An addendum to this minute has been included at the end of the document.

5.03 CANNABIDIOL, Oral solution, 100 mg per mL, 100mL Epidyolex®, Emerge Health Pty Ltd.

1 Purpose of submission

1.1 The submission requested a Section 100, Highly Specialised Drugs Program (Community Access) Authority Required (STREAMLINED) listing for cannabidiol for use as adjunctive therapy to treat seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), also known as severe myoclonic epilepsy in infancy (SMEI), for patients 2 years of age and older.

1.2 Listing was requested on the basis of a cost-effectiveness analysis of cannabidiol plus standard care versus placebo plus standard care.

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

Component	Description
Population	Patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS).
Intervention	Cannabidiol oral solution 100 mg/mL as adjunctive therapy to standard care, which includes current anti-epileptic drugs alone.
Comparator	Standard care, which includes oral anti-epileptic drugs, and non-pharmacotherapy interventions (vagus nerve stimulation, ketogenic diet, and colostomy).
Outcomes	Primary: Reduction in seizure frequency during 14 weeks of treatment compared to 28-day baseline seizure frequency (drop seizures for LGS and convulsive seizures for DS). Secondary: Change from baseline in responder rates, seizure-free days, seizure frequency, global impression of change, quality of life and Vineland II behavioural assessment.
Clinical claim	Cannabidiol as adjunctive therapy is superior in terms of efficacy and inferior in terms of safety compared to standard care (current anti-epileptic drugs alone) in patients with seizures associated with LGS or DS who have trialled two other appropriate anti-epileptic drugs to a maximally tolerated dose and failed to achieve seizure freedom.

Source: Table 8, pp3-4 of the submission.

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration**: not registered.

2.2 The submission was made under the TGA/PBAC Parallel Process. The requested indication was for "adjunctive therapy of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome for patients 2 years of age and older". At the time of PBAC consideration, the TGA Clinical Evaluation Report and Delegate's Overview were available.

2.3 The Delegate's Overview indicated support for the registration of cannabidiol but noted the clinical evaluator had proposed amending the indication to be in combination with clobazam for treatment of DS and LGS. The Delegate made a number of requests for advice from the Advisory Committee on Medicines (ACM).

2.4 Cannabidiol was registered by members of the European Economic Area (31 countries) for the treatment of seizures associated with DS or LGS in conjunction with clobazam for patients 2 years of age or older (19 September 2019). In the USA, the FDA approved cannabidiol for the treatment of seizures associated with DS or LGS in patients 2 years of age or older on 25 June 2018. There is some evidence which points towards potential synergistic efficacy from concurrent use of cannabidiol and clobazam[1], and the NICE health technology assessment for cannabidiol in DS[2] and LGS[3] considered the combination of cannabidiol and clobazam specifically.

2.5 The PBAC noted an outstanding issue for consideration by the ACM is whether cannabidiol should only be registered for use in combination with clobazam and considered this may have implications for the clinical positioning of cannabidiol.

Previous PBAC consideration

2.6 The PBAC recommended stiripentol for the treatment of DS at its March 2020 meeting.

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

3 Requested listing

3.1 The sponsor requested PBS listing of a maximum quantity of 1 pack with 5 repeats for patients with DS, and 2 packs with 5 repeats for patients with LGS.

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

[1] Draft Product Information
[2] https://www.nice.org.uk/guidance/ta614
[3] https://www.nice.org.uk/guidance/ta615

MEDICINAL PRODUCT medicinal product pack	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price. Max Qty	Available brands
CANNABIDIOL cannabidiol 100 mg/mL oral liquid, 100 mL	1	1	5	$[redacted]	Epidyolex

Category / Program: ~~Section 100 – Highly Specialised Drugs Program (Community Access)~~ *GENERAL – General Schedule (Code GE)*
Prescriber type: ☒Medical Practitioners
Restriction type / Method: ☒*Authority Required – immediate/real time assessment (telephone/online)* ☒~~Authority Required - Streamlined~~
Condition: ~~Dravet syndrome~~ *Severe myoclonic epilepsy of infancy (Dravet syndrome)*
Indication: ~~Adjunctive therapy of seizures associated with Dravet syndrome (DS) for patients 2 years of age and older.~~ *Severe myoclonic epilepsy of infancy (Dravet syndrome)*
Treatment Phase: Initial and continuing treatment
Clinical criteria:
The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs.
AND
Clinical criteria:
~~The treatment must be adjunctive treatment.~~ *The treatment must be in combination with at least one anti-epileptic drug.*
AND
Clinical criteria:
If patients have achieved a ≥30% reduction in convulsive seizures at 12 months versus baseline they are eligible for continuation.
AND
Treatment criteria:
Must be treated by a physician or paediatrician with experience in the treatment of epilepsy.
Population criteria:
Patient must be ~~under the~~ 2 years of age or older.
Prescribing Instructions:
~~Care must be taken to comply with the provisions of State and Territory law when prescribing cannabidiol.~~
Administrative Advice: ~~Note: No applications for increased maximum quantity and/or repeats will be authorised~~
Administrative Advice: *Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*
Caution: Maximum recommended dose of cannabidiol should not be exceeded.

MEDICINAL PRODUCT medicinal product pack	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price Max. Qty	Available brands
CANNABIDIOL cannabidiol 100 mg/mL oral liquid, 100 mL	2	2	5	$[redacted]	Epidyolex

Category / Program: ~~Section 100 – Highly Specialised Drugs Program (Community Access)~~ *GENERAL – General Schedule (Code GE)*
Prescriber type: ☒ Medical Practitioners
Restriction type / Method: ☒*Authority Required – immediate/real time assessment (telephone/online)* ☒~~Authority Required - Streamlined~~
Condition: *Seizures of the* Lennox-Gastaut syndrome
Indication: ~~Adjunctive therapy of seizures associated with Lennox-Gastaut syndrome for patients 2 years of age and older.~~ *Seizures of the Lennox-Gastaut syndrome*
Treatment Phase: Initial and continuing treatment

Clinical criteria:
The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs.
AND
Clinical criteria:
~~The treatment must be adjunctive treatment.~~ *The treatment must be in combination with at least one anti-epileptic drug.*
AND
Clinical criteria:
If patients have achieved a ≥30% reduction in drop seizures at 12 months versus baseline they are eligible for continuation.
AND
Treatment criteria:
Must be treated by a physician or paediatrician with experience in the treatment of epilepsy.
AND
Population criteria:
Patient must be ~~under the~~ 2 years of age or older.
Prescribing Instructions:
~~Care must be taken to comply with the provisions of State and Territory law when prescribing cannabidiol.~~
Administrative Advice: ~~Note: No applications for increased maximum quantity and/or repeats will be authorised~~
Administrative Advice: *Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*
Caution: Maximum recommended dose of cannabidiol should not be exceeded.

3.3 No special pricing arrangement was proposed.

3.4 The requested PBS restriction was consistent with the sponsor proposed TGA indication at the time of submission. However it was not in line with the clinical trial evidence. The trials for DS required patients to have convulsive seizures that were not completely controlled by current anti-epileptic drugs (AEDs) and to have been taking one or more AEDs at a stable dose for 4 weeks prior to randomisation. Similarly, in the LGS trials, patients must have had seizures which were refractory to treatment, with documented failures on more than one AED, and patients needed to be taking one or more AEDs at a stable dose for 4 weeks prior to randomisation.

3.5 The Pre-Sub-Committee Response (PSCR) agreed with the evaluation proposal to include the clinical criterion "patients must have trialled two other appropriate AEDs to a maximally tolerated dose and failed to achieve seizure freedom", to align the restriction more closely with the clinical claim in the submission. The ESC considered that prevalent patients would likely have trialled a number of prior therapies and so the inclusion of this clinical criteria would not create a barrier to treatment.

3.6 The ESC considered that the criterion of a 30% reduction in seizures would be difficult for caregivers to monitor for patients experiencing multiple seizures per day.

3.7 The PBAC considered an Authority Required (telephone/online), Section 85 (General Schedule) listing for cannabidiol would be more appropriate than an Authority Required (streamlined), Section 100 Highly Specialised Drugs Program (Community Access) listing.

3.8 The PBAC noted the proposed maximum quantity for DS and LGS was based on patients receiving an average dose of 15mg/kg/day which was not consistent with the 10mg/kg/day dose assumed in the economic and financial models.

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

4 Population and disease

4.1 DS is a rare, refractory and genetic form of epilepsy that is characterised by febrile or afebrile prolonged generalised clonic or tonic-clonic seizures (grand mal seizures) starting in the first year of life. Patients typically display cognitive and psychomotor retardation with attention deficit and hyperactivity and absent language skills by the age of 2 years, and they may also have arrhythmias and cardiac structural abnormalities. Up to 85% of patients with DS have a genetic defect in their SCN1A gene. The submission estimated the incidence rate to be 3.0 births per 100,000 with a prevalence rate of 4.0 per 100,000 of the population. Seizures in patients with DS can lead to status epilepticus and Sudden Unexplained Death in Epilepsy (SUDEP). In patients under 18 years of age, mortality rates can range from 7% to 18%, with the most common cause of death being SUDEP. Australian studies have reported a death rate of up to 17% in the first 17 years of life. Few patients with DS live beyond 30 years of age.

4.2 LGS is a rare severe form of epileptic encephalopathy that has its onset in early childhood. The submission estimated an incidence rate of 1.9 per 100,000 and a prevalence rate of 16.1 per 100,000 of the population. The syndrome typically manifests in patients by 8 years of age with a peak incidence occurring between the ages of 3 and 5 years. Seizures persist into adulthood in more than 90% of patients. The disease is characterised by slow spike-and-wave activity, and moderate to severe cognitive impairment. Seizures in patients with LGS include atonic and tonic seizures, which can lead to drop seizures, and atypical absence seizures, as well as a variety of other seizures. Seizures are often disabling, despite treatment. As patients with LGS can have different types of seizures they often require therapy with multiple types of AEDs. Children with LGS have a 14 times higher risk of death compared to the risk of death in the general population, with a mortality rate of approximately 5%. High seizure frequency is a significant predictor of early death.

