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

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule, Authority Required listing for fenfluramine (FEN) for the treatment of patients with Lennox-Gastaut Syndrome (LGS) who are not adequately controlled with at least two other antiseizure medications (ASMs).

1.2 Listing was requested on the basis of a cost-minimisation approach versus cannabidiol (CBD).

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

Component	Description
Population	Patients with LGS not adequately controlled despite treatment with at least two other ASMs
Intervention	Fenfluramine 2.2mg/mL oral solution Phase: Dose First week: 0.2 mg/kg/day (0.1 mg/kg twice daily) Second week: 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 (as tolerated): 26 mg daily (13 mg twice daily)
Comparator	Cannabidiol 100 mg/mL oral solution: titrated to a maintenance dose of up to 20 mg/kg/day
Outcomes	Drop 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	Similar and noninferior efficacy Different but noninferior safety Economic claim: cost minimisation Financial claim: Small incremental budget impact

Source: Table 1.1, p13 of the submission. LGS= Lennox-Gastaut syndrome; ASMs = antiseizure medications.

2 Background

Registration status

2.1 Fenfluramine was TGA registered on 28 November 2024 as add-on therapy in the treatment of seizures associated with Dravet syndrome (DS) and LGS in patients 2 years of age and older.

Previous PBAC consideration

2.2 Fenfluramine was recommended by the PBAC for the treatment of DS in November 2024 and was listed for that indication on 1 May 2025.

2.3 The PBAC recommended cannabidiol for LGS in September 2022 for use in patients who satisfied both clinical and electroencephalogram (EEG) criteria for LGS, who have not achieved adequate seizure control with at least two other ASMs, who are taking at least two other ASMs, and who are under the care of, or being cared for in consultation with a neurologist or paediatric neurologist. Listing occurred on 1 June 2023.

2.4 At its meeting in July 2025 the PBAC recommended amending the restriction level of cannabidiol[1] for the treatment of seizures associated with LGS from Authority Required (Telephone/online PBS Authorities system) to Authority Required (STREAMLINED). The PBAC also recommended amendments to the current PBS criteria for cannabidiol to improve access for patients with LGS. These include easing the requirement for an EEG to confirm diagnosis, removing specific EEG features, seizure frequency and type, and reducing the number of concomitant ASMs required. The PBAC further supported allowing prescribing by a paediatrician for both initial and continuing treatment.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

[1] https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2025-07/cannabidiol-epidyolex-psd-july-2025

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
FENFLURAMINE					
Fenfluramine, 2.2 mg/mL oral solution, 360 mL.	$4,637.44 published price $[redacted] effective price	1	1	5	Fintepla

Category / Program: General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
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: Special Pricing Arrangements apply
Indication: Seizures of the Lennox-Gastaut Syndrome
Clinical criteria:
~~Patient must have a diagnosis of Lennox-Gastaut syndrome confirmed by an electroencephalogram (EEG) that showed a pattern of slow (less than 3.0 hertz) spike-and-wave discharges with generalised paroxysmal fast activity (sleep recording should be obtained where it is possible)~~ *Patient must have a diagnosis of Lennox-Gastaut syndrome. The diagnosis should be confirmed by an electroencephalogram (EEG) where possible.*

AND
Clinical criteria:
Patient must have (as an initiating patient)/have had (as a continuing patient) more than one type of ~~generalised~~ seizures *that are not adequately controlled with at least two other antiseizure medication prior to initiating treatment with this medicine*
~~AND~~
~~Clinical criteria~~
~~Patient must have had at least two drop seizures (atonic, tonic or tonic-clonic) per week that are not adequately controlled with at least two other anti-epileptic drugs prior to initiating treatment with this medicine~~
AND
Clinical criteria
The treatment must be as adjunctive therapy to ~~at least two~~ other ~~anti-epileptic drugs~~ *antiseizure medication*
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;~~
OR
Must be treated by a prescriber who is either (i) a neurologist, (ii) a paediatrician if treatment is being initiated; or
OR
Must be treated by a prescriber who is either (i) a neurologist, (ii) a paediatrician if treatment is being continued or re-initiated; or
OR
Must be treated by a general practitioner in consultation with either (i) a neurologist, (ii) a paediatrician if treatment is being continued
OR
Must be treated by a registered nurse in partnership with an authorised health practitioner under a clinical governance framework and an active prescribing agreement if treatment is being continued.
~~**Administrative Advice:** Tonic seizures must have been recorded on video-EEG or have been clearly observed and reported by a witness.~~
Administrative Advice: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
Administrative Advice: Cardiac monitoring must be carried out in accordance with the approved Product Information while on treatment with this drug for this condition.

3.2 The proposed restriction provided in the submission was the same as the PBS restriction for cannabidiol for LGS prior to the July 2025 PBAC meeting, with the additional requirement for cardiac monitoring, consistent with the current PBS listing for fenfluramine in DS. The revised listing proposed by the Secretariat (above) was aligned with the PBAC recommended listing for CBD in July 2025. The Pre-Sub-Committee Response (PSCR) accepted updating the restriction to be consistent with the cannabidiol changes recommended by the PBAC at its July 2025 meeting.

3.3 The submission proposed a Special Pricing Arrangement (SPA) for fenfluramine for LGS; the product currently has a SPA for its listing for DS. The published price proposed

in the submission was the same as the current published price for DS. The submission stated that following a positive recommendation to list fenfluramine for LGS patients, once the effective price for cannabidiol was revealed, the sponsor would propose an effective price for fenfluramine to ensure that the cost minimisation approach would be realised.

3.4 At its July 2025 meeting, the PBAC recommended amending the restriction level of cannabidiol for LGS from Authority Required (telephone/online PBS Authorities system) to Authority Required (STREAMLINED) (paragraph 5.1, cannabidiol Public Summary Document [PSD], July 2025 PBAC meeting).

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

4 Population and disease

4.1 Lennox-Gastaut Syndrome is a lifelong condition characterised by childhood onset of multiple types of epileptic seizures, treatment-resistance of seizures, and intellectual disability. Mortality is increased and impacts on quality of life and parent/caregiver burden are severe. Most patients require multiple ASMs, and changes of treatment because of intolerance or lack of efficacy are common.

4.2 The proposed treatment algorithm positioned FEN as an alternative to CBD as third-line treatment in patients whose seizures are inadequately controlled on at least two of valproate, lamotrigine and topiramate, or as fourth-line treatment in addition to CBD and two other drugs.

4.3 Fenfluramine and its metabolite norfenfluramine are agonists at serotonin (5-HT) receptors, which enhances GABAergic neurotransmission, and inhibit 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 CBD was nominated as the main comparator. The submission justified this in terms of the proposed restriction and proposed treatment algorithm, which position FEN and CBD as alternative third-line treatments in patients who have received at least two other ASMs.

5.2 The PBS-listed ASMs commonly used for LGS, other than cannabidiol, are valproate, topiramate and lamotrigine. Valproate is not restricted by type of epilepsy and there is no requirement for prior use of other treatments. Lamotrigine is not restricted as to type of epilepsy, but "[t]he condition must have failed to be controlled satisfactorily by other anti-epileptic drugs" (or the patient must be a woman of child-bearing potential). Topiramate is PBS-listed for LGS and "[t]he condition must have failed to be controlled satisfactorily by other anti-epileptic drugs". Clobazam and rufinamide are not PBS-listed but are included in treatment guidelines for LGS as first- or second-line options.

5.3 The submission conceded that any of valproate, topiramate and lamotrigine could be comparators, but that "given the limitations of the available evidence base, as previously recognised by PBAC, (Cannabidiol PSD, March 2022), it was considered unlikely that clinical comparisons would be either technically feasible or particularly informative for PBAC decision making".

