

**5.11 FENFLURAMINE,
Oral solution 2.2 mg (as hydrochloride) per mL,
360 mL
Fintepla[®],
UCB Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 1 submission requested an Authority Required (telephone/online) listing for fenfluramine for the treatment of seizures associated with Dravet Syndrome.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus cannabidiol. The components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description		
Population	Patients with Dravet Syndrome not adequately controlled despite treatment with at least 2 other antiepileptic drugs.		
Intervention	Fenfluramine 2.2 mg/mL oral solution (as below)		
	Dose	With stiripentol	Without stiripentol
	First week	0.2 mg/kg/day (0.1 mg/kg twice daily)	0.2 mg/kg/day (0.1 mg/kg twice daily)
	Second week	0.4 mg/kg/day (0.2 mg/kg twice daily)	0.4 mg/kg/day (0.2 mg/kg twice daily)
	Ongoing treatment		0.7 mg/kg/day (0.35 mg/kg twice daily)
Maximum recommended	17 mg daily (8.6 mg twice daily)	26 mg daily (13 mg twice daily)	
Comparator	Main: Cannabidiol 100 mg/mL oral solution: titrated to a maintenance dose of up to 20 mg/kg/day.		
Outcomes	Convulsive and total seizure frequency (and associated responder analyses). Seizure-free days and intervals. Patient-reported outcomes and health-related quality of life. Incidence and severity of adverse events. Long-term safety.		
Clinical claim	Superior efficacy and similar safety compared to cannabidiol. Uncertain comparative efficacy versus stiripentol.		

Source: Table 1-1, p16 of the submission.

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** not registered. The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the Delegate’s Overview and ACM advice were available. The proposed indication is:

‘Fintepla is indicated for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older’.

- 2.2 Fenfluramine was previously registered for weight loss in adults and withdrawn from the Australian market in 1997 due to its potential for causing valvular damage in the heart and pulmonary hypertension.¹

Previous PBAC consideration

- 2.3 The PBAC has not previously considered fenfluramine for listing on the PBS for any condition.
- 2.4 The PBAC has previously recommended the PBS listing of cannabidiol and stiripentol for the treatment of seizures associated with Dravet Syndrome in November 2020 and March 2020, respectively. Both cannabidiol and stiripentol are currently PBS listed as adjunctive therapy to at least 2 other anti-epileptic drugs and are therefore placed as third-line therapy options.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FENFLURAMINE					
Fenfluramine, 2.2 mg/mL oral solution, 360 mL	\$4,636.97 published price \$█ effective price (Pre-PBAC Response)	1	1	5	Fintepla

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Severity: Severe
Condition: Myoclonic epilepsy in infancy (Dravet Syndrome)
Indication: Severe myoclonic epilepsy in infancy (Dravet syndrome)
Clinical criteria:
Patient must have (as an initiating patient)/have had (as a continuing patient, or as a patient receiving non-PBS-subsidised treatment with this drug for this condition prior to [PBS Listing Date]), generalised tonic-clonic seizures or generalised clonic seizures that are not adequately controlled with at least two other anti-epileptic drugs.
AND
The treatment must be as adjunctive therapy to at least two other anti-epileptic drugs.
Treatment criteria:
Must be treated by a neurologist if treatment is being initiated; OR
Must be treated by a neurologist if treatment is being continued or re-initiated; OR
Must be treated by a paediatrician in consultation with a neurologist if treatment is being continued; OR
Must be treated by a general practitioner in consultation with a neurologist if treatment is being continued.
Notes: Special Pricing Arrangements apply

¹ <https://www.tga.gov.au/safety/product-recalls/slimming-factor-also-known-easy-trim-que-she-and-chinese-herbal-diet-pills#:~:text=Fenfluramine%20was%20withdrawn%20from%20the,with%20its%20long%2Dterm%20use.>

- 3.1 The submission proposed a Special Pricing Arrangement (SPA). The submission requested an effective dispensed price for maximum quantity (DPMQ) of \$█████ which equates to an ex-manufacturer price of \$█████. The Pre-PBAC Response provided a revised effective approved ex-manufacturer price (AEMP) of \$█████ (DPMQ \$█████).
- 3.2 The submission proposed fenfluramine for PBS listing as a General Schedule item with an Authority Required (telephone/online) restriction. The requested authority level was consistent with cannabidiol but differed from stiripentol, which was PBS listed as Authority Required (Streamlined). The submission proposed an Authority Required restriction to: 1) limit the treatment to patients with generalised tonic-clonic seizures or generalised clonic seizures that are not adequately controlled with at least 2 other anti-epileptic drugs, 2) prevent off-label use in weight management in obese patients, and 3) ensure that prescribing physicians are aware of the need for periodic cardiac monitoring.
- 3.3 The submission did not request PBS listing for Lennox-Gastaut Syndrome and stated that a separate PBAC application will be submitted for the indication.
- 3.4 Due to the risk of valvopathy and/or pulmonary arterial hypertension associated with fenfluramine, cardiac monitoring using echocardiogram is required. A prescriber instruction may be required recommending echocardiogram monitoring (aligned to the final Product Information [PI]). The Pre-Sub-Committee Response (PSCR) argued the TGA Guidance was clear and well-understood by specialists who manage patients with Dravet Syndrome and such a requirement in the PBS listing was not necessary.
- 3.5 The clinical and treatment criteria included in the proposed restriction are consistent with the stiripentol and cannabidiol PBS listings, except 'or as a patient receiving non-PBS-subsidised treatment with this drug for this condition prior to [PBS Listing Date]' which was included to allow patients receiving non-PBS treatment to transition to PBS subsidised treatment.
- 3.6 The proposed listing did not restrict the population by age group. However, the results presented in the submission may not be generalisable to adults with Dravet Syndrome because the included clinical evidence was based on a population aged 2–18 years with Dravet Syndrome. The ESC considered it was appropriate to not include an age restriction for fenfluramine to allow for flexibility in individual clinical decision-making.
- 3.7 The ESC considered that fenfluramine, cannabidiol, and stiripentol could be used in combination or sequentially, depending on patient response and side effect profile, and that clinicians are likely try a range of treatment options to attempt to achieve the best possible disease control for patients and therefore it was reasonable to not preclude combination use of these therapies. The Pre-PBAC Response agreed use of treatments for Dravet Syndrome in such a manner would be consistent with international guidelines and local expert advice, however reiterated there is very limited available evidence to support combination use of fenfluramine and cannabidiol.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Dravet syndrome is a rare, progressive and life-limiting form of developmental and epileptic encephalopathy and is one of the most severe and difficult-to-treat forms of epilepsy. It is typically associated with de novo variants of the SCN1A gene, which codes for the alpha-1 subunit of the neuronal voltage-gated sodium channel responsible for initiating action potentials in neurons. A recent systematic review of 21 studies on Dravet Syndrome reported an incidence rate of 2.17 to 6.5 per 100,000 persons and a prevalence rate of 1.2 to 6.5 per 100,000 persons (Sullivan 2024).²
- 4.2 The first symptoms of Dravet Syndrome typically present between 5 and 8 months of age, as prolonged, febrile and/or afebrile seizures. These seizures are frequently generalised clonic (causing loss of consciousness and violent muscle contractions) or hemiclonic (unilateral seizure with convulsive movements affecting only one side of the body). In contrast, tonic seizures cause the stiffening of muscles. The most common initial seizure type is tonic-clonic, and the second most common is hemiclonic (Li 2021).³ Non-seizure symptoms, including neurodevelopmental delays, typically emerge soon after seizures begin. All seizure and non-seizure symptoms progress and persist into adulthood. The average age at diagnosis ranges from 1.6 to 9.2 years (Sullivan 2024).⁴ The diagnosis is usually made by observation, occurs within one year of the first seizure in about 88% of infants, but is commonly delayed in adults (Lagae 2018).⁵
- 4.3 Due to high seizure frequency, Dravet Syndrome is associated with higher mortality rates – up to 13 times higher than the general population and the general epilepsy population. Mortality in Dravet Syndrome population was estimated around 15.8 per 1000 person-years and the median age at death was between 4.7 and 7 years (Sullivan 2024). These estimates were based on data from 67 studies in Dravet Syndrome populations, of which one reported a standardised incidence of mortality and only 4 reported the median age at death. These studies found that few patients had died during the follow-up period, with an incidence of mortality between 4–21% over 2 to 26 years of study follow-up. Further, one Japanese survey of 623 individuals with

² Sullivan J, Benítez A, et al. A systematic literature review on the global epidemiology of Dravet syndrome and Lennox-Gastaut syndrome: Prevalence, incidence, diagnosis, and mortality. *Epilepsia*. 2024.

³ Li W, Schneider AL, Scheffer IE. Defining Dravet syndrome: An essential pre-requisite for precision medicine trials. *Epilepsia*. 2021;62(9):2205-2217.

⁴ Sullivan J, Benítez A, et al. A systematic literature review on the global epidemiology of Dravet syndrome and Lennox-Gastaut syndrome: Prevalence, incidence, diagnosis, and mortality. *Epilepsia*. 2024;65:1240-1263.

⁵ Lagae, L., Brambilla, I., et al., Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. *Dev Med Child Neurol*. 2018; 60: 63-72.

Dravet Syndrome found prevalence of sudden death reached a first peak at 1–3 years of age and a second peak at ≥ 18 years of age (Sakauchi 2011).⁶

- 4.4 Given the high symptom burden of Dravet Syndrome, it has a major impact on the health-related quality of life (HRQoL) of patients, caregivers, and the whole family. Children with Dravet Syndrome experience poorer overall HRQoL compared to healthy children or those with other epilepsy syndromes. Given the young age of onset, the parent/carer's quality of life is also severely impacted.
- 4.5 The submission proposed the addition of fenfluramine as a third or later-line treatment option, substituting mainly cannabidiol and to a lesser extent stiripentol. This positioning of fenfluramine in the treatment algorithm was in line with that of cannabidiol and was reasonable (para. 11.1, cannabidiol, Public Summary Document [PSD], July 2020 PBAC meeting). However, the proposed treatment algorithm did not align with the International Consensus Statement⁷ or the NICE guidelines⁸ both positioning fenfluramine as a second-line add-on therapy in the treatment algorithm for patients for whom clobazam or clobazam-containing regimens were not a desirable option.
- 4.6 The key difference between the current and the proposed algorithm was the addition of fenfluramine when seizure control was not achieved after first- or second-line therapies. In the current algorithm based on their PBS listing structure, only cannabidiol or stiripentol could be considered as the third-line treatment. While in the proposed algorithm fenfluramine would also be considered, with or without concomitant treatment with stiripentol. In these circumstances, the submission anticipated that fenfluramine would replace rather than displace cannabidiol and stiripentol and would have a limited impact on either first/second or later-line treatment pathways. The evaluation considered that this assumption may not be reasonable for later-line treatments. Treatment for Dravet Syndrome is often additive, which means that fenfluramine, cannabidiol, and stiripentol may be used in combination or sequentially, depending on patient response and side effect profile. The PSCR argued that given the limited evidence available for combination use of fenfluramine and cannabidiol, such use would not occur frequently in practice. The ESC agreed with the evaluation and considered that clinicians would likely try a range of treatment options, including combination treatment, to attempt to achieve the best possible disease control for patients.
- 4.7 Positioning fenfluramine as third-line therapy for the treatment of Dravet Syndrome was consistent with the restriction proposed in the submission, the economic

⁶ Sakauchi, M., Oguni, H., et al. Mortality in Dravet syndrome: search for risk factors in Japanese patients. *Epilepsia*. 2011; 52:50-4.

⁷ Wirrell EC, Hood V et al. International consensus on diagnosis and management of Dravet syndrome. *Epilepsia*. 2022; 63: 1761–1777.

⁸ NICE Technology Appraisal Guidance. Fenfluramine for treating seizures associated with Dravet syndrome. July 2022. <https://www.nice.org.uk/guidance/ta808>.

evaluation presented, and the estimated use and costs. Section 3 of the submission did not assess the cost-effectiveness of fenfluramine (without concomitant stiripentol) compared with stiripentol.

- 4.8 Fenfluramine has a dual mechanism of action: 1) It acts as an agonist at specific serotonin (5-HT) receptors which enhances GABAergic neurotransmission. 2) It also inhibits excitatory glutamatergic signalling by mediating the interaction of the sigma-1 receptor with the N-methyl-D-aspartate receptor.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated cannabidiol as the main comparator. The submission provided the following arguments to support this nomination: cannabidiol was the most frequently prescribed PBS-listed therapy for treatment-refractory Dravet Syndrome, and local clinical feedback strongly suggested that fenfluramine was most likely to replace cannabidiol in Australian clinical practice.

- 5.2 Fenfluramine is also likely to replace or displace stiripentol in some circumstances in clinical practice, and therefore should also be considered a comparator. The submission acknowledged that stiripentol was currently listed on the PBS for the treatment of refractory Dravet Syndrome. While stiripentol was not considered a primary comparator, the submission provided additional analyses using stiripentol as a comparator. The submission claimed that transitivity issues between the respective sets of placebo-controlled trials for fenfluramine and stiripentol resulted in unreliable comparisons that would be uninformative for decision-making purposes. However, the ESC considered stiripentol to be a relevant comparator as it can and would (in some instances) be replaced by fenfluramine, and further considered that exchangeability issues between the clinical trials was not an adequate reason to exclude it as a comparator. The Pre-PBAC Response maintained that the appropriate main comparator for the submission was cannabidiol. However, noted that in a real-world Australian setting, stiripentol may be considered an alternative secondary comparator for fenfluramine.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The Sponsor requested a hearing for this item. The clinician discussed their experience of using fenfluramine for Dravet Syndrome and described the transformative effects of treatment, including a substantially reduced seizure burden and other benefits including improved mobility, cognition and learning ability. The clinician also discussed the comparative effectiveness and safety of fenfluramine to other therapies for Dravet Syndrome, including cannabidiol and stiripentol, and outlined that patients treated

with fenfluramine are more likely to achieve a 50% reduction in convulsive seizure frequency than cannabidiol, and that stiripentol is associated with a range of cognitive side effects that are not experienced with fenfluramine.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health professionals (7), individuals, parents, family members and caregivers of patients (21), consumer organisations (1) and specialist medical organisations (2) via the Consumer Comments facility on the PBS website.
- 6.3 The PBAC noted the input from health professionals that described fenfluramine as having high-quality evidence for reducing seizures in Dravet Syndrome and being more effective than other available treatment options. The health professionals considered that better seizure control was likely to have additional benefits including a reduced risk of sudden unexpected death in epilepsy (SUDEP) and the ability to reduce or cease other anti-epileptic drugs that have significant side effects. The Committee also noted the input from health professionals acknowledged the need for ongoing cardiovascular monitoring for patients while being treated with fenfluramine, and the potential for drug interactions with other agents that act on the serotonin pathway that must be managed.
- 6.4 The PBAC welcomed the experiences shared by individuals, parents, family members and caregivers discussing both life with Dravet Syndrome and treatment with fenfluramine and noted consistent themes expressed including the transformative effects of treatment, including improved seizure control, improved language and cognitive development, improved physical function and motor skills. The Committee also recognised the input highlighted how fenfluramine treatment had allowed children impacted by Dravet Syndrome to be able to go outside and have a life similar to other children, as sensitivity to sun and warmer temperatures in terms of triggering seizures had diminished.
- 6.5 The PBAC noted the input from the consumer group Epilepsy Action Australia supporting the listing of fenfluramine, and discussed the results of an anonymous patient survey that highlighted that patients and their caregivers were aware of fenfluramine and its positive clinical trial results, but were concerned about access to treatment and the prohibitive cost of treatment without PBS listing. The group also highlighted the annual cost without PBS listing or another funding mechanism ranging between \$█████ for an infant on a low dose, to over \$█████ for an adult on the maximum recommended dose.
- 6.6 The PBAC acknowledged the input from the National Paediatric Medicines Forum (NPMF) and the Epilepsy Society of Australia, which both supported the listing of fenfluramine. The NPMF input included an evaluation of the available evidence for fenfluramine for Dravet Syndrome, with the organisation stating that they believe the PBS listing would be immensely beneficial to all relevant paediatric patients. The input from the Epilepsy Society outlined that there remains a significant unmet need for

additional effective treatment options for Dravet Syndrome, and fenfluramine has demonstrated efficacy, safety and tolerability in three randomised controlled trials, with identified improvements in convulsive seizures, quality of life and cognitive function. The input also noted the known historical risk of cardiac valvular disease and pulmonary hypertension associated with fenfluramine when used at higher doses than in the Dravet Syndrome trials, and noted that to the Society's knowledge, only one patient has had a suspected cardiac complication identified during a detailed follow-up and highlighted that patients currently on treatment in Australia have a well-organised approach to cardiac screening during treatment.

Clinical trials

- 6.7 No head-to-head trials comparing fenfluramine (any dose) with cannabidiol (any dose) were identified. Therefore, the submission conducted a series of pairwise, frequentist indirect treatment comparisons using meta-analysed outcomes for fenfluramine and cannabidiol in comparison to placebo.
- 6.8 The submission was based on 3 randomised controlled trials that compared fenfluramine (as adjunctive therapy) to placebo in participants with Dravet Syndrome:
- Study 1 [N=119] compared fenfluramine 0.7 mg/kg/day (max 26 mg/day) plus standard care, and fenfluramine 0.2 mg/kg/day plus standard care, to placebo plus standard care. The participants in this study did not receive concomitant stiripentol.
 - Study 3 [N=143] compared fenfluramine 0.7 mg/kg/day (max 26 mg/day) plus standard care, and fenfluramine 0.2 mg/kg/day plus standard care, to placebo plus standard care. The participants in this study did not receive concomitant stiripentol.
 - Study 2 [N=87] compared fenfluramine 0.4 mg/kg/day (max 17 mg/day) plus standard care, to placebo plus standard care. All the participants in this study received concomitant stiripentol.
 - The indirect comparisons in the submission excluded participants in the fenfluramine 0.2 mg/kg/day (without stiripentol) treatment arm as this was not a recommended maintenance dose in Australia.
- 6.9 The submission also presented 2 randomised controlled trials that compared cannabidiol (as adjunctive therapy) to placebo in participants with Dravet Syndrome:
- The GWPCARE1 Part B trial [N=120] compared cannabidiol 20 mg/kg/day (plus standard care) to placebo (plus standard care)
 - The GWPCARE2 trial [N=198] compared cannabidiol 10 mg/kg/day and 20 mg/kg/day (plus standard care) to placebo (plus standard care).
- 6.10 Additionally, the submission identified 2 open-label extension studies, one for each therapy:

- Study 1503 [N=375] enrolled participants from Study 1, Study 3 and Study 2, along with a subgroup of de novo participants (i.e. participants who were not part of the randomised controlled trial period of Study 1, 3 or 2). All the participants in this study received fenfluramine, while a few participants also received stiripentol.
 - The GWPCARE5 [N=315] open-label extension study provided long-term data on participants enrolled in the GWPCARE1 and GWPCARE2, where the average dose of cannabidiol was more than 20 mg/kg/day.
- 6.11 The submission described 2 randomised controlled trials comparing stiripentol to placebo:
- The STICLO-France trial [N=41] compared stiripentol 50 mg/kg/day (plus standard care) to placebo (plus standard care).
 - The STICLO-Italy trial [N=23] compared stiripentol 50 mg/kg/day (plus standard care) to placebo (plus standard care).
- 6.12 Standard care in the fenfluramine and cannabidiol trials comprised of existing AEDs or non-pharmacologic treatments. Standard care in the stiripentol trials comprised of valproate and clobazam.
- 6.13 The submission also identified 12 systematic reviews and meta-analyses— 7 network meta-analyses presented comparative efficacy and safety of fenfluramine, cannabidiol and stiripentol, 2 meta-analyses compared the efficacy of fenfluramine vs placebo, and 3 meta-analyses compared the efficacy of cannabidiol vs placebo.
- 6.14 The PBAC has previously considered the cannabidiol trials GWPCARE1, GWPCARE2, and GWPCARE5 (para. 6.8, cannabidiol, PSD, July 2020 PBAC Meeting) and the stiripentol trials STICLO-France and STICLO-Italy (para. 6.4, stiripentol, PSD, March 2020 PBAC Meeting).
- 6.15 Details of the trials and studies presented in the submission are provided in Table 2.

