# 7.02 CANNABIDIOL, Oral liquid 100 mg per mL, 100 mL, Epidyolex®, Chiesi Australia Pty Ltd.

## 1 Purpose of submission

1.1 The standard re-entry submission requested Authority Required listing for cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS).

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

1.3 The key components of the proposed listing were unchanged from the previous submission.

**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) |
| Intervention | Cannabidiol oral solution 100 mg/mL as adjunctive therapy to standard care |
| Comparator | Standard of care, which includes oral anti-epileptic drugs, and non-pharmacotherapy interventions |
| Outcomes | Reduction in frequency of drop seizures |
| Clinical claim | Cannabidiol, as adjunctive therapy, is superior in terms of efficacy and inferior in terms of safety compared to standard of care (current anti-epileptic drugs alone) in patients with seizures associated with LGS |

Source: Table 1-1, p2 of the submission.

## 2 Background

### *Registration status*

2.1 Cannabidiol was TGA registered on 21 September 2020 "for use as adjunctive therapy of seizures associated with LGS or Dravet syndrome (DS) for patients 2 years of age or older".

### *Previous PBAC consideration*

2.2 In July 2020, the PBAC deferred making a decision to list cannabidiol for DS and LGS. In November 2020, the PBAC recommended the listing of cannabidiol for DS but did not recommend listing for LGS. The outstanding key matters of concern are summarised in the table below.

**Table 2: Summary of key matters of concern**

| Component | Matter of concern (July 2020 PSD) | How the resubmission addresses it |
|---|---|---|
| PBS restriction | Paragraph 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).<br>Paragraph 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 criterion that appropriately identifies people with LGS. | A more specific definition of LGS, which includes a requirement for patients to have an EEG that showed a pattern of slow (<3.0 Hz) spike-and-wave discharges, was included in the requested restriction. [redacted] |
| | Paragraph 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 revised restriction did not incorporate a stopping rule. The revised restriction was the same as that approved for DS. |
| Clinical evidence | Paragraph 7.6: 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 resubmission provided additional analyses of the trials, including the proportions of patients achieving ≥25% and ≥75% threshold reductions in the number of drop seizures at the end of the treatment period (14 weeks) along with the proportions achieving ≥50% threshold reduction, as had been presented in the July 2020 submission. |
| Economic analysis | Paragraph 6.43: Overall, the ESC considered the models were uninformative for decision making……<br>Paragraph 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. | A revised modelled economic analysis was presented. The structure of the revised model was aligned with the structure of the model presented for stiripentol, as advised by ESC (para 6.50). See Table 7 and Table 8 for further detail. |
| Financial implications | Paragraph 11.17: 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.<br>Paragraph 11.18: 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). | The resubmission provided additional evidence to address identification of the patient population (see Table 13 and Table 14 for detail). |

Source: Table 1-3, p5 of the resubmission; July 2020 cannabidiol PSD.

DS = Dravet syndrome; EEG = electroencephalogram; Hz = hertz; LGS = Lennox-Gastaut syndrome; PSD = Public Summary Document

# 3 Requested listing

3.1 The requested listing is presented below. Suggested additions are in italics and deletions are in strikethrough.

| Name, Restriction, Manner of administration and form | PBS item code | Max. qty packs | Max. qty units | №.of Rpts | Proprietary Name and Manufacturer | |
|---|---|---|---|---|---|---|
| CANNABIDIOL<br><br>cannabidiol 100 mg/mL oral liquid, 100 mL | NEW (or amend 12467E) | 1 | 1 | 5 | Epidyolex® | Chiesi Australia Pty Ltd |