5.4 The PSCR reiterated the submission had acknowledged other treatments could be considered comparators, however argued the same limitations that applied to the consideration of CBD (noted in paragraph 5.3) apply for FEN, thus, it is unlikely clinical comparisons to other treatment options would either be technically feasible or informative to the current decision context. The ESC considered other therapies could be considered comparators, but agreed with the PSCR that comparisons to these would likely be uninformative and was satisfied that CBD is the most appropriate comparator.

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 the severity of LGS, impact on patients, and highlighted that response to different treatments and combinations was individualised, and there was a clinical need for new and effective therapies to help some patients achieve better control of their condition.

Consumer inputs

6.2 The PBAC noted and welcomed the input from health care professionals (5), medical organisation the National Paediatric Medicines Forum (NPMF) and consumer organisations Epilepsy Action Australia and SCN2A Australia.

6.3 The input from health care professionals described LGS as a severe, treatment-resistant form of epilepsy with significant risks including intellectual disability, frequent and dangerous seizures that often cause injury, and sudden unexpected death in epilepsy (SUDEP) with a devastating impact on quality of life for patients, parents and caregivers, and stated FEN showed promise as an important new addition in a limited treatment landscape, with risk of side effects that are generally manageable with appropriate clinical oversight.

6.4 Input from the NPMF stated that FEN would be beneficial to all relevant paediatric patients with LGS, as these patients are often medication resistant and in need of further treatment options to manage their condition.

6.5 Input from Epilepsy Action Australia noted the severity of LGS and the physical, social and financial impact on patients, parents and families and highlighted the clinical need for new and effective therapies. The input discussed the results of the pivotal FEN trial, which included some Australian patients, and the reduction in tonic and atonic

seizures experienced by patients treated with FEN.

6.6 Input from SCN2A Australia discussed the burden of LGS, including frequent dangerous seizures and injury, the impact on schooling and community participating and the impact on carers. The input also discussed the current management of LGS and the potential benefits of FEN including improved symptom control and life stability, simplified administration compared to some treatments, and reduced disruption on daily life and reduced burden on caregivers.

Clinical trials

6.7 The submission was based on one trial comparing two doses of FEN to placebo (Study 1601, N = 263). Study 1601 included a randomised, double-blind phase (Part 1) and an open-label extension phase (Part 2). Subjects were enrolled in North America, Europe, Australia and Japan. Because enrolment was more rapid than expected, a protocol amendment increased the total sample size, separated patients from sites in Europe, North America and Australia (Cohort A) from patients from sites in Japan (Cohort B), and specified that Cohorts A and B were to be analysed separately. Only data from Cohort A were presented in the submission.

6.8 Results from Cohort B (N = 33) were reviewed during the evaluation. Differences between placebo, FEN 0.2 mg/kg/day and FEN 0.7 mg/kg/day were broadly similar to those of Cohort A, both in regard to efficacy and safety, although differences that were statistically significant in Cohort A were not statistically significant in Cohort B because of the small sample size.

6.9 The submission presented an indirect treatment comparison (ITC) of FEN 0.7 mg/kg/day vs CBD 10 mg/kg/day and 20 mg/kg/day, using two placebo-controlled trials of CBD (GWPCARE 3 and 4). These CBD trials have been previously considered by PBAC in its consideration of CBD for LGS.

6.10 The submission stated that no ITC of CBD vs FEN 0.2 mg/kg/day was presented "as this is not a TGA recommended maintenance dose". However, there is no "recommended" maintenance dose in the PI, only a starting dose and a maximum.

6.11 Study 1601 was designed using results from a small (N = 13) Phase 2, open-label, dose-finding study, S58545 (NCT02655198) of FEN in treatment-refractory LGS. The submission presented results from this study as supportive data.

6.12 Numerous systematic reviews and meta-analyses were identified, which the submission stated were considered to show " general consistency of data sources, results and conclusions with the present clinical evaluation"; results were not presented in the submission.

6.13 Details of the trials relied on in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study 1601, Part 1 NCT03355209	A Randomized, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults with LGS. Part 1, Cohort A: 11 September 2021 Knupp, KG, et al. Efficacy and safety of fenfluramine for the treatment of seizures associated with Lennox-Gastaut Syndrome: a randomized clinical trial.	JAMA, 2022; 79:554–564.
Study 1601, Part 2 NCT03355209	An open-label, flexible-dose extension for patients who completed Part 1 that will assess long-term safety of ZX008 (Fenfluramine Hydrochloride) in Children and Adults with LGS. Part 2, Cohort A: 14 September 20211 Knupp, KG, et al. Efficacy and safety of fenfluramine for the treatment of seizures associated with Lennox-Gastaut Syndrome: a randomized clinical trial.	JAMA, 2022; 79:554–564.
S58545 NCT02655198	Add-on therapy with low dose Fenfluramine in Lennox Gastaut Epilepsy (FEN-LGS). Lagae L, Schoonjans AS, Gammaitoni AR, Galer BS, Ceulemans B. A pilot, open-label study of the effectiveness and tolerability of low-dose ZX008 (fenfluramine HCl) in Lennox-Gastaut syndrome.	*Epilepsia* 2018; 59:1881-1888.
GWPCARE3 NCT02224560	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome.	*N Engl J Med* 2018; 378:1888-1897
GWPCARE4 NCT02224690	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial.	*Lancet* 2018; http://dx.doi.org/10.1016/S0140-6736(18)30136-3
GWPCARE5 NCT02224573	An Open Label Extension Study of Cannabidiol (GWP42003-P) in Children and Adults With Dravet or Lennox-Gastaut Syndromes (GWPCARE5) Patel AD, Mazurkiewicz-Beldzinska M, Chin RF, et al. Long- term safety and efficacy of add-on cannabidiol in patients with Lennox–Gastaut syndrome: Results of a long- term open- label extension trial.	*Epilepsia* 2021; 62:2228–39.

Source: Table 2-2, p41 of the submission.

6.14 The key features of the included trials are summarised in Table 3.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Fenfluramine vs placebo					
Study 1601, Part 1	263	R, DB, MC; randomised 1:1:1 to placebo (N = 87), FEN 0.2 mg/kg/day (N = 89) or FEN 0.7 mg/kg/day (N = 87); 4 week baseline, 2 week titration period (T), 12 week maintenance period (M)	Low	Age 2-35 years; LGS by EEG and clinical criteria with recent drop seizures despite 1-4 ASMs at stable dose	Primary: Median % CFB in DSF over T+M; Key Secondary: % subjects with ≥50% reduction in DSF over T+M
Study 1601, Part 2 = OLE	247	OL, 2 week transition to FEN 0.2 mg/kg/day, then 1 month at 0.2 mg/kg/day with no change to other ASMs, then 4 months with FEN titrated to effect and tolerability up to 0.7 mg/kg/day or 26 mg/day with other ASMs stable, then 6 months with dose reduction or discontinuation of other ASMs (at least one other had to be continued), then follow-up with FEN discontinued.	Unclear	Patients completing Part 1	Safety, especially valve disease and pulmonary hypertension; DSF was a secondary outcome.
Cannabidiol vs placebo					
GWPCARE3	252	R, DB, MC; randomised 1:1:1 to placebo (N = 76) or CBD 10 mg/kg/day (N = 73) or 20 mg/kg/day (N = 76); 4 week baseline, 2 week dose titration (T), 12 week maintenance (M).	Low	Age 2-55 years; diagnosis of LGS including typical EEG with recent drop seizures; at least *one* failed ASM and taking one or more ASMs at stable dose.	Primary: Mean % CFB in DSF over M Secondary: Patients with ≥25%, ≥50%, ≥75% reduction in DSF
GWPCARE4	171	R, DB, MC; randomised 1:1 to placebo (N = 85) or CBD 20 mg/kg/day (N = 86); 4 week baseline, 2 week dose titration (T), 12 week maintenance (M).	Low	Age 2-55 years; diagnosis of LGS including typical EEG with recent drop seizures; at least *two* failed ASMs *including* prior and current treatment, taking one to four ASMs at stable dose.	Primary: Mean % CFB in DSF over T+M; Secondary: Patients with ≥25%, ≥50%, ≥75% reduction in DSF
GWPCARE5	366	OLE; CBD 20 mg/kg/day; dose of CBD or other ASMs could be reduced and dose of CBD could be increased to 30 mg/kg/day; mean duration 826 days, median 1090 days.	Unclear	Completion of GWPCARE 3 or 4.	DSF events per 28 days for 12 week periods.