4.3 The proposed clinical management algorithms suggested that sodium valproate is the first-line treatment of choice for patients with seizures due to either DS or LGS, and that cannabidiol could be used in addition to either sodium valproate ± other AEDs (if seizures are inadequately controlled) or in addition to any of the listed therapies if sodium valproate is not tolerated. The ESC noted that LGS and DS do not have linear treatment protocols and that there are no traditional lines of treatment. The ESC considered that the proposed clinical management algorithm, although simplistic, reflected current practice and the dynamic management of DS and LGS.

4.4 The intervention is a highly purified oral solution containing cannabidiol (ATC N03AW24) extracted from *Cannabis sativa* L., folium cum flore (cannabis leaf and flower). The cannabidiol is solubilised in oil and alcohol with each mL containing 100 mg of cannabidiol.

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

5 Comparator

5.1 The submission nominated the comparator to be "standard care, which includes ALL current oral anti-epileptic drugs (AEDs)". The main arguments provided in support of this nomination were that cannabidiol is intended to be used as an adjunct to existing therapies rather than to replace them, and that pharmacological treatment of refractory epilepsy is often dynamic with the need to alter anti-epileptic therapies as efficacy wanes or as drug/drug interactions reduce tolerability.

5.2 Cannabidiol may both replace and displace the use of other adjunctive therapies in patients with DS or LGS. Adjunctive therapies include PBS-listed lamotrigine, levetiracetam, topiramate and sodium valproate and non-PBS listed clobazam, rufinamide (LGS only) and stiripentol (DS only). Some of these therapies are less costly than cannabidiol. Such use was not considered in the economic analysis and financial estimates, and there was no clinical comparison made to any of these therapies.

5.3 The ESC noted cannabidiol may also substitute for other medicinal cannabis products, available via the TGA Special Access Scheme (Category B) or Authorised Prescriber programs, in practice.

5.4 In its recent consideration of stiripentol, the PBAC considered that standard care, consisting of a range of AEDs and treatments including topiramate and levetiracetam, was the appropriate main comparator, but that due to the limited evidence evaluating the efficacy of these treatments in DS patients, placebo (plus sodium valproate and clobazam) was used as the comparator in the clinical comparison and economic model. Noting the variable and individualised nature of standard care in DS, the PBAC considered that the evidence presented compared to placebo was still informative in demonstrating the incremental benefit of stiripentol against a standardised trial comparator (paragraph 7.4, stiripentol Public Summary Document (PSD), March 2020 PBAC meeting).

5.5 The ESC noted that, similar to stiripentol, the limited evidence available meant that placebo (plus standard care) was the appropriate comparator for the clinical and economic model (paragraph 7.4, stiripentol PSD, March 2020 PBAC meeting).

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 presented clinical case studies and discussed the natural history of DS and LGS, the impact of these conditions on patients, carers and the broader community, how cannabidiol would be used in practice and its place in the treatment algorithm, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating these uncommon diseases.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with cannabidiol including an improvement in seizure control for patients who generally do not have seizure control, leading to a substantial increase in quality of life for both patients and carers.

6.3 The PBAC noted the advice of the Epilepsy Society of Australia that prescribing should be restricted to neurologists and paediatric neurologists experienced in the treatment of epilepsy, to ensure appropriate use as part of patients' comprehensive management strategy. The Epilepsy Society considered that definitions for DS and LGS should be included in a PBS listing so that use is limited to patient populations with clinical data supporting the risk and benefit of cannabidiol.

6.4 The PBAC noted the advice of the Epilepsy Foundation that cost of treatment is a barrier for most patients.

6.5 The PBAC noted the advice of the National Paediatric Medicines Forum that a significant number of paediatric patients across Australia are currently prescribed cannabidiol for DS and LGS.

Clinical trials

6.6 The submission was based on four direct randomised trials (Table 3). Two direct randomised trials (GWPCARE2 (n=198) and GWPCARE1 Part B (n=120)) compared cannabidiol (plus standard care) to placebo (plus standard care) in patients with DS and two direct randomised trials (GWPCARE3 (n=225) and GWPCARE4 (n=171)) compared cannabidiol (plus standard care) to placebo (plus standard care) in patients with LGS. Standard care in all trials was continuation of existing stable AED regimens, with no dose adjustments. The ESC noted that adjustments to existing AEDs were permitted if cannabidiol was found to impact on the plasma levels of existing AEDs.

6.7 The submission designated GWPCARE2 and GWPCARE3 as key trials, and GWPCARE1 Part B and GWPCARE4 to be supplementary trials, given that only the key trials randomised patients to the proposed maintenance dose of cannabidiol of 10 mg/kg/day, with others randomising to 20 mg/kg/day. As the maximum

recommended dose of cannabidiol in the draft PI is 10 mg/kg twice daily (20 mg/kg/day), all trials were considered relevant in the evaluation.

6.8 The submission also presented safety data from an open-label extension study (for patients enrolled in these four direct randomised trials), GWPCARE5.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
GWPCARE2	A randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome. NCT02224703 Miller I, Scheffer IE, Gunning B, et al. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial	12 December 2018; Amendment 1 15 March 2019 *JAMA Neurol*. 2020 Mar 2: e200073.
GWPCARE1 Part B	A double-blind, placebo-controlled, two-part study to investigate the dose-ranging safety and pharmacokinetics, followed by the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome. NCT02091375 Devinsky, O., et al. Trial of cannabidiol for drug-resistant seizures in the Dravet Syndrome.	11 November 2016 *NEJM* 2017: 376(21): 2011-2020
GWPCARE3	A randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults. NCT02224560 Devinsky O et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome.	19 July 2017 *NEJM* 2018: 378(20):1888-1897
GWPCARE4	A randomised, 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. NCT02224690 Theile EA et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial.	24 February 2017; Addendum 3 13 December 2018 *The Lancet* 2018: 391(10125): 1085-1096
GWPCARE5	An open label extension study to investigate the safety of cannabidiol (GWP42003-P; CBD) in children and young adults with inadequately controlled Dravet or Lennox-Gastaut Syndromes.NCT02224573 Devinsky O et al. Long-term cannabidiol treatment in patients with Dravet syndrome: An open-label treatment label. Thiele EA et al. Cannabidiol in patients with Lennox-Gastaut syndrome: interim analysis of an open-label extension study.	May 2017 *Epilepsia* 2019: 60(2): 294-302 *Epilepsia* 2019: 60(3): 419-428

Source: Tables 22 and 23, pp37-38 of the submission.

6.9 The key features of the direct randomised trials are summarised in Table 3. The two DS trials had the same design, although the GWPCARE2 trial had a different primary endpoint to the GWPCARE1 Part B trial. The two LGS trials had the same design.

Table 3: Key features of the included evidence

Trial	N	Design / duration	Bias	Population	Outcomes
Dravet syndrome					
GWPCARE2	198	R, DB, PC, MC, 14 weeks Titration to either 10 mg/kg/day or 20 mg/kg/day cannabidiol	Low	DS; age 2.1-18.9 years Median (interquartile range) baseline convulsive seizures per 28 days: 12 (6-33) Median (range) AEDs 3 (1-5)	1°: change in total convulsive seizures from baseline
GWPCARE1 Part B	120	R, DB, PC, MC, 14 weeks Titration to 20 mg/kg/day cannabidiol	Low	DS; age 2.3-18.4 years Median (range) baseline convulsive seizures per month: 13.0 (3.7-1717) Median (range) AEDs: 3 (1-5)	1°: percentage change from baseline in convulsive seizure frequency
Lennox-Gastaut syndrome					
GWPCARE3	225	R, DB, PC, MC, 14 weeks Titration to either 10 mg/kg/day or 20 mg/kg/day cannabidiol	Low	LGS; age 2.6-48 years Median (range) baseline drop seizures per 28 days 85 (38.3-190.0) Median (range) AEDs: 3 (0-5)	1°: percentage change from baseline in drop seizure frequency
GWPCARE4	171	R, DB, PC, MC, 14 weeks Titration to 20 mg/kg/day cannabidiol	Low	LGS; age 2.7-45 years; Median (range) baseline drop seizures per month: 71 – 75 (27.0-156.0); Median (range) AEDs: 3 (1-5)	

AED = antiepileptic drug; DB = double-blind; DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome; MC = multi-centre; PC = placebo-controlled; R = randomised;
Note: The 14 week duration included the titration phase for all trials
Source: Tables 27 and 28, p49 of the submission, Miller 2020, Devinsky 2017, Devinsky 2018, Thiele 2018 and compiled from Section 2 of the submission.

6.10 GWPCARE1 was a two-part trial, with Part A evaluating dose-ranging safety and pharmacokinetics of cannabidiol compared with placebo, and Part B evaluating the efficacy and safety of cannabidiol compared to placebo.

Comparative effectiveness

Dravet Syndrome (DS)

6.11 Table 4 summarises the trial results for the primary endpoints for patients enrolled in the DS trials of percentage reduction in convulsive seizure frequency from baseline for GWPCARE2 and the estimated median difference in convulsive seizure frequency from baseline for GWPCARE1 Part B. Also presented is the proportion of patients with a ≥50% reduction in convulsive seizures per 28 days from baseline at the end of the 14-week period of the trials, which the submission proposed as a clinically relevant outcome. Convulsive seizures were defined as tonic, clonic, tonic-clonic, and atonic seizures.

