	**Base Case**
1	Discontinuation based on available OLE data: Fenfluramine + SoC: 1.2356% per cycle after the 4th cycle (13.85% per annum) Cannabidiol + clobazam + SoC: 4.028% after the 4th cycle (36.38% per annum)	Discontinuation for both interventions at 1.2356% per annum after the 4th cycle (13.85% per annum)
2	Equal efficacy for all doses of cannabidiol and fenfluramine (54.1% reduction in convulsive seizure frequency)	Based on the ITC, base case reductions in seizure frequency from baseline vs placebo are as follows: Cannabidiol + clobazam + SoC: 39.14% Fenfluramine 0.32mg/kg/day + SoC: 54.1% Fenfluramine 0.44mg/kg/day + SoC: 62.3%
3	Equal efficacy for all doses of cannabidiol and fenfluramine (62.3% reduction in convulsive seizure frequency)	
4	Fenfluramine dose according to trial doses: 0.4mg/kg/day with stiripentol 0.7mg/kg/day without stiripentol	Fenfluramine dose according to OLE study: Fenfluramine 0.32mg/kg/day with stiripentol Fenfluramine 0.44mg/kg/day without stiripentol
5	Scenario 4 + cannabidiol dose 15mg/kg/day	Cannabidiol dose 17.5mg/kg/day

6	Scenario 5 + discontinuation rates from RWE for fenfluramine and SMC2262 for cannabidiol: Fenfluramine + SoC: 1.0599% per cycle after the 4th cycle (12% per annum) Cannabidiol + clobazam + SoC: 0.4266% (5% per annum)	
7	Scenario 5 + Scenario 1	
8	Scenario 6 + carer disutility included	No carer disutility included
9	Scenario 7 + care giver disutility included	

SoC = standard of care; OLE = open label extension; RWE = real world evidence; ITC = indirect treatment comparison.

6.4. Key strengths

The strengths of the analysis were identified as being:

- The model structure was appropriate to the heterogeneous seizure patterns inherent to the nature of the condition.
- The comparator in the model was appropriate.
- Sources of randomised placebo controlled evidence for the intervention and the comparator were available to inform an ITC.

6.5. Key uncertainties

The analysis is associated with the flowing uncertainties:

- The estimates of relative treatment effect versus the comparator from the NMA have wide credible intervals indicating uncertainty in the results. The company have explored equal efficacy for fenfluramine and cannabidiol in a sensitivity analysis but with favourable assumptions regarding fenfluramine and cannabidiol dosing. In sensitivity analyses the cost-effectiveness conclusions were highly sensitive to varying dosing assumptions when equal efficacy was assumed.
- The OLE study for fenfluramine shows a lower dose in practice than the dose used in the pivotal trials that informed the efficacy of fenfluramine. The company have assumed that the efficacy at these lower doses is equal to that in the randomised study but costed for the lower dose. This assumption is highly uncertain and likely to bias the results in favour of fenfluramine.
- The dose of cannabidiol in routine Scottish clinical practice is uncertain. The company have identified evidence that this may be higher than in the evidence considered by SMC for the cannabidiol submission in this indication (SMC2262). Clinical experts consulted by SMC stated that cannabidiol doses assumed in the company's base case were higher than those observed in Scottish clinical practice and that 10-12/mg/kg/day doses were more appropriate assumptions. The results of the analysis are sensitive to varying cannabidiol

dosing assumptions. The Committee noted scenario 5 explored more conservative dosing assumptions, with fenfluramine trial doses and a lower cannabidiol dose of 15mg/kg/day.

- The rate at which patients discontinue treatment with fenfluramine and cannabidiol is highly uncertain and the results of the analysis are highly sensitive to different sources of evidence for this parameter. The Committee noted the scenarios which had the largest impact on the ICER were when OLE discontinuation rates were used. In these scenarions the cannabidiol discontinuation rate was much higher than that of fenfluramine and higher than the rate used in the cannabidiol submission to SMC. Given this and the conflicting rates observed in the RWE study, the Committee concluded the company's assumption of equal discontinuation rates was reasonable.
- There is limited evidence to support the assumptions made with regards to the impact of reducing seizure frequency on other outcomes that are important to patients, such as seizure-free days and mortality.

7. Conclusion

The Committee considered the benefits of fenfluramine in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as fenfluramine is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted fenfluramine for restricted use in NHSScotland.

8. Guidelines and Protocols

The National Institute of Health and Clinical Excellence (NICE) published in April 2022 national guideline 217, epilepsies in children, young people and adults.[3]

9. Additional Information

9.1. Product availability date

June 2021

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Fenfluramine	**0.2 to 0.7mg/kg/day**	**For a 12kg child: 6,009 to 20,778** **For a 70kg adult: 34,782 to 64,633**

Costs from BNF online/eMC Dictionary of Medicines and Devices Browser on 6 June 2023. Costs do not take any patient access schemes into consideration. The maximum recommended daily dose of fenfluramine is 26mg for patients not taking stiripentol and 17mg for patients taking stiripentol.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 37 patients eligible for treatment with fenfluramine in year 1 and 36 patients eligible for treatment in year 5. The uptake rate was estimated to be 17% in year 1 (3 patients) and 45% in year 5 (6 patients) with a discontinuation rate of 46% in year 1 and 63% in year 5 applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 July 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.