Source: Study 1601 Part 1 CSR, pp3-5; Study 1601 Part 2 CSR, pp2-5. ASM = antiseizure medication; CBD = cannabidiol; CFB = change from baseline; DB = double blind; DSF = drop seizure frequency; EEG = electro-encephalogram; FEN = fenfluramine; LGS = Lennox-Gastaut Syndrome; MC = multi-centre; OLE = open label extension; R = randomised.

6.15 Subjects without a diagnosis of LGS could be enrolled in Study 1601 if they met the study's diagnostic criteria; this is important because although patients had to have been treated with at least one ASM it did not have to be an ASM recommended for

LGS.[2] Patients had to have at least 4 seizures in both the first two weeks and second two weeks of the baseline period. The PSCR argued that the requirement for patients without a formal diagnosis of LGS to meet all other diagnostic criteria was likely more stringent than for patients recruited through a confirmed LGS diagnosis.

6.16 In all studies drop seizures were defined as seizures considered to typically result in drops (falling, slumping in a chair, or hitting the head on a surface) and adjudicated as causing drops for an individual patient by the Epilepsy Study Consortium (https://epilepsyconsortium.org/). Drop seizures were chosen as the primary outcome because they are an important cause of morbidity and because they can be counted reliably.

6.17 In all studies drop seizure frequency (DSF) per 28 days was calculated by adding all seizures recorded in seizure diaries for the relevant period, dividing the number by the number of days with non-missing data, and multiplying by 28. Although the submission stated that there was no imputation of missing data for efficacy outcomes in Study 1601, this procedure is equivalent to assuming the average frequency of seizures on days with missing data.

6.18 Concomitant ASM treatment could not be changed during the study, except that a reduction of dose to manage adverse events was allowed.

Comparative effectiveness

Fenfluramine

6.19 Efficacy outcomes in Study 1601 Part 1 are shown in Table 4, with change in drop seizure frequency from baseline presented in Figure 1.

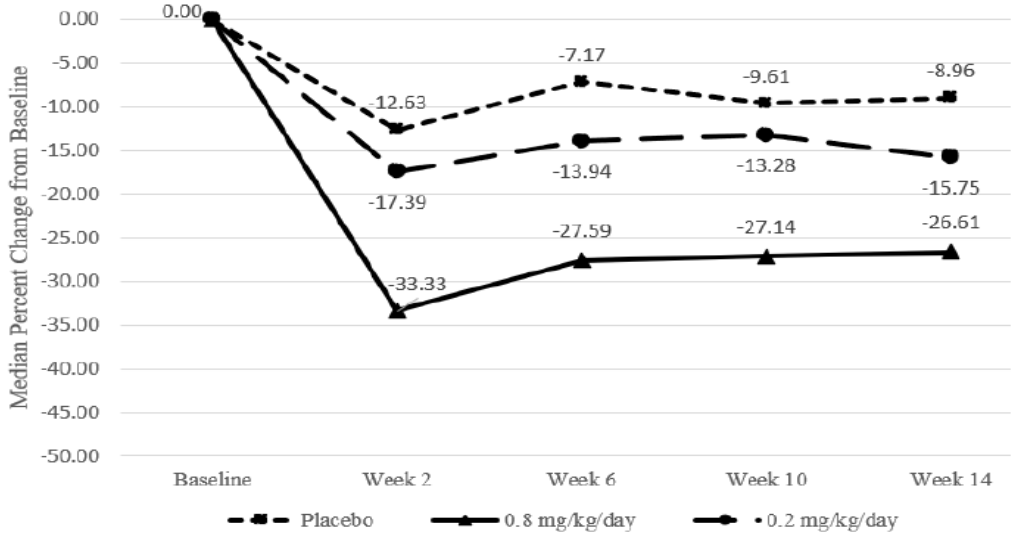
[2] In Study 1601 64/261 patients (24.5%) had received carbamazepine and 40/261 (15.3%) had received phenytoin, which guidelines recommend should be avoided because they can worsen drop seizures (Study 1601 Part 1 CSR, Table 14.1.4.3.1 and Figures 1-9, p28 and 1-10, p30 of the submission).

Table 4: Efficacy Outcomes in Study 1601 Part 1

	Placebo N = 87	**Fenfluramine 0.2 mg/kg/day N = 89**	**Fenfluramine 0.7 mg/kg/day N = 87**
Baseline DSF, events per 28 days[2] Mean (SD) Median (range)	 164.4 (309.8) 53.0 (2.0, 1761.0)[1]	 233.0 (435.5) 85.0 (4.1, 2943.0)	 195.0 (308.9) 83.0 (6.5, 1803.0)
T+M DSF, events per 28 days Mean (SD) Median (range)	 145.2 (263.2) 46.8 (0.0, 1683.8)	 247.3 (609.0) 61.8 (0.0, 5110.9)	 162.6 (285.3) 54.6 (0.3, 1562.0)
% change from baseline in DSF, T+M Median (range) P vs placebo	 -7.6 (-100.0, 557.1) -	 -14.2 (-100.0, 3307.3) 0.094	 **-26.5 (-95.2, 402.1)** **0.001**
Estimated median (95% CI) difference vs placebo in % change from baseline in DSF, T+M[3]	-	10.5 (-25.0, 4.0)	**19.9 (-31.0, -8.7)**
Patients with ≥50% change from baseline in DSF, T+M n (%) OR (95% CI) P vs placebo	 9 (10.3%) - -	 **25 (28.1%)** **3.30 (1.43, 7.59)** **0.0051**	 **22 (25.3%)** **2.87 (1.23, 6.70)** **0.0150**
Patients with ≥25% change from baseline in DSF, T+M n (%) OR (95% CI) P vs placebo	 27 (31.0%) - -	 **42 (47.2%)** **1.91 (1.02, 3.57)** **0.042**	 **45 (51.7%)** **2.39 (1.28, 4.49)** **0.006**
Patients with ≥75% change from baseline in DSF, T+M n (%) OR (95% CI) P vs placebo	 4 (4.6%) - -	 9 (10.1%) 2.7 (0.8, 9.2) 0.12	 7 (8.0%) 2.0 (0.6, 7.1) 0.30
CGI Minimally Improved, Much Improved or Very Much Improved at end of T+M, investigator rating n (%) OR (95% CI) P vs placebo	 27 (33.8%) - -	 38 (44.7%) 1.6 (0.8, 3.0) 0.16	 39 (48.8%) 1.9 (1.0, 3.5) 0.057
CGI Much Improved or Very Much Improved at end of T+M, investigator rating n (%) OR (95% CI) P vs placebo	 5 (6.3%) - -	 **17 (20.0%)** **3.73 (1.31, 10.65)** **0.010**	 **21 (26.3%)** **5.30 (1,89, 14.87)** **0.0007**
CGI Much Improved or Very Much Improved at end of T+M, parent/caregiver rating n (%) OR (95% CI) P vs placebo	 4 (4.9%) - -	 **23 (27.1%)** **7.26 (2.39, 22.03)** **<0.0001**	 **27 (33.8%)** **9.96 (3.29, 30.17)** **<0.0001**

Source: Table 21, p115, Table 39, p148, Table 46, p164-5, Table 14.2.4.4.1.1, Table 14.2.5.1.1, Table 14.2.12.1.1, Table 14.2.13.1.1, Study 1601 Part 1 CSF. **Bold** indicates statistically significant results.
[1] Six patients with baseline DSF of <4 per 28 days enrolled in breach of the protocol were included in the mITT population (Study 1601 Part 1 CSR, Table 12, p105).
[2] Seizures per 28 days were calculated from the total seizures recorded in seizure diaries over the 4 week baseline or the 14 week T+M period, divided by the number of days with non-missing data, multiplied by 28.
[3] Hodges-Lehmann method.
CGI = Clinical Global Impression of Improvement; CI = confidence interval; DSF = drop seizure frequency (drop seizures were seizure of any type resulting in falls to the floor or slumping in a chair or similar event); OR = odds ratio; SD = standard deviation; T+M = titration plus maintenance.