Table 4: Key results across the DS trials (ITT analyses)

	Cannabidiol 10 mg/kg/day	Cannabidiol 20 mg/kg/day	Placebo
GWPCARE2*			
Median convulsive seizure frequency (average per 28 days) at baseline (Q1, Q3)	13.53 (6.0, 31.2)	9.03 (6.03, 21.2)	16.63 (7.0, 51.1)
Median convulsive seizure frequency (average per 28 days) at end of treatment period (Q1, Q3)	6.30 (2.7, 18.6)	4.86 (2.3, 21.8)	14.00 (5.7, 49.3)
Percentage change from baseline in convulsive seizure frequency (28 day average)			
% reduction[a], (95% CI)	48.7 (37.9, 57.6)	45.7 (34.2, 55.2)	26.9 (11.9, 39.4)
Difference from placebo in percentage change from baseline in convulsive seizure frequency (28 day average)			
% reduction[a], (95% CI)	**29.8 (8.4, 46.2)**	**25.7 (2.9, 43.2)**	NA
Treatment ratio versus placebo			
% reduction[a], (95% CI)	**0.702 (0.538, 0.916)**	**0.743 (0.568, 0.971)**	NA
Proportion of patients experiencing ≥50% reduction in convulsive seizure frequency from baseline, n/N (%)	29/66 (43.9)	33/67 (49.3)	17/65 (26.2)
OR vs placebo (95% CI)	**2.21 (1.06, 4.62)**	**2.74 (1.32, 5.70)**	NA
RR vs placebo (95% CI)	**1.68 (1.03, 2.75)**	**1.88 (1.17, 3.03)**	NA
RD vs placebo (95% CI)	**0.18 (0.02, 0.34)**	**0.23 (0.07, 0.39)**	NA
GWPCARE1 Part B*			
Median convulsive seizure frequency (average per 28 days) at baseline (Q1, Q3)	NA	12.44 (6.2, 28.0)	14.88 (7.0, 36.0)
Median convulsive seizure frequency (average per 28 days) at end of treatment period (Q1, Q3)	NA	5.92 (3.2, 17.3)	14.14 (4.2, 31.1)
Median percentage change during treatment (Q1, Q3)	NA	**-38.94 (-69.5, -4.8)**	-13.29 (-52.5, 20.2)
Estimated median percentage difference from placebo[b] (95% CI)	NA	**-22.79 (-41.06, -5.43)**	NA
Proportion of patients experiencing ≥50% reduction in convulsive seizure frequency from baseline, n/N (%)	NA	26/61 (42.6)	16/59 (27.1)
OR of patients experiencing ≥50% reduction in convulsive seizure frequency from baseline compared to placebo (95% CI)	NA	2.00 (0.93, 4.30)	-

CI = confidence interval; NA = not applicable; OR = odds ratio; Q1 = lower quartile; Q3 = upper quartile; RD = risk difference; RR = relative risk

[a] using negative binomial regression approach

[b] using Wilcoxon rank-sum test with Hodges-Lehmann approach

Bold indicates statistically significant differences.

* 66 patients (10 mg/kg/day), 67 patients (20 mg/kg/day), 65 patients (placebo) in GWPCARE2 and 61 patients (20 mg/kg/day) and 59 patients (placebo) in GWPCARE1 Part B

Source: Table, 57, p101 and Table 61, p109 of the submission. Page 124-125, p145 of the GWPCARE2 CSR, p125 pf the GWPCARE1 Part B CSR, Table 58, pp102-103 of the submission.

6.12 GWPCARE2 demonstrated that patients treated with cannabidiol 10 mg/kg/day experienced, on average, an additional 29.8% reduction in the frequency of convulsive seizures per 28 days from baseline (primary endpoint) at 14 weeks compared to patients treated with placebo.

6.13 Patients treated with placebo reported overall positive improvement in the percentage change from baseline in convulsive seizure frequency (28 day average) (reduction of 26.9%, 95% CI 11.9%, 39.4%). Given that GWPCARE2 did not allow patients to use any new medications or interventions for epilepsy (including ketogenic

diet and vagus nerve stimulation) and only allowed changes in dosages of concomitant AED in certain circumstances, the improvement from baseline convulsive seizure frequency in patients using placebo could not be explained. Miller et al (2020) also noted that the placebo response rate in GWPCARE2 was higher than in GWPCARE1 (-26.9% vs -13%) without a clear explanation. The ESC noted that there was a significant placebo effect which may or may not be present to the same degree outside the intense monitoring of the clinical trials.

6.14 For secondary outcomes, compared to placebo, an additional 18% (95% CI: 2%, 34%) of patients treated with cannabidiol 10 mg/kg/day had a 50% or more reduction in convulsive seizure frequency from baseline. The PBAC has previously indicated that a 50% reduction in seizures is likely to be clinically important in patients with intractable epilepsy (paragraph 12, lacosamide PSD November 2009). The ESC considered that an additional 18% of patients achieving a ≥50% reduction in convulsive seizures was clinically meaningful. Two patients (3.0%) treated with the 10 mg/kg/day dose of cannabidiol were free from convulsive seizures by the end of the trial, compared to one patient treated with placebo (1.5%).

6.15 Other trial results for cannabidiol 10 mg/kg/day for DS showed that:

- there was a statistically significant improvement in the Caregiver Global Impression of Change score, with 18.5% of caregivers reporting that patients treated with cannabidiol were very much improved compared to 3.1% for placebo treated patients at Day 57; and
- total seizures (convulsive and non-convulsive) were reduced by 56.4% compared to placebo patients where the total reduction in seizure frequency from baseline was 29.7%.

6.16 For the 20 mg/kg/day dose, the results for trial GWPCARE2 showed that the percentage reduction in convulsive seizures from baseline (primary endpoint) (45.7%) was less than for the 10 mg/kg/day dose (48.7%). A higher proportion of patients treated with 20 mg/kg/day (49.3%) had a 50% or more percentage reduction in convulsive seizures from baseline compared to patients treated with 10 mg/kg/day (43.9%).

Lennox-Gastaut syndrome (LGS)

6.17 Table 5 summarises the trial results for the primary endpoint for patients enrolled in the LGS trials. Also presented is the proportion of patients with a ≥50% reduction in drop seizures (an epileptic seizure including atonic, tonic or tonic-clonic that leads or could lead to a fall, injury or slumping in a chair) per 28 days from baseline at the end of the 14-week period of the trials, which the submission proposed as a clinically relevant outcome.

Table 5: Key results of the LGS trials (ITT analyses)

	Cannabidiol 10 mg/kg/day	Cannabidiol 20 mg/kg/day	Placebo
GWPCARE3*			
Median drop seizure frequency (average per 28 days) at baseline (Q1, Q3)	86.90 (40.6, 190.0)	85.53 (38.2, 161.5)	80.25 (47.8, 148.0)
Median drop seizure frequency (average per 28 days) at end of treatment period (Q1, Q3)	50.00 (20.5, 113.2)	44.86 (14.4, 117.4)	72.66 (35.3, 125.0)
Median percentage change during treatment (Q1, Q3)	-37.16 (-63.8, -5.6)	-41.86 (-72.4, -1.3)	-17.17 (-37.1, 0.9)
Estimated median difference compared to placebo (95% CI)	**-19.19 (-31.24, -7.69)**	**-21.57 (-34.79, -6.67)**	NA
Proportion of patients experiencing ≥50% reduction in drop seizure frequency from baseline, n/N (%)	26/73 (35.6%)	30/76 (39.5%)	11/76 (14.5%)
OR vs placebo (95% CI)	**3.27 (1.47, 7.26)**	**3.85 (1.75, 8.47)**	NA
RR vs placebo (95% CI)	**2.46 (1.31, 4.61)**	**2.73 (1.48, 5.04)**	NA
RD vs placebo (95% CI)	**0.21 (0.08, 0.35)**	**0.25 (0.11, 0.39)**	NA
GWPCARE4*			
Median drop seizure frequency (average per 28 days) at baseline (Q1, Q3)	NA	71.43 (27.0, 156.0)	74.67 (47.3, 144.0)
Median drop seizure frequency (average per 28 days) at end of treatment period (Q1, Q3)	NA	31.38 (14.4, 92.0)	56.29 (29.7, 129.3)
Median percentage change during treatment (Q1, Q3)	NA	**-43.90 (-69.6, -1.9)**	-21.80 (-45.7, 1.7)
Estimated median percentage difference compared to placebo (95% CI),	NA	**-17.21 (-30.32, -4.09)**	-
Proportion of patients experiencing ≥50% reduction in drop seizure frequency from baseline, n/N (%)	NA	38/86 (44.2)	20/ 85 (23.5)
OR vs placebo (95% CI)	NA	**2.57 (1.33, 4.97)**	-
RD vs placebo (95% CI)	NA	**0.21 (0.07, 0.35)**	

CI = confidence interval; NA = not applicable; OR = odds ratio; Q1 = lower quartile; Q3 = upper quartile; RD = risk difference; RR = relative risk

Bold indicates statistically significant differences.

Median values were reported in the submissions rather than means

* 73 patients (10 mg/kg/day), 76 patients (20 mg/kg/day), 76 patients (placebo) in GWPCARE3 and 86 patients (20 mg/kg/day) and 85 patients (placebo) in GWPCARE4. Wilcoxon rank-sum test with Hodges-Lehmann approach used for primary outcome.

Source: Table 59, pp104-105, Table 60, pp105-107 and Table 63, p112 of the submission.

6.18 GWPCARE3 demonstrated that patients treated with cannabidiol 10 mg/kg/day experienced a difference in median percentage reduction in drop seizure frequency (the primary endpoint) of 19.19% compared with patients treated with placebo at 14 weeks.

6.19 An additional 21% of patients treated with cannabidiol 10 mg/kg/day in GWPCARE3 had a 50% or more reduction in drop seizure frequency from baseline compared to placebo.

6.20 No patients being treated with either cannabidiol 10 mg/kg/day or placebo were seizure-free at the end of GWPCARE3. A statistically significant reduction in total (drop and non-drop) seizure frequency from baseline of 36.44% for cannabidiol treated patients versus 18.47% for placebo treated patients, and an overall improvement in the combined Caregiver/subject Global Impression of Change score at the last visit were also reported.

6.21 For patients treated with the higher dose of 20 mg/kg/day cannabidiol in GWPCARE3, there was a statistically significant median reduction in drop seizure frequency (primary endpoint) of 21.57% compared to placebo treated patients during the 14 week period of the trial. A similar estimated median reduction of 17.21% was seen in GWPCARE4. A higher proportion of patients treated with 20 mg/kg/day (39.5%) had a 50% or more percentage reduction in convulsive seizures from baseline compared to patients treated with 10 mg/kg/day (35.6%).

6.22 Quality of life data was collected in the trials. For the key trials (GWPCARE2 for DS and GWPCARE3 for LGS), while the adjusted mean difference between treatments was in favour of cannabidiol over placebo, none of the differences in the subscales or the overall quality of life in childhood epilepsy scores were statistically significant.

6.23 There was no statistically significant difference in the rate of hospitalisations due to epilepsy in the key trials. This was inconsistent with the submission's assumption that treatment with cannabidiol would reduce epilepsy-related hospitalisations in the modelled economic evaluations.