Table 2: Trials, studies and associated reports presented in the submission

Trial ID	Publication title	Publication citation
Fenfluramine trials		
Study 1 ZX008-1501/1502 NCT02682927 NCT02826863 EUCTR2015-004167-37	A Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial.	Zogenix Clinical Study Report 28 August 2019 Lancet. 2019;394(10216):2243-54.
Study 3ZX008-1501/1502 NCT02682927 NCT02826863 EUCTR2015-004167-37	A Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome. Sullivan J, Lagae L, Cross J.H et al. Fenfluramine in the treatment of Dravet syndrome: Results of a third randomized, placebo-controlled clinical trial.	Zogenix Clinical Study Report 12 November 2021 Epilepsia, 64(10), 2653–2666.
Study 2 ZX008-1504 NCT02926898 EUCTR2016-000474-38	A Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled Evaluation of the Efficacy, Safety, and Tolerability of ZX008 (Fenfluramine Hydrochloride) Oral Solution, as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, et al. Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial.	Zogenix Clinical Study Report 21 December 2018 JAMA Neurol. 2020;77(3):300-8.
Study 1503 ZX008-1503 NCT02823145; EUCTR2016-002804-14	An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome: - Interim report: Dec 2018 (March 2018 data cut) - Main report: July 2023 (Jan 2023 data cut). Agarwal A, Farfel GM, Gammaitoni AR, Wong PC, Pinto FJ, Galer BS. Long-term cardiovascular safety of fenfluramine in patients with Dravet syndrome treated for up to 3 years: Findings from serial echocardiographic assessments. Lai WW, Galer BS, Wong PC, Farfel G, Pringsheim M, Keane MG, et al. Cardiovascular safety of fenfluramine in the treatment of Dravet syndrome: Analysis of an ongoing long-term open-label safety extension study. Sullivan J, Scheffer IE, Lagae L, Nabbout R, Pringsheim M, Talwar D, et al. Fenfluramine HCl (Fintepla®) provides long-term clinically meaningful reduction in seizure frequency: Analysis of an ongoing open-label extension study.	Zogenix Clinical Study Report - December 2018 - July 2023 Eur J Paediatr Neurol. 2022;39:35-9. Epilepsia. 2020;61(11):2386-95 Epilepsia. 2020;61(11):2396-404.
Post-hoc, subgroup and pooled analyses	Bishop KI, Isquith PK, Gioia GA, Knupp KG, Scheffer IE, Nabbout R, et al. Fenfluramine treatment is associated with improvement in everyday executive function in preschool-aged children (<5 years) with Dravet syndrome: a critical period for early neurodevelopment. Sullivan J, Perry MS, Wheless JW, Galer B, Gammaitoni A. Fenfluramine responder analyses and numbers needed to treat: translating epilepsy trial data into clinical practice. Sullivan J, Specchio N, Devinsky O, Auvin S, Perry MS, Strzelczyk A, et al. Fenfluramine significantly reduces day-to-day seizure burden by increasing number of seizure-free days and time between seizures in patients with Dravet syndrome: A time-to-event analysis.	Epilepsy & behavior. 2023; 138:108994. European journal of paediatric neurology: EJPN. 2021;31:10-4. Epilepsia. 2022;63(1):130-8.

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Trial ID	Publication title	Publication citation
Cannabidiol trials		
GWPCARE1 NCT02091375 (Part B) NCT02091206 (Part A) EUCTR2014- 002941-23	Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome.	N Engl J Med. 2017;376(21):2011-20 Neurology. 2018;90(14):e1204-e11.
GWPCARE2 NCT02224703 EUCTR2014- 002939-34	Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, et al. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: a Randomized Clinical Trial.	JAMA neurology. 2020;77(5):613-21.
GWPCARE5 NCT02224573 EUCTR2014- 001834-27	Devinsky O, Nabbout R, Miller I, Laux L, Zolnowska M, Wright S, et al. Long-term cannabidiol treatment in patients with Dravet syndrome: An open-label extension trial. Scheffer IE, Halford JJ, Miller I, Nabbout R, Sanchez-Carpintero R, Shiloh-Malawsky Y, et al. Add-on cannabidiol in patients with Dravet syndrome: Results of a long-term open-label extension trial.	Epilepsia. 2019;60(2):294-302. Epilepsia. 2021;62(10):2505-17.
Stiripentol trials		
STICLO France	Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, Dulac O, Pons G. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group.	Lancet. 2000 Nov 11;356(9242):1638-42
STICLO Italy	Guerrini R, Tonnelier S, d'Athis P, Rey E, Vincent J, Pon G, Dalla Bernardina B, Ferrari AR, Veggiotti P, Veneselli E, Pascottoli E, Vigeveno F. Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial.	Epilepsia 2002; 43(8):155
Post-hoc, subgroup & pooled analyses	Guerrini R, Chancharme L et al. Additional Results from Two Randomized, Placebo-Controlled Trials of Stiripentol in Dravet Syndrome Highlight a Rapid Antiseizure Efficacy with Longer Seizure-Free Periods. Cross JH, Chiron C et al. ≥75% Seizure Reduction with Stiripentol: Data from the Pivotal Trials.	Neurol Ther. 2024. Devel Med and Child Neur. 2023; 65:32-3.
Systematic reviews and meta-analyses		
Comparative network meta-analysis	Lattanzi S, Trinkka E et al. Pharmacotherapy for Dravet Syndrome: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials.	Drugs.2023; 83 (15):1409-1424.
Comparative network meta-analysis	Guerrini R, Chiron C. et al. Comparative efficacy and safety of stiripentol, cannabidiol and fenfluramine as first-line add-on therapies for seizures in Dravet syndrome: a network meta-analysis.	Epilepsia open. 2024; 9(2):689-703.

Source: Table 2-2, p42; Table 2-3 p43; Appendix 1 of the submission

6.16 The key features of the placebo-controlled randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence in the indirect comparison

Trial	N	Design/duration/ intervention dose	Bias	Population	Key outcomes ^a	Outcome used in modelled evaluation
Fenfluramine vs. placebo						
Study 1	119	R, DB, PC, 14 weeks. ^b Titration to either 0.2 mg/kg/day or 0.7 mg/kg/day FFA (-STP).	Low	Age 2-18 years. ≥4 convulsive seizures (tonic, tonic- atonic, tonic-clonic, or clonic) at baseline. ^c Did not receive STP in 21 days before screening.	Percentage change from baseline in CSF	No
					Responder analyses ^e	No
Study 3	143	R, DB, PC, 14 weeks. Titration to either 0.2 mg/kg/day or 0.7 mg/kg/day FFA (- STP). ^b	Low	Age 2-18 years. ≥4 convulsive seizures (tonic, tonic- atonic, tonic-clonic, or clonic) at baseline. ^c Did not receive STP in 21 days before screening.	Percentage change from baseline in CSF	No
					Responder analyses ^e	No
Study 2	87	R, DB, PC, 14 weeks. Titration 0.4 mg/kg/day FFA (+STP). ^b	Low	Age 2-18 years. ≥4 convulsive seizures (tonic-clonic, tonic or clonic) at baseline. ^c Receiving STP + clobazam and/or valproate at baseline. ^d	Percentage change from baseline in CSF	Yes
					Responder analyses ^e	No
Meta- analysis	176	Meta-analysis of FFA 0.7 mg/kg/day (-STP) arms in Study 1 and Study 3 for pooled least square mean difference from baseline vs. placebo.		Percentage change from baseline in CSF	Yes	
Meta- analysis	176	Meta-analysis of FFA 0.7 mg/kg/day (-STP) arms in Study 1 and Study 3 for pooled odds ratio, risk ratio and risk difference for the proportion of participants with ≥50%, ≥25%, and ≥75%, reduction in monthly CSF from baseline.		Responder analyses ^e	No	
Cannabidiol vs. placebo						
GWPCARE1	120	R, DB, PC, 14 weeks. Titration to 20 mg/kg/day CBD (+/- STP). ^f	Low	Age 2-18 years. ≥4 convulsive seizures (tonic, clonic, tonic-clonic, or atonic) at baseline. ^g Did not receive cannabis-based drugs in 3m before screening.	Percentage change from baseline in CSF	No
					Responder analyses ^e	No
GWPCARE2	198	R, DB, PC, 14 weeks Titration to either 10 or 20 mg/kg/day cannabidiol (+/-STP). ^f	Low	Age 2-18 years. ≥4 convulsive seizures (tonic, clonic, tonic-clonic, or atonic) at baseline. ^g Did not receive cannabis-based drugs in 3m before screening.	Percentage change from baseline in CSF	No
					Responder analyses ^e	No
Meta- analysis	263	Meta-analysis of CBD 20 mg/kg/day (±STP) arms in GWPCARE1 and GWPCARE2.		Percentage change from baseline in CSF	Yes	
Meta- analysis	263	Meta-analysis of CBD 20 mg/kg/day (±STP) arms in GWPCARE1 and GWPCARE2 for pooled odds ratio, risk ratio and risk difference for the proportion of participants with ≥50%, ≥25%, and ≥75%, reduction in monthly CSF from baseline.		Responder analyses ^e	No	
Stiripentol vs. placebo						
STICLO- France	42	R, DB, PC, 8 weeks. 50 mg/kg/day STP.	Low	Age 3-18 years. ≥4 convulsive seizures (clonic or tonic-clonic) per month.	Percentage change from baseline in CSF	No
STICLO- Italy	23				Responder analyses ^h	No
Meta- analysis	55	Meta-analysis of STP 50 mg/kg/day arms in STILCO-France and STILCO-Italy trials		Percentage change from baseline in CSF	No	

Source: Compiled during evaluation from Table 2-7 and Table 2-8, pp52-54, Table 2-9 p55, Table 2-10 p56, Table 2-11 p57 of the submission, Table A-9, p9 of Appendix 1 of the submission; cannabidiol PSD, July 2020 PBAC Meeting; stiripentol, PSD, March 2020 PBAC Meeting. Italicised text indicates new information added during the evaluation.

CBD = cannabidiol; CSF =convulsive seizure frequency; DB = double-blind; FFA = fenfluramine; MC =multicentre; N = number of participants; NR = not reported; PC = placebo-controlled; R = randomised; STP = stiripentol.

^a This table reports only the key outcomes reported in the included trials, used in the economic evaluation and the meta-analyses used in the indirect treatment comparisons

^b Trial duration included 2 weeks of titration and 12 weeks of maintenance. After the primary outcome assessment, there were 2 weeks of taper/transition.

^c In a 4-week period during the 12 weeks prior to screening.

^d For at least 4 weeks prior to screening.

^e Percentage of participants achieving $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, or 100% reduction in monthly CSF.

^f Trial duration included 2 weeks titration and 12 weeks maintenance. After the primary outcome assessment, there were 10 days taper/transition and 4 weeks of safety follow-up.

^g 28-day baseline period.

^h Percentage of participants achieving $\geq 50\%$ reduction of seizure frequency during the second month of the double-blind period compared to baseline.

6.17 The sample sizes were small in the treatment arms across all the included trials. This was expected given that Dravet Syndrome is a rare disease. However, the small sample sizes reduced the statistical power to detect differences across treatment arms in the included trials, creating additional uncertainty for the indirect comparisons.

6.18 Key differences between the fenfluramine, cannabidiol and stiripentol trials were differences in: concomitant use of stiripentol (Study 1/3 = no stiripentol; Study 2 = stiripentol; GWPCARE1 and GWPCARE2 = stiripentol permitted) and AEDs (higher use in fenfluramine vs cannabidiol trials) and the types of convulsive seizures included at baseline (Study 1/3 = tonic-clonic, tonic, clonic, or tonic-atonic seizures; Study 2 = tonic-clonic, tonic, or clonic seizures; GWPCARE1 and GWPCARE2 = tonic-clonic, tonic, clonic, or atonic seizures; STICLO-France/-Italy = tonic-clonic, clonic seizures), which impact the interpretation of the indirect treatment comparisons.

6.19 The primary outcome was similar across the trials: percent change from baseline in monthly CSF (mean or median), compared to placebo. The secondary outcomes in the submission were responder analyses reflecting the proportion of participants achieving $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, or 100% reduction in monthly CSF, and additional assessments of seizure-based outcomes and patient- and carer-reported quality of life outcomes. However, the timepoint for primary assessment differed between trials (14 weeks in the fenfluramine and cannabidiol trials, and 8 weeks in the stiripentol trials) and the types of convulsive seizures included at follow-up differed across the trials (as noted above). Furthermore, the statistical modelling strategies to compute the mean percentage change in monthly CSF differed across the trials (ANCOVA in GWPCARE1 and negative binomial regression in GWPCARE2). These differences were a further source of uncertainty for the indirect treatment comparisons.

6.20 The submission proposed either of the following as a minimally clinically important difference (MCID):

- A statistically significant difference compared to placebo of $\geq 50\%$ reduction in mean/median monthly CSF; or

- A statistically significant difference in the proportion of participants achieving a $\geq 50\%$ reduction in mean/median CSF.
- 6.21 The submission stated the following reasons to suggest a $\geq 50\%$ reduction in seizures to be clinically important:
- The PBAC previously considered a 50% reduction as clinically important (para. 11.7, cannabidiol, PSD, July 2020 PBAC Meeting).
 - It was consistent with contemporary literature and guidelines (Sullivan et al. 2021).⁹ The study by Sullivan et al. (2021) used data from the Study 1 and Study 2 trials to calculate numbers needed to treat with fenfluramine to achieve clinically desirable response—dichotomised for 50% and 75% reductions. This study predefined the ‘clinically meaningful’ response as a reduction in seizure frequency by $\geq 50\%$. The study did not employ standard methodologies to derive an MCID using patient and clinician-reported outcome measures.
- 6.22 Overall, the evaluation considered that the submission did not justify the choice of MCID using a statistically robust method or a systematic review. Previously, based on clinical advice, the PBAC considered a reduction in the number of seizures of at least 25% was likely to be clinically significant and, for Dravet Syndrome, could be determined in clinical practice by clinicians, patients and carers (para. 11.7, cannabidiol PSD, July 2020 PBAC Meeting). Therefore, the MCID may be lower than a $\geq 50\%$ reduction in seizures.
- 6.23 A claim of superior efficacy vs cannabidiol 10 mg/kg/day or 20 mg/kg/day (+/- stiripentol) was made based on the following outcomes: Change in monthly convulsive and total seizure frequency and associated responder analyses reflecting the proportion of participants achieving $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, or 100% reduction in monthly CSF, seizure-free days and intervals, and patient-reported outcomes and health-related quality of life. The submission did not provide an indirect comparison for seizure-free days and intervals or patient-reported outcomes. The PSCR argued there was insufficient publicly available information from the GWPCARE studies to undertake these analyses.
- 6.24 A claim of ‘similar’ safety vs cannabidiol 10 mg/kg/day or 20 mg/kg/day (+/- stiripentol) was made based on the outcomes of incidence and severity of adverse events and long-term safety. The submission did not provide an indirect comparison for safety outcomes but rather provided an ‘informal assessment’ (i.e. a side-by-side comparison of safety data) claiming that the trials were not sufficiently detailed or comparable to facilitate a formal indirect comparison.
- 6.25 The PBAC agreed with the ESC that stiripentol was a relevant comparator (paragraph 5.3), however considered the comparative effectiveness and safety of fenfluramine

⁹ Sullivan, J., Perry, M. S. et al. Fenfluramine responder analyses and numbers needed to treat: Translating epilepsy trial data into clinical practice. *European Journal of Paediatric Neurology*. 2021;31:10-14.

and stiripentol was not able to be reliably assessed. This was because the stiripentol trials were older, with a different standard of care and range of anti-epileptic drugs available, which when considered alongside the other transitivity issues identified including differences in trial eligibility criteria, treatment settings outcome measures, trial duration and follow-up and statistical methodology, precluded a reliable comparative assessment of these two agents.

Comparative effectiveness

6.26 The primary outcome (percent change in monthly CSF from baseline) in the fenfluramine trials is presented in Table 4.

Table 4: Change in 28-day CSF from baseline across the fenfluramine trials: continuous outcome

Trial ID Intervention and comparator	Study 1		Study 3		Study 2	
	FFA 0.7 mg/kg/day (-STP)	PBO (-STP)	FFA 0.7 mg/kg/day (-STP)	PBO (-STP)	FFA 0.4 mg/kg/day (+ STP)	PBO (+STP)
Number of participants	N=40	N=40	N=48	N=48	N=43	N=44
Median (range) baseline	20.7 (4.8, 124.0)	27.3 (3.3, 147.3)	13.0 (2.7, 2700.7)	12.7 (4.0, 229.3)	14.0 (2.7, 213.3)	10.7 (2.7, 162.7)
Median (range) at follow-up ^a	4.7 (0.0, 169.9)	22.0 (3.0, 164.0)	3.1 (0, 3498.6)	12.0 (0.9, 137.8)	5.2 (0, 458.6)	11.4 (2.2, 170.1)
Median % change from baseline, p-value vs. placebo	-74.9, <0.0001	-19.2	-73.7, <0.0001	-7.6	-63.1, <0.001	-1.1
LS mean difference from placebo, % (95% CI), p-value vs. placebo [ANCOVA]	-62.3 (-72.8, -47.7), <0.001	-	-64.8 (-74.2, -51.9), <0.0001	-	-54.0 (-67.2, -35.6), <0.001	-
Ratio vs. placebo (95% CI)	0.38 (0.27, 0.52)	-	0.35 (0.26, 0.48)	-	0.46 (0.33, 0.64)	-
LS mean difference from placebo, p-value vs. placebo [Rank ANCOVA] ^{b,c,d}	<0.001	-	<0.0001	-	<0.001	-

Source: Compiled during the evaluation using Table 2-22, p70, Table 2-28, p75, and Table 2-34, p79 of the submission, p224 of Study 1 CSR, p118 of Study 3 CSR, p222 of Study 2 CSR. **Bold** indicates statistically significant results.