Figure 1: Change from baseline drop seizure frequency (DSF) (Study 1601 Part 1)



Source: Figure 2-8 of the submission. *The 0.8mg/kg/day dose in this figure refers to fenfluramine hydrochloride and is equivalent to 0.7 mg/kg/day of the fenfluramine free base.*

6.20 The observed changes in DSF were difficult to interpret because of very large variability among patients.

6.21 Although drop seizures are generally easy to count, some patients with LGS experience clusters of back-to-back seizures. In these cases, only the duration of the episode was recorded and to allow the cluster to be included in seizure frequency calculations a number of seizures was imputed. Excluding seizure clusters and changing the method of imputation did not materially reduce the variability or change the results. Exclusion of outliers also did not materially reduce variability or change the results.

6.22 The types of seizures considered as typically resulting in drops were generalised tonic-clonic (GTC), secondarily generalised tonic-clonic (sGTC), tonic (TS), atonic (AS) and tonic/atonic (TA). The effect of FEN 0.7 mg/kg/day was similar for all seizure types, but the effect of FEN 0.2 mg/kg/day was more variable.

6.23 Seizures that do not typically result in drops, such as absence seizures, cause morbidity but are difficult to count reliably, and the study was not powered to detect an effect of FEN on non-drop seizures. The recorded frequency of absence/atypical absence seizures declined markedly during the treatment period, but FEN had no greater effect

than placebo: median (range) % change from baseline for placebo was -43.4% (-100.0, 1056.5), for FEN 0.2 mg/kg/day -50.1% (-100.0, 2128.6), and for FEN 0.7 mg/kg/day -52.3% (-100.0, 769.9).

6.24 The proportion of patients with at least a 50% reduction in DSF was defined as a key secondary outcome. The proportions of patients with a 25% and with a 75% reduction in DSF were also secondary outcomes.

6.25 The PBAC has previously determined that a 25% reduction in DSF would be clinically meaningful (paragraph 11.7, Cannabidiol PSD, July 2020 PBAC Meeting), and NICE has used a 30% reduction in drop seizures as a criterion for continued use of CBD.[3]

6.26 Although the average frequency of seizures affects quality of life in LGS, the number of seizure-free days is also relevant to the burden of illness.[4] There were no large or statistically significant differences among treatment groups in the number of drop seizure-free days or the longest seizure-free interval.

6.27 Two patients were seizure-free during the trial, one randomised to placebo and one to FEN 0.2 mg/kg/day; two further patients had only one observed seizure during the trial, one randomised to FEN 0.2 mg/kg/day and one to FEN 0.7 mg/kg/day.

Cannabidiol

6.28 The design of the CBD trials was similar to that of the FEN trial. As in Study 1601, concomitant ASM treatment at baseline could not be changed during the study. Results of the CBD trials are shown in Table 5.

6.29 There were some differences between Study 1601 and the CBD trials in concomitant ASM use, with valproate being used more frequently in patients in the FEN study (147/263, 56% in Study 1601 vs 85/225, 38% in GWPCARE3 and 69/171, 40% in GWPCARE4) and rufinamide less frequently (53/263, 20% in Study 1601 vs 65/225, 29% in GWPCARE3 and 46/171, 27% in GWPCARE4).

[3] NICE TA 615, Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome. 18 December 2019.

[4] Strzelczyk A, Zuberi SM, Striano P, Rosenow F, Schubert-Bast S. The burden of illness in Lennox–Gastaut syndrome: a systematic literature review. *Orphanet J Rare Dis* 2023; 18: 42.

Table 5: Efficacy Outcomes in CBD Trials

GWPCARE3			
	Placebo N = 76	**CBD 10 mg/kg/day N = 73**	**CBD 20 mg/kg/day N = 76**
Baseline DSF, events per 28 days Median (IQR)	80.3 (47.8, 148.0)	86.9 (40.6, 190.0)	85.5 (38.3, 161.5)
% Change from baseline in DSF, T+M, median	-17.2	-37.2	-41.9
Estimated median (95% CI) difference in % change from baseline in DSF vs placebo[a] P vs placebo	- -	**19.2 (-31.2, -7.7)** **0.002**	**21.6 (-34.8, -6.7)** **0.005**
Patients with ≥50% change from baseline in DSF, T+M n (%) OR (95% CI) P vs placebo	11 (14%) - -	**26 (36%)** **3.27 (1.47, 7.26)** **0.003**	**30 (39%)** **3.85 (1.75, 8.47)** **<0.001**
Patients with ≥25% change from baseline in DSF, T+M n (%) OR (95% CI)	33 (43.4%) -	**46 (63%)** **2.22 (1.15, 4.28)**	**47 (61.8%)** **2.11 (1.10, 4.04)**
Patients with ≥75% change from baseline in DSF, T+M n (%) OR (95% CI)	2 (2.6%) -	8 (11.0%) 4.55 (0.93, 22.2)	**19 (25.0%)** **12.33 (2.76, 55.1)**
CGI Much Improved or Very Much Improved at end of T+M, parent/caregiver rating n (%)	9 (12%)	23 (31.5%)	21 (28%)
GWPCARE4			
BL DSF, events per 28 days Median (IQR)	74.7 (47.3, 144.0)	NA	71.4 (27.0, 156.0)
% change from baseline in DSF, T+M, median	21.8		43.9
Estimated median (95% CI) difference in % CFB in DSF vs placebo[3] P vs placebo	-		**-17.21 (-30.3, -4.1)** **0.014**
Patients with ≥50% change from baseline in DSF, T+M n (%) OR (95% CI) P vs placebo	20 (24%) - -		**38 (44%)** **2.57 (1.33, 4.97)** **0.004**
Patients with ≥25% change from baseline in DSF, T+M n (%) OR (95% CI) P vs placebo	37 (44%) - -		**55 (64%)** **2.30 (1.24, 4.26)** **0.008**
Patients with >25% worsening of DSF vs BL, T+M n (%)	9 (10.6%)		12 (14.0%)
CGI Much Improved or Very Much Improved at end of T+M, parent/caregiver rating n (%)	15 (17%)		29 (35%)

Source: Devinsky O, et al. N Engl J Med 2018; 378:1888-1897. Thiele EA, et al. Lancet 2018 http://dx.doi.org/10.1016/S0140-6736(18)30136-3.
; CGI = clinical global improvement; CI = confidence interval; DSF = drop seizure frequency; IQR = inter-quartile range; OR = odds ratio; T+M = titration + maintenance periods. **Bold** indicates statistically significant results.
[a] Hodges-Lehmann method.

Indirect Treatment Comparison (ITC)

6.30 The submission stated that the ITC "should not be interpreted as a definitive statement on the comparative efficacy and safety of the two therapies". No non-inferiority margin was nominated, and "it is unlikely that any ITC could realistically support a formal claim of noninferiority, subject to a theoretically defensible margin".