Comparative harms

6.24 Significantly more patients treated with cannabidiol experienced at least one adverse event (AE) compared with placebo in the randomised trials (see Table 6). The most common AEs included somnolence, decreased appetite, diarrhoea, need for investigations, and fatigue.

6.25 The safety profile for cannabidiol 10 mg/kg/day relative to placebo appears to be more favourable than the safety profile for cannabidiol 20 mg/kg/day relative to placebo. The ESC noted the significant rates of adverse events for cannabidiol 20mg/kg/day, particularly fatigue, diarrhoea and psychiatric disorders, which may have significant negative impacts on patient's and carer's quality of life.

6.26 The ESC considered long-term safety data would be useful in light of the rates of adverse events; however, acknowledged it would be challenging to conduct longer-term trials given participation in the trials were burdensome to patients and carers. The ESC considered that open label extension and post marketing surveillance would be important to inform long-term safety of cannabidiol.

Benefits/harms

6.27 A summary of the comparative harms for cannabidiol and standard care (continuation of patient's existing AED therapies) versus placebo and standard care is presented in Table 6 for statistically significant differences in trials GWPCARE2 and GWPCARE1 Part B (for DS) and GWPCARE3 and GWPCARE4 (for LGS).

Table 6: Summary of comparative harms for cannabidiol and standard care versus placebo and standard care

	Cannabidiol 10 mg/kg/day	Placebo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Cannabidiol 10 mg/kg/day	Placebo	
Psychiatric disorders (irritability, insomnia, aggression)						
GWPCARE3	9/67	2/76	**5.10 (1.14, 22.8)**	13.4	2.6	**0.11 (0.02, 0.21)**
	Cannabidiol 20 mg/kg/day	**Placebo**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Cannabidiol 20 mg/kg/day	**Placebo**	
Fatigue						
GWPCARE2	14/69	4/65	**3.30 (1.14, 9.50)**	20.3	6.2	**0.14 (0.03, 0.26)**
GWPCARE1 Part B	10/61	1/59	**9.67 (1.28, 73.2)**	16.4	1.7	**0.15 (0.05, 0.26)**
Diarrhoea						
GWPCARE2	15/69	4/65	**3.53 (1.24, 10.09)**	21.7	6.2	**0.16 (0.04, 0.28)**
GWPCARE1 Part B	13/61	2/59	**6.29 (1.48, 26.7)**	21.3	5.1	**0.18 (0.07, 0.30)**
GWPCARE4	11/86	3/85	**3.62 (1.05, 12.5)**	12.8	3.5	**0.09 (0.01, 0.18)**
Investigations						
GWPCARE2	17/69	6/65	**2.67 (1.12, 6.35)**	24.6	9.2	**0.15 (0.03, 0.28)**
GWPCARE1 Part B	14/61	1/59	**13.5 (1.84, 99.7)**	23.0	1.7	**0.21 (0.11, 0.34)**
GWPCARE3	14/82	2/76	**6.49 (1.52, 27.6)**	17.1	2.6	**0.14 (0.06, 0.24)**
GWPCARE4	18/86	4/85	**4.45 (1.57, 12.6)**	20.9	4.7	**0.16 (0.07, 0.27)**
Somnolence						
GWPCARE2	16/69	6/65	**2.51 (1.05, 6.03)**	23.2	9.2	**0.14 (0.01, 0.27)**
GWPCARE1 Part B	19/61	4/59	**4.59 (1.66, 12.7)**	31.1	6.8	**0.24 (0.11, 0.38)**
GWPCARE3	21/82	2/76	**9.73 (2.36, 40.1)**	25.6	2.6	**0.23 (0.13, 0.34)**
Decreased appetite						
GWPCARE3	13/82	2/76	**6.02 (1.41, 25.8))**	15.9	2.6	**0.13 (0.05, 0.23)**
GWPCARE4	8/86	1/85	**7.91 (1.01, 61.9)**	9.3	1.2	**0.08 (0.02, 0.16)**
Psychiatric disorders (irritability, insomnia, aggression)						
GWPCARE1 Part B	9/61	1/59	**8.70 (1.14, 66.6)**	14.8	1.7	**0.13 (0.04, 0.24)**

RD = risk difference; RR = risk ratio. Bold signifies a statistically significant difference.

* Median duration of follow-up: 14 weeks

Source: Tables 65-68, pp116-125 of the submission. CSRs for each trial

6.28 On the basis of direct evidence presented by the submission as detailed in Table 4, Table 5 and Table 6, for every 100 patients treated with cannabidiol 10 mg/kg/day as an adjunct to standard care compared to every 100 patients treated with placebo and standard care, over a median duration of exposure of 14 weeks:

- Approximately 18 additional DS patients would have a 50% or greater reduction in convulsive seizures per 28 days from baseline.
- Approximately 21 additional LGS patients would have a 50% or greater reduction in drop seizures per 28 days from baseline.
- Approximately 11 additional LGS patients would experience psychiatric disorders such as irritability or aggression or difficulty sleeping (insomnia).

6.29 On the basis of direct evidence presented by the submission, for every 100 patients treated with cannabidiol 20 mg/kg/day as an adjunct to standard care compared to

every 100 patients treated with placebo and standard care, over a median duration of exposure of 14 weeks:

- Approximately 16 to 23 additional patients with DS would have a 50% or greater reduction in convulsive seizure frequency per 28 days from baseline[4].
- Approximately 21 to 25 additional patients with LGS would have a 50% or greater reduction in drop seizure frequency per 28 days from baseline[5].
- For DS, 15 to 21 additional patients would require investigations, 14 to 15 additional patients would experience fatigue, 13 additional patients would experience psychiatric disorders (such as irritability, or aggression or difficulty sleeping (insomnia)), 15 to 16 additional patients would experience diarrhoea, and 14 to 24 would experience somnolence (sleepiness).
- For LGS, approximately 8 to 13 additional patients would experience decreased appetite, 23 additional patients would experience sleepiness (somnolence), 15 to 16 additional patients would require investigations, and 9 additional patients would experience diarrhoea.

Clinical claim

6.30 The submission described cannabidiol as adjunctive therapy to standard oral AEDs as superior in terms of effectiveness compared with standard oral AEDs alone and inferior in terms of safety in patients with seizures associated with DS or LGS who have trialled two other appropriate AEDs to a maximally tolerated dose and failed to achieve seizure freedom. The claim was based on evidence provided in the randomised placebo-controlled trials, GWPCARE2 and GWPCARE1 Part B for DS and GWPCARE3 and GWPCARE4 for LGS.

6.31 The evaluation considered the therapeutic conclusion in relation to inferior safety was adequately supported by the evidence presented.

6.32 The evaluation considered the claim regarding superior efficacy, was not supported for the following reasons:

- There was no requirement for patients with DS in GWPCARE2 and GWPCARE1 Part B to have trialled two other AEDs, although the ESC noted that all patients had trialled at least one other AED and the median previously trialled AEDs was 3;
- Patients enrolled in the trials did not need to have failed to respond to a maximally tolerated dose of AEDs prior to entry in the trials;
- The randomised trials presented were of short duration (14 weeks). While the trial evidence supported an assertion that cannabidiol as adjunctive therapy to standard oral AEDs is superior in terms of comparative effectiveness to standard oral AEDs

[4] Based on results from both the GWPCARE2 and GWPCARE1 Part B secondary outcome of 50% or greater reduction in convulsive seizures.

[5] Based on results from both GWPCARE3 and GWPCARE4 secondary outcome of 50% or greater reduction in drop seizures.

alone, no randomised trial evidence was provided to support the view that superior efficacy would be maintained over a longer time frame. The ESC considered that while the trials where of short duration, it is unlikely that longer randomised trials will be forthcoming. The ESC agreed with the PSCR that extending the trials beyond 14 weeks with placebo would not be ethical. In the Pre-PBAC response, the sponsor noted that stiripentol had been recommended by the PBAC in March 2020 based on two clinical trials which ran for only two months and with a smaller trial population (pre-PBAC response);

- Standard care in the trials may not reflect standard care in clinical practice due to limitations in changing concomitant medications.

6.33 The ESC considered that, overall, the claim that cannabidiol as adjunctive therapy to standard oral AEDs was superior in terms of effectiveness compared with standard oral AEDs was reasonable in these difficult to treat patient populations. However, the ESC considered the magnitude of benefit may be uncertain in clinical practice given the issues raised in paragraph 6.32.

6.34 The PBAC agreed with the ESC that the claim that cannabidiol as adjunctive therapy was superior in terms of effectiveness was reasonable but the magnitude of the benefit was uncertain.

6.35 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.36 The submission presented stepped economic evaluations of cannabidiol 10 mg/kg/day that were stated to have been based on the direct randomised trials (GWPCARE2 for DS and GWPCARE3 for LGS). Very little of the trial based data used to inform the analyses could be verified. The workings of the model were also difficult to elucidate given the use of VBA code and subsequent lack of transparency. However, numerous issues were identified during the evaluation with the data used to populate the models, both for data that was said to have been extracted from these trials, and for assumptions that were used to extrapolate the outcomes out to 30 years. Patients treated with cannabidiol 20 mg/kg/day were not included in the economic analysis.

6.37 The type of economic evaluations presented were cost-utility analyses designed to estimate the incremental cost and benefits of cannabidiol 10 mg/kg/day as an adjunct to standard care, versus placebo and standard care.