ANCOVA = Analysis of covariance; CI = confidence interval; CSF = convulsive seizure frequency; FFA = fenfluramine; LS = least square; N = total participants in the treatment arm; PBO = placebo; STP = stiripentol.

The results of the fenfluramine 0.2 mg/kg/day (without stiripentol) arm were not presented in this table because the dose was not relevant to the assessment.

^a 14-week titration + maintenance period.

^b The Study 1 trial presented a sensitivity analysis using a non-parametric rank ANCOVA model with the ranks of baseline CSF as covariates, and treatment arms and age groups (<6 years, ≥6 years) as factors. LS mean % difference was not reported (Sec 6.3.1.1., p30 of Appendix 16.1.9 of Study 1 CSR).

^c The study 3 trial presented a sensitivity analysis using a non-parametric rank ANCOVA model with the ranks of baseline CSF as covariates, and treatment arms (3 levels) and age groups (<6 years, ≥6 years) as factors. LS mean % difference was not reported (Study 3 CSR).

^d The study 2 trial presented a sensitivity analysis using a non-parametric rank ANCOVA model with the rank of baseline CSF as covariates, and treatment arms and age groups (<6 years, ≥6 years) as factors. LS mean % difference was not reported (Study 2 CSR).

6.27 The fenfluramine trials reported a statistically significant decrease in CSF from baseline, compared to placebo, for all doses of fenfluramine tested in the trials (-32% to -65%). Of all the fenfluramine doses tested, the magnitude of change compared to placebo was the highest for fenfluramine 0.7 mg/kg/day (without stiripentol), with

Study 3 reporting the largest improvement in CSF (-64.8%, 95% CI: 74.2%, 51.9%). This was considered as clinically important by the submission, based on the nominated MCID. The improvements were statistically significant across the trials and fenfluramine doses when tested using rank ANCOVA models in a sensitivity analysis.

6.28 The secondary outcome (responder analysis) in the fenfluramine trials is presented in Table 5.

Table 5: Results of responder analyses in fenfluramine trials for ≥25%, ≥50%, ≥75% and 100% reduction from baseline in monthly CSF: dichotomous data

Trial ID	Study 1		Study 3		Study 2	
Intervention and comparator	FFA 0.7 mg/kg/day (-STP)	PBO (-STP)	FFA 0.7 mg/kg/day (-STP)	PBO (-STP)	FFA 0.4 mg/kg/day (+STP)	PBO (+STP)
Number of participants	N=40	N=40	N=48	N=48	N=43	N=44
≥50% reduction in monthly CSF						
n/N (%)	27/40 (67.5)	5/40 (12.5)	35/48 (72.9)	3/48 (6.3)	23/43 (53.5)	2/44 (4.5)
Odds ratio (95% CI), p-value vs. placebo	15.0 (4.5, 49.9), <0.001	-	53.3 (12.9, 220.5), <0.0001	-	26.0 (5.5, 123.2), <0.0001	-
≥25% reduction in monthly CSF^b						
n/N (%)	36/40 (90.0)	14/40 (35.0)	40/48 (83.3)	13/48 (27.1)	30/43 (69.8)	12/44 (27.3)
Odds ratio (95% CI), p-value vs. placebo	22.3 (5.9, 84.1), <0.001	-	15.7 (5.6, 44.1), <0.0001	-	6.4 (2.5, 16.5), <0.001	-
≥75% reduction in monthly CSF^b						
n/N (%)	20/40 (50.0)	1/40 (2.5)	23/48 (47.9)	2/48 (4.2)	15/43 (35.0)	1/44 (2.3)
Odds ratio (95% CI), p-value vs. placebo	55.1 (5.8, 526.3), <0.001	-	27.7 (6, 130.9), <0.0001	-	23.7 (2.9, 191.8), 0.003	-
100% reduction in monthly CSF^b						
n/N (%)	3/40 (7.5)	0/40 (0.0)	6/48 (12.5)	0/48 (0.0)	1/43 (2.3)	0/44(0.0)
Odds ratio (95% CI), p-value vs. placebo	NR	NR	NR	NR	NR	NR

Source: Compiled during the evaluation using Table 2-23, p71, Table 2-29, p76, and Table 2-35, p80 of the submission. **Bold** indicates statistically significant results.

CI = confidence interval; CSF = convulsive seizure frequency; FFA = fenfluramine; n = number of participants with event; N = total participants in the group; NR = not reported; PBO =placebo; STP = stiripentol.

The results of the fenfluramine 0.2 mg/kg/day (without stiripentol) arm were not presented in this table because the dose was not relevant to the assessment.

^a14 weeks titration = maintenance period.

^b Study 1, Study 3 and Study 2 described these as 'other secondary endpoints' but did not propose alpha levels to ascertain the statistical significance of the difference between the fenfluramine and placebo arms Study 1 CSR, pp77-78 of the Study 3 CSR, p69 of the Study 2 CSR). Therefore, these are not presented in **bold** font.

6.29 The fenfluramine trials reported a statistically significant higher proportion of participants in the fenfluramine treatment arms (53.5% to 72.9%) than placebo (6.3% to 12.5%) who achieved ≥50% reduction in CSF during the titration + maintenance

- period (14 weeks) compared with the baseline. However, the confidence intervals of the odds ratios were wide, indicating uncertainty in the magnitude of clinical benefit.
- 6.30 The fenfluramine trials also reported a statistically significant higher proportion of participants across all fenfluramine doses than placebo who achieved $\geq 25\%$ and $\geq 75\%$ reduction in CSF during the titration +maintenance period (14 weeks) compared with the baseline. Confidence intervals of the odds ratios were wide, indicating uncertainty in the magnitude of clinical benefit.
- 6.31 The fenfluramine trials also reported a numerically greater proportion of participants in the fenfluramine 0.7 mg/kg/day (without stiripentol) arm (7.5%) than placebo (0%) who achieved a 100% reduction in CSF, also called 'seizure freedom' during the titration +maintenance period (14 weeks).
- 6.32 Long-term follow-up indicated that the beneficial effects of fenfluramine on decrease in seizure frequency were likely maintained. The fenfluramine open-label extension Study 1503 reported 64.4% of participants (any dose) reported $\geq 50\%$ reduction in monthly CSF at the end of 3 years.
- 6.33 The patient-reported outcomes in the fenfluramine trials are presented in Table 6.

Table 6: Patient-reported outcomes and quality of life in fenfluramine trials, number (%) of participants with the rating at the end of the study period

Trial ID	Study 1		Study 3		Study 2	
Intervention and comparator	FFA 0.7 mg/kg/day (-STP)	PBO (-STP)	FFA 0.7 mg/kg/day (-STP)	PBO (-STP)	FFA 0.4 mg/kg/day (+STP)	PBO (+STP)
Number of participants	N=40	N=40	N=48	N=48	N=43	N=44
Clinical Global Impression of Improvement (CGI-I)						
Parent or caregiver rating: "Very much improved or much improved", n (%)	22 (55.0)	4 (10.0)	30 (62.5)	4 (8.3)	14 (33.0)	9 (21.0)
Odds ratio vs. PBO (95% CI), p-value	12.0 (CI NR), <0.001	-	16.1 (5.0, 52.0), <0.0001	-	2.1 (0.8, 5.7), 0.142	-
Parent or caregiver rating: Any improvement, n (%)	26 (65.0)	12 (30.0)	40 (83.3)	13 (27.1)	19 (44.0)	7 (16.0)
Odds ratio vs. PBO (95% CI), p-value	4.6 (CI NR), 0.002	-	15.1 (5.2, 44.3), <0.0001	-	NR, 0.008	-
Investigator rating: "Very much improved or much improved", n (%)	25 (62.5)	4 (10.0)	31 (64.6)	4 (8.3)	26 (60.5)	16 (36.4)
Odds ratio vs. PBO (95% CI), p-value	19.6 (CI NR), <0.001	-	16.1 (5.0, 51.9), <0.0001	-	3.9 (1.4, 10.6), 0.008	-
Investigator rating: Any improvement, n (%)	31 (77.5)	16 (40.0)	36 (75.0)	4 (8.3)	31 (72.1)	14 (31.8)
Odds ratio vs. PBO (95% CI), p-value	6.9 (CI NR), <0.001	-	8.4 (3.3, 21.8), <0.0001	-	NR, <0.001	-
Quality of Life in Childhood Epilepsy (QOLCE)						
Change from baseline, mean (SD), p-value vs. PBO	5.8 (11.7), 0.280	1.5 (8.7)	5.5 (13.2), 0.045	1.2 (9.0)	-3.5 (10.3), 0.191	0.1 (8.5)
Paediatric Quality of Life Inventory (PedsQL) generic core – Total score						
Change from baseline, mean (SD), p-value vs. PBO	5.9 (15.1), 0.020	-1.6 (10.4)	2.1 (14.7), 0.908	1.9 (13.3)	-0.9 (11.8), 0.618	-0.3 (12.4)
PedsQL Family Impact Module – Parent report – Total score						
Change from baseline, mean (SD), p-value vs. PBO	5.4 (15.6), 0.058	-4.4 (13.0)	6.3 (14.6), 0.242	1.3 (14.9)	3.4 (12.3), 0.240	-1.2 (13.1)
Caregiver QoL: (EQ-5D-5L)						
Mobility – Problems, n (%)						
Baseline	21 (52.5)	26 (65.0)	NR	NR	18 (41.9)	14 (31.8)
End of study visit	18 (45.0)	21 (52.5)			13 (30.2)	15 (34.1)
Self-care - Problems n (%)						
Baseline	24 (60.0)	29 (72.5)	NR	NR	25 (58.1)	22 (50.0)
End of study visit	19 (47.5)	25 (62.5)			25 (58.1)	31 (70.5)
Usual activities - Problems n (%)						
Baseline	25 (62.5)	30 (75.0)	NR	NR	20 (46.5)	17 (38.6)
End of study visit	19 (47.5)	26 (65.0)			18 (41.9)	20 (45.5)
Pain/discomfort - Problems n (%)						
Baseline	21 (52.5)	20 (50.0)	NR	NR	4 (9.3)	3 (6.8)
End of study visit	13 (32.5)	18 (45.0)			2 (4.7)	4 (9.1)

Trial ID	Study 1		Study 3		Study 2	
	FFA 0.7 mg/kg/day (-STP)	PBO (-STP)	FFA 0.7 mg/kg/day (-STP)	PBO (-STP)	FFA 0.4 mg/kg/day (+STP)	PBO (+STP)
Anxiety/depression - Problems n (%)						
Baseline	17 (42.5)	10 (25.0)	NR	NR	1 (2.3)	3 (6.8)
End of study visit	12 (30.0)	12 (30.0)			2 (4.7)	5 (11.4)
EQ-5D-5L VAS, change from baseline						
Mean (SD)	7.4 (20.3)	-1.7 (25.7)	5.9 (30.1)	9.0 (26.2)	9.4 (27.6)	1.6 (26.0)
Median (range)	5.0 (-29, 69)	-1.5 (-76, 65)	NR	-1.5 (-76, 65)	0.5 (-32, 60)	0 (-71, 50)
p-value vs PBO	0.059	-	0.797	-	0.423	-

Source: Table 2-27, p74, Table 2-33, p78, Table 2-40, p83 of the submission, p143 of Study 3 CSR. Odds ratios of CGI-I scores from Study 1 were extracted from Table 27, p115 and Table 28, p117 of Study 1 CSR of Study 1 CSR. PedsQL Family impact score for Study 3 extracted from p146 of Study 3 CSR. EQ-5D-5L VAS scores for Study 3 extracted from p147 of Study 3 CSR.

CGI-C= Clinical Global Impression of Change; CGI-I= Clinical Global Impression – Improvement; CSF = convulsive seizure frequency; EQ-5D-5L= EuroQOL –5 Dimensions – 5 Levels scale produced by the European Quality of Life Group; FFA = fenfluramine; NR= not reported; PedsQL= Paediatric Quality of Life Inventory; PBO = placebo; QoL = quality of life; QOLCE = Quality of Life in Childhood Epilepsy; SD= standard deviation; STP =stiripentol.

- 6.34 The Study 1 and Study 3 trials reported statistically significant improvement in parent and investigator Clinical Global Impression - Improvement (CGI-I) rating after 14 weeks of follow-up in fenfluramine 0.7 mg/kg/day (without stiripentol) compared to placebo. The fenfluramine trials claimed that a rating of ‘very much improved’ or ‘much improved’ in the CGI-I was a clinically meaningful improvement.
- 6.35 The fenfluramine open-label extension study also reported an increase in the proportion of parents/caregivers rating ‘much or very much improved’ from 50.5% in month 1 of the open-label extension period, to 62.5% over the 3 years of follow-up.
- 6.36 Only the Study 3 trial reported a significant change from baseline than placebo, in the Quality of Life in Childhood Epilepsy (QOLCE) scores in the fenfluramine 0.7 mg/kg/day (without stiripentol) treatment arm (mean 5.5 (SD 13.2)). The QOLCE instrument was specific to epilepsy and, therefore, was sensitive to the impact of epilepsy on quality of life (QoL).¹⁰ However, the effect sizes were small (the scale was scored from 0 to 100) and it is unclear whether the differences were clinically meaningful. Further, the follow-up duration of these trials was likely too short to observe meaningful change in quality of life measures.

Meta-analyses

- 6.37 The submission presented random-effects meta-analyses to pool data from the treatment arms randomised to the same drug dose for the 3 treatments (fenfluramine, cannabidiol and stiripentol) to inform the indirect treatment comparisons.

¹⁰ Goodwin SW, Ferro MA, Speechley KN. Development and assessment of the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-16). *Epilepsia*. 2018; 59: 668–678.

6.38 Table 7 presents the meta-analyses of fenfluramine, cannabidiol and stiripentol treatment arms, for the outcome of change in 28-day CSF from baseline.

Table 7 Results of meta-analyses for the outcome of change in 28-day CSF from baseline across fenfluramine, cannabidiol and stiripentol trials

Population	Trial ID	Active treatment LS mean % difference from baseline compared to placebo (95% CI)
FFA 0.7 mg/kg/day (- STP)	Study 1	-62.3 (-74.9, -49.8) ^a
	Study 3	-64.80 (-76.0, -53.6) ^a
	Meta-analysis results	-63.7 (-72.1, -55.3)
	I ² with 95% uncertainty interval	0.0%
FFA 0.4 mg/kg/day (+ STP)	Study 2	-54.0 (-69.8, -38.2) ^a
	Meta-analysis results [results from one trial]	-54.0 (-69.8, -38.2)
	I ² with 95% uncertainty interval	NA
CBD 10 mg/kg/day (±STP)	GWPCARE1	-29.8 (-48.7, -10.9) ^b
	Meta-analysis results [results from one trial]	-29.8 (-48.7, -10.9)
	I ² with 95% uncertainty interval	NA
CBD 20 mg/kg/day (±STP)	GWPCARE1	-22.0 (-45.2, 1.2) ^a
	GWPCARE2	-25.7 (-45.9, -5.6) ^b
	Meta-analysis results	-24.1 (-39.3, -8.9)
	I ² with 95% uncertainty interval	0.0%
STP 50 mg/kg/day	STICLO- France	-74.1 (-104.4, -43.8) ^c
	STICLO-Italy	-61.2 (-101.7, -20.6) ^c
	Meta-analysis results	-70.4 (-94.7, -46.1)^c
	I ² with 95% uncertainty interval	NR

Source: Table compiled during the evaluation using Section 2.6.3.1, p119 of the submission. **Bold** indicates statistically significant results. CBD = cannabidiol; CI = confidence interval; CSF = convulsive seizure frequency; FFA =fenfluramine; LS = least square; n = number of participants with event; N = total participants in group; NA= not applicable; STP = stiripentol.

^a ANCOVA model.

^b Negative binomial regression model.

^c The submission calculated mean difference in 30-day CSF using Mann-Whitney U test but did not report the workings of the method used (Table A-9, p9, Appendix 1 of the submission). This result was not reported in the trial publication.

6.39 Table 8 presents the meta-analyses of fenfluramine, cannabidiol and stiripentol treatment arms, for the outcome of responder analyses for proportion of participants with for ≥50%, ≥25%, and ≥75% reduction in monthly CSF from baseline. The submission did not report the responder analyses for a 100% reduction in seizure frequency because the placebo event rates were zero in all of the trials, preventing any meaningful statistical comparisons from being conducted.