| |
|---|
| **Category / Program:**<br>GENERAL – General Schedule (Code GE) |
| **Prescriber type:** ☒Medical Practitioners |
| **Restriction Level / Method:**<br>☒Authority Required – Telephone/Electronic/Emergency |
| **Administrative Advice:**<br>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:**<br>Requests for increased quantities may be sought based on daily doses not exceeding 20 mg/kg/day (in line with the Product Information) for up to 4 weeks per dispensing. |
| **Administrative Advice:**<br>No increase in the maximum number of repeats may be authorised. |
| **Administrative Advice:**<br>Special Pricing Arrangements apply. |
| **Episodicity:** optional |
| **Severity:** optional |
| **Condition:** Seizures of the Lennox-Gastaut syndrome |
| **Indication:** Seizures of the Lennox-Gastaut syndrome |
| **Treatment Phase:** ~~Initial and continuing treatment~~ |
| **Clinical criteria:** |
| Patient must have a diagnosis of ~~LGS~~ *Lennox-Gastaut syndrome* confirmed by an electroencephalogram *(EEG*) that showed a pattern of slow (less than 3.0 hertz) spike-and-wave discharges |
| **AND** |
| **Clinical criteria:** |
| Patient must have (as an initiating patient)/have had (as a continuing patient) more than one type of generalised seizures, including drop seizures (atonic, tonic or tonic-clonic) 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 one other anti-epileptic drug.~~<br>*The treatment must be in combination with at least one anti-epileptic drug.* |
| **AND** |
| **Treatment criteria:** |
| Must be treated by a neurologist if treatment is being initiated; or |

| |
|---|
| Must be treated by a neurologist if treatment is being continued or re-initiated; or<br>Must be treated by a paediatrician in consultation with a neurologist if treatment is being continued; or<br>Must be treated by a general practitioner in consultation with a neurologist if treatment is being continued. |
| **AND** |
| ~~**Population criteria:**~~ |
| ~~Patient must be 2 years of age or older.~~ |

3.2 The resubmission proposed a special pricing arrangement (SPA). The proposed effective price per 100 mL pack is the same as the agreed price for DS.

3.3 The restriction in the resubmission was modelled on that approved for DS, with the addition of the EEG criteria for diagnosis of LGS as advised by the PBAC (paragraph 9.19, Cannabidiol Public Summary Document (PSD); July 2020 PBAC meeting). The ESC considered the proposed restriction appropriately identified LGS patients suitable for initial and continuing treatment with cannabidiol. The ESC agreed with the Secretariat's proposal to remove the population criteria related to age.

3.4 The Pre-Sub-Committee Response (PSCR) confirmed that 86 patients will require transitioning to PBS-subsidised treatment.

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

# 4 Population and disease

4.1 The resubmission provided the same treatment algorithm as previously reviewed and accepted by the PBAC. As noted in paragraph 4.3 of the July 2020 PSD, the proposed clinical management algorithms suggested that sodium valproate is the preferred first-line treatment for patients with seizures and that cannabidiol could be used either in addition to sodium valproate with or without other AEDs if seizures are inadequately controlled, or in addition to any of the listed therapies if sodium valproate is not tolerated.

4.2 The precise mechanisms by which cannabidiol exerts its anticonvulsant effects in humans are unknown, but it is known that the anticonvulsant effects are not exerted through interaction with cannabinoid receptors. It is likely that the anticonvulsant actions of cannabidiol are achieved through inhibition of adenosine reuptake and modulation of intracellular calcium ($Ca^{2+}$) concentration.

# 5 Comparator

5.1 The resubmission proposed the same comparator, standard care, as previously accepted by the PBAC.

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

# 6 Consideration of the evidence

## *Sponsor hearing*

6.1 There was no hearing for this item.

## *Consumer comments*

6.2 The PBAC noted and welcomed the input from individuals (9), health care professionals (7) and organisations (4) via the Consumer Comments facility on the PBS website. The comments highlighted the severity of LGS and the impact of the condition on patients' lives and outlined the demonstrated effectiveness of cannabidiol in managing the symptoms of LGS, particularly in terms of reducing the number of drop seizures many patients experience. The comments also noted the prohibitive costs of accessing cannabidiol privately for LGS. The PBAC noted the advice from the National Paediatric Medicines Forum (NPMF) that a significant number of paediatric patients across Australia are currently prescribed cannabidiol for LGS and the NPMF were supportive of a PBS listing in this population.