6.38 A summary of the model structures and key inputs is presented in Table 7.

Table 7: Summary of model structures and key inputs

Component	Summary
Treatments	Cannabidiol 10 mg/kg/day as an adjunct to standard care, versus placebo and standard care
Time horizon	30 years in the base case of each model versus 14 weeks in the trials
Outcomes	QALYS
Methods used to generate results	Markov state-transition cohort models
Health states	For DS, patients entered the model in two age cohorts, <12 years (split further into 2-5 and 6-11 years) or ≥12 years (split further into 12-17 and 18-55 years) of age into 1 of 9 health states based on convulsive seizures per month (≤18; >18 - ≤25 and >25), each sub-categorised by the number of days without convulsive seizures (<18 days; >18 - <24 days; >24 days). From Cycle 1, there were 25 health states: • 12 based on the number of convulsive seizures per month (seizure-free, ≤18; >18 - ≤25 and >25), each sub-categorised by the number of days without convulsive seizures (<18 days; >18 - <24 days; >24 days); • 12 discontinued health states (seizure-free, ≤18; >18 - ≤25 and >25), each sub-categorised by the number of days without convulsive seizures (<18 days; >18 - <24 days; >24 days); and • Death (from three possible causes: SUDEP, non-SUDEP and background). Death was an absorbing state. For LGS, patients entered the model in two age cohorts, <12 years (split further into 2-5 and 6-11 years) or ≥12 years (split further into 12-17 and 18-55 years) of age into 1 of 9 health states based on the number of drop seizures per month (≤45; >45 - ≤110 and >110) and the number of days without drop seizures (<3 days; >3 - ≤15 days; >15 days). From Cycle 1, there were 25 health states: • 12 based on the number of drop seizures per month (seizure-free, ≤45; >45 - ≤110 and >110) each sub-categorised by the number of days without drop seizures (<3 days; >3 - ≤15 days; >15 days); • 12 discontinued health states (seizure-free, ≤45; >45 - ≤110 and >110) each sub-categorised by the number of days without drop seizures (<3 days; >3 - ≤15 days; >15 days); and • Death (from three possible causes: SUDEP, non-SUDEP and background). Death was an absorbing state. The models additionally separated all states based on whether the patient was spending their 'first' or a 'subsequent' cycle in any given health state, except for 'background' death. The health states were considered to be too wide in terms of number of seizures per month to adequately capture changes in seizure frequency between cycles. The ranges were selected to ensure the patients in the trials were split into three equal groups, and therefore, for the analyses to have sufficient statistical power. There is no indication that these ranges represent clinically important groups that subsequently attract different costs and utilities.
Cycle length	3 months. Inappropriately, no half cycle correction was applied.
Transition probabilities	For Cycle 1, the transition probabilities were based on a re-cut analysis of data for the 10 mg/kg/day cannabidiol and placebo treatment groups from GWPCARE2 and GWPCARE3. Transition probabilities were also dependent on the cycle number and the age of the patient at the particular cycle. The transition probabilities could not be verified, and from cross-checks undertaken during the evaluation, the data did not appear to reconcile. It was claimed that data from GWPCARE5 was used from Cycle 2 to Cycle 9 for cannabidiol. GWPCARE5 used a higher dose of cannabidiol (mean modal dose was 23 mg/kg/day). Transition probabilities after Cycle 9 for cannabidiol assumed no waning of treatment effect. This was not reasonable given that efficacy of AEDs is thought to decline over time. For placebo treated patients, response to placebo was assumed to only apply in Cycle 1, and patients remained in that health state to Cycle 8, unless they died. Patients who were alive and discontinued from cannabidiol and patients treated with placebo reverted to baseline seizure/seizure-free days health states in Cycle 9.
Health related quality of life	Health state utilities were derived based on a questionnaire with a visual analogue scale (VAS) of patients and/or caregivers of patients with DS, LGS or other epilepsies. Vignettes were provided to the

Component	Summary
	patients and/or caregivers describing 23 health states for DS and 39 health states for LGS, and these were scored by 28 to 30 respondents for each disease state. The utility values were key drivers of the modelled economic evaluations. As the vignettes were not provided in the submission, it was not possible to determine whether they would have appropriately represented patients in the health states scored. In some cases the values appeared to lack face validity with small differences in utility values despite a large difference in seizures per month. The submission also used carer disutilities collected using the same approach for three health states, however these were not considered appropriate for inclusion in the base case ICERs.
Costs	The cost of cannabidiol was calculated using the requested price per mg multiplied by the median weights of patients in the age groups of 2-5, 6-11, 12-17, and 18 or more years from the key trials, and an assumed dose of cannabidiol of 10 mg/kg/day. It was unreasonable for the submission to assume that all patients would take this dose in practice, since the dose may be increased up to 20 mg/kg/day. The models were sensitive to the dose of cannabidiol used and to the average weights of patients in the models given that the cost of cannabidiol accounts for most of the incremental difference between treatment arms. Drug costs for standard care were assumed to be the same between treatment groups. This may not accurately reflect clinical practice, as cannabidiol may be used instead of other AEDs. The other key component of costs in the models was the cost of hospitalisation due to epilepsy, with the models assuming that treatment with cannabidiol would reduce hospitalisations, which favoured cannabidiol. The trial evidence did not support an assertion that cannabidiol would reduce hospital admissions.

AED = anti-epileptic drugs; DS = Dravet Syndrome; ICER = incremental cost effectiveness ration; LGS = Lennox Gasault Syndrome; QALY = quality adjusted life year; SUDEP = sudden unexplained death in epilepsy
Source: constructed during the evaluation from Section 3 of the submission and the cost-utility workbooks provided with the submission.

6.39 The ESC noted that the costs accounted for in the economic model were likely underestimated as:

- there was no allowance for the cost of treating adverse events, which was unreasonable considering the adverse event outcomes of the clinical trials;
- monitoring of plasma levels of other AEDs following the initiation of cannabidiol (as recommended in the draft PI) was not accounted for;
- the included costs were variously based on MBS prices, AR-DRGS, UK prices and provider websites with no justification for the source selection; and
- the model assumed all patients received 10mg/kg/day.

6.40 The ESC noted the response in the PSCR that only patients who respond to a 10 mg/kg/day dose and wish to further reduce seizure burden would be titrated to 20 mg/kg/day. However, the ESC considered that the clinical trials, including the long term effectiveness trial GWPCARE5, the draft PI and the requested listing allowed doses of cannabidiol up to 20 mg/kg/day, therefore considered that the model assumption that all patients would receive 10 mg/kg/day was an underestimate.

6.41 The ESC considered that the modelled health states did not align with the outcomes from the key trials and additionally did not align with established meaningful health states.

6.42 The ESC noted that the health state utilities were derived from an unpublished study, with a small sample size (n=38) and the actual vignettes (23 for DS and 39 for LGS) used were not provided in the submission. The ESC noted the single vignette provided

with the PSCR but considered this was uninformative and the use of this data was considered an area of significant uncertainty.

6.43 Overall, the ESC considered the models were uninformative for decision making given:

- The extrapolation of 14 week trial data to a 30-year time horizon, which magnified the uncertainties;
- The wide range of assumptions used in the models that could not be verified or lacked face validity, or did not reconcile with data reported in the key trials;
- The potential for changes in seizure response over time were not adequately captured in the models, given the assumption that a waning of treatment effect for cannabidiol did not occur;
- The rationale for the health states selected was not considered to have been adequately justified, and the ranges for seizure frequency were considered to be too wide;
- The assumption that patients would cease treatment with cannabidiol at 12 months if seizure frequency was not at least 30% was not adequately supported given that: (i) additional therapies could be added onto existing therapies to contribute to reduction in seizure frequency; (ii) given the Streamlined listing requested that does not require specific documentation to be submitted related to treatment response; (iii) clinicians are likely to cease treatment earlier than 12 months if no response achieved;
- The vignettes used to derive the nominated utility values were not provided, and therefore it was not possible to determine if they included information on other seizures that patients may continue to experience (e.g. non-convulsive seizures for patients with DS, and non-drop seizures for patients with LGS) and on ability for self-care. It is likely that the utility values were overestimated, and this potentially favoured cannabidiol;
- The cost of cannabidiol was likely underestimated given the models did not account for use of doses of cannabidiol of more than 10 mg/kg/day, and this favoured cannabidiol.

6.44 There were a large number of inconsistencies between inputs into the models and the clinical trial data informing the models. For example:

- The transition probabilities used in the models could not be verified, and from the cross-checking that was possible (limited due to non-availability of the individual patient data, and re-cut data used in the models), the number of patients in some of the health states in the models could not be reconciled with the trial data.
- The adverse event rates used in the models to inform disutilities and associated management costs were not consistent with the rates reported in the key trials.
- The models assumed that patients would have improved utility values and reduced hospitalisations due to epilepsy, however these assumptions were not supported by the data from the key trials which did not report any statistically significant differences between arms in overall quality of life, or in rates of hospitalisation due to epilepsy.

6.45 Key drivers of the models are summarised in Table 8.

Table 8: Key drivers of the models

Description	Method/Value	Impact
Base case (no carer utilities): $75,000 to < $95,000/QALY gained for DS and $155,000 to < $255,000/QALY gained for LGS over 30 years		
Extrapolation	Treatment effect of cannabidiol 10 mg/kg/day assumed to continue beyond 14 weeks in the randomised controlled trials. Transition probabilities could not be verified for any cycle. No waning of treatment effect after Cycle 9. Placebo response ceased after Cycle 1.	**High, favours cannabidiol** Using a 1 year time horizon instead of 30 years in the base case increased the ICER to $455,000 to < $555,000/QALY gained for DS (+514%) and to $555,000 to < $655,000//QALY gained for LGS (+260%). The ESC noted that the March 2020 stiripentol submission used a 5 year time horizon.
Utilities	Use of the utility values as detailed in the submission through scoring of vignettes using a visual analogue scale. The ESC noted that this data was from an unpublished study with a small sample size. The clinical trial data showed no significant difference in quality of life.	**High, favours cannabidiol** Use of the submission's assignment of Verdian et al 2008 utility values instead of the vignettes in the base case increased the ICERs to $135,000 to < $155,000/QALY gained for DS (+65%) and to $255,000 to < $355,000/QALY gained for LGS (+78%)
Cost of cannabidiol	Assumed dose of 10 mg/kg/day and patient weights based on medians in the key trials for each disease state. Draft PI and clinical trial data allows a maximum maintenance dose of 20 mg/kg/day.	**High, favours cannabidiol** Assuming a dose of 15 mg/kg/day increased the ICERs to $155,000 to < $255,000/QALY gained for DS (+103%) and to $255,000 to < $355,000/QALY gained for LGS (+57%)
Cost of hospitalisations due to epilepsy	The ESC noted that the model assumed cannabidiol reduced the frequency of hospitalisations, however no reduction in hospitalisations was observed in the key trials. Furthermore, it was not apparent where the estimates of resource use for the submission for hospitalisation in Australia were derived.	**High, favours cannabidiol** The ICER for DS was particularly sensitive to the cost of hospitalisation. Assuming no hospitalisation costs (a proxy for no difference in hospitalisation between treatment arms) increased the ICER to $155,000 to < $255,000/QALY gained for DS (+73%) and to $155,000 to < $255,000/QALY gained for LGS (+6%)
Assumption of discontinuation in cannabidiol beyond Cycle 10	The submission assumed that 0.5% of all seizure-free patients and 10% of patients in all other health states discontinued from cannabidiol beyond Cycle 9, with no corresponding reduction in efficacy.	**High, favours cannabidiol** Assuming no discontinuation from treatment in Cycles 10-120, the ICER increased to $135,000 to < $155,000/QALY gained (+59%) in DS and $155,000 to < $255,000/QALY gained in LGS (+41%)

AED = anti-epileptic drugs; DS = Dravet Syndrome; ESC = economic sub-committee ICER = incremental cost effectiveness ration; LGS = Lennox Gastaut Syndrome; PI = product information; QALY = quality adjusted life year

Source: constructed during the evaluation from Section 3 of the submission, and the cost-utility workbooks provided with the submission.