Table 8 Results of meta-analyses for the outcome of responder analyses for $\geq 50\%$, $\geq 25\%$, and $\geq 75\%$ reduction in monthly CSF from baseline across fenfluramine, cannabidiol and stiripentol trials

Trial	Intervention	Treatment arm n/N (%)	Placebo ^b n/N (%)	Relative and absolute difference vs Placebo		
				OR (95% CI)	RR (95% CI)	RD (95% CI)
$\geq 50\%$ reduction from baseline monthly CSF						
Study 1	FFA 0.7 mg/kg/day (- STP)	27/40 (67.5)	5/40 (12.5)	14.54 (4.62, 45.78)	5.40 (2.31, 12.60)	0.55 (0.37, 0.73)
Study 3	FFA 0.7 mg/kg/day (- STP)	35/48 (72.9)	3/48 (6.3)	40.38 (10.67, 152.83)	11.67 (3.85, 35.37)	0.67 (0.52, 0.81)
Pooled estimates for FFA 0.7 mg/kg/day (- STP) used in indirect comparison				22.87 (8.46, 61.83)	7.28 (3.49, 15.19)	0.62 (0.51, 0.73)
Study 2	FFA 0.4 mg/kg/day (+ STP)	23/43 (53.5)	2/44 (4.5)	24.15 (5.18, 112.64)	11.77 (2.95, 46.89)	0.49 (0.33, 0.65)
Pooled estimates for FFA 0.4 mg/kg/day (+STP) used in indirect comparison				24.15 (5.18, 112.64)	11.77 (2.95, 46.89)	0.49 (0.33, 0.65)
GWPCARE1	CBD 20 mg/kg/day (+/- STP)	26/61 (42.6)	16/59 (27.1)	2.00 (0.93, 4.30)	1.57 (0.94, 2.62)	0.16 (-0.01, 0.32)
GWPCARE2	CBD 20 mg/kg/day (+/- STP)	33/67 (49.3)	17/65 (26.2)	2.74 (1.32, 5.70)	1.88 (1.17, 3.03)	0.23 (0.07, 0.39)
Pooled estimates for CBD 20 mg/kg/day (+/-STP) used in indirect comparison				2.36 (1.39, 4.00)	1.73 (1.22, 2.45)	0.19 (0.08, 0.31)
GWPCARE2	CBD 10 mg/kg/day (+/- STP)	29/66 (43.9)	17/65 (26.2)	2.21 (1.06, 4.62)	1.68 (1.03, 2.75)	0.18 (0.02, 0.34)
Pooled estimates for CBD mg/kg/day (+/-STP) used in indirect comparison				2.21 (1.06, 4.62)	1.68 (1.03, 2.75)	0.18 (0.02, 0.34)
STICLO- France & Italy	STP 50 mg/kg/day	23/32 (71.9)	2/29 (6.9)	34.5 (6.76, 176.08)	10.42 (2.69, 40.39)	0.65 (0.47, 0.83)
Pooled estimates for STP 50 mg/kg/day used in indirect comparison				34.5 (6.76, 176.08)	10.42 (2.69, 40.39)	0.65 (0.47, 0.83)
$\geq 25\%$ reduction from baseline monthly CSF						
Study 1	FFA 0.7 mg/kg/day (- STP)	36/40 (90.0)	14/40 (35.0)	16.71 (4.93, 56.63)	2.57 (1.66, 3.97)	0.55 (0.38, 0.72)
Study 3	FFA 0.7 mg/kg/day (- STP)	40/48 (83.3)	13/48 (27.1)	13.46 (5.00, 36.25)	3.08 (1.90, 4.98)	0.56 (0.40, 0.73)
Pooled estimates for FFA 0.7 mg/kg/day (- STP) used in indirect comparison				14.67 (6.80, 31.66)	2.79 (2.02, 3.85)	0.56 (0.44, 0.68)
Study 2	FFA 0.4 mg/kg/day (+ STP)	30/43 (69.8)	12/44 (27.3)	6.15 (2.43, 15.59)	2.56 (1.52, 4.31)	0.42 (0.23, 0.62)
Pooled estimates for FFA 0.4 mg/kg/day (+ STP) used in indirect comparison				6.15 (2.43, 15.59)	2.56 (1.52, 4.31)	0.42 (0.23, 0.62)
GWPCARE1	CBD 20 mg/kg/day (+/- STP)	38/61 (62.3)	26/59 (44.1)	2.1 (1.01, 4.35)	1.41 (1.00, 2.00)	0.18 (0.01, 0.36)
GWPCARE2	CBD 20 mg/kg/day (+/- STP)	47/67 (70.1)	32/65 (49.2)	2.42 (1.19, 4.95)	1.42 (1.06, 1.91)	0.21 (0.05, 0.37)
Pooled estimates for CBD 20 mg/kg/day (+/- STP) used in indirect comparison				2.26 (1.36, 3.76)	1.42 (1.14, 1.78)	0.20 (0.08, 0.32)
GWPCARE2	CBD 10 mg/kg/day (+/- STP)	37/66 (56.1)	32/65 (49.2)	1.32 (0.66, 2.62)	1.14 (0.82, 1.58)	0.07 (-0.1, 0.24)
Pooled estimates for CBD 10 mg/kg/day (+/- STP) used in indirect comparison				1.32 (0.66, 2.62)	1.14 (0.82, 1.58)	0.07 (-0.1, 0.24)
$\geq 75\%$ reduction from baseline monthly CSF						
Study 1	FFA 0.7 mg/kg/day (- STP)	20/40 (50.0)	1/40 (2.5)	39 (4.87, 312.01)	20 (2.82, 141.99)	0.47 (0.31, 0.64)

Trial	Intervention	Treatment arm n/N (%)	Placebo ^b n/N (%)	Relative and absolute difference vs Placebo		
				OR (95% CI)	RR (95% CI)	RD (95% CI)
Study 3	FFA 0.7 mg/kg/day (- STP)	23/48 (47.9)	2/48 (4.2)	21.16 (4.61, 97.21)	11.5 (2.87, 46.1)	0.44 (0.29, 0.59)
Pooled estimates for FFA 0.7 mg/kg/day (- STP) used in indirect comparison				26.20 (7.66, 89.62)	13.84 (4.46, 42.96)	0.46 (0.34, 0.57)
Study 2	FFA 0.4 mg/kg/day (+ STP)	15/43 (35)	1/44 (2.3)	23.04 (2.88, 184.29)	15.35 (2.12, 111.18) 45.35 (2.12, 111.18) ^a	0.33 (0.18, 0.48)
Pooled estimates for FFA 0.4 mg/kg/day (+ STP) used in indirect comparison				23.04 (2.88, 184.29)	15.35 (2.12, 111.18) 45.35 (2.12, 111.18)	0.33 (0.18, 0.48)
GWPCARE1	CBD 20 mg/kg/day (+/- STP)	14/61 (23.0)	7/59 (11.9)	2.21 (0.82, 5.95)	1.93 (0.84, 4.45)	0.11 (-0.02, 0.24)
GWPCARE2	CBD 20 mg/kg/day (+/- STP)	12/67 (17.9)	4/65 (6.2)	3.33 (1.01, 10.92)	2.91 (0.99, 8.56)	0.12 (0.01, 0.23)
Pooled estimates for CBD 20 mg/kg/day (+/- STP) used in indirect comparison				2.61 (1.22, 5.59)	2.25 (1.17, 4.36)	0.11 (0.03, 0.20)
GWPCARE2	CBD 10 mg/kg/day (+/- STP)	20/66 (30.3)	4/65 (6.2)	6.63 (2.12, 20.73)	4.92 (1.78, 13.62)	0.24 (0.12, 0.37)
Pooled estimates for CBD 10 mg/kg/day (+/- STP) used in indirect comparison				6.63 (2.12, 20.73)	4.92 (1.78, 13.62)	0.24 (0.12, 0.37)

Source: Table compiled during the evaluation using Table 2-66, p118, Section 2.6.3. pp119-129 of the submission, Table A-13, p13, Table A-14, p13 of Appendix 1 of the submission. **Bold** text shows statistically significant results.

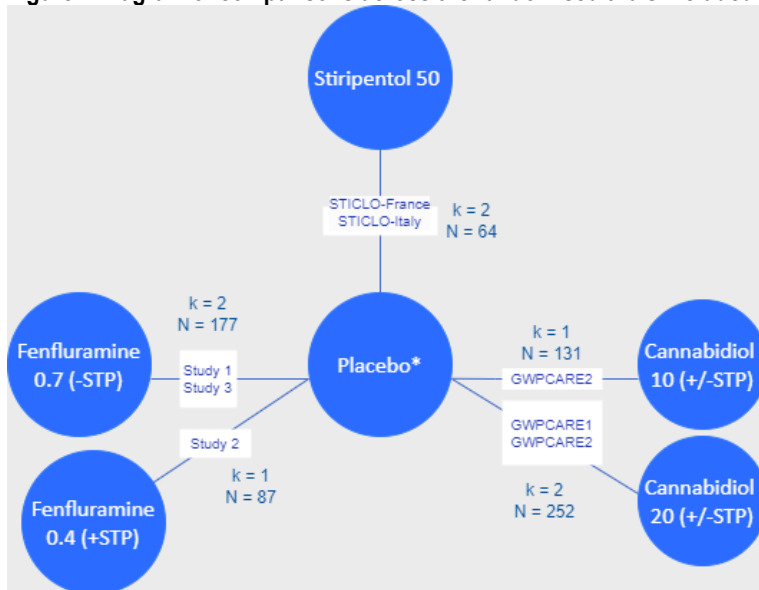
CBD = cannabidiol; CI = confidence interval; CSF = convulsive seizure frequency; FFA =fenfluramine; LS = least square; n = number of participants with event; N = total number of participants in the group; NA= not applicable; OR = Odds ratios; RR= risk ratio; RD= risk difference; STP = stiripentol.

^a In Study 1 and Study 3 the participants in the placebo arm did not receive stiripentol. In Study 2 all the participants in the placebo arm received stiripentol. In the GWPCARE1 and GWPCARE2 trials some participants in the placebo arm received stiripentol (42% and 36%, respectively).

Indirect treatment comparison

6.40 In the absence of direct randomised controlled trials, the submission presented indirect treatment comparisons using placebo as a common comparator. A diagram of all the included drug regimens is shown in Figure 1. Each node in the diagram represents a drug regimen, and the lines between the nodes reflect direct comparisons.

Figure 1 Diagram of comparisons across the randomised trials included in the indirect treatment comparisons



Source: Figure compiled during the evaluation from Figure 2-3, p44 of the submission, and Figure A-2 in Appendix 1 of the submission. Comparisons with stiripentol only included fenfluramine 0.7 mg/kg/day (without stiripentol) dose from Study 1 and Study 3 trials (k=2, N=261). k=number of randomised controlled trials, N= total number of participants across the trials; STP = stiripentol.

* In Study 1 and Study 3 the participants in the placebo arm did not receive stiripentol. In Study 2 all the participants in the placebo arm received stiripentol. In the GWPCARE1 and GWPCARE2 trials some participants in the placebo arm received stiripentol (42% and 36%, respectively).

6.41 The variable inclusion/exclusion of stiripentol in the treatment arms across the fenfluramine and cannabidiol trials could introduce uncertainty in comparing the clinical effectiveness of fenfluramine vs cannabidiol. The common comparator used in the indirect comparison of fenfluramine with cannabidiol was not the same across the included trials: the comparator vs fenfluramine 0.7 mg/kg/day (without stiripentol) was placebo without stiripentol (0% patients received stiripentol), the comparator vs fenfluramine 0.4 mg/kg/day (with stiripentol) was placebo with stiripentol (100% participants received stiripentol), and the comparator vs cannabidiol 10 and 20 mg/kg/day was placebo of which 36-42% received stiripentol. It is difficult to predict the direction of bias. However, assuming that stiripentol has superior efficacy to cannabidiol (described in a network meta-analysis of 8 trials),¹¹ it is possible that the inclusion of stiripentol with fenfluramine in the intervention and unknown inclusion of stiripentol with cannabidiol in the indirect comparison could bias the results in favour of fenfluramine 0.4 mg/kg/day (with stiripentol). The PSCR noted this important limitation was acknowledged by the submission and reiterated that patient level data based on stiripentol use in the cannabidiol trials was not available.

6.42 In the indirect treatment comparisons between fenfluramine and stiripentol the submission excluded a subgroup of fenfluramine trial participants who received

¹¹ Lattanzi S, Trinka E, et al. Pharmacotherapy for Dravet Syndrome: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. *Drugs*. 2023 Oct;83(15):1409-1424.

fenfluramine 0.4 mg/kg/day (with stiripentol) because it was not informative to an indirect comparison of fenfluramine and stiripentol.

- 6.43 The submission presented random-effects meta-analyses to pool data from the treatment arms randomised to the same dose for the 3 treatments (fenfluramine, cannabidiol and stiripentol) to inform the indirect treatment comparisons. The method of calculating the outcomes in the individual and pooled analyses of stiripentol trials was not reported, and therefore, could not be validated and it was not possible to determine how this may influence the results.
- 6.44 The submission conducted a placebo-adjusted indirect treatment comparison using the Bucher single pairwise method, with inputs derived from the consolidated efficacy outcomes from the relevant trials (described in the meta-analyses).
- 6.45 Table 9 presents the indirect comparison results for the change in monthly (28-day) CSF from baseline and the responder analyses for $\geq 50\%$, $\geq 25\%$, and $\geq 75\%$ reduction in monthly CSF from baseline. The stiripentol trials used a 30-day period to estimate the study outcomes.

Table 9: Results of pairwise indirect treatment comparisons

Continuous outcome: LS mean % difference in change from baseline monthly CSF			
Comparison	Estimate (95% CI)		
FFA 0.7 mg/kg/day (-STP) vs. CBD 20 mg/kg/day	-39.6 (-56.9, -22.3)		
FFA 0.7 mg/kg/day (-STP) vs. CBD 10 mg/kg/day	-33.9 (-54.6, -13.2)		
FFA 0.4 mg/kg/day (-STP) vs. CBD 20 mg/kg/day	-29.9 (-51.8, -8.0)		
FFA 0.4 mg/kg/day (+STP) vs. CBD 10 mg/kg/day	-24.2 (-48.8, 0.4)		
FFA 0.7 mg/kg/day (-STP) vs. STP 50 mg/kg/day	6.7 (-19.0, 32.4)		
Categorical outcomes			
Comparison	OR (95 % CI)	RR (95% CI)	RD (95% CI)
≥50% reduction from baseline monthly CSF			
FFA 0.7 mg/kg/day vs. CBD 20 mg/kg/day	9.69 (3.14, 29.89)	4.21 (1.86, 9.50)	0.43 (0.27, 0.59)
FFA 0.7 mg/kg/day vs. CBD 10 mg/kg/day	10.35 (3.00, 35.66)	4.33 (1.79, 10.49)	0.44 (0.25, 0.63)
FFA 0.4 mg/kg/day vs. CBD 20 mg/kg/day	10.23 (2.01, 52.12)	6.80 (1.63, 28.32)	0.30 (0.10, 0.50)
FFA 0.4 mg/kg/day vs. CBD 10 mg/kg/day	10.93 (1.98, 60.21)	7.01 (1.61, 30.40)	0.31 (0.08, 0.54)
FFA 0.7 mg/kg/day vs. STP 50 mg/kg/day	0.66 (0.98, 4.47) ^a	0.70 (0.15, 3.26)	-0.30 (-0.24, 1.81)
≥25% reduction from baseline monthly CSF^b			
FFA 0.7 mg/kg/day vs. CBD 20 mg/kg/day	6.49 (2.59, 16.25)	1.96 (1.33, 2.91)	0.36 (0.19, 0.53)
FFA 0.7 mg/kg/day vs. CBD 10 mg/kg/day	11.11 (3.97, 31.10)	2.45 (1.54, 3.88)	0.49 (0.28, 0.70)
FFA 0.4 mg/kg/day vs. CBD 20 mg/kg/day	2.72 (0.94, 7.85)	1.80 (1.02, 3.17)	0.22 (0.08, 0.32)
FFA 0.4 mg/kg/day vs. CBD 10 mg/kg/day	4.66 (1.46, 14.82)	2.25 (1.21, 4.15)	0.35 (0.01, 0.69)
≥75% reduction from baseline monthly CSF^b			
FFA 0.7 mg/kg/day vs. CBD 20 mg/kg/day	10.04 (2.36, 42.63)	6.15 (1.67, 22.79)	0.35 (0.21, 0.49)
FFA 0.7 mg/kg/day vs. CBD 10 mg/kg/day	3.95 (0.74, 21.14)	2.81 (0.61, 12.89)	0.22 (0.05, 0.39)
FFA 0.4 mg/kg/day vs. CBD 20 mg/kg/day	8.83 (0.96, 80.81)	6.82 (0.85, 54.95)	0.22 (0.05, 0.39)
FFA 0.4 mg/kg/day vs. CBD 10 mg/kg/day	3.47 (0.32, 37.27)	3.12 (0.34, 28.90)	0.09 (-0.10, 0.28)

Source: Table 2-68, p130 of the submission, Table A-15, p13 of Appendix 1 of the submission. **Bold** indicates statistically significant results. PBO = placebo; CBD = cannabidiol; CI = confidence interval; CSF = convulsive seizure frequency; FFA =fenfluramine; LS = least square; n = number of participants with event; N = total participants in group; NA= not applicable; STP = stiripentol.

^a It was noted during PBAC consideration that the point estimate lies outside of the reported confidence interval (Appendix 1 of the submission) and therefore may be an error.

^b The submission did not present a comparison between fenfluramine 0.7 mg/kg/day and stiripentol 50 mg/kg/day for this outcome.

6.46 The indirect comparisons showed a statistically significant improvement across most outcomes for fenfluramine compared to cannabidiol:

- Fenfluramine 0.7 mg/kg/day (without stiripentol) and 0.4 mg/kg/day (with stiripentol) resulted in a statistically significantly larger decrease in the 28-day CSF compared with cannabidiol 20 mg/kg/day (+/- stiripentol) (mean change from baseline in CSF -39.6% (95% CI -56.9%, -22.3%) and -29.9% (95% CI -51.8%, -8.0%), respectively). These results did not meet the nominated MCID.

- Fenfluramine 0.4 mg/kg/day (with stiripentol) resulted in a similar decrease (difference was not statistically significant) in the 28-day CSF compared with cannabidiol 10 mg/kg/day (+/- stiripentol).
 - Fenfluramine 0.7 mg/kg/day (without stiripentol) and 0.4 mg/kg/day (with stiripentol) resulted in a statistically significantly larger increase in the proportion of participants who achieved $\geq 50\%$ reduction in CSF, compared to those on cannabidiol 10 mg/kg/day (+/- stiripentol) or cannabidiol 20 mg/kg/day (+/- stiripentol).
 - Fenfluramine 0.7 mg/kg/day (without stiripentol) resulted in a statistically significantly larger proportion of participants who achieved $\geq 75\%$ reduction in CSF, compared to those on cannabidiol 20 mg/kg/day (+/- stiripentol), but the results were similar in the other comparisons based on the relative estimates.
- 6.47 The indirect comparisons showed a similar improvement (differences were not statistically significant) for fenfluramine 0.7 mg/kg/day (without stiripentol) vs stiripentol:
- Fenfluramine 0.7 mg/kg/day (without stiripentol) resulted in a similar decrease in the monthly CSF compared with stiripentol 50 mg/kg/day. However, numerically it favoured stiripentol.
 - Fenfluramine 0.7 mg/kg/day (without stiripentol) resulted in a similar proportion of participants who achieved $\geq 50\%$ reduction in CSF, compared to those on stiripentol 50 mg/kg/day. Numerically, most of the results favoured stiripentol.
- 6.48 However, the results of the indirect treatment comparisons were highly uncertain due to the small sample sizes across all the included trials and the differences across the trials that affected the assumption of transitivity (paragraphs 6.18 and 6.19).

Comparative harms

- 6.49 The key safety outcomes for the fenfluramine trials are presented in Table 10.