6.3 The Epilepsy Society of Australia (ESA) stated that patients with LGS usually have a severe form of epilepsy, with frequent drug-resistant seizures, cognitive impairment and high rates of morbidity and mortality. The ESA noted many clinicians incorrectly use the term "Lennox-Gastaut Syndrome" to describe any severe, early-onset epilepsy with intractable seizures leading to falls. The ESA stated it was important to appropriately define LGS to ensure subsidised treatment is restricted to the appropriate population with LGS for whom there is Class I evidence of efficacy. The Young Epilepsy Section and Epilepsy Nurse Specialist Interest Group of Australasia also expressed their support for ESAs comments.

6.4 The ESA stated it would be appropriate to require patients to have an electroclinical diagnosis of LGS confirmed by a neurologist with expertise in epilepsy and include the following diagnostic criteria (1) typical EEG features of LGS: Generalised slow spike and wave with Generalised Paroxysmal Fast Activity (GPFA) (where possible to get a sleep recording) and (2) Tonic seizures recorded on video-EEG or clearly reported by a witness. The ESA stated this is consistent with the definition of the International League Against Epilepsy.

## *Clinical trials*

6.5 The resubmission presented the same clinical evidence as in the previous submission, two randomised trials, GWPCARE3 and GWPCARE4, plus an open label follow-up study GWPCARE5. Details of the trials are provided in the table below.

**Table 3: Trials and associated reports presented in the resubmission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| 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<br>Devinsky O et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. | 19 July 2017<br><br>*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<br>Thiele 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<br><br>*The Lancet* 2018: 391(10125): 1085-1096 |
| GWPCARE5[a] | 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<br>Devinsky O et al. Long-term cannabidiol treatment in patients with Dravet syndrome: An open-label treatment label.<br>Thiele EA et al. Cannabidiol in patients with Lennox-Gastaut syndrome: interim analysis of an open-label extension study. | May 2017<br><br>*Epilepsia* 2019: 60(2): 294-302<br><br>*Epilepsia* 2019: 60(3): 419-428 |

Source: Table 2, July 2020 cannabidiol PSD.

[a] An additional publication, described as the final analysis of efficacy and safety (Patel 2021), was identified during the evaluation.

6.6 The key features of the randomised trials are summarised in the table below. The PBAC previously accepted the assessment of the clinical evidence.

**Table 4: Key features of the included evidence**

| Trial | N | Design / duration | Bias | Population | Outcomes |
|---|---|---|---|---|---|
| GWPCARE3 | 225 | R, DB, PC, MC,<br>14 weeks<br>Titration to either 10 mg/kg/day or 20 mg/kg/day | Low | LGS; age 2.6-48 years<br>Median (min, max) baseline drop seizures per 28 days 85 (8.7, 7494.0)<br>Median (min, max) AEDs: 3 (0, 5) | Percentage change from baseline in drop seizure frequency |
| GWPCARE4 | 171 | R, DB, PC, MC,<br>14 weeks<br>Titration to 20 mg/kg/day | Low | LGS; age 2.7-45 years;<br>Median (min, max) baseline drop seizures per 28 days: 73.8 (10.3, 3174.6);<br>Median (min, max) AEDs: 3 (1, 5) | |
| GWPCARE5 | 366 | Open-label extension of GWPCARE3 and GWPCARE4 | | | |

Source: Table 3, July 2020 cannabidiol PSD; Table 3.2.1, p30 of GWPCARE3 CSR final tables; Table 3.2.1, p24 of GWPCARE4 CSR final tables.

AED = anti-epileptic drug; DB = double-blind; LGS = Lennox-Gastaut syndrome; MC = multi-centre; PC = placebo-controlled; R = randomised

## *Comparative effectiveness*

6.7 The main results from the trials are as presented in the previous submission (reproduced below, Table 6). The additional data presented were estimates of the proportion of patients with ≥ 25% and ≥ 75% reduction in drop seizure frequency.