6.31 The ITC included only patients allocated to 0.7 mg/kg/day, although only about half the patients in that group received that dose (mostly due to the maximum daily dose of 26 mg/kg).

6.32 The results of the Bucher method ITC for efficacy outcomes are shown in Table 6.

Table 6: Results of the ITC for efficacy of FEN vs CBD

	Fenfluramine 0.7 mg/kg/day vs Cannabidiol 10 mg/kg/day	**Fenfluramine 0.7 mg/kg/day vs Cannabidiol 20 mg/kg/day**
Median (95% CI) difference in % CFB in DSF (events per 28 days)	-0.78 (-16.97, 15.41) P = 0.92	-0.74 (-15.42, 13.94) P = 0.92
≥25% reduction of DSF from BL		
OR (95% CI)	1.02 (0.42, 2.51)	1.03 (0.48, 2.2)
RR (95% CI)	1.12 (0.69, 1.83)	1.12 (0.73, 1.73)
RD (95% CI)	0.00 (-0.16, 0.18)	0.01 (-0.16, 0.18)
≥50% reduction of DSF from BL		
OR (95% CI)	1.09 (0.34, 3.47)	1.17 (0.43, 3.15)
RR (95% CI)	1.17 (0.44, 3.11)	1.35 (0.59, 3.09)
RD (95% CI)	-0.04 (-0.21, 0.13)	-0.06 (-0.21, 0.09)
≥75% reduction of DSF from BL		
OR (95% CI)	0.54 (0.07, 4.2)	0.47 (0.07, 3.34)
RR (95% CI)	0.56 (0.07, 4.19)	0.55 (0.09, 3.6)
RD (95% CI)	-0.03 (-0.13, 0.07)	-0.12 (-0.25, 0.01)

Source: Table 2-56, p120 of the submission.
BL = baseline; CFB = change from baseline; CI = confidence interval; DSF = drop seizure frequency; OR = odds ratio; RD = risk difference; RR = risk ratio.

6.33 Most outcome measures showed clinically insignificant differences between FEN and CBD.

Comparative harms

Fenfluramine

6.34 Adverse events reported in the trial are shown in Table 7.

Table 7: Summary of key adverse events in Study 1601, Part 1

	Fenfluramine 0.2 mg/kg/day N = 89	**Fenfluramine 0.7 mg/kg/day N = 87**	**Placebo N = 87**
Subjects with any TEAE, n (%)	69 (77.5%)	78 (89.7%)	65 (74.7%)
Subjects with any TESAE, n (%)	4 (4.5%)	10 (11.5%)	4 (4.6%)
Subjects with any severe TEAE, n (%)	1 (1.1%)	3 (3.4%)	1 (1.1%)
TEAE leading to death, n (%)	0	0	1 (1.1%)
TEAE leading to discontinuation, n (%)	4 (4.5%)	5 (5.7%)	1 (1.1%)
Diarrhoea, n (%)	10 (11.2%)	12 (12.6%)	4 (4.6%)
Vomiting, n (%)	12 (13.5%)	7 (8.0%)	5 (5.7%)
Fatigue, n (%)	8 (9.0%)	16 (18.4%)	9 (10.3%)
Somnolence, n (%)	9 (10.1%)	15 (17.2%)	9 (10.3%)
Decreased appetite, n (%)	18 (20.2%)	31 (35.6%)	10 (11.5%)
Weight loss ≥7% during T+M, n (%)	6 (7%)	8 (9%)	0

Source: Study 1601 Part 1 CSR, Table 49, p180, Table 50, p181; p239.
TEAE = treatment-emergent adverse event; TESAE = treatment emergent serious adverse event; T+M = titration + maintenance periods.

6.35 The most prominent adverse events associated with fenfluramine were loss of appetite and weight loss. Feeding difficulties in patients with LGS are common, median BMI was less than 19 at baseline and some patients were seriously underweight. In such underweight patients, the evaluation considered 7% weight loss could have serious consequences.

6.36 In the open-label extension of Study 1601 (Part 2), 43/247 (17.4%) patients were observed at some point in the open-label extension to have lost 7% or more of body weight from their Part 2 baseline. Weight loss was reported as an adverse event in 13/247 (5.3%) patients. Weight loss as an adverse event appeared to be dose-related, reported in 2/68 (3%) patients receiving a mean daily dose of FEN between 0.2 mg/kg and 0.4 mg/kg, in 7/110 (6.4%) receiving 0.4 mg/kg/day to 0.6 mg/kg/day, and in 4/62 (6.4%) receiving 0.6 mg/kg/day or more.

Extended Assessment of Safety of Fenfluramine

6.37 The Periodic Safety Update Report for FEN [redacted]

6.38 [redacted]

6.39 [redacted]

6.40 [redacted]

6.41 The PSCR provided an extract of the Periodic Safety Update Report (PSUR) [redacted][5] The PBAC noted the TGA Product Information for FEN includes a black box warning regarding VHD and PAH and the following statement in the 'special warnings and precautions for use' heading: "VHD and PAH have been reported from post-marketing surveillance of [fenfluramine] used at the doses recommended for patients with Dravet syndrome and Lennox-Gastaut syndrome".

Cannabidiol

6.42 Adverse events reported in the CBD trials are shown in Table 8.

[5] Information will be unredacted in full when the Periodic Safety Update Report to June 2024 is published.

Table 8: Summary of key adverse events in cannabidiol trials

GWPCARE3			
	Cannabidiol 10 mg/kg/day N = 67	**Cannabidiol 20 mg/kg/day N = 82**	**Placebo N = 76**
Patients with any TEAE, n (%)	56 (84%)	77 (94%)	55 (72%)
Patients with any TESAE, n (%)	13 (19%)	13 (16%)	7 (9%)
TEAE leading to death, n (%)	0	0	0
TEAE leading to discontinuation, n (%)	1 (1.5%)	6 (7%)	1 (1.3%)
Serum transaminase >3x ULN, n (%)	3 (4.5%)	11 (13%)	0
Diarrhoea, n (%)	7 (10%)	12 (15%)	6 (8%)
Vomiting, n (%)	4 (6%)	10 (12%)	9 (12%)
Somnolence, n (%)	14 (21%)	25 (30%)	4 (5%)
Decreased appetite, n (%)	11 (16%)	21 (26%)	6 (8%)
GWPCARE4			
	NA	**Cannabidiol 20 mg/kg/day**	**Placebo**
Patients with any TEAE, n (%)		74 (86%)	59 (69.4%)
TEAE leading to discontinuation, n (%)		12 (14%)	1 (1.2%)
Serum transaminase > 3 x ULN, n (%)		20 (24%)	1 (1.2%)
Diarrhoea, n (%)		16 (19%)	7 (8%)
Vomiting, n (%)		9 (10.5%)	14 (16.5%)
Somnolence, n (%)		13 (15%)	8 (9%)
Fatigue, n (%)		5 (6%)	2 (2.4%)
Decreased appetite, n (%)		11 (13%)	2 (2.4%)

Source: Devinsky O, et al. N Engl J Med 2018; 378:1888-1897. Thiele EA, et al. Lancet 2018 http://dx.doi.org/10.1016/S0140-6736(18)30136-3.

NA = not applicable; TEAE = treatment-emergent adverse event; TESAE = treatment emergent serious adverse event; ULN = upper limit of normal.

6.43 Elevations of serum transaminases were more common in patients also receiving valproate: 11/14 (78.6%) CBD-treated patients with elevation > 3 x ULN in GWPCARE3 and 16/20 (80%) in GWPCARE4 were taking valproate, about twice the proportion taking valproate in the studies as a whole.