6.46 The ESC noted that the cost of cannabidiol was a key driver of the model, and considered that the use of median patient weights did not reflect the large weight range represented by the patient population, and likely led to an underestimate of the cost.

6.47 The ESC noted that the time horizon was also a significant driver of the model, and considered that a 30 year time horizon was not supported by the available clinical evidence. While the ESC considered that it is was unlikely that longer term trial data would become available, due to the difficulties of conducting clinical trials in the patient population, it considered that a 5 year time horizon, as was submitted for stiripentol, would be more appropriate given the length of the trial data.

6.48 Table 9 and Table 10 present the results of the stepped economic evaluations for DS and LGS respectively. Steps 3 and 4 were modified during the evaluation from that presented in the submission, to remove the carer utilities that were included in the submission's estimates, given the PBAC's preference for use of a healthcare perspective, and outcomes which are beyond the treated patient population should only be included as supplementary analyses. The ESC acknowledged the significant impact of DS and LGS on caregiver's quality of life, however considered it was not appropriate to include this utility in the base case.

Table 9: Results of the stepped economic evaluation: DS

Step and component	Cannabidiol 10 mg/kg/day	Placebo	Increment
DS trial-based costs and outcomes			
Cannabidiol costs	$[redacted]	$0	$[redacted]
Proportion of patients with at least a 50% reduction in convulsive seizures	43.9%	26.2%	17.7%
Proportion of patients seizure-free	3.0%	1.5%	1.50%
Incremental cost over the trial period of 98 days			$[redacted]
Incremental cost per patient with a 50% or greater reduction in convulsive seizures over 98 days (cost/17.7%)			$[redacted]
Incremental cost per patient free from convulsive seizures over 98 days (cost/1.5%)			$[redacted]
	Cannabidiol 20 mg/kg/day	**Placebo**	**Increment**
Cannabidiol costs*	$[redacted]	$0	$[redacted]
Proportion of patients with at least a 50% reduction in convulsive seizures	49.3%	26.2%	23.1%
Proportion of patients seizure free	4.5%	1.5%	3.0%
Incremental cost over 98 days			$[redacted]
Incremental cost per patient with a 50% or greater reduction in convulsive seizures over 98 days (cost/23.1%)			$[redacted]
Incremental cost per patient free from convulsive seizures over 98 days (cost/3.0%)			$[redacted]
Time horizon extended to 1 year using modelled data (no carer disutilities)			
Costs	$[redacted]	$56,299	$[redacted]
QALYs	0.47	0.43	0.03
Incremental cost/extra QALY gained			$[redacted]
Time horizon extended to 30 years using modelled data (no carer disutilities)			
Costs	$[redacted]	$446,757	$[redacted]
QALYs	6.24	5.77	0.47
Incremental cost/extra QALY gained (base case)			**$[redacted]**
Time horizon extended to 30 years using modelled data (with carer disutilities) – base case in the submission			
Costs	$[redacted]	$446,757	$[redacted]
QALYs	0.43	-0.50	0.93
Incremental cost/extra QALY gained			**$[redacted]**

DS Dravet Syndrome; QALY = quality adjusted life year

*Cost for 20 mg/kg/day over 98 days plus 2 physician treatment visits at $195 per visit, in line with the submission's assumptions for the 10 mg/kg/day dose

Source: Table 110, p191 of the submission and constructed during the evaluation.

The redacted table shows the base case ICER (no carer disutilities) in the range of $75,000 to < $95,000 per QALY, versus an ICER (with carer disutilities) in the range of $35,000 to < $45,000 per QALY.

6.49 The ESC noted the ICER for the 30 year time horizon without allowing for carer disutilities was approximately twice that of stiripentol ($35,000 to < $45,000 per QALY gained) (Table 11, stiripentol PSD, March 2020 PBAC meeting).

Table 10: Results of the stepped economic evaluation: LGS

Step and component	Cannabidiol 10 mg/kg/day	Placebo	Increment
LGS trial-based costs and outcomes			
Cannabidiol costs	$[redacted]	$0	$[redacted]
Proportion of patients with at least a 50% reduction in drop seizures	35.6%	14.5%	21.1%
Incremental cost over 98 days			$[redacted]
Incremental cost per patient with a 50% or greater reduction in convulsive seizures over 98 days (cost/21.1%)			$39,872
	Cannabidiol 20 mg/kg/day	**Placebo**	**Increment**
Cannabidiol costs	$[redacted]	$0	$[redacted]
Proportion of patients with at least a 50% reduction in drop seizures	39.5%	14.5%	25.0%
Incremental cost over 98 days			$[redacted]
Incremental cost per patient with a 50% or greater reduction in convulsive seizures over 98 days (cost/25.0%)			$65,740
Time horizon extended to 1 year (no carer disutilities) as reported by the submission			
Costs	$[redacted]	$17,808	$[redacted]
QALYs	0.47	0.44	0.03
Incremental cost/extra QALY gained			$[redacted]
Time horizon extended to 30 years using modelled data (no carer disutilities)			
Costs	$[redacted]	$231,994	$[redacted]
QALYs	5.31	4.79	0.52
Incremental cost/extra QALY gained (base case)			**$[redacted]**
Time horizon extended to 30 years using modelled data (with carer disutilities) – base case in the submission			
Costs	$[redacted]	$231,994	$[redacted]
QALYs	-1.46	-2.76	1.3
Incremental cost/extra QALY gained			**$[redacted]**

LGS = Lennox Gastaut Syndrome; QALY = quality adjusted life year

Cost for 20 mg/kg/day over 98 days plus 2 physician treatment visits at $195 per visit, in line with the submission's assumptions for the 10 mg/kg/day dose

Source: Table 100, p191 of the submission and constructed during the evaluation and Table 110, pp191-192 of the submission.

The redacted table shows the base case ICER (no carer disutilities) in the range of $155,000 to < $255,000 per QALY, versus an ICER (with carer disutilities) in the range of $55,000 to < $75,000 per QALY.

6.50 The ESC considered the March 2020 PBAC recommendation for stiripentol for DS may provide a useful framework for consideration of the cost-effectiveness of cannabidiol for DS and LGS. The ESC advised that a simpler economic model, as was used in the stiripentol submission, with a 5 year time horizon, 4 health states clearly linked with health outcomes from the clinical trials, and applying utilities sourced from peer reviewed literature (Verdian 2008) could be a more appropriate approach, noting that addressing other issues raised in paragraphs 6.43 and 6.44 would also be required.

Drug cost/patient/year

Table 11: Drug cost per patient for cannabidiol

	Trial dose and duration	Trial-based analyses in Section 3	Modelled economic evaluations	Financial estimates
Mean dose	DS: 32.8 kg x 10.06 mg/kg/day LGS: 44.25 kg x 9.94 mg/kg/day	10 mg/kg/day and mean weight of 32.8 kg and 44.25 kg for DS and LGS	10 mg/kg/day based on median weights by age in the trials (average DS 32.1 kg, LGS 41.3 kg)	10 mg/kg/day based on average weight of 33 kg for DS and 43 kg for LGS
Mean duration	DS: 98.3 days LGS: 98.4 days	98 days	1 year less discontinuations for DS of 4.35% in Cycle 1 and between 0.50% and 5.41% in Cycle 2, and for LGS of 6.25% in Cycle 1 and between 0.50 and 4.69% in Cycle 2 and mortality of 1.58%	1 year
Cost/patient/ trial-based period	DS: $[redacted] LGS: $[redacted]	DS: $[redacted] LGS: $[redacted]	-	-
Cost/patient/ year	-	-	Based on using a 1-year model duration* DS: $[redacted] LGS: $[redacted]	DS: $[redacted]** LGS: $[redacted]**

DS = Dravet Syndrome; LGS = Lennox Gastaut Syndrome;
Source: constructed during the evaluation from Sections 2, 3 and 4 of the submission.
* calculated as treatment cost cannabidiol minus placebo with a 1-year model duration
** based on total cost to PBS/number of patients

6.51 The cost of cannabidiol per patient for the first year of treatment (based on the economic model) was estimated to be $[redacted] for patients with LGS and $[redacted] for patients with DS. This cost was lower compared to the financial estimates, due to the models' use of median weights rather than mean weights, and the assumption in the models that some patients will discontinue treatment.

6.52 The PBAC recalled stiripentol had been recommended for the treatment of DS at a modelled cost per patient per year of $[redacted] (Table 12, stiripentol PSD, March 2020 PBAC meeting).

Estimated PBS usage & financial implications

6.53 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate both the incidence and prevalence of DS and LGS in Australia, the utilisation of cannabidiol and the associated financial implications to the PBS and the health budget. It was assumed that cannabidiol would be prescribed as adjunctive therapy to other AEDs, that patients would cease treatment without tapering of the dose should they not have at least a 30% reduction in seizure frequency per month from baseline within 12 months of initiating therapy, and that there would be no change in the dose of cannabidiol or in the use of any other AEDs over time. It was also assumed that there would be net savings to the health budget associated with reduced hospitalisation for patients becoming seizure free on cannabidiol.