Table 10: Safety profile of fenfluramine in the placebo-controlled trials (participants with ≥1 event: n (%))

Trial ID	Study 1		Study 3		Study 2	
	FFA 0.7 mg/kg/day (-STP), n (%)	PBO (-STP)	FFA 0.7 mg/kg/day (-STP), n (%)	PBO (-STP)	FFA 0.4 mg/kg/day (+STP), n (%)	PBO (+STP)
Number of participants	N=40	N=40	N=48	N=48	N=43	N=44
TEAE	38 (95.0)	26 (65.0)	44 (91.7)	40 (83.3)	42 (97.7)	42 (95.5)
Treatment-related TEAE	27 (67.5)	7 (17.5)	32 (66.7)	17 (35.4)	31 (72.1)	15 (34.1)
Treatment-related serious TEAE	2 (5.0)	0 (0.0)	1 (2.1)	0 (0)	1 (2.3)	1 (2.3)
TEAE leading to discontinuation	5 (12.5)	0 (0.0)	2 (4.2)	1 (2.1)	2 (4.7)	1 (2.3)
Serious AE	5 (12.5)	4 (10.0)	3 (6.3)	2 (4.2)	6 (14.0)	7 (15.9)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0)	0 (0)
Adverse events of special interest ^a	18 (45.0)	10 (25.0)	21 (43.8)	20 (41.7)	10 (23.3)	10 (22.7)

Source: Table 2-49, p98, Table 2-50, p98, Table 2-54, p101, Table 2-56, p103, Table 2-58, p104, Table 2-60, p106 of the submission.

FFA = fenfluramine; n= number of participants with the event; PBO = placebo; SAE = serious adverse event; TEAE = treatment emergent adverse event.

^a At study initiation, any AE, lab finding or test value that could be related to cardiovascular effects or effects on weight were denoted as adverse events of special interest (AESIs) (Study 1 CSR).

6.50 The most common adverse outcomes in fenfluramine trials were decreased appetite, diarrhea, pyrexia, abnormal echocardiogram, nasopharyngitis, lethargy, somnolence, seizure, vomiting, diastolic blood pressure increased, and weight decrease. The fenfluramine trials reported a higher proportion of participants in fenfluramine 0.7 mg/kg/day (without stiripentol) and 0.2 mg/kg/day (without stiripentol) treatment arms than placebo with decreased appetite, decreased weight, abnormal echocardiogram, metabolism and nutrition disorders, and at least one adverse event of special interest. These adverse events (AEs) may be difficult to manage with minimal medical intervention in children with epilepsy. Abnormal echocardiograms were especially important in the context of this submission given that fenfluramine was previously registered for weight loss in adults and withdrawn from the Australian market due to its potential for causing valvular damage in the heart and pulmonary hypertension.¹² The fenfluramine long-term open-label extension Study 1503 indicated that these AEs persisted at the end of 3 years.

6.51 The submission provided an informal side-by-side comparison of common summary safety outcomes from the relevant active treatment arms across the trials. Table 11 presents the comparative summary of safety outcomes across the included trials.

¹² <https://www.tga.gov.au/safety/product-recalls/slimming-factor-also-known-easy-trim-que-she-and-chinese-herbal-diet-pills#:~:text=Fenfluramine%20was%20withdrawn%20from%20the,with%20its%20long%2Dterm%20use.>

Table 11: Comparative summary of safety outcomes (Safety populations)

n (%)	Fenfluramine			Cannabidiol			Stiripentol
	0.7 mg/kg/day (-STP)		0.4 mg/kg/day (+STP)	20 mg/kg/day (+/-STP)		10 mg/kg/day (+/-STP)	50 mg/kg/day
	Study 1 (n=40)	Study 3 (n=48)	Study 2 (N=43)	GWPCA RE1 (N=61)	GWPCARE2 (N=69)	GWPCARE2 (N=64)	STICLO-France & Italy (n=33)
AE	38 (95.0)	44 (91.7)	42 (97.7)	57 (93.4)	62 (89.9)	56 (87.5)	33 (100)
SAE	5 (12.5)	3 (6.3)	6 (14.0)	10 (16.3)	13 (18.8)	17 (26.5)	2 (6.1)
AE >DC	5 (12.5)	2 (4.2)	2 (4.7)	8 (13.1)	3 (4.6)	6 (8.7)	NR
Deaths	0 (0.0)	0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	NR
Decreased appetite	15 (37.5)	18 (37.5)	19 (44.2)	17 (28.0)	20 (29.0)	11 (17.0)	15 (45.5)
Echocardiogram abnormal	9 (22.5)	8 (16.7)	4 (9.3)	NR	NR	NR	NR
Weight decrease	2 (5.0)	0	4 (9.3)	NR	NR	NR	9 (27.3)
Metabolism and nutrition disorders	17 (42.5)	20 (41.7)	21 (48.8)	NR	NR	NR	NR
Somnolence	4 (10.0)	10 (20.8)	3 (7.0)	22 (36.0)	16 (23.0)	16 (25.0)	22 (66.7)
Upper respiratory tract infection	0 (0.0)	4 (8.3)	4 (9.3)	7 (11.0)	8 (12.0)	4 (6.0)	NR
Vomiting	3 (7.5)	3 (6.3)	2 (4.7)	9 (15.0)	11 (16.0)	4 (6.0)	NR
Status epilepticus ^a	14 (35)	5 (10.4)	8 (18.6)	3 (4.9)	7 (10.0)	5 (8.0)	NR
Diarrhoea	7 (17.5)	7 (14.6)	10 (23.3)	19 (31.0)	18 (26.0)	11 (17.0)	NR
ALT level increased	NR	NR	NR	NR	3 (5.0)	9 (13.0)	NR
AST level increased	NR	NR	NR	NR	3 (5.0)	8 (12.0)	NR

Source: Table compiled during the assessment from Table 2-49, p98, Table 2-50, p98, Table 2-54, p101, Table 2-56, p103, Table 2-58, p104, Table 2-60, p106, Table 2-63, p110, Table 2-64, p112, Table 2-69, p132, Table A-11, p11, Appendix 1 of the submission, Guerrini et al 2024. GWPCARE1 and GWPCARE2 data was from trial publications Devinsky et al (2017) and Miller et al (2020), respectively, and STICLO trials' data was from Guerrini et al 2024.

>DC = leading to discontinuation of study treatment; AE = adverse event; ALT= Alanine Transaminase; AST=Aspartate Aminotransferase; NR = not reported; SAE = serious adverse event; STP = stiripentol; TE = treatment emergent.

^a Status epilepticus was defined as an outcome, as opposed to an adverse event, in the fenfluramine trials.

6.52 While the overall incidence of AEs across the trials appeared similar, the types of AEs were different.

- The common AEs reported in the fenfluramine trials may have a long-lasting impact on children with epilepsy and may be difficult to manage with minimal medical intervention (e.g. metabolism and nutrition disorders and abnormal echocardiogram indicating valvular damage).
- On the other hand, the common AEs reported in the cannabidiol trials such as diarrhoea and vomiting may be treated with minimal medical intervention.
- The safety of fenfluramine 0.7 mg/kg/day (without stiripentol) was uncertain compared to stiripentol 50 mg/kg/day—while some AEs had a higher incidence in the fenfluramine arm, others were higher in the stiripentol arm. The stiripentol trials reported very few types of AEs making the comparison difficult with fenfluramine.
- The safety of fenfluramine 0.4 mg/kg/day (with stiripentol) was uncertain compared to placebo (stiripentol unknown dose) [Study 2 trial results]—serious

AEs had a higher incidence in the placebo arm, but specific AEs such as abnormal echocardiogram and metabolism and nutritional disorders were higher in the fenfluramine (with stiripentol) arm.

- 6.53 In the absence of a formal indirect comparison between safety outcomes, an unanchored indirect comparison was conducted during the evaluation, to quantify comparative harms. To use pooled effects for the same interventions, a random-effects meta-analysis was used. The unanchored comparisons were only feasible for outcomes presented across the fenfluramine, cannabidiol and stiripentol trials.
- 6.54 Table 12 presents the unanchored indirect treatment comparison for serious adverse events reported in the trials.

Table 12: Unanchored indirect treatment comparison for safety of fenfluramine vs cannabidiol and stiripentol.

Harms						
	FFA	Comparator/ PBO	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				FFA	PBO	
Serious adverse events						
FFA 0.7 mg/kg/day (-STP) vs CBD 20 mg/kg/day (+/-STP)						
Study 1 (FFA vs PBO)	5/40	4/40	NR	12.5	10.0	0.06 (NR)
Study 3 (FFA vs PBO)	3/48	2/48	NR	6.3	4.2	0.02 (NR)
Pooled meta-analysis for FFA 0.7 mg/kg/day vs PBO ^b						0.02 (-0.05, 0.10)
GWPCARE1 (CBD vs PBO)	10/61	3/51	NR	16.4	5.1	0.11
GWPCARE2 (CBD vs PBO)	13/67	10/65	NR	18.8	15.4	0.03
Pooled meta-analysis for CBD 20 mg/kg/day vs PBO used in the indirect comparison ^a						0.08 (-0.01, 0.16)
Indirect comparison: FFA 0.7 mg/kg/day vs CBD 20 mg/kg/day ^b						-0.06 (NR)
FFA 0.7 mg/kg/day (-STP) vs CBD 10 mg/kg/day (+/-STP)						
Study 1 (FFA vs PBO)	5/40	4/40	NR	12.5	6.3	0.06 (NR)
Study 3 (FFA vs PBO)	3/48	2/48	NR	6.3	4.2	0.02
Pooled meta-analysis for FFA 0.7 mg/kg/day vs PBO used in the indirect comparison ^a						0.02 (-0.05, 0.10)
GWPCARE2 (CBD vs PBO)	17/66	10/65	NR	26.5	15.4	0.11
Pooled meta-analysis for CBD 10 mg/kg/day vs PBO used in the indirect comparison						0.11
Indirect comparison: FFA 0.7 mg/kg/day vs CBD 10 mg/kg/day ^c						-0.09 (NR)
FFA 0.4 mg/kg/day (+STP) vs CBD 20 mg/kg/day (+/-STP)						
Study 2 (FFA vs PBO)	6/43	7/44	NR	14.0	15.9	-0.02
Pooled meta-analysis for FFA 0.4 mg/kg/day vs placebo used in the indirect comparison						-0.02
GWPCARE1 (CBD vs PBO)	10/61	3/51	NR	16.4	5.1	0.11
GWPCARE2 (CBD vs PBO)	13/67	10/65	NR	18.8	15.4	0.03
Pooled meta-analysis for CBD 20 mg/kg/day vs PBO used in the indirect comparison ^a						0.08 (-0.01, 0.16)
Indirect comparison: FFA 0.4 mg/kg/day vs CBD 20 mg/kg/day ^b						-0.06 (NR)
FFA 0.4 mg/kg/day (+STP) vs CBD 10 mg/kg/day (+/-STP)						
Study 2 (FFA vs PBO)	6/43	7/44	NR	14.0	15.9	-0.02
Pooled meta-analysis for FFA 0.4 mg/kg/day vs placebo used in the indirect comparison						-0.02
GWPCARE2 (CBD vs PBO)	17/66	10/65		26.5	15.4	0.11
Pooled meta-analysis for CBD 10 mg/kg/day vs PBO used in the indirect comparison						0.11
Indirect comparison: FFA 0.4 mg/kg/day vs CBD 10 mg/kg/day						-0.13 (NR)
FFA 0.7 mg/kg/day (-STP) vs STP 50 mg/kg/day						
Study 1 (FFA vs PBO)	5/40	4/40	NR	12.5	10.0	0.06 (NR)
Study 3 (FFA vs PBO)	3/48	2/48	NR	6.3	4.2	0.02 (NR)
Pooled meta-analysis for FFA 0.7 mg/kg/day vs PBO ^a						0.02 (-0.05, 0.10)
STICLO – France & Italy (STP vs PBO)	10/61	3/51	NR	16.4	5.1	-0.04 (-0.17, 0.10)
Pooled meta-analysis for STP 50 mg/kg/day vs PBO used in the indirect comparison ^a						-0.04 (-0.17, 0.10)
Indirect comparison: FFA 0.7 mg/kg/day vs STP 50 mg/kg/day ^b						0.06 (NR)
FFA 0.4 mg/kg/day (+STP) vs PBO (STP unknown dose) [Study 2 trial results]						
Study 2 (FFA vs PBO)	6/43	7/44	NR	14.0	15.9	-0.02
Pooled meta-analysis for FFA 0.4 mg/kg/day vs STP						-0.02
Comparison: FFA 0.4 mg/kg/day (+STP) vs STP (unknown dose) ^b						-0.02 (NR)

Source: Compiled during the evaluation Table 2-49, p98, Table 2-50, p98, Table 2-54, p101, Table 2-56, p103, Table 2-58, p104, Table 2-60, p106, Table 2-63, p110, Table 2-64, p112, Table 2-69, p132, Table A-11, p11, Appendix 1 of the submission, Guerrini et al 2024, p119 of the submission.

AE= adverse event; CBD = cannabidiol; CI= confidence interval; FFA = fenfluramine; n= number of participants with event; N= total number of participants in the treatment arm; NR = not reported; PBO = placebo; RD= risk difference; RR= risk ratio; SAE = serious adverse event; STP = stiripentol; TE = treatment emergent.

^a Pooled risk difference calculated during the evaluation using random-effects meta-analyses.

^b Results of unanchored indirect treatment comparison conducted during the evaluation.

- 6.55 The results indicated that fenfluramine (all doses) resulted in numerically fewer severe adverse events compared to cannabidiol (any dose) and resulted in numerically higher severe adverse events compared to stiripentol. Due to the nature of the analysis, confidence intervals or statistical tests for significance were not feasible. The PSCR reiterated the submission argument that there is insufficient information available from the respective comparator trials to conduct a meaningful comparison of safety outcomes and argued the data supports the submission conclusion that fenfluramine is generally well tolerated and can be added to most other AED regimens.

Benefits/harms

- 6.56 The small sample sizes and transitivity issues between the included trials presented in the submission introduced significant uncertainty in the comparison of the benefits and harms of fenfluramine vs cannabidiol or fenfluramine vs stiripentol.
- 6.57 The trials included in the submission did not present safety outcomes of abnormal echocardiogram and pulmonary hypertension or metabolism and nutrition disorders for the cannabidiol and stiripentol trials, with a relatively high frequency reported in the fenfluramine trials.
- 6.58 A summary of the comparative benefits and harms for fenfluramine, cannabidiol and stiripentol is presented in Table 13.

Table 13 Summary of the comparative benefits and harms for fenfluramine, cannabidiol and stiripentol

	RR (95% CI)	RD (95% CI)
Dichotomous outcome I: ≥50% reduction in monthly CSF		
FFA 0.7 mg/kg/day (-STP) vs CBD 20 mg/kg/day (+/- STP)	4.21 (1.86, 9.50)	0.43 (0.27, 0.59)
FFA 0.7 mg/kg/day (-STP) vs CBD 10 mg/kg/day (+/- STP)	4.33 (1.79, 10.49)	0.44 (0.25, 0.63)
FFA 0.4 mg/kg/day (+STP) vs CBD 20 mg/kg/day (+/- STP)	6.80 (1.63, 28.32)	0.30 (0.10, 0.50)
FFA 0.4 mg/kg/day (+STP) vs CBD 10 mg/kg/day (+/- STP)	7.01 (1.61, 30.40)	0.31 (0.08, 0.54)
FFA 0.7 mg/kg/day (-STP) vs STP 50 mg/kg/day	0.70 (0.15, 3.26)	-0.30 (-0.24, 1.81)
FFA 0.4 mg/kg/day (+STP) vs. PBO (STP unknown dose) [Study 2]	11.77 (2.95, 46.89)	0.49 (0.33, 0.65)
Continuous outcome I: Change in CSF from baseline [indirect comparison]^a		
FFA 0.7 mg/kg/day (-STP) vs CBD 20 mg/kg/day (+/- STP)	NR	-39.6 (-56.9, -22.37)
FFA 0.7 mg/kg/day (-STP) vs CBD 10 mg/kg/day (+/- STP)	NR	-33.9 (-54.6, -13.2)
FFA 0.4 mg/kg/day (+STP) vs CBD 20 mg/kg/day (+/- STP)	NR	-29.9 (-51.8, -8.0)
FFA 0.4 mg/kg/day (+STP) vs CBD 10 mg/kg/day (+/- STP)	NR	-24.2 (-48.8, 0.4)
FFA 0.7 mg/kg/day (-STP) vs STP 50 mg/kg/day	NR	6.7 (-19.0, 32.4)
FFA 0.4 mg/kg/day (+STP) vs. PBO (STP unknown dose) [Study 2]	NR	-54.0 (-67.2, -35.6)
Harms: Serious adverse events [unanchored indirect comparison]		
FFA 0.7 mg/kg/day (-STP) vs CBD 20 mg/kg/day (+/- STP)	NR	-0.06 (NR)
FFA 0.7 mg/kg/day (-STP) vs CBD 10 mg/kg/day (+/- STP)	NR	-0.09 (NR)
FFA 0.4 mg/kg/day (+STP) vs CBD 20 mg/kg/day (+/- STP)	NR	-0.06 (NR)
FFA 0.4 mg/kg/day (+STP) vs CBD 10 mg/kg/day (+/- STP)	NR	-0.13 (NR)
FFA 0.7 mg/kg/day (-STP) vs STP 50 mg/kg/day	NR	0.06 (NR)
FFA 0.4 mg/kg/day (+STP) vs. PBO (STP unknown dose) [Study 2]	NR	-0.02 (NR)

Source: Compiled during the evaluation from para. 6.38 and para. 6.47.

CBD = cannabidiol; CI= confidence interval; CSF = convulsive seizure frequency; FFA = fenfluramine; n= number of participants with event; N= total number of participants in the treatment arm; NR = not reported; PBO = placebo; RD= risk difference; RR= risk ratio; SAE = serious adverse event; STP = stiripentol; TE = treatment emergent.

^a mean difference between intervention and comparator.

- 6.59 The data presented is from the published cannabidiol and stiripentol trials. The only relevant and comparable safety outcome available across the fenfluramine, cannabidiol and stiripentol trials was incidence of serious adverse events.