6.44 Somnolence was more common among patients also taking clobazam: 26/39 (66.7%) of CBD-treated patients with somnolence in GWPCARE3 and 9/13 (69%) in GWPCARE4 were also taking clobazam, compared to about 50% in the studies as a whole.

6.45 In the open-label extension study (GWPCARE5) elevations of serum transaminases greater than three times the upper limit of normal were seen in 55/366 (15%) patients, of whom 40 (73%) were also taking valproate. Liver enzyme abnormalities resolved in 52/55 (95%): in 25 patients spontaneously, in 14/15 who stopped CBD and withdrew from the study, and in 13/13 whose dose of CBD or another ASM was reduced.[6]

[6] Patel AD, Mazurkiewicz-Beldzinska M, Chin RF, et al. Long-term safety and efficacy of add-on cannabidiol in patients with Lennox–Gastaut syndrome: Results of a long-term open-label extension trial. *Epilepsia* 2021; 62:2228-39.

Indirect Treatment Comparison of Safety

6.46 Only data for serious adverse events was provided in the ITC. There were no clinically meaningful or statistically significant differences in the rate of serious adverse events, but the evaluation considered this does not adequately establish non-inferior safety in and of itself.

Benefits/harms

6.47 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

6.48 The submission described fenfluramine as non-inferior in terms of effectiveness compared to cannabidiol. This evaluation considered the claim was uncertain and may not be adequately supported. More patients in the CBD trials than in the FEN trial had 25%, 50% and 75% reductions in DSF, but these differences did not reach statistical significance, for either CBD 10 mg/kg/day or 20 mg/kg/day. However, there was very marked variability of response to treatment. On balance, the ESC considered the claim of non-inferior comparative effectiveness may be reasonable, considering the rarity of LGS and low likelihood of future clinical data to inform the claims.

6.49 The submission described fenfluramine as having "different but non-inferior" safety compared to cannabidiol. The evaluation considered the claim was not adequately supported. As PBAC noted in its consideration of fenfluramine for Dravet Syndrome, although the overall frequency of adverse events with FEN and CBD was similar, the adverse events were different (Paragraph 6.52, Fenfluramine PSD, November 2024 PBAC Meeting), with FEN associated with cardiovascular and nutritional adverse events that may have a long-lasting impact on children with epilepsy and may be difficult to manage (Paragraph 6.68, Fenfluramine PSD, November 2024 PBAC Meeting). Transaminase levels more than three times the upper limit of normal were seen more commonly in the CBD trials in LGS than in Dravet Syndrome, but they resolved either spontaneously (in half of the patients) or after CBD was withdrawn or the dose reduced. The ESC considered views of the PBAC regarding the safety profiles of FEN and CBD for Dravet Syndrome were generally also applicable to the LGS indication (Paragraph 7.9, Fenfluramine PSD, November 2024 PBAC meeting).

6.50 The PBAC considered that the claim of non-inferior comparative effectiveness was, on balance, likely to be reasonable.

6.51 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported, and considered that while the safety profiles of FEN and CBD were different, the type and potential severity of adverse events observed for FEN supports a conclusion that FEN is of inferior comparative safety to CBD.

Economic analysis

6.52 The submission presented a cost minimisation approach. The key components of the approach are shown in Table 9.

Table 9: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in the submission, effectiveness is assumed to be similar.
Therapeutic claim: safety	Based on evidence presented in the submission, safety is assumed to be comparable but different
Evidence base	Pairwise, frequentist, adjusted (Bucher) ITC using similarly well-designed placebo controlled randomised controlled trials of fenfluramine 0.7 (max 26 mg/day) (Study 1601) and cannabidiol 10 AND/OR 20 mg/kg/day (GWPCARE3/4) all of which included 14 weeks of treatment (2 weeks titration + 12 weeks maintenance) and appropriate follow-up/analysis of similar clinically relevant efficacy and safety outcomes.
Equi-effective doses	Fenfluramine 0.7 mg/kg/day (max 26 mg/day) is considered equi-effective to cannabidiol at a fixed dose of either 10 mg/kg/day OR 20 mg/kg/day. While the average stable dose of cannabidiol in the real world PBS setting likely approaches the TGA recommended maximum of 20 mg/kg/day, the CMA has been conducted using a relativity of fenfluramine 0.7 mg/kg/day (max 26 mg/day) to cannabidiol 12 mg/kg/day, as this was the average dose at which PBAC assessed the comparator to be acceptably cost effective at its September 2022 meeting. CBD titration = 7.5 mg/kg/day for 14 days Fenfluramine titration = 0.3 mg/kg/day for 14 days
Direct medicine costs	Equivalent total treatment costs, over 2 years of titration and maintenance therapy. The analysis is based on the June 2025 published dispensed price of cannabidiol (100 m x 100 mg/mL).
Other costs or cost offsets	Differential monitoring costs included as per TGA recommendations and MBS items. The PBAC noted the PI states that plasma drug concentration should be considered but and considered it is rarely done in clinical practice.

Source: Table 3.1, p129 of the submission.

6.53 The equi-effective doses were estimated as fenfluramine 0.7 mg/kg/day mg over two years and cannabidiol 12 mg/kg/day over 2 years, with the latter dose based on the PBAC consideration of cannabidiol in September 2022. The submission constructed a stratified CMA, using ten discrete population subgroups defined by patient weights, which were estimated from a post hoc analysis of Study 1601. The average weight derived from the stratified analysis was [redacted]kg (consistent with the average weight of patients in the trial).

6.54 This analysis is shown in Table 10 and Table 11, based on the published price of cannabidiol. The submission also included the costs of monitoring for both cannabidiol and fenfluramine: for cannabidiol, 6 liver function tests over 2 years (MBS Item 66512, fee $17.70) and 2 measurements of plasma drug concentration (MBS item 66626, fee $24.10), and for fenfluramine, 5 echocardiograms over 2 years (MBS Item 55133, $232.80).

Table 10: Weights by decile of patients in Study 1601, Cohort A, mITT

Cohort,1 (n)	Mean weight (kg)	Weighting
[redacted]	15.08	[redacted]%
[redacted]	20.93	[redacted]%
[redacted]	26.55	[redacted]%
[redacted]	31.37	[redacted]%
[redacted]	36.28	[redacted]%
[redacted]	41.52	[redacted]%
[redacted]	48.88	[redacted]%
[redacted]	54.97	[redacted]%
[redacted]	63.49	[redacted]%
[redacted]	84.92	[redacted]%

Source: Table 3.3, p131 of the submission.
mITT=modified intention to treat

Table 11: Summary weighted average results for the whole population

	Cannabidiol	Fenfluramine
Total mg over 2 years	372,345	[redacted]
Weighted average mg per day	510.1	[redacted]
Weighted average mg per kg	11.91	[redacted]
Total drug cost over 2 years	$57,167	$[redacted]
Monitoring costs	$154	$1,164
Total cost over 2 years	$57,321	$[redacted]
DPMQ per pack	$1,535.31	$[redacted]
EMP per pack	$1,400.00	$[redacted]

Source: Table 3.6, p132 of the submission
DPMQ = dispensed price for maximum quantity; EMP = ex-manufacturer price

6.55 The mean patient weight in the pivotal FEN trial (Study 1601 Part 1) was [redacted] kg. Based on the cost minimised price per mg proposed in the submission (calculated at DPMQ level, $0.15 for CBD and $[redacted] for FEN), for a patient of average weight this would result in a drug cost over 2 years of approximately $56,291 for CBD (12 mg/kg/day, previously accepted average dose, (see paragraph 11.2, CBD PSD, September 2022 PBAC meeting) and $[redacted] for FEN (26 mg/day). This would result in FEN being more costly over 2 years for an average patient with LGS (excluding dose titration and monitoring costs). The PSCR argued using a single weight input like mean patient weight would not account for the heterogeneity of the target patient population nor for the reality that the daily dose of fenfluramine is capped, whilst it is uncapped for cannabidiol. The ESC considered the use of a stratified weight distribution to determine dose inputs to the CMA may, in principle, better reflect the range of patients being treated with cannabidiol and/or fenfluramine.