6.54 Table 12 summarises the key inputs used in the financial estimates.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incidence/prevalent population	LGS: Incidence rate 0.0019%, prevalence rate 0.016% from systematic review of publications. DS: 0.003%, prevalence 0.004% from Rosander 2015	The ESC noted the prevalence of DS in the Rosander 2015 paper was reported as 1/45,700 or 0.002%. The ESC noted the incidence and prevalence of LGS was based on a systemic review but minimal detail regarding the review or associated publications were provided in the submission.
% who are inadequately controlled on current AEDs	85%, based on Ostendorf 2017	Not a requirement for use of cannabidiol. Unreasonable to apply this assumption. Corrected in the revised base case to 100%
% medically eligible for cannabis	90%, based on clinician feedback in the UK	Considered unreasonable to apply this assumption given no justification for it and no definition of it. Corrected in the revised base case to 100%
Uptake rate	LGS: Prevalent: 48% in 2021, increasing to 64%, 74%, 82%, 88% and 96% in years up to 2026. Incident: 0% in 2021 and 5% thereafter. DS: Prevalent: 60% in 2021, increasing to 78%, 84%, 87%, 92% and 96% in years up to 2026. Incident: 0% in 2021 and 5% thereafter. From sponsor projections from UK and US uptake.	Considered highly uncertain and likely underestimated.
Patients continuing after 12 months	LGS: 63% (from GWPCARE2 trial) DS: 44% (stated to be from GWPCARE3 trial)	The proportion of patients achieving at least a 25% reduction from baseline in drop seizures for LGS and convulsive seizures for DS was equal to 63% and 56% at 14 weeks. The proportions could be substantially higher than estimated based on the requested streamlined listing, lack of detail required for patients before they could continue on treatment, and higher response rates in DS patients taking 20 mg/kg/day dose in GWPCARE2
Grandfathered patients	< 500 patients: 80% LGS and 20% DS from NSW and QLD compassionate access scheme	Reasonable, although mortality rates were not applied to these patients, which was inconsistent.
Dose/duration	Ongoing dose of 10 mg/kg/day for patients at initiation and in those who continue on therapy after 12 months, based on recommended maintenance dose in draft PI	Consistent with the economic evaluation, however this is likely to be an underestimate of the likely dose in practice.
Patient weight	LGS: 43 kg and DS: 33 kg, based on mean weight in GWPCARE1-4 trials	Unreasonable, since the average age and weight of patients likely to use cannabidiol on the PBS is unknown, and since the assumptions included no allowance for the average weight to increase as younger patients who commence on cannabidiol age over time.
Bottles of cannabidiol required per month	1.29 bottles for LGS and 1.00 for DS	Annual units were 12.05 for DS and 15.7 for LGS. No allowance was made for wastage in discontinuing patients, which was inappropriate. This underestimated the expected cost of cannabidiol to the PBS.
Offsets for other drug therapies	None	Consistent with the economic evaluation, however there may be changes in the dose and or use of other AEDs in practice.

Parameter	Value applied and source	Comment
Hospitalisations	Assumed 13% of patients would become seizure free and avoid an average 3 day hospital stay, based on general ward daily cost of $1,700.42 per day from National Hospital Cost Data Collection Round 22, DRG B76A and B76B	Not considered appropriate. Cost offsets due to reduced hospitalisations may not be realised.

AED = anti-epileptic drug; DS = Dravet Syndrome; ESC = economic sub-committee; LGS = Lennox Gastaut Syndrome; PBS = Pharmaceutical Benefits Scheme; PI = product information
Source: Table 130, pp213-214 of the submission.

6.55 Table 13 summarises the estimated use and financial implications of the proposed PBS listing for cannabidiol.

Table 13: Estimated use and financial implications

	2021	2022	2023	2024	2025	2026
DS treated patients at the end of year*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised script numbers – DS (one 100 mL bottle per script)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised PBS/RPBS cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
LGS treated patients at end of year**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised script numbers – LGS (two 100 mL bottles per script)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised PBS/ RPBS cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Revised estimated financial implications of cannabidiol (based on above)						
Revised cost to PBS/ RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/ RPBS* **	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

* Based on assuming all diagnosed patients are medically eligible and otherwise eligible for cannabidiol, and the continuation rate is 56% at the end of 2021 rather than 44% to be consistent with the approach for LGS
** Based on assuming all diagnosed patients are medically eligible and otherwise eligible for cannabidiol
*** The net change in services and costs to the MBS and health budgets associated with an assumed reduced number of hospitalisations due to more patients becoming seizure free are not presented as these costs were not considered likely to be realised
LGS: DPMQ of $[redacted] for 2 x 100 mL bottles per script
DS: DPMQ of $[redacted] for 1 x 100 mL bottle per script
Estimates that were updated during the evaluation assuming all patients are medically eligible for cannabidiol and that treatment is not limited to patients inadequately controlled on other AEDs, and that 56% of patients will continue on treatment for DS rather than 44% to be consistent with the approach for LGS
Source: constructed during the evaluation from Table 137, p219 and Tables 139- 141, pp220-221 of the submission.

The redacted table shows that at Year 6, the estimated number of scripts was 500 to < 5,000 and 5,000 to < 10,000 for DS and LGS respectively.

6.56 The revised (assuming all patients would be medically eligible, and one and two bottles per script for DS and LGS, respectively) total net cost to the PBS/RPBS of listing cannabidiol was estimated to be $30 million to < $40 million in Year 6, and a total net cost of $200 million to < $300 million in the first 6 years of listing.

6.57 The revised total cost to the PBS/RPBS was considered to be highly uncertain and potentially underestimated, despite the evaluation's increase to the number of patients medically eligible and otherwise eligible for cannabidiol since: (i) the proportion of patients continuing on therapy after 12 months may be greater than

that estimated by the submission; (ii) the dose of cannabidiol used is likely to be higher than estimated by the submission; and (iii) the weight of patients (and therefore the cost of cannabidiol, being based on weight) is likely to increase over time as the cohort initiating treatment on cannabidiol ages. This underestimation of costs may have been partly offset by the submission's inclusion of grandfathered patients separate to the estimation of prevalent patient numbers, and there could also be some cost offsets in the use of other AEDs should cannabidiol replace the use of some currently PBS-listed AEDs for patients with DS or LGS.

6.58 The ESC considered the financial estimates to be highly uncertain and likely underestimated due to a lack of data and unsupported assumptions:

- The prevalence and incidence of LGS in the Australian population was an estimation based on a systematic review of publications and minimal details regarding the review or publications identified were provided in the submission;
- The prevalence of DS appeared to be incorrectly applied (0.004%, rather than 0.002%);
- The uptake rates were considered highly uncertain as they were based on unsubstantiated sponsor projections;
- The weight of patients was uncertain, and did not allow for the increasing weight of patients over time;
- The costs of monitoring plasma levels of other AEDs was not accounted for;
- Dosage was based on the assumption that all patients would receive 10 mg/kg/day, although the restriction and PI allow up to 20 mg/kg/day;
- No allowance was made for wastage.

6.59 The PBAC noted the prevalence and incidence of LGS was based on a systematic review (conducted in October 2018) but minimal discussion was included in the submission. The PBAC considered the estimate of the prevalence of LGS (2,996 people in 2021) was likely to be significantly underestimated given the wide range of aetiologies associated with condition. The PBAC noted there may be 5,000 to < 10,000 patients in Australia with LGS[6].

Quality Use of Medicines

6.60 The sponsor proposed to undertake a prescriber education program covering safety, dose and titration, treatment criteria and the targeted patient population.

[6] http://www.health.vic.gov.au/healthvictoria/apr19/epilepsy.htm

Financial Management – Risk Sharing Arrangements

6.61 Given that there will likely be a proportion of patients using a dose greater than the proposed 10 mg/kg/day, the evaluation noted a risk sharing arrangement for these patients may be required.

6.62 The sponsor advised that they were open to a risk sharing arrangement in their pre-PBAC response.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of cannabidiol for the treatment of Dravet Syndrome (DS) and Lennox Gastaut Syndrome (LGS) in combination with other anti-epileptic drugs (AEDs) on the PBS to enable consultation with stakeholders regarding the role of cannabidiol in the treatment of these rare forms of epilepsy. The PBAC considered further clarity on the clinical place of cannabidiol in therapy is required to inform the appropriate initial and continuing restriction criteria, cost-effectiveness and financial implications of listing cannabidiol on the PBS.

7.2 The PBAC considered there was a clinical need for additional effective and safe treatment options for people with DS and LGS. The PBAC noted the consumer comments received indicated the benefits of treatment with cannabidiol included improvement in seizure control in difficult to treat patients and an increase in quality of life for both patients and carers.

7.3 The PBAC noted that the TGA Delegate was supportive of the registration of cannabidiol but a number of issues were referred to the Advisory Committee on Medicines for advice. The PBAC noted the clinical evaluator was supportive of registration only in combination with clobazam and this may have an impact on the clinical place in therapy of cannabidiol. The PBAC noted clobazam is not currently listed on the PBS.

7.4 The PBAC noted the sponsor proposed amending the restriction criteria to identify patients with DS and LGS who have trialled two other appropriate AEDs to a maximally tolerated dose and failed to achieve seizure freedom in their pre-sub-committee response to be consistent with the clinical claim. The PBAC noted this was not consistent with the patients included in the clinical trials (paragraph 3.4) who were not required to have trialled two other AEDs to maximally tolerated doses and it was unclear whether it defined the appropriate clinical place in therapy for cannabidiol.

7.5 The proposed restriction criteria required patients to cease treatment after 12 months if a 30% reduction in convulsive (for DS) or drop (for LGS) seizures had not been achieved. The PBAC considered it may be unreasonable for clinicians, patients and their carers to determine if a 30% reduction in seizures had been achieved. The PBAC considered the proposed continuation criteria may not capture additional benefits of

treatment with cannabidiol, such as a reduction in uncountable non-convulsive or non-drop seizures, and may result in patients experiencing a meaningful benefit being required to cease treatment. The PBAC considered that further consultation was required as to the appropriate initial and continuing restriction criteria for cannabidiol for DS and LGS.

7.6 The PBAC noted the clinical claims in the submission were based on two randomised double-blind, placebo-controlled studies of cannabidiol conducted over 14 weeks for each patient population. The trials used fixed doses of cannabidiol (10 and/or 20mg/kg/day). Data from an open-label extension study provided support for the longer-term use of cannabidiol in DS and LGS. The PBAC noted there were limitations in the clinical studies (paragraph 6.32) but, on balance, considered that the evidence presented demonstrated cannabidiol is likely to be beneficial; however, the magnitude of the benefit was unclear. The PBAC noted that compared with placebo, an additional 16% to 23% of DS patients and 21% to 25% of LGS patients treated with cannabidiol 10mg/kg/day or 20mg/kg/day achieved a 50% reduction in seizure frequency over 14 weeks. The PBAC considered this was an important outcome in patients with refractory seizures but noted the results were not statistically significant in all studies and the confidence intervals around the estimates were wide.