Fenfluramine vs cannabidiol

- 6.60 On the basis of indirect comparison evidence presented by the submission comparing fenfluramine 0.7 mg/kg/day (without stiripentol) and cannabidiol 20 mg/kg/day (+/- stiripentol), for every 100 patients treated over 14 weeks:
- Approximately 43 additional patients would have a reduction in monthly convulsive seizures by $\geq 50\%$.
 - Patients would experience approximately a 39.6% reduction in 28-day seizure frequency from baseline.
 - Approximately 6 fewer patients would experience a serious adverse event (but the adverse events likely to be experienced would differ).
- 6.61 On the basis of indirect comparison evidence presented by the submission comparing fenfluramine 0.7 mg/kg/day (without stiripentol) and cannabidiol 10 mg/kg/day (+/- stiripentol) for every 100 patients treated over 14 weeks:
- Approximately 44 additional patients would have a reduction in monthly convulsive seizures by $\geq 50\%$.
 - Patients would experience approximately a 33.9% reduction in 28-day seizure frequency from baseline.
 - Approximately 9 fewer patients would experience a serious adverse event.
- 6.62 On the basis of indirect comparison evidence presented by the submission comparing fenfluramine 0.4 mg/kg/day (with stiripentol) and cannabidiol 20 mg/kg/day (+/- stiripentol), for every 100 patients treated over 14 weeks:
- Approximately 30 additional patients would have a reduction in monthly convulsive seizures by $\geq 50\%$.
 - Patients would experience approximately a 29.9% reduction in 28-day seizure frequency from baseline.
 - Approximately 6 fewer patients would experience a serious adverse event.
- 6.63 On the basis of indirect comparison evidence presented by the submission comparing fenfluramine 0.4 mg/kg/day (with stiripentol) and cannabidiol 10 mg/kg/day (+/- stiripentol), for every 100 patients treated over 14 weeks:
- Approximately 31 additional patients would have a reduction in monthly convulsive seizures by $\geq 50\%$.
 - Patients would experience a similar reduction in 28-day seizure frequency from baseline.

- Approximately 13 fewer patients would experience a serious adverse event.

Fenfluramine vs stiripentol

- 6.64 On the basis of indirect comparison evidence presented by the submission comparing fenfluramine 0.7 mg/kg/day (without stiripentol) and stiripentol 50 mg/kg/day, for every 100 patients treated with fenfluramine over 14 weeks and stiripentol over 8 weeks:
- A similar proportion of patients would have a reduction in monthly convulsive seizures by $\geq 50\%$.
 - Patients would experience a similar change in monthly CSF from baseline.
 - Approximately 6 more patients would experience a serious adverse event.
- 6.65 On the basis of comparative evidence (Study 2) presented by the submission comparing fenfluramine 0.4 mg/kg/day (with stiripentol) and placebo (stiripentol unknown dose), for every 100 patients treated with fenfluramine over 14 weeks:
- Approximately 49 additional patients would have a reduction in monthly convulsive seizures by $\geq 50\%$.
 - Patients would experience approximately a 54.0% reduction in 28-day seizure frequency from baseline.
 - Approximately 2 fewer patients would experience a serious adverse event.

Clinical claim

Fenfluramine vs cannabidiol

- 6.66 The submission described fenfluramine as superior in terms of effectiveness compared with cannabidiol and similar in terms of safety compared to cannabidiol.
- 6.67 The therapeutic conclusion regarding efficacy presented in the submission was reasonably supported for fenfluramine vs cannabidiol. The indirect comparisons indicated that fenfluramine 0.7 mg/kg/day (without stiripentol) resulted in a greater decrease in the 28-day CSF and a greater increase in the proportion of participants who achieved $\geq 50\%$ reduction in CSF compared with cannabidiol 10 or 20 mg/kg/day. The magnitude of benefit and clinical significance of the results was highly uncertain because the sample sizes were small in the treatment arms across all the included trials and there were significant between-trial differences that limit the exchangeability of the included fenfluramine and cannabidiol trials (paragraphs 6.18 and 6.19). The ESC considered that for the comparison with cannabidiol that whilst there were numerous uncertainties with the indirect treatment comparison, that a claim of superior comparative effectiveness was likely to be reasonable.
- 6.68 The therapeutic conclusion regarding safety presented in the submission was not adequately supported for fenfluramine vs cannabidiol because while the overall incidence of AEs across trials appear similar, the types of AEs were different. In

particular, the incidence of AEs that may have long-lasting impact on children with epilepsy and may be difficult to manage with minimal medical intervention was numerically higher in the fenfluramine trials than the cannabidiol trials (e.g. metabolism and nutrition disorders and abnormal echocardiogram indicating valvular damage). On the other hand, the common AEs reported in the cannabidiol trials, such as diarrhoea and vomiting, may be treated with minimal intervention.

- 6.69 The ESC considered the claim of similar comparative safety to cannabidiol to be uncertain, given the adverse event profiles of these agents were different and the long-term safety of fenfluramine, especially with respect to its impact on cardiac outcomes, remained unclear.
- 6.70 The PBAC considered that the claim of superior comparative effectiveness to cannabidiol was reasonable.
- 6.71 The PBAC considered that the claim of similar comparative safety to cannabidiol to be uncertain, but the available evidence did not allow a clear assessment of whether one could be considered superior (or inferior) to another.

Fenfluramine vs stiripentol

- 6.72 The submission described fenfluramine 0.7 mg/kg/day (without stiripentol) as uncertain in terms of effectiveness compared with stiripentol 50 mg/kg/day and did not make a clinical claim in terms of safety to stiripentol. The indirect comparisons suggested that fenfluramine 0.7 mg/kg/day (without stiripentol) resulted in a similar decrease in the 28-day CSF and a similar increase in the proportion of participants who achieved $\geq 50\%$ reduction in CSF compared with stiripentol 50 mg/kg/day. On the other hand, the placebo-controlled RCT Study 2 trial showed that fenfluramine 0.4 mg/kg/day (with stiripentol) resulted in a significant decrease in the 28-day CSF and a significant increase in the proportion of participants who achieved $\geq 50\%$ reduction in CSF compared with placebo with stiripentol (unknown dose).
- 6.73 The PSCR stated it was incorrect to describe the evidence networks connecting fenfluramine and cannabidiol and fenfluramine to stiripentol as being similar, and argued additional differences between the fenfluramine and stiripentol trials that undermine reliable comparison included differences in eligibility criteria, treatment settings, concurrent AED regimens, outcome measures, time points, length of follow up, assessment window for seizure frequency outcomes and statistical methods.
- 6.74 The ESC acknowledged these additional issues for the indirect comparison of fenfluramine and stiripentol, however considered that whilst these differences impact the robustness of the indirect treatment comparisons, the fact that stiripentol is a reasonable comparator for the proposed listing necessitates consideration of the comparative effectiveness and safety of these two agents. Based on the available data, the ESC considered a claim of superior comparative effectiveness or safety to stiripentol may be challenging to support.

- 6.75 Further to above, the ESC considered it important to reiterate that whilst the comparisons to cannabidiol and stiripentol have substantial uncertainties, the available evidence supports a conclusion that fenfluramine is an effective therapy for Dravet Syndrome, and there remains a substantial unmet clinical need for effective treatments in this rare and devastating disease.
- 6.76 The PBAC agreed stiripentol was a reasonable comparator, however considered that given the magnitude of the transitivity issues between the fenfluramine data and the pivotal stiripentol trial, that it was not possible to draw meaningful conclusions regarding the comparative effectiveness and safety of these therapies. The Committee did note, however, that the available safety data highlights the different adverse event profiles of fenfluramine, cannabidiol and stiripentol, and the long-term safety of fenfluramine with respect to risk of pulmonary hypertension or valvular heart disease is not yet clear. In addition, the PBAC agreed with the ESC that the available evidence supports a conclusion that fenfluramine is an effective therapy and there is a substantial unmet need for additional effective treatment options in Dravet Syndrome.

Economic analysis

- 6.77 The ESC noted the economic model used a weighted ICER approach based on two cohorts stratified by use of concomitant stiripentol (either 100% for both fenfluramine and cannabidiol, or none), which individually produced vastly different ICERs (dominant in the + stiripentol cohort and \$155,000 to < \$255,000 per QALY in the no stiripentol cohort) and considered this highlighted major uncertainties with the model. In particular, the ESC noted the model was very sensitive to parameters that determine the cost of treatment with cannabidiol (+/- stiripentol) in both cohorts. Further, the ESC noted that the relevant inputs were inconsistent with prior PBAC considerations for stiripentol and cannabidiol including time horizon, starting age, cannabidiol dose and extent of combination use of cannabidiol and stiripentol.
- 6.78 The ESC considered a model structure with health states relevant to frequency and/or reduction to seizure frequency was likely to have more accurately captured the incremental clinical benefits of treatment, compared to the current structure with health states based on treatment status. The Pre-PBAC Response acknowledged the possibility that a model structure with health states relevant to seizure free days or seizure freedom might have better captured the incremental benefits of treatment.
- 6.79 The ESC considered that given the clinical comparisons were uncertain due to the available data and exchangeability issues that limit the robustness of the indirect treatment comparisons (discussed above), the results of the model also reflect this uncertainty. Overall, the ESC considered the weighted ICER approach to be inappropriate and given the resultant ICERs in the individual cohorts to the aforementioned parameters, considered the submission approach to be unreliable for decision-making.

- 6.80 However, the ESC recognised that Dravet Syndrome is a rare and devastating illness and there was a clinical need for additional effective therapies, and that the evidence supports a conclusion that fenfluramine is likely an effective treatment. Therefore, the ESC considered an alternative, simplified approach to determining an acceptably cost-effective price for fenfluramine may be justified in recognition of the available evidence and clinical need. The Pre-PBAC Response acknowledged the advice of the ESC, however reiterated it was reasonable for fenfluramine to have a price premium over relevant comparisons (where appropriate).
- 6.81 The PBAC agreed with the ESC and considered the economic model in the submission was unreliable for decision-making and agreed a simpler alternative approach to assess the cost-effectiveness of fenfluramine was reasonable, in the context of the rarity and high clinical need for additional effective therapies in Dravet Syndrome. The approach relied upon by the PBAC to consider the cost-effectiveness of fenfluramine is discussed in the 'cost per responder analyses' section below, following the summary of the model included in the submission.
- 6.82 The submission presented a modelled economic evaluation based on indirect comparisons between fenfluramine (0.7 mg/kg/day without stiripentol and 0.4 mg/kg/day with stiripentol) and cannabidiol (10 or 20 mg/kg/day +/- stiripentol) for the outcome of percentage change from baseline in CSF. The indirect comparisons were informed by a meta-analysis of the Study 1 and 3 trials (fenfluramine 0.7 mg/kg/day without stiripentol), the Study 2 trial (fenfluramine 0.4 mg/kg/day with stiripentol), the GWPCARE1 trial (cannabidiol 10 mg/kg/day +/- stiripentol) and a meta-analysis of the GWPCARE1 and GWPCARE2 trials (cannabidiol 20 mg/kg/day +/- stiripentol) (Table 9).
- 6.83 The type of economic evaluation presented was a cost-utility analysis, consistent with the clinical claim of superior effectiveness of fenfluramine compared with cannabidiol.
- 6.84 The economic model was stratified into two cohorts:
- Cohort 1 (patients receiving a background AED regimen including stiripentol 50 mg/kg/day):
 - Intervention arm: Fenfluramine 0.4 mg/kg/day; versus
 - Comparator arm: Cannabidiol weighted average of 10 and 20 mg/kg/day.
 - Cohort 2 (patients receiving a background AED regimen excluding stiripentol):
 - Intervention arm: Fenfluramine 0.7 mg/kg/day; versus
 - Comparator arm: Cannabidiol weighted average of 10 and 20 mg/kg/day.
- 6.85 Stratification into two cohorts based on concomitant stiripentol was consistent with the fenfluramine trials. However, this stratification did not align with the cannabidiol trial where some patients received concomitant stiripentol. This modelling approach did not account for the treatment effect of adding stiripentol to cannabidiol.

6.86 Stiripentol was not considered as a comparator in the economic model provided in the submission. This was inconsistent with the treatment algorithm and the financial estimates, which both consider substitution from stiripentol to fenfluramine.

6.87 A summary of the model structure and key inputs is presented in Table 14.

Table 14: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Cohort 1: FFA 0.4 mg/kg/day + STP 50 mg/kg/day vs CBD (10 mg/kg/day or 20 mg/kg/day) + STP 50 mg/kg/day Cohort 2: FFA 0.7 mg/kg/day vs CBD (10 mg/kg/day or 20 mg/kg/day) CBD dose distribution: 50%:50% 10 mg/kg/day vs 20 mg/kg/day. This may not be appropriate. The PBAC previously noted clinical advice that a dose of 10 mg/kg/day or less was likely to be used in most patients with Dravet Syndrome (para. 11.5, cannabidiol, PSD, addendum to the July 2020 PBAC Minutes).
Type of analysis	Cost-utility analysis.
Time horizon	16 years in the model base case versus 14 weeks in the key trials (Study 1-3 and GWPCARE1 & 2). The modelled time horizon was long compared to the duration of follow-up in the fenfluramine and cannabidiol trials. The stiripentol model previously considered by the PBAC included a time horizon of 5 years (para 6.24, stiripentol, PSD, March 2020 PBAC Meeting). The ESC previously advised that a time horizon of 5 years would be appropriate for the cannabidiol model (para. 6.50, cannabidiol, PSD, July 2020 PBAC Meeting).
Outcomes	Quality-adjusted life years, convulsive seizure events, status epilepticus events, and deaths
Methods used to generate results	Stratified Markov model, with stratification into two cohorts based on concomitant stiripentol treatment. Patients in Cohort 1 received concomitant stiripentol 50 mg/kg/day, while patients in Cohort 2 did not receive concomitant stiripentol. ICERs for each cohort were calculated separately, then a weighted ICER was estimated by assuming 31% of patients were in Cohort 1, based on PBS utilisation data for cannabidiol and stiripentol as concomitant treatment for Dravet Syndrome. The use of a Markov model was appropriate, although there were issues with the model structure (see para. 6.90).
Health states	3 health states: Alive on treatment, Alive discontinued, Dead. The health states do not align with the health outcomes from the key trials. The health states were consistent with the 3 fenfluramine models identified by the submission; however, the cannabidiol and stiripentol models for Dravet Syndrome identified by the submission utilised health states relating to seizure frequency or reduction. Further, two systematic reviews cited in the submission identified 11 economic evaluations of paediatric drug-resistant epilepsy treatments; 7 used Markov models with health states relating to seizure frequency or reduction, 4 used decision trees, and none used health states linked to treatment (Elliott 2019 and Erku 2021).
Cycle length	Cycle 0: 14 weeks (2 weeks titration + 12 weeks maintenance). Subsequent cycles: 12 weeks. The cycle lengths were reasonable. No half cycle correction was applied. This was not appropriate.
Population	Starting age: 9.2 years, based on the Study 1-3 trials. This was consistent with the trials and reasonable due to patients needing to be refractory to multiple AEDs before commencing treatment with fenfluramine. However, it was inconsistent with the financial estimates that estimated an age distribution from 2 to 25 years. Weight: 29 kg, based on ANZSPED weight chart. Baseline CSF: 45.6 per month, based on a weighted average of all patients in the Study 1-3 trials. Applied to fenfluramine and cannabidiol arms in Cohorts 1 and 2. Applying different baseline CSF values for each cohort based on the relevant fenfluramine trials would be more appropriate.

Component	Summary
Transition probabilities	<p>Treatment effect (mean reduction in monthly CSF):</p> <p>Cohort 1, FFA 0.4 mg/kg/day (+ STP) (Study 2 trial):</p> <ul style="list-style-type: none"> - 54.00% <p>Cohort 1, CBD 10 mg/kg/day and 20 mg/kg/day (+/- STP) (indirect comparison results vs FFA 0.4 mg/kg/day (+ STP), weighted by CBD dose 50%:50%):</p> <ul style="list-style-type: none"> - 26.96% <p>Cohort 2, FFA 0.7 mg/kg/day (- STP) (meta-analysis of the Study 1 & 3 trials):</p> <ul style="list-style-type: none"> - 63.69% <p>Cohort 2, CBD 10 mg/kg/day and 20 mg/kg/day (+/- STP) (indirect comparison results vs FFA 0.7 mg/kg/day (- STP), weighted by CBD dose 50%:50%):</p> <ul style="list-style-type: none"> - 26.96% <p>Status epilepticus events: Assumed to be 0.17% of convulsive seizure events, based on post-hoc analysis from Studies 1 & 2. The post-hoc analysis was not provided and could not be verified during the evaluation. The use of only Study 1 & 2 to estimate status epilepticus events was inconsistent with trial-based model sources, which included Study 3 and stratified results based on concomitant stiripentol. The trial data was presented as the number of participants with events, not the total number of events. The impact of including Study 3 cannot be determined based on the evidence provided in the submission. The weighted ICER was sensitive to the proportion of convulsive seizure events that were status epilepticus.</p> <p>Disease-specific mortality: Assumed to be linked to convulsive seizures. Modelled survival calibrated to fit Cooper (2016), which estimated a mortality rate of 15.84 per 1,000 person years.</p> <p>Adherence: 100% (assumption).</p> <p>Treatment discontinuation:</p> <ul style="list-style-type: none"> - Cycle 0 based on Studies 1-3 for fenfluramine and GWPCARE1 & 2 for cannabidiol <ul style="list-style-type: none"> o Fenfluramine: Cohort 1 = 16.28%, Cohort 2 = 10.55% o Cannabidiol: 10 mg/kg/day = 4.50%, 20 mg/kg/day = 11.90% - Subsequent cycles: 5% per annum (expert clinical advice). <p>These were reasonable.</p> <p>Age-specific background mortality: Australian life tables. This was reasonable.</p>
Extrapolation method	<p>Treatment discontinuation was based on the key trials for Cycle 0, then assumed to be 5% per annum thereafter. This was reasonable. Modelled long-term discontinuations were compared to data from the fenfluramine open-label extension study (Study 1503) during the evaluation. The Study 1503 study did not stratify fenfluramine by concomitant stiripentol. Model Cohort 1 (with stiripentol) appeared to overestimate discontinuations at 12 months but aligned with trial data at 24 and 36 months. Model Cohort 2 (without stiripentol) appeared to align with trial data at 12 months but underestimated discontinuations at 24 and 36 months.</p> <p>The submission assumed that the treatment effects observed in the 14-week trials would remain constant while patients remained on treatment to the 16-year modelled time horizon. Patients returned to baseline CSF (and mortality) upon entering the 'alive discontinued' health state. Assuming constant treatment effect while on treatment may be reasonable based on the long-term data from the Study 1503 study; assuming patients return to baseline mean CSF upon discontinuation may not be reasonable given the placebo effect observed in the fenfluramine and cannabidiol trials.</p>

Component	Summary
	98.53% of QALYs gained, 99.97% of LY gained, and 99.94% of costs (undiscounted) occurred in the extrapolated period.
Health related quality of life	PedsQL data from fenfluramine Study 1-3 trials was mapped to EQ-5D-Y. A regression equation linked CSF to EQ-5D-Y. Linking EQ-5D-Y to CSF added complexity but reasonable given no utility data were collected in the cannabidiol trials.
Costs	<p>Doses:</p> <p>Fenfluramine:</p> <ul style="list-style-type: none"> - Cohort 1: 0.4 mg/kg/day (max dose 17 mg/day) based on Study 2 - Cohort 2: 0.7 mg/kg/day (max dose 26 mg/day) based on Study 1 & 3 - The maximum daily doses for fenfluramine were reached when patients were 13 years (46 kg) in Cohort 1 and 12 years (42 kg) in Cohort 2. <p>Cannabidiol: assumed to be an evenly weighted average of 10 and 20 mg/kg/day regimens (50%:50%), i.e., 15 mg/kg/day. The cohort-level ICERs and the weighted ICER were sensitive to changes in the proportion of patients receiving cannabidiol 10 mg/kg/day.</p> <p>Stiripentol: assumed to be 50 mg/kg/day. The cost of stiripentol was applied to 100% of patients in the cannabidiol arm of Cohort 1 and 0% of the patients in the cannabidiol arm of Cohort 2. This was inconsistent with the GWPCARE1 and GWPCARE2 trials, where 42% and 34% of patients were treated with stiripentol, respectively.</p> <p>Wastage was not considered. Excluding wastage was not reasonable.</p> <p>Treatment costs: As proposed for fenfluramine. Published DPMQ for stiripentol. The submission assumed a Special Pricing Arrangement (SPA) reduction of [redacted] % applied to the published price of cannabidiol (assumed effective DPMQ = \$ [redacted] * [redacted] = \$ [redacted]).</p> <p>Costs of monitoring and hospitalisation for status epilepticus included. The treatment, monitoring, status epilepticus costs included and excluded were reasonable.</p> <p>Background AEDs (e.g., valproate) were excluded. This may not be reasonable given differences in background AEDs across the included trials. Assuming no difference may not accurately reflect clinical practice.</p> <p>The model did not include adverse events. Excluding adverse events may not be reasonable, given the different types of events experienced in the fenfluramine vs cannabidiol trials.</p>
Weighted ICER	Cohort 1 was dominant: associated with a QALY gain and was less costly (0.1085 QALY gained, \$ [redacted] less costly) and therefore had a negative ICER (representing the south-east quadrant on the CE plane). The ICER for Cohort 1 was -\$755,000 to < \$855,000/QALY (i.e., fenfluramine + stiripentol was less costly and more effective than cannabidiol +/- stiripentol) and the ICER for Cohort 2 was \$255,000 to < \$355,000/QALY (fenfluramine was more costly and more effective than cannabidiol). The weighted ICER was \$15,000 to < \$25,000/QALY. Many sensitivity analyses had strong impacts at the Cohort level ICER but minimal impact on the weighted ICER. Key drivers of the weighted ICER were the proportion of patients in each Cohort, the starting age of patients, and the proportion of patients receiving cannabidiol 10 mg/kg/day vs 20 mg/kg/day.