6.56 The CMA provided in the submission was based on the dispensed price for maximum quantity (DPMQ). Pricing agreements are made by Government under the *National Health Act 1953* at the ex-manufacturer level and, as such, the prices would be agreed on this basis. It is not usually the case that pharmacy and wholesaler mark-ups are considered for the purpose of cost-minimisation as they do not relate to the cost of the medicine. Using the published EMP for CBD in the CMA provided in the submission results in an EMP of $[redacted] for FEN.

6.57 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with fenfluramine would be no more than the cost per patient of cannabidiol. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe. In this case, the PBAC should consider the following parameters: uncertain dose in practice, frequency of adverse events.

Drug cost/patient/year

6.58 The cost per patient per year based on the published price of CBD to calculate the price of FEN and using the weighted average dose of FEN as calculated in the economic analysis (see Table 11) was $[redacted].

Estimated PBS usage & financial implications

6.59 This submission was not considered by DUSC.

6.60 The submission presented a mixed market share and epidemiological model to estimate utilisation and cost of fenfluramine. The key inputs used in the model are shown in Table 12.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Existing market for cannabidiol for LGS	PBS item reports 2024, Item 13277T, 100*100mg/mL	Limited to cannabidiol – market likely to be larger as other treatments are also PBS listed for LGS. The population was based on 100% growth from 2024 scripts, with further growth applied in the estimates model. The rationale for this assumption was unclear.
Uptake rate	year / Substitution / Additional population 2025 [redacted]% [redacted]% 2026 [redacted]% [redacted]% 2027 [redacted]% [redacted]% 2028 [redacted]% [redacted]% 2029 [redacted]% [redacted]% 2030 [redacted]% [redacted]% 2031 [redacted]% [redacted]%	Basis for estimate of combination use, ie additional population, unclear. The PBAC considered the estimated use of FEN and CBD in combination was likely overestimated.
Growth rate	Sponsor assumption, also notes estimates in cannabidiol PSD. year / Growth 2025 [redacted]% 2026 [redacted]% 2027 [redacted]% 2028 [redacted]% 2029 [redacted]% 2030 [redacted]% 2031 [redacted]%	Assumes that current market is still expanding and that growth will then stabilise.
Drug prices	**Medicine** / **Dose form** / **DPMQ** Fenfluramine / 360 mL x 2.2 mg/mL / $[redacted] Cannabidiol / 100 mL x 100 mg/mL / $1,535.31	Based on published price for CBD and the price of FEN calculated using the published price CBD.
Dose/duration	As per PI	
Script equivalence	Based on CMA: [redacted] packs of fenfluramine (360 mL*2.2 mg/mL) = 1 pack of cannabidiol (100 mL*100 mg/mL) The financial estimates applied a 'more realistic relativity': 1.71 bottles cannabidiol dispensed every 28 days compared to 1 bottle of fenfluramine every 32.77 days i.e. 0.777 scripts of fenfluramine = 1 script of cannabidiol For the incremental cohort – assumes 1 pack every 36.05 days.	Very difficult to determine what the actual dose equivalence will be in practice so this may or may not be reasonable. Titration dosing was not considered in the estimates model.
MBS item	Costs of monitoring for fenfluramine and cannabidiol: MBS items 66512, LFTs for CBD 66626: plasma drug concentration monitoring for CBD 55133: echocardiogram for fenfluramine	Consistent with CMA.

Source: Table 4.1, p135; Table, 4.4, p 136. Table 4.5, p137 and associated text of Section of the submission.

6.61 A number of assumptions in the analysis were not well supported: estimates of substitution and additional population, which did not account for switching from other ASMs or use in combination with products other than cannabidiol; the overall growth rate of the market, the number of MBS items per script and the script equivalence. The latter in particular is uncertain given the problems in determining actual dose used

on the trials as well as the estimated equivalence between cannabidiol and fenfluramine in practice.

6.62 The estimated use and cost, as presented in the submission, using the published price of cannabidiol to calculate the effective price of fenfluramine as derived from the CMA (noting its limitations) is shown in Table 13. The submission stated that for these estimates, the incremental cost to the PBS was due to the estimated use of fenfluramine in combination with cannabidiol. The ESC was of the view the financial implications may be underestimated, as the submission does not assume switching from other anti-seizure medications.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed - substitution	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Number of scripts dispensed- incremental	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total items/packs	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]
Estimated financial implications of fenfluramine						
Cost to PBS/RPBS less copayments	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]	$[redacted][7]	$[redacted][8]
Estimated financial implications for cannabidiol						
Cost to PBS/RPBS less copayments	-$[redacted][5]	-$[redacted][5]	-$[redacted][6]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Net cost to MBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Net cost to PBS/RPBS/MBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]

Source: Tables 4.6, 4.7 and 4.8, pp138-9; Tables 4.9 and 4.19, pp140 and 141 of the submission.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *5,000 to < 10,000*

[4] *10,000 to < 20,000*

[5] *$0 to < $10 million*

[6] *$10 million to < $20 million*

[7] *$20 million to < $30 million*

[8] *$30 million to < $40 million*

6.63 The submission presented sensitivity analyses for the estimates, varying market growth rates, the number of CBD bottles per script, the substitution rate and the script equivalence. These analyses, using the fenfluramine price derived from the cannabidiol published price, demonstrated that the estimates of financial impact were highly variable and illustrate the fundamental uncertainty of the estimation of use of fenfluramine for LGS. The ESC considered the assumptions around patient weight/dose and likely uptake in practice were highly uncertain. The Pre-PBAC Response (pg 1) acknowledged the changes to the CBD restriction had the potential to alter the LGS market and a willingness to engage with the Department to manage the impact of these changes on the financial estimates. The PBAC recalled it had previously considered the revised PBS restrictions were not expected to result in a substantial financial impact (paragraph 5.8, cannabidiol PSD, July 2025 PBAC meeting).

Financial Management – Risk Sharing Arrangements

6.64 The submission did not formally propose a risk sharing arrangement, but noted that the sponsor was aware that a RSA had been implemented for cannabidiol for LGS, and therefore that they were prepared to work with the PBAC and Department to address the issues concerning the uncertainty of use and cost of listing of fenfluramine. The ESC considered inclusion of fenfluramine in the existing RSA for cannabidiol for LGS may partially mitigate some of the uncertainties regarding the financial estimates.

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 (Streamlined) listing of fenfluramine (FEN) for the treatment of seizures associated with Lennox Gastaut Syndrome (LGS). In making this recommendation, the PBAC considered the available evidence, whilst uncertain, on balance likely supports a conclusion that FEN is of non-inferior comparative effectiveness to cannabidiol (CBD). However, the PBAC considered that fenfluramine is associated with more serious safety concerns than CBD, including nutritional impacts (e.g., weight loss) and the risk of serious cardiac events. The PBAC considered it was appropriate for these concerns to be reflected in the price at which it considered FEN would be cost effective. The PBAC advised FEN should be included in the risk sharing arrangement (RSA) currently in place for LGS with no increase in expenditure caps.