7.7 The PBAC noted the economic model presented in the submission was unreliable given the substantial issues noted by ESC, and further that it was not possible to verify a number of the key inputs as part of the evaluation of the submission. The PBAC noted stakeholder input regarding the patient population and circumstances of use of cannabidiol (including initial and continuing restriction criteria, concomitant therapies and dose) will need to be considered in a revised economic evaluation.

7.8 The PBAC considered the estimated number of patients with LGS likely to be treated with cannabidiol to be uncertain, given the limited discussion in the submission regarding the systematic literature review used to inform the incidence and prevalence estimates and the uncertain clinical place of cannabidiol in therapy. The PBAC noted no criteria were proposed to define LGS and considered that as it is a heterogeneous condition, the number of prevalent patients could be significantly higher than estimated in the submission.

7.9 The PBAC noted DS was a smaller, better defined population than LGS but the number of patients who would be treated with cannabidiol is uncertain given the clinical place in therapy is unclear, particularly relative to stiripentol which was recommended for PBS listing for DS in March 2020.

7.10 The PBAC considered that any future resubmission should be a major submission and the proposed restriction criteria, economic evaluation and financial estimates should be informed by the outcome of consultation with stakeholders regarding the role of cannabidiol in the treatment of DS and LGS.

Outcome:
Deferred

8 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.

9 Sponsor's Comment

The outcome is disappointing for DS and LGS patients in Australia. The sponsor continues to be committed to collaborating with the PBAC to find a way to make Epidyolex® available for this patient population with such high unmet medical need.

Chiesi Australia (formerly Emerge Health Pty Ltd) also believe that in disease areas such as DS and LGS that a carer utility (thus QALY) should be able allowed to be included in an economic evaluation

Addendum to the July 2020 PBAC Minutes:

4.02 CANNABIDIOL, Oral solution, 100 mg per mL, 100mL Epidyolex®, Chiesi Australia Pty Ltd.

10 Background

10.1 At its July 2020 meeting, the PBAC considered further clarity on the clinical place of cannabidiol in the treatment of DS and LGS was required to inform the appropriate initial and continuing restriction criteria, cost-effectiveness and financial implications of listing cannabidiol on the PBS (paragraph 7.1).

10.2 A discussion with clinicians to inform the clinical place of cannabidiol in therapy was held on 9 October 2020 with representatives of the PBAC present and advice from this discussion informed PBAC consideration at the November 2020 meeting.

10.3 Cannabidiol was included on the Australian Register of Therapeutic Goods on 25 September 2020. The approved indication is "for use as adjunctive therapy of seizures associated with LGS or DS for patients 2 years of age or older".

11 PBAC Outcome

Dravet Syndrome

11.1 The PBAC recommended the listing of cannabidiol for the treatment of Dravet Syndrome (DS) in combination with at least two other anti-epileptic drugs (AEDs) on the PBS. The PBAC considered the appropriate place in therapy for cannabidiol is as a third line treatment and that cannabidiol was likely to be cost-effective at a cost per patient per year that is less than, or is not significantly higher than, that for stiripentol. The PBAC considered the financial impact could be reliably estimated based on the number of eligible patients in this small, well defined population.

11.2 The PBAC considered that standard care, consisting of a range of AEDs (paragraph 5.2), was the appropriate main comparator. The PBAC recalled it had previously considered cannabidiol as adjunctive therapy was superior in terms of effectiveness compared to standard care (but the magnitude of the benefit was uncertain) and inferior in terms of safety (paragraph 7.6).

11.3 The PBAC was satisfied that cannabidiol provides, for some patients, an improvement in efficacy over standard care for DS.

11.4 The PBAC recalled the economic model considered in July 2020 was unreliable (paragraph 7.7). However, given a similar clinical positioning as stiripentol (i.e., as a third line treatment), the PBAC considered cannabidiol would be of acceptable cost-

effectiveness for DS if it were listed at a cost per patient per year that is less than, or is not significantly higher than, that for stiripentol.

11.5 The PBAC recalled the cost of cannabidiol may have been underestimated in the July 2020 submission as the economic and financial models did not account for doses higher than 10mg/kg/day (paragraph 6.43, paragraph 6.58). The PBAC noted clinical advice that a dose of 10mg/kg/day or less was likely to be used in most DS patients and considered that not accounting for doses higher than 10mg/kg/day was reasonable.

11.6 The PBAC considered the financial impact of listing for DS could be reliably estimated based on the number of eligible patients in this small, well defined population.

11.7 The PBAC previously considered it may be unreasonable for clinicians, patients and their carers to determine if a 30% reduction in seizures had been achieved (paragraph 7.5). However, 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 DS, could be determined in clinical practice by clinicians, patients and carers. The PBAC noted the stiripentol restriction did not include a response criteria for continuing therapy and considered that, given the similar clinical positioning to stiripentol, it was appropriate to exclude the response criteria from the cannabidiol restriction.

11.8 The PBAC considered that an Authority Required (telephone/online), Section 85 (General Schedule) listing was appropriate for the DS population.

11.9 The PBAC advised that the restriction criteria for DS should:

- provide for a maximum quantity of 1 bottle (100 mL) and five repeats;
- include the clinical criteria “Patient must have, or have had, generalised tonic-clonic seizures or generalised clonic seizures that are not adequately controlled with at least two other anti-epileptic drugs at initiating treatment”;
- include the clinical criteria “The treatment must be as adjunctive therapy to at least two other anti-epileptic drugs”;
- not include the population criteria “Patient must be 2 years of age or older”.

11.10 The PBAC advised the following flow on changes are required to the stiripentol restriction:

- change “Patient must have, or have had, generalised tonic-clonic seizures or generalised clonic seizures that are not adequately controlled with a benzodiazepine and valproate” to “Patient must have, or have had, generalised tonic-clonic seizures or generalised clonic seizures that are not adequately controlled with at least two other anti-epileptic drugs”.
- change “The treatment must be as adjunctive therapy to a benzodiazepine and valproate” to “The treatment must be as adjunctive therapy to at least two other anti-epileptic drugs”.

11.11 The PBAC advised that initial prescribing should be limited to neurologists, and that paediatricians and general practitioners, in addition to neurologists, could also continue treatment, but only in consultation with a neurologist.

11.12 The PBAC advised that cannabidiol is not suitable for prescribing by nurse practitioners.

11.13 The PBAC recommended that the Early Supply Rule should not apply.

11.14 The PBAC recommended that cannabidiol should not be treated as interchangeable on an individual patient basis with any other drugs.

11.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for cannabidiol:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over standard of care. The PBAC considered this criteria was not met as the available data did not allow a reliable assessment of the magnitude of the incremental benefit (paragraph 7.6).

b) Treatment with cannabidiol is not expected to address a high and urgent unmet clinical need;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

11.16 The PBAC noted that this submission was not eligible for an Independent Review as it received a positive recommendation.

<u>Lennox Gastaut Syndrome</u>

11.17 The PBAC did not recommend the listing of cannabidiol for treatment of Lennox Gastaut Syndrome (LGS) on the PBS. The PBAC considered the place in therapy as a third line treatment was appropriate but the cost-effectiveness of cannabidiol for LGS remained uncertain. The PBAC considered the financial estimates provided in the submission were high and uncertain and that further information was required to appropriately define this potentially large, heterogeneous patient population.

11.18 The PBAC noted the clinical advice that LGS was a heterogeneous condition and is often not consistently defined in clinical practice, outside of the research setting. The PBAC considered the appropriate restriction criteria for LGS and estimated number of patients likely to be treated with cannabidiol continued to be uncertain (paragraph 7.8). The PBAC reiterated its previous consideration that the number of prevalent patients with LGS may be significantly higher than estimated in the submission (paragraph 6.59).

11.19 The PBAC noted the clinical advice that electroencephalogram (EEG) is the most definitive diagnostic measure for LGS. The PBAC noted the clinical trials for LGS required patients to have an EEG that showed a pattern of slow (<3.0 Hz) spike-and-wave complexes. The PBAC considered that any resubmission should propose a criteria that appropriately identifies people with LGS.

11.20 The PBAC noted clinical advice that a reduction in the number of seizures of at least 25% was likely to be clinically significant for LGS but it may be more challenging (compared to DS) for clinicians, patients and carers to determine if this has been achieved due to the nature of seizures experienced. The PBAC considered that any resubmission for LGS should address this issue.

11.21 The PBAC recalled the economic model considered in July 2020 was unreliable (paragraph 7.7) and the cost-effectiveness of cannabidiol in this population remained uncertain.

11.22 The PBAC considered that any future submission for LGS should be a major submission and should propose appropriate restriction criteria, address the uncertain cost-effectiveness and high and uncertain financial estimates.

Outcome:
Recommended for DS.

12 Recommended listing

12.1 Add new medicinal product:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
CANNABIDIOL cannabidiol 100 mg/mL oral liquid, 100 mL	New	1	1	5	Epidyolex

Restriction Summary [new] / Treatment of Concept: [new]

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ Authority Required – immediate/real time assessment by Services Australia (telephone/online)
	Episodicity: [blank]
	Severity: Severe
	Condition: myoclonic epilepsy of infancy (Dravet syndrome)
	Indication: Severe myoclonic epilepsy of infancy (Dravet syndrome)
	Treatment Phase: [blank]
	Clinical criteria:
	Patient must have, or have had, generalised tonic-clonic seizures or 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/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: 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: Requests for increased maximum quantities will be considered based on daily doses not exceeding 20 mg/kg/day (in line with the Product Information) and requested quantities not taking treatment duration beyond 30 days per prescription.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.

12.2 Flow on changes to stiripentol listing (12088F, 12103B, 12106E 12107F) as outlined in paragraph 9.10.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

13 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.

14 Sponsor's Comment

Chiesi Australia welcomes the PBAC's decision to recommend Epidyolex® for Dravet Syndrome. We look forward to working with the PBAC to ensure the successful PBS listing of Epidyolex for Lennox Gastaut Syndrome patients in Australia.