Source: Tables 3-1 & 3-2, pp142 & 148 of the submission; pp140, 149-151, 153, 155-158 & 166 of the submission; Sheets 'Totals_undiscounted' and 'Results' of the Section 3 workbook.

AEDs = anti-epileptic drugs; ANZSPED = Australia and New Zealand Society for Paediatric Endocrinology and Diabetes; CBD = cannabidiol; CAF = convulsive seizure frequency; EQ-5D-Y = child specific version of EuroQol – 5 Dimension; FFA = fenfluramine; ICER = Incremental Cost Effectiveness Ratio; LYs = Life Years; PedsQL = Pediatric Quality of Life Inventory; QALYs = Quality Adjusted Life Years; RCTs = Randomised Controlled Trials; STP = stiripentol.

6.88 The economic model presented in the submission was structured as a stratified Markov process with three health states (alive on treatment, alive discontinued,

- dead). Transitions between ‘alive on treatment’ and ‘alive discontinued’ were informed by discontinuation rates in the fenfluramine and cannabidiol trials for cycle 0 and expert clinical advice for subsequent cycles.
- 6.89 Transitions to ‘dead’ were estimated by first estimating age-specific background mortality, then estimating a relative risk of death due to Dravet syndrome using a linear regression, with monthly CSF as an explanatory variable. This meant treatment effects (in terms of a reduction in monthly CSF) were linked to survival gains via a reduction in the risk of death due to Dravet Syndrome.
- 6.90 The model’s health states were not consistent with the clinical trials that had primary outcomes related to seizure frequency. The model’s health states were consistent with the 3 fenfluramine models identified by the submission literature review, including the model considered by NICE (TA808)¹³ and the Scottish Medicines Consortium¹⁴. However, the cannabidiol and stiripentol models for Dravet Syndrome identified by the submission utilised health states directly relating to seizure frequency or reduction. Further, two systematic reviews cited in the submission identified 11 economic evaluations of paediatric drug-resistant epilepsy treatments; 7 used Markov models with health states linked to seizure frequency or reduction, 4 used decision trees, and none used health states linked to treatment (Elliott 2019 and Erku 2021).^{15,16}
- 6.91 The submission presented a Markov model calculated as a cohort expected value analysis. Costs, composite outcomes, and incremental results were presented on an average per patient basis. No individual simulation methods were employed and there was no consideration of patient heterogeneity beyond the primary stratification by concomitant stiripentol use.
- 6.92 The model estimated the treatment effect as the difference in percentage change from baseline in mean monthly CSF, which was the primary outcome in the fenfluramine and cannabidiol trials (Table 15). The model assumed 50% of patients in the cannabidiol arm received the 10 mg/kg/day and 50% received 20 mg/kg/day. The model therefore estimated a weighted average change from baseline for the cannabidiol arm in Cohorts 1 and 2 using the indirect comparison results presented in Table 9.

¹³ NICE, <https://www.nice.org.uk/guidance/ta808>

¹⁴ Scottish Medicines Consortium, <https://scottishmedicines.org.uk/medicines-advice/fenfluramine-fintepla-full-smc2569/>

¹⁵ Elliot, J., van Katwyk, S., et al. Decision Models for Assessing the Cost Effectiveness of Treatments for Paediatric Drug-Resistant Epilepsy: A Systematic Review of Economic Evaluations. *PharmacoEconomics*. 2019; 37:1261-76.

¹⁶ Erku, D., Shrestha, S., & Scuffam, P. Cost-Effectiveness of Medicinal Cannabis for Management of Refractory Symptoms Associated with Chronic Conditions: A Systematic Review of Economic Evaluations. *Value In Health*. 2021; 24(10):1520-30.

Table 15: Summary of treatment effect estimated used in the model

Treatment regimen	LS mean difference in change from baseline monthly CSF versus fenfluramine, % (95% CI)	Estimated reduction in mean monthly CSF applied in the model, % (95% CI)	Source/method
Cohort 1 (with stiripentol 50 mg/kg/day)			
Fenfluramine 0.4 mg/kg/day	-	54.00 (38.20, 69.80)	Observed LS mean difference from placebo in the Study 2 trial
Cannabidiol 10 mg/kg/day	24.20 (-0.43, 48.83)	-	Indirect treatment comparison with FFA
Cannabidiol 20 mg/kg/day	29.89 (7.99, 51.79)	-	
Cannabidiol 15 mg/kg/day with stiripentol 50 mg/kg/day	-	26.96	Weighted average LS mean difference between FFA and CBD 10 and 20 mg/kg/day) * (reduction in mean monthly CSF for FFA versus placebo.
Cohort 2 (without stiripentol 50 mg/kg/day)			
Fenfluramine 0.7 mg/kg/day	-	63.69 (55.34, 72.05)	Meta-analysis of observed LS mean difference from placebo in the Study 1 & 3 trials.
Cannabidiol 10 mg/kg/day	33.89 (13.22, 54.55)	-	Indirect treatment comparison with FFA.
Cannabidiol 20 mg/kg/day	39.58 (22.27, 56.89)	-	
Cannabidiol 15 mg/kg/day	-	26.96	Weighted average LS mean difference between FFA and CBD 10 and 20 mg/kg/day) * (reduction in mean monthly CSF for FFA versus placebo.

Source: Table 3-5, p152 of the submission, Sheet 'model inputs' of the Section 3 workbook.
 CBD = cannabidiol; CSF = convulsive seizure frequency; FFA = fenfluramine; LS = Least Squares.

6.93 The sources used to estimate the treatment effect were reasonable. However, the magnitude of the treatment effect estimated by the indirect comparisons was highly uncertain. The ICER was sensitive to the treatment effect.

6.94 The model applied trial-based utilities by first mapping PedsQL data from the Study 1–3 trials to EQ-5D-Y. A regression equation linked mean monthly CSF to EQ-5D-Y with age (categorical) and baseline stiripentol use as covariates. An example of the regression equation for an individual aged 21 years with mean monthly CSF of 33 and concomitant stiripentol use was provided in the economic model workbook (Table 16).

Table 16: Example conversion of regression results to utility

	Variable	Value when monthly CSF = 33	Value when monthly CSF = 0	Source/method
A	Intercept	0.3978	0.3978	Table 3-6, p155 of the submission
B	Monthly CSF	-0.0029 * 33	-0.0029 * 0	Table 3-6, p155 of the submission * sample input
C	Baseline age ≥ 12	-0.3267	-0.3267	Table 3-6, p155 of the submission
D	Stiripentol use	0.1329	0.1329	Table 3-6, p155 of the submission
E	Term on log odds scale	0.1083	0.1083	= A + B + C + D
D	Utility	0.5270	0.5508	= exp (E)/(1 + EXP (E))

Source: Sheet 'Util' of the Section 3 workbook.
 CSF = convulsive seizure frequency.

6.95 The regression equation was tested during the evaluation to estimate the utility of a 21 year old patient who was seizure-free (0.5508). This appeared low but the evaluation considered may be consistent with a patient experiencing the long-term

quality of life impact of chronic convulsive seizures. The results also suggest that reducing monthly CSF from 33 to 0 makes a difference of 0.02 to the utility value, which appeared small considering the expected quality of life impact of reducing seizure frequency from at least daily to none.

- 6.96 In each model cycle, mean CSF was estimated for each intervention in each cohort based on the proportions in the 'alive on treatment' and 'alive discontinued' health state. In each model cycle, the utility for each intervention in each cohort was re-estimated using the regression equation and the cycle-specific estimate of mean CSF. Linking EQ-5D-Y to CSF added complexity but was reasonable given no utility data were collected in the cannabidiol trials.
- 6.97 The submission estimated treatment costs (weight-based dosing) for fenfluramine, cannabidiol, and stiripentol using the ANZSPED age/weight chart. The submission stated that the proposed pack size for fenfluramine (360 mL of 2.2 mg/mL solution) would accommodate both the recommended titration and weight-based dosing schedules across a heterogeneous patient population. Individuals aged 12 and over receiving fenfluramine without stiripentol (Cohort 2) will use approximately one pack per month. However, for younger children or individuals receiving fenfluramine with stiripentol (Cohort 1), each pack of fenfluramine will last much longer than one month.
- 6.98 The submission assumed that patients receiving fenfluramine in Cohort 1 would receive 0.4 mg/kg/day, with a maximum daily dose of 17 mg. The submission assumed that patients receiving fenfluramine in Cohort 2 would receive 0.7 mg/kg/day, with a maximum daily dose of 26 mg.
- 6.99 The submission assumed an average cannabidiol dose of 15 mg/kg/day. The PBAC previously noted clinical advice that a dose of 10 mg/kg/day or less of cannabidiol was likely to be used in most patients with Dravet Syndrome (para. 11.5, cannabidiol, PSD, addendum to the July 2020 PBAC Minutes). Assuming an average cannabidiol dose of 15 mg/kg/day was inconsistent with previous PBAC advice.
- 6.100 The submission assumed an average stiripentol dose of 50 mg/kg/day. The cost of stiripentol was applied to 100% of patients in Cohort 1 and 0% of the patients in Cohort 2. This was inconsistent with the GWPCARE1 and GWPCARE2 trials, where 42% and 34% of patients were treated with stiripentol, respectively. In Cohort 1, the model applied the cost of stiripentol to all patients, when the effectiveness estimates for cannabidiol included trial participants who did not receive stiripentol. Conversely in Cohort 2, the model assumed no cost for stiripentol, when the effectiveness estimates for cannabidiol included patients who also received stiripentol. This evaluation and ESC considered this was not reasonable.
- 6.101 The cost of medicine (fenfluramine and cannabidiol) was the key cost driver in the model. In Cohort 1 the per cycle cost of cannabidiol with stiripentol was greater than the cost of fenfluramine with stiripentol. In Cohort 2, after 9 years (when patients reach age 19) the per cycle cost of cannabidiol was greater than the cost of fenfluramine. The modelled start age was 9 years and the estimated daily dose of

cannabidiol is 15 mg/kg/day, which means from the first model cycle, patients were treated with a cannabidiol dose that would require more than one bottle per month, which continued to increase as patients became older. The cohort-level ICERs and the weighted ICER were sensitive to changes in the proportion of patients receiving cannabidiol 10 mg/kg/day. The ESC considered the inputs that determined the price of cannabidiol (+/- stiripentol) in the model to be questionable and inconsistent with prior PBAC advice, which likely overestimated its cost.

- 6.102 The model did not consider wastage. Excluding wastage in discontinuing patients underestimated the costs of fenfluramine, cannabidiol, and stiripentol.
- 6.103 The submission base case assumed an effective price for cannabidiol that was [REDACTED] % lower than the published price.
- 6.104 The submission estimated a weighted ICER across Cohorts 1 and 2 by weighting costs and QALYs for each cohort separately (31%:69%), then dividing weighted costs by weighted QALYs.
- 6.105 The submission did not present a stepped evaluation. The stepped economic evaluation presented in Table 17 was prepared during the evaluation.

Table 17: Results of the stepped economic evaluation

Step and component	Cohort 1			Cohort 2			Weighted Increment
	Fenfluramine	Cannabidiol	Increment	Fenfluramine	Cannabidiol	Increment	
Step 1: Trial-based costs and outcomes^a							
Costs (\$)							
mCSF	20.98	33.31	-12.33	16.56	33.31	-16.75	-15.38
Incremental cost/unit reduction in mCSF			\$			\$	\$
Step 2: Convert to LYG^b							
Costs							
LYG	0.2683	0.2683	0	0.2683	0.2683	0	0
Incremental cost/extra LYG gained			Undefined			Undefined	Undefined
Step 3: Time horizon extended to 16 years^c							
Costs (\$)							
LYG	15.3238	15.1585	0.1653	15.4181	15.1585	0.2596	0.2303
Incremental cost/extra LYG gained			Dominant			¹	Dominant
Step 4: Discounting (5%) included^d							
Costs (\$)							
LYG	11.0369	10.9387	0.0982	11.0928	10.9387	0.1541	0.1367
Incremental cost/extra LYG gained			Dominant			²	³
Step 5: Incorporation of medical resource costs							
Costs (\$)							
LYG	11.0369	10.9387	0.0982	11.0928	10.9387	0.1541	0.1367
Incremental cost/extra LYG gained			Dominant			²	⁴
Step 6: Utility weights applied							
Costs (\$)							
QALYs	5.8120	5.7035	0.1085	5.5054	5.3402	0.1652	0.1476
Incremental cost/extra QALY gained (base case)			Dominant			²	⁴

Source: Sheets 'Results', 'Outcomes_Costs', 'Totals_undiscounted' and 'Totals_disc' of the Section 3 workbook.

mCSF = mean convulsive seizure frequency; LYG = Life Years Gained; QALYs = Quality Adjusted Life Years.

^a Cells G10, L10, Q10 and V10, Sheet 'Outcomes_Costs'; L9 of Sheets 'Cohort1_Engine - FFA', 'Cohort1_Engine - CBD', 'Cohorts_Engine - FFA', 'Cohort2_Engine - CBD', and D24, Sheet 'Model inputs' of the Section 3 workbook.

^b Cells G10, L10, Q10 and V10, Sheet 'Outcomes_Costs'; G10, M10, S10, and Y10, Sheet 'Outcomes_Health', and D24, Sheet 'Model inputs' of the Section 3 workbook.

^c Calculated from cells in columns G, L, Q and V, Sheet 'Outcomes_Costs' and cells in row 74, Sheet 'Totals_undiscounted' of the Section 3 workbook.

^d Calculated from cells in row 74, Sheet 'Totals_disc' of the Section 3 workbook. To disaggregate medicine costs from other medical resource use, the formulas in columns E, M, U, and AC of 'Totals_undiscounted' were modified to only reference columns G, L, Q and V, Sheet 'Outcomes_Costs'.

The redacted values correspond to the following ranges:

1 \$155,000 to < \$255,000

2 \$255,000 to < \$355,000

3 \$45,000 to < \$55,000

4 \$15,000 to < \$25,000

6.106 The results in Table 17 were based on the assumed effective price of the comparator (% less than the published price).

Cost per responder analyses

6.107 Noting the advice of the ESC that an alternative, simplified approach to determining an acceptably cost-effective price for fenfluramine may be justified in recognition of the available evidence and clinical need (paragraph 6.80), cost per responder analyses are shown below. These analyses are based on a responder definition of a 50% reduction in convulsive seizure frequency and apply the effective AEMP offered in the

Pre-PBAC Response (AEMP \$ [REDACTED], DPMQ \$ [REDACTED]). Cost per responder scenarios were tested based on trial results from Study 1, Study 2 and Study 3 separately using the median age in each trial and model weights from Australia and New Zealand Society for Paediatric Endocrinology and Diabetes (ANZSPED) growth charts (male/female weighted). The calculated annual fenfluramine treatment costs at these weights and results of the cost per responder analyses are presented below.