7.2 The PBAC considered the equi-effective doses were:

FEN 0.7 mg/kg/day (up to a maximum dose of 26 mg/day) = CBD 12 mg/kg/day

7.3 The PBAC acknowledged the input from individuals, healthcare professionals and organisations highlighting the devastating impact of LGS as a rare and serious epileptic encephalopathy, often manifesting with dangerous tonic-clonic (convulsive) and atonic ('drop') seizures, which carry a significant risk of injury, the developmental delays that typically occur, and the urgent need for additional effective treatment options. The Committee also acknowledged the significant caregiver burden for parents and family members of children with LGS. The PBAC noted current treatments for LGS, which includes standard anti-seizure medications (ASMs) and CBD, are often not effective or sub-optimally effective, and considered there was an unmet need for additional therapies to allow patients to optimise therapy for their individual circumstances. The PBAC accepted there was a clinical place for FEN and it may be effective for some patients; however, the Committee considered the safety profile of FEN would likely lead to it being reserved for use until after most other options had been tried.

7.4 The PBAC considered the listing of FEN should be aligned with the restriction recommended for CBD in July 2025, as proposed in Section 3.

7.5 The PBAC considered the nominated comparator of CBD was reasonable, but noted sequencing of ASMs could occur in any order, and any could be used as third-line treatment. However, the Committee recalled in its consideration of CBD the view that comparisons to other ASMs would likely not be informative (paragraph 5.3 refers) and considered this view was also applicable to FEN.

7.6 The Committee noted the submission was primarily supported by a single, randomised head-to-head trial comparing FEN to placebo (Study 1601), where background ASMs were continued in both arms of the trial over a period of 12 weeks following dose titration. Additional longer-term data was provided from an open label extension of this study. The PBAC also noted the CBD data was informed by two randomised head-to-head trials (GWPCARE 3 and 4), with a similar 12-week duration (after dose titration) and supported by an open label extension stage (GWPCARE5). The FEN and CBD studies both measured change in drop seizure frequency (DSF) from baseline as the primary outcome, with proportion of patients with a ≥25%, ≥50%, ≥75% reduction in DSF and clinical global improvement assessments also collected.

7.7 The PBAC noted the FEN trial did not require a formal diagnosis of LGS if they otherwise met the study's diagnostic criteria, and considered this added some uncertainty regarding the population recruited to Study 1601. Furthermore, the Committee also considered the nomination of change in DSF as the main seizure type of interest may mean important information about changes in other seizure types may not have been captured. However, given the overall similarity in primary outcomes between the FEN and CBD trials, the PBAC considered the available data was sufficient for assessing the clinical claims, albeit with some uncertainty.

7.8 The PBAC noted that for the primary outcome of change in DSF from baseline, FEN (at a dose of 0.7 mg/kg/day) was superior to placebo (7.6% reduction from baseline for placebo vs 26.5% reduction from baseline for FEN) and the odds ratio of achieving a 25% reduction in DSF from baseline was 2.39 (95% CI: 1.28, 4.49) for FEN (at a dose of 0.7 mg/kg/day) compared to placebo.

7.9 Based on the indirect treatment comparison (ITC) presented using the Bucher method, the PBAC noted there were no statistically significant differences between FEN and CBD for the outcomes of median change in DSF, or proportion with a greater than 25%, 50% or 75% reduction in DSF from baseline (see Table 8).The PBAC considered that, on balance, a claim of non-inferior comparative effectiveness of FEN and CBD was likely to be reasonable.

7.10 With respect to comparative safety, the PBAC noted the available data indicated FEN was associated with nutritional side effects such as loss of appetite and weight loss, which was of particular concern in LGS given median baseline body mass index (BMI) was less than 19 in Study 1601 (paragraph 6.35 refers), and was concerned that ~17% of patients were observed to have lost 7% or more body weight during the open label extension phase of the FEN trial (paragraph 6.36 refers).The PBAC noted valvulopathy and pulmonary arterial have been reported at doses used in patients with LGS (and Dravet syndrome) in post-marketing studies and the long term risk remained

uncertain. For CBD, the Committee noted the most common side effects were elevated serum transaminases and somnolence (paragraphs 6.45 and 6.46 refer). The PBAC considered FEN to be of inferior comparative safety to CBD, with a higher risk of more serious and impactful adverse events.

7.11 The PBAC noted the submission presented a cost minimisation approach (CMA) of FEN and CBD, reflecting the submission claims of non-inferior comparative effectiveness and safety. The Committee noted the CMA was conducted over two years and included offsets for cardiac monitoring for FEN and liver function monitoring and plasma drug concentration monitoring for CBD. The PBAC considered the inclusion of cardiac and liver function monitoring costs in the CMA was appropriate; however, blood plasma monitoring for CBD is not required in the Product Information and is rarely undertaken in clinical practice. The PBAC advised blood plasma monitoring should be removed from the CMA. Additionally, the PBAC considered the CMA should be based on the ex-manufacturer price (as discussed in paragraph 6.56).

7.12 The PBAC noted the CMA was based on patient weight distribution in Study 1601 grouped by deciles to determine the overall amounts of FEN and CBD used over 2 years, based on the equi-effective doses of FEN 0.7 mg/kg/day (up to a maximum of 26 mg/day) and CBD 12 mg/kg/day. The PBAC noted the applicability of the weight distributions to the Australian population was uncertain but considered that, on balance, this approach was reasonable.

7.13 Noting the inferior safety profile of FEN, the PBAC advised the cost per patient for FEN (as calculated in the CMA) should be aligned with the comparable efficacy and uncertainty around its comparative safety.

7.14 The PBAC noted the submission presented a mixed market share (based on current CBD scripts) and epidemiological model (to capture patients using FEN and CBD in combination) to estimate the utilisation of FEN. The PBAC considered the utilisation estimates were uncertain, as the prescribing of cannabinoids including CBD was complex in Australia, its use had been lower than expected (paragraph 5.7, cannabidiol PSD, July 2025 PBAC meeting) and it was unclear how reliable its current use was for estimating the LGS market. Additionally, the Committee considered the assumptions around market growth, script equivalence and extent of use in combination with CBD to be uncertain. However, on balance, the PBAC considered the incremental cost of listing FEN on the PBS for LGS was likely to be small and it would be appropriate to include FEN in the RSA in place for LGS with no change in the expenditure caps.

7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because FEN is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over CBD, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

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:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
FENFLURAMINE					
fenfluramine hydrochloride 2.2 mg/mL oral liquid, 360 mL	NEW	1	1	5	Fintepla

Restriction Summary NEW / Treatment of Concept: NEW1A	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction type: ☒Authority Required (STREAMLINED)
Prescribing rule level	**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.
	Indication: Seizures of the Lennox-Gastaut syndrome
	Clinical criteria:
	Patient must have a diagnosis of Lennox-Gastaut syndrome; the diagnosis should be confirmed by an electroencephalogram (EEG) where possible.
	AND
	Clinical criteria:
	Patient must have (as an initiating patient)/have had (as a continuing patient) more than one type of seizures that are not adequately controlled with at least two other antiseizure medication prior to initiating treatment with this medicine
	AND
	Clinical criteria:
	The treatment must be as adjunctive therapy to other antiseizure medication
	Treatment criteria:
	Must be treated by a prescriber who is either (i) a neurologist, (ii) a paediatrician if treatment is being initiated; or
	Must be treated by a prescriber who is either (i) a neurologist, (ii) a paediatrician if treatment is being continued or re-initiated; or
	Must be treated by a general practitioner in consultation with either (i) a neurologist, (ii) a paediatrician if treatment is being continued
	Administrative Advice: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records

	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

UCB welcomes the PBAC recommendation for Fintepla in Lennox-Gastaut Syndrome, a lifelong, rare and serious form of epilepsy. UCB is committed to the highest standards of patient safety and actively monitors adverse events, minimises risk and ensures quality use of medicines is maintained through the Controlled Access Program for Fintepla. Cumulative and ongoing data collection in Australia and internationally ensure the safety profile for Fintepla is well-characterised and indicates that the risk-benefit balance for Fintepla remains favourable.