6.8 The dose of cannabidiol in the open label study (GWPCARE5) was expressed as 'modal dose'. In the publication of this study (Patel 2021), mean modal dose was defined as "the average of doses each patient was on the most".

6.9 The results from the additional analyses suggested that more patients will achieve a 75% reduction in seizures at the 20 mg/kg/day dose compared to the 10 mg/kg/day dose, but the number of events in the trial was small with resulting wide confidence intervals. The evaluation considered that although the evidence for a dose response effect is limited, it would be likely that increasing the dose would be done in practice. A study from NSW (Chen 2018[1]) of the use of cannabidiol in 40 children with drug resistant epilepsy, including 8 children with LGS, described dosing of up to 25 mg/kg/day. The ESC noted expert advice provided with the PSCR that a majority of patients with LGS will be treated with doses less than 20 mg/kg/day in clinical practice, in part due to dose-related adverse events.

[1] Chen KA, Farrar M, Cardamone M, Gill D et al. Cannabidiol for treating drug-resistant epilepsy in children: the New South Wales experience. *Med J Aust* 2018; 209(5): 217-221.

**Table 5: Results of GWPCARE3 and GWPCARE4**

| GWPCARE3 | | | |
|---|---|---|---|
| | **Cannabidiol 10 mg/kg/day (N=73)** | **Cannabidiol 20 mg/kg/day (N=76)** | **Placebo (N=76)** |
| 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 percentage difference compared to placebo (95% CI) | **-19.19 (-31.24, -7.69)** | **-21.57 (-34.79, -6.67)** | NA |
| **Proportion of patients experiencing reduction in drop seizure frequency from baseline** | | | |
| ≥25% reduction in drop seizure frequency n (%) | 46 (63.0%) | 47 (61.8%) | 33 (43.4%) |
| OR vs placebo (95% CI) | **2.22 (1.15, 4.27)** | **2.11 (1.11, 4.03)** | NA |
| RR vs placebo (95% CI) | **1.45 (1.06, 1.98)** | **1.42 (1.04, 1.94)** | NA |
| RD vs placebo (95% CI) | **0.20 (0.04, 0.35)** | **0.18 (0.03, 0.24)** | NA |
| ≥50% reduction in drop seizure frequency n (%) | 26 (35.6%) | 30 (39.5%) | 11 (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 |
| ≥75% reduction in drop seizure frequency n (%) | 8 (11.0%) | 19 (25.0%) | 2 (2.6%) |
| OR vs placebo (95% CI) | **4.55 (1.05, NC)** | **12.33 (3.04, NC)** | NA |
| RR vs placebo (95% CI) | **4.16 (0.91, 18.96)** | **9.5 (2.29, 39.38)** | NA |
| RD vs placebo (95% CI) | **0.08 (0.03, 0.16)** | **0.22 (0.12, 0.33)** | NA |
| **GWPCARE4** | | | |
| | | **Cannabidiol 20 mg/kg/day (N=86)** | **Placebo (N=85)** |
| 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) | | **-17.21 (-30.32, -4.09)** | NA |
| **Proportion of patients experiencing reduction in drop seizure frequency from baseline** | | | |
| ≥25% reduction in drop seizure frequency n (%) | | 55 (64.0%) | 37 (43.5%) |
| OR vs placebo (95% CI) | | **2.30 (1.25, 4.24)** | NA |
| RR vs placebo (95% CI) | | **1.47 (1.10, 1.96)** | |
| RD vs placebo (95% CI) | | **0.20 (0.06, 0.35)** | |
| ≥50% reduction in drop seizure frequency n (%) | NA | 38 (44.2%) | 20 (23.5%) |
| OR vs placebo (95% CI) | | **2.57 (1.33, 4.97)** | NA |
| RR vs placebo (95% CI) | | **1.87 (1.20, 2.95)** | |
| RD vs placebo (95% CI) | | **0.21 (0.07, 0.35)** | |
| ≥75% reduction in drop seizure frequency n (%) | | 17 (19.8%) | 7 (8.2%) |
| OR vs placebo (95% CI) | | **2.74 (1.10, 6.84)** | NA |
| RR vs placebo (95% CI) | | **2.40 (1.05, 5.49)** | NA |
| RD vs placebo (95% CI) | | **0.16 (0.01, 0.22)** | NA |