Table 18: Treatment cost per patient per year (effective DPMQ)

	Fenfluramine 0.7mg/kg/day Monotherapy	Fenfluramine 0.4mg/kg/day In combination with STIRI (cost not included)
9-year-old, 29 kg	\$ [REDACTED]	\$ [REDACTED]
12-year-old, 42 kg	\$ [REDACTED] ¹	\$ [REDACTED]
16-year-old, 58 kg	\$ [REDACTED]	\$ [REDACTED] ²

¹Same cost per patient from 42 kg

²Same cost per patient from 46 kg

Abbreviations: mg/kg/day = mg per kg (body weight) per day; STIRI = stiripentol; kg = kilogram

Table 19: Cost and clinical outcome ratios: Study 1 – Median age = 8 years

Step and component	Fenfluramine 0.7mg/kg/day Monotherapy	Placebo	Increment
Fenfluramine costs per year	\$ [REDACTED]	\$0	\$ [REDACTED]
Proportion of patients with at least a 50% reduction in monthly CSF ¹	67.5%	12.5%	55.0%
Incremental cost per patient with a 50% or greater reduction in convulsive seizures over 14 weeks (14-week cost/0.55)			\$ [REDACTED]

¹Trial period = 2-week titration + 12-week maintenance period = 14 weeks in total

ANZSPED growth chart (weighted) weight of 26 kg used

Abbreviations: mg/kg/day = mg per kg (body weight) per day, CSF = convulsive seizure frequency

Table 20: Cost and clinical outcome ratios: Study 3 – Median age = 9 years

Step and component	Fenfluramine 0.7mg/kg/day Monotherapy	Placebo	Increment
Fenfluramine costs per year	\$ [REDACTED]	\$0	\$ [REDACTED]
Proportion of patients with at least a 50% reduction in monthly CSF ¹	72.9%	6.3%	66.6%
Incremental cost per patient with a 50% or greater reduction in convulsive seizures over 14 weeks (14-week cost/0.666)			\$ [REDACTED]

ANZSPED growth chart (weighted) weight of 29 kg used

Abbreviations: mg/kg/day = mg per kg (body weight) per day, CSF = convulsive seizure frequency

Table 21: Cost and clinical outcome ratios: Study 2 – Median age = 9 years

Step and component	Fenfluramine 0.4mg/kg/day +STIRI (cost not included)	Placebo +STIRI (cost not included)	Increment
Fenfluramine costs per year	\$ [REDACTED]	\$0	\$ [REDACTED]
Proportion of patients with at least a 50% reduction in monthly CSF ¹	53.5%	4.5%	49.0%
Incremental cost per patient with a 50% or greater reduction in convulsive seizures over 15 weeks (15-week cost/0.49)			\$ [REDACTED]

ANZSPED growth chart (weighted) weight of 29 kg used

Abbreviations: mg/kg/day = mg per kg (body weight) per day, CSF = convulsive seizure frequency

6.108 The PBAC noted previous decisions it had made using an incremental cost per responder analysis (Table 10, osildrostat PSD, March 2024 PBAC meeting).

Drug cost/patient/year

6.109 The cost per patient per year based on the Pre-PBAC Response price at three different age/weight scenarios for both fenfluramine dose options (assuming 100% compliance) are detailed in Table 19 above.

Estimated PBS usage & financial implications

6.110 This submission was considered by DUSC.

6.111 The submission used a market share approach to predict the financial impact of including fenfluramine on the PBS as an add-on therapy for patients with Dravet Syndrome who are not adequately controlled with at least 2 other AEDs. A supplementary epidemiological component of the analysis was included for < 500 patients to be included under a grandfathering restriction, who were already receiving fenfluramine for Dravet Syndrome by 31 December 2023 and will transition to PBS supply when listing occurs. The submission stated that patients who commenced treatment with fenfluramine for Dravet Syndrome on or after 1 January 2024 were captured in the market share analysis. The evaluation considered this was reasonable, given the market share approach was estimated using 2023 data for cannabidiol and stiripentol and the proposed grandfathered population would not be counted in those data.

6.112 The submission assumed uptake from stiripentol of ██████% in Year 1, increasing to ██████% in Year 6.

6.113 The evaluation and DUSC were concerned the submission did not consider whether fenfluramine would grow the market for Dravet Syndrome by being used as an add-on therapy to cannabidiol and/or stiripentol. The DUSC further considered this was inappropriate given combination therapy was not precluded by the proposed restriction.

6.114 Table 22 presents key inputs for the financial estimates.

Table 22: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Scripts in the current market (cannabidiol and stiripentol)	2,548, based on PBS item reports for cannabidiol (12467E) and stiripentol (12088F, 12103B, 12106E, 12107F) in calendar year 2023.	This was reasonable.
Proportion of patients receiving combination therapy with cannabidiol and stiripentol	31%, based on PBS utilisation data provided by the Department of Health	This was reasonable.
Market growth	20% in Year 1, 15% in Year 2, 10% in Year 3 and 5% thereafter, based on historical data, expert opinion, internal market research and commercial forecasts.	Assumption
Uptake rate from cannabidiol	█% in Year 1, increasing to █% in Year 6, based on historical data, expert opinion, internal market research and commercial forecasts.	Assumption
Uptake rate from stiripentol	█% in Year 1, increasing to █% in Year 6, based on historical data, expert opinion, internal market research and commercial forecasts.	Assumption
Patient age distribution	Estimated as a skewed pyramid with a mean of approx. 9 years. Local demographic data, current utilisation of stiripentol, the average age of patients in the RCTs, local expert opinion and broader clinical literature.	The mean age in the fenfluramine trials was approximately 9 years. Local demographic data, expert opinion and broader literature were not cited to support this claim. The DUSC noted that the trial only included patients aged 2 to 18 years old, but there was no age limit included in the proposed PBS restriction.
Stiripentol dose	35 mg/kg/day, assumed halfway between recommended minimum and maximum dose.	
Script equivalence	vs CBD: 0.464, vs STP 250 mg: 0.758, vs STP 500 mg: 1.285. Calculated using assumed distribution of ages from 2 to 25, weight-based dosing, 50%:50% distribution of CBD doses, and 31% receiving FFA with STP.	The financial estimates were sensitive to the script equivalence estimate for cannabidiol.
Fenfluramine discontinuation	5% per annum, based on an assumption.	
Fenfluramine monitoring	\$34.40 based on MBS item 11707 (electrocardiogram).	The MBS fee for item 11707 is \$20.95, not \$34.40. The evaluation considered MBS item 55133 (echocardiogram, \$232.80) is more appropriate.

Source: Tables 4-1, 4-5, 4-6, 4-7, pp171, 173-175 of the submission, pp 159, 172 & 174 of the submission.

CBD = cannabidiol; FFA = fenfluramine; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; STP = stiripentol.

6.115 The submission estimated the prevalent treated population as < 500 patients (█ + █). The DUSC noted PBS utilisation data indicated < 500 was the correct number of prevalent patients being treated with cannabidiol and/or stiripentol.

6.116 Table 23 presents the estimated financial implications for the PBS listing of fenfluramine as treatment for Dravet Syndrome based on the proposed effective price for fenfluramine from the submission and the assumed effective price for cannabidiol.

Table 23: Estimated use and financial implications – proposed effective price for fenfluramine and assumed effective price for cannabidiol (submission estimates)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of grandfathered patients treated ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total Number of scripts dispensed (substitution plus grandfathered patients) ^b	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of fenfluramine						
Cost to PBS/RPBS less copayments	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Estimated financial implications for cannabidiol and stiripentol						
Cost to PBS/RPBS less copayments ^b	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net financial implications						
Net cost to PBS/RPBS ^c	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to MBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to Australian Government ^b	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³

Source: Tables 4-8, 4-9, 4-10 & 4-12, pp176, 177 & 179 of the submission; Sheet '2c. Patients – GF' of the Section 4 workbook. Italicised text (net cost to PBS/RPBS and Australian Government using proposed effective price for fenfluramine, assumed effective for cannabidiol, and published price for stiripentol in July 2024 added during the evaluation).

DPMQ = Dispensed Price for Maximum Quantity; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a The submission proposed that < 500 patients would be eligible for the grandfathering restriction, and of these 5% would discontinue treatment, leaving < 500 patients to be treated under the PBS grandfathering restriction in Year 1 (2024).

^b Assuming 7.71 scripts per year for grandfathered patients, script substitution from cannabidiol = 0.464, stiripentol 250 mg = 0.758, and stiripentol 500 mg = 1.285.

^c The submission applied DPMQs from June 2024. Applying July 2024 DPMQs had minimal impact on the financial estimates.

The redacted values correspond to the following ranges:

1 < 500

2 500 to < 5,000

3 \$0 to < \$10 million

4 net cost saving

6.117 The total cost to the PBS/RPBS of listing fenfluramine at the price proposed in the submission was estimated to be \$0 to < \$10 million in Year 6, and a total of \$10 million to < \$20 million in the first 6 years of listing when the assumed effective price of cannabidiol was used.

6.118 The DUSC considered use by adult patients may have been underestimated, as an analysis of PBS prescriptions for Dravet syndrome suggested the mean age of treated patients was 16 and the median was 14.

6.119 The Pre-PBAC Response acknowledged the advice of the DUSC, however argued that while higher than expected use in adults may increase the use of fenfluramine, it also means the use of stiripentol and cannabidiol were likely underestimated, as there is no maximum daily dose for these agents with increasing weight. Furthermore, the Response acknowledged that whilst some combination use of fenfluramine and cannabidiol (in any combination) may occur in practice, the lack of available evidence is likely to limit such use, and argued any use in this manner would likely be offset by

lower estimated costs given the DUSC advice the prevalent treated population was smaller than estimated by the submission.

Quality Use of Medicines

6.120 The submission did not present a quality use of medicines section. Dosing of liquid medicines can be challenging, and educational materials for patients and caregivers regarding measuring and administering these medicines (i.e., working in mL, using a dose adaptor and supplied syringes) would be beneficial.

6.121 The DUSC considered educational materials for patients and caregivers regarding the measurement and administration of fenfluramine would be beneficial. The Pre-PBAC Response stated the consumer medicines information (CMI) documentation for fenfluramine will include instructions on the measurement and administration for patients.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule, Authority Required (telephone/online) listing of fenfluramine for the treatment of seizures associated with Dravet Syndrome, to be used in combination with at least two other anti-epileptic drugs (AEDs). In making this recommendation, the PBAC recognised the high unmet clinical need for effective therapies for this refractory and severe form of epilepsy. The PBAC considered the available evidence supported a conclusion that fenfluramine is an effective therapy for the treatment of Dravet Syndrome and was satisfied that fenfluramine provides, for some patients, a significant improvement in efficacy over cannabidiol. The PBAC considered fenfluramine would be acceptably cost-effective at the price proposed in the Pre-PBAC Response.

7.2 The Committee considered there remained a high and unmet clinical need for additional effective therapies for Dravet Syndrome. The PBAC acknowledged Dravet Syndrome was a rare and severe developmental and epileptic encephalopathy which manifests through frequent, severe seizures, as well as cognitive and physical developmental delays and regression, which has a considerable impact on patients, parents, families and caregivers. The Committee welcomed the input from individuals, parents and caregivers that discussed the life-altering impact of Dravet Syndrome and the substantial improvements in terms of seizure symptoms, cognitive and physical ability and quality of life that fenfluramine had provided for those who had accessed it either through clinical trials or compassionate access programs (discussed further in 'Consumer Comments'). The PBAC also acknowledged that Dravet Syndrome is associated with a significant risk of sudden unexpected death in epilepsy (SUDEP) which is commonly associated with major seizures, therefore a reduced seizure burden may reduce the risk of SUDEP events when treated with a more efficacious therapy, but such a benefit was difficult to quantify.

- 7.3 The PBAC considered the listing should be aligned with that of stiripentol and cannabidiol, with no restrictions on potential combination use or patient age. The PBAC noted patients with Dravet Syndrome were typically managed by a small number of expert neurologists and the PBS listings require a neurologist to initiate treatment, therefore the risk of inappropriate polypharmacy was low. Given the maximum daily dose of fenfluramine resulted in no more than 1 bottle per month being required, the PBAC considered it was appropriate for standard 'no increases' clauses to maximum quantities or repeats to be included in the listing. The PBAC considered it was appropriate to include an administrative advice regarding the need for ongoing cardiac function testing as outlined in the Product Information whilst being treated with fenfluramine.
- 7.4 The Committee considered the proposed clinical place as a third (or later) line therapy after patients had not responded to two or more prior AEDs, similar to stiripentol and cannabidiol, was reasonable.
- 7.5 The PBAC considered the nominated comparator of cannabidiol was reasonable, however considered stiripentol was also a reasonable comparator.
- 7.6 The PBAC noted the clinical evidence for fenfluramine was based on three randomised controlled trials (RCTs) (Study 1, Study 2 and Study 3) comparing fenfluramine to placebo (as add-on to background therapy), with Study 1 and Study 3 requiring no concomitant stiripentol (assessing the 0.7 mg/kg/day dose), and Study 2 assessing fenfluramine (at the 0.4 mg/kg/day dose) added onto a background regimen containing stiripentol. The Committee noted the clinical evidence for cannabidiol (GWPCARE1 and 2) and stiripentol (STICLO France and STICLO Italy) had previously been used to support the PBAC submissions for these agents. The PBAC noted that for the comparison of fenfluramine and cannabidiol, there were exchangeability issues that created uncertainty with the indirect treatment comparisons, including different composition of background AEDs (particularly with respect to proportion of stiripentol use), different definitions of convulsive seizures, and different statistical approaches. Furthermore, the Committee noted additional issues for the comparison of fenfluramine and stiripentol, including differences in trial eligibility criteria, treatment settings, the range of available AEDs at time of study (as the stiripentol trials were older) and differences in outcome measures and timepoints and length of follow-up. Given these additional transitivity issues, the PBAC formed the view that the indirect treatment comparisons of fenfluramine and stiripentol were unlikely to be reliable for assessing the comparative effectiveness and safety of these therapies or for determining the magnitude of any clinical benefit.
- 7.7 With respect to the effectiveness of fenfluramine, the PBAC noted the pooled results of Study 1 and Study 3 (fenfluramine monotherapy) found patients treated with fenfluramine were statistically more likely to achieve a 50% or more reduction from baseline monthly CSF (50% CSF) for both relative and absolute statistics compared to placebo (RR 7.28 (95% CI 3.49, 15.19), RD 0.62 (95% CI 0.51, 0.73)), with a similarly statistically significant result from Study 2 for fenfluramine + stiripentol compared to

placebo + stiripentol (RR 11.77 (95% CI 2.95, 46.89), RD 0.49 (95% CI 0.33, 0.65)). The Committee also noted statistically significant results across Studies 1–3 for fenfluramine (+/- stiripentol) over placebo (+/- stiripentol) in terms of reducing the number of seizures over 28 days compared to baseline. On that basis, the PBAC considered the evidence supported a conclusion that fenfluramine is an effective therapy for the treatment of Dravet Syndrome.

- 7.8 When considering the comparative effectiveness of fenfluramine and cannabidiol, the PBAC noted the results of the indirect treatment comparisons (ITCs) were statistically in favour of fenfluramine (both +/- stiripentol) over both cannabidiol 10 mg/kg/day and 20 mg/kg/day, with similar results against each of these cannabidiol doses for the comparison of 50% CSF, with some comparisons for 25% CSF and 75% CSF favouring fenfluramine (but none statistically significantly favouring cannabidiol, see Table 9). The PBAC noted fenfluramine (both +/- stiripentol) also achieved a statistically significant result over cannabidiol (10 and 20 mg/kg/day) in terms of percentage change in monthly CSF from baseline (see Table 9). Whilst there were uncertainties with the indirect treatment comparisons, the PBAC considered the available evidence supported a conclusion that fenfluramine is likely to be superior to cannabidiol in terms of achieving a 50% reduction in CSF and percentage change in number of CSF from baseline.
- 7.9 With regards to comparative safety, the PBAC noted the submission described fenfluramine as having 'similar' safety to cannabidiol. The PBAC noted the available evidence was difficult to assess in comparative terms for fenfluramine vs. cannabidiol, however considered the safety profiles of these agents are different (see Table 11) but could not be considered superior (or inferior) to another. The PBAC considered it was not possible to draw meaningful conclusions regarding the comparative effectiveness and safety of fenfluramine and stiripentol, as there were substantial transitivity issues with the available evidence that precluded a robust comparison of these therapies. The PBAC noted long-term data with respect to cardiac outcomes such as pulmonary hypertension and valvular heart disease was not available at the time of consideration and considered that given the known safety profile of fenfluramine from historical use (at higher doses), this risk continued to be a relevant consideration.
- 7.10 The PBAC agreed with the ESC and considered the economic model provided in the submission, which used a weighted ICER approach based on cohorts that either included or excluded use of stiripentol, to be unreliable for decision-making (discussed further in paragraphs 6.77 - 6.80). The PBAC considered a simpler approach to assessing the cost-effectiveness of fenfluramine was justified. The PBAC considered that this was appropriate given the clinical need and the available evidence supporting a conclusion of superior comparative effectiveness compared to cannabidiol. The Committee considered it may be reasonable to consider a cost per responder approach (defined as a 50% reduction in CSF from baseline). The PBAC noted the results of the cost per responder analyses (Table 19 - Table 21) based on the populations of the three fenfluramine trials and considered that given the clinical and

quality of life benefit associated with a 50% reduction in CSF, that fenfluramine likely represented a cost-effective therapy at the price proposed in the Pre-PBAC Response, noting the small, well-defined population, the clinical need and additional benefit to patients likely to be realised over cannabidiol.

- 7.11 The PBAC considered that, on balance, and noting the small, well-defined population, the fenfluramine utilisation estimates provided in the submission were reasonable. The PBAC noted the financial implications of listing fenfluramine will need to be updated to include the price proposed in the pre-PBAC response. The PBAC noted the cost-offsets for stiripentol and cannabidiol were unlikely to be fully realised as fenfluramine may be used in combination with, or displace, these therapies.
- 7.12 The PBAC advised fenfluramine should not be treated as interchangeable with any other drugs.
- 7.13 The PBAC advised that fenfluramine is not suitable for prescribing by nurse practitioners.
- 7.14 The PBAC advised the Early Supply Rule should not apply to fenfluramine as it is an oral liquid formulation.
- 7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for fenfluramine:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over cannabidiol, based on the results of the ITCs suggesting a statistically significantly higher chance of achieving a 50% reduction in CSF and an improved reduction in monthly seizures from baseline.
 - b) The treatment is expected to address a high and urgent unmet clinical need because Dravet Syndrome is a rare and severe epileptic encephalopathy and current treatments typically have limited effectiveness and many patients do not respond to currently available treatments.
 - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FENFLURAMINE					
fenfluramine hydrochloride 2.2 mg/mL oral liquid, 360 mL	NEW	1	1	5	Fintepla
Restriction Summary variant of 11681 [+GF] / Treatment of Concept: variant of 11681 [+GF]					
Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment)					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Severity: Severe					
Condition: Myoclonic epilepsy in infancy (Dravet syndrome)					
Indication: Severe myoclonic epilepsy in infancy (Dravet syndrome)					
Treatment Phase:					
Clinical criteria:					
Patient must have (if initiating) generalised tonic-clonic seizures ore generalised clonic seizures that are not adequately controlled with at least two other anti-epileptic drugs; or					
Patient must have had (if continuing) generalised tonic-clonic seizures ore generalised clonic seizures that are not adequately controlled with at least two other anti-epileptic drugs.					
AND					
Clinical criteria:					
The treatment must be as adjunctive therapy to at least two other anti-epileptic drugs					
AND					
Treatment criteria:					
Must be treated by a neurologist if treatment is being initiated; OR Must be treated by a neurologist if treatment is being continued or re-initiated; OR Must be treated by a paediatrician in consultation with a neurologist if treatment is being continued; OR Must be treated by a general practitioner in consultation with a neurologist if treatment is being continued					
Administrative Advice: Cardiac monitoring must be carried out in accordance with the approved Product Information while on treatment with this drug for this condition.					

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in

relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.