Source: Table 2-1, p10; Table 2-2, p12 of the resubmission.

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

**Bold** indicates statistically significant differences; blue shading indicates data previously seen by the PBAC.

6.10 The PSCR argued the results of the 10 mg/kg/day and 20 mg/kg/day doses in the GWPCARE3 study indicated there was a lack of a strong dose-response relationship and stated that an improved response with increased dose was observed in less than 25% of patients. The ESC agreed there was not a strong dose-response relationship but noted more patients treated with 20 mg/kg/ day achieved a 75% reduction in drop seizures (RD 16% to 22%) compared to patients treated with 10 mg/ kg/ day (RD 8%). The ESC considered that, given there appears to be a dose-response relationship for

adverse events, it remained uncertain the extent clinicians would escalate dose in clinical practice.

## *Comparative harms*

6.11 No new evidence was provided in the resubmission. As noted in the July 2020 PSD (paragraph 6.24), the most common adverse events (AEs) included somnolence, decreased appetite, diarrhoea, need for investigations, and fatigue and these appear to be somewhat dose related.

6.12 The publication by Patel 2021 provided a comprehensive listing of adverse events from GWPCARE5. According to the authors, the most common AEs included somnolence, decreased appetite, diarrhoea, need for investigations, and fatigue. The evaluation noted adverse events did not appear to be related to dose, except for early withdrawals due to adverse events in the group of patients whose modal dose was <20 mg/kg/day. The ESC considered AEs were likely to be dose-related and noted this was consistent with the expert advice provided with the PSCR (see paragraph 6.5).

## *Benefits/harms*

6.13 A summary of the comparative benefits and harms for cannabidiol and standard care versus placebo and standard care is presented below. The harms table is reproduced from the previous PBAC consideration.

6.14 On the basis of direct evidence presented for every 100 patients with LGS 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 21 additional patients would have a 50% or greater reduction in drop seizures and 8 additional patients would have a 75% or greater reduction in drop seizures per 28 days from baseline.
- Approximately 11 additional patients would experience psychiatric disorders such as irritability or aggression or difficulty sleeping (insomnia).

6.15 On the basis of direct evidence presented by the submission, for every 100 patients with LGS 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 21 to 25 additional patients would have a 50% or greater reduction in drop seizure frequency and 16 to 22 additional patients would have a 75% or greater reduction in drop seizure frequency per 28 days from baseline.
- 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.

**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** | |
| **Diarrhoea** | | | | | | |
| GWPCARE4 | 11/86 | 3/85 | **3.62 (1.05, 12.5)** | 12.8 | 3.5 | **0.09 (0.01, 0.18)** |
| **Investigations** | | | | | | |
| 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** | | | | | | |
| 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)** |

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

* Median duration of follow-up: 14 weeks

Source: Table 6, cannabidiol PSD, July 2020 PBAC meeting

## *Clinical claim*

6.16 The resubmission made no change to the claim previously accepted by the PBAC, that in patients with refractory LGS, cannabidiol (added to background anti-epileptic therapy) is superior in terms of effectiveness compared with placebo (added to background anti-epileptic therapy) but inferior in terms of safety. While this was previously accepted by the PBAC, the magnitude of the benefit was uncertain (paragraph 6.34, cannabidiol PSD, July 2020). The additional analyses presented in the resubmission demonstrate that use of a more stringent threshold for benefit (i.e., 75% response) still results in a significant improvement in clinical outcomes.

6.17 The adverse effects of cannabidiol in the open label data set were convulsion, diarrhoea, pyrexia, somnolence, and vomiting; and as noted above, there appear to be some patients who withdraw relatively early in treatment due to intolerance.

6.18 The ESC considered the dose likely to be used in clinical practice remained uncertain but acknowledged the dose was likely to be no higher than 20 mg/kg/day for a majority of patients.

6.19 Noting the clinical claim had not changed in the re-submission, the PBAC reaffirmed its previously expressed view that the claim of superior comparative effectiveness and inferior comparative safety compared to placebo was reasonable.

## *Economic analysis*

6.20 Similar to the July 2020 submission, the economic model presented in the resubmission was a cost utility analysis comparing cannabidiol as adjunctive therapy to placebo. However, the model structure was revised; the table below provides a

summary of PBAC and ESC consideration of the July 2020 model, and the corresponding structure and content of the revised model. The ESC noted the revised model had addressed a number of previous concerns and considered the revised model structure was reasonable.

**Table 7: Issues raised by PBAC and ESC in regard to the July 2020 cannabidiol model and the March 2020 stiripentol model**

| Component | Issue identified by ESC and/or PBAC in July 2020 cannabidiol PSD and March 2020 stiripentol PSD | How revised model addressed the issues/comment |
|---|---|---|
| Overall | Paragraph 6.43: Overall, the ESC considered the models were uninformative for decision making…… Paragraph 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. | A revised model has been presented, based on the March 2020 stiripentol model. The revised model has 6 health states, a time horizon of 5 years and utility values sourced from Verdian 2008. |
| Computational methods | Paragraph 6.36: 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. | Transition probabilities are sourced from patient-level data from the GWPCARE3, GWPCARE4 and GWPCARE5 trials. There is no use of VBA code in the Excel workbook. |
| Time horizon | Paragraphs 6.43 and 6.47: The extrapolation of 14-week trial data to a 30-year time horizon magnified uncertainties; the ESC considered that a 5 year time horizon, as submitted for stiripentol, would be more appropriate. | The revised model used a 5-year time horizon. |
| Cycle length | Table 7: 3 months. Inappropriately, no half cycle correction was applied. | 28-day cycle, consistent with frequency of dispensing of therapy. In addition, the revised model assumed that treatment effect for cannabidiol will wane. |
| Health states | Paragraph 6.41, Paragraph 6.50: ESC considered that the modelled health states did not align with the outcomes from the trials and additionally did not align with established meaningful health states. ESC advised that a simpler economic model, as was used in the stiripentol submission, with 4 health states linked with outcomes from the trials and applying utilities from the literature (Verdian 2008) could be a more appropriate approach. | The revised model is similar to the structure in the stiripentol model, with 6 health states based on percentage reduction in drop seizure frequency, and utilities sourced from Verdian 2008. |
| Dosing | Paragraph 6.36: Patients treated with cannabidiol 20 mg/kg/day were not included in the economic analysis Paragraph 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. | Dosing was based on the distribution of the weight of patients enrolled in the GWPCARE3 and GWPCARE4 trials. The calculations were based on all patients in the trials, including placebo-treated patients, using both 10 mg/kg/day and 20 mg/kg/day doses. |
| Costs | Paragraph 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 AEs or monitoring plasma levels of other AEDs, included costs were from a range of sources that were not justified and the model assumed all patients received 10 mg/kg/day. | Costs and disutilities associated with management of AEs were not incorporated in the revised model on the grounds that the adverse events are reversible and are managed by discontinuing or reducing the dose of cannabidiol. The resubmission did not provide any discussion or justification for this claim. |

| Component | Issue identified by ESC and/or PBAC in July 2020 cannabidiol PSD and March 2020 stiripentol PSD | How revised model addressed the issues/comment |
|---|---|---|
| | | The revised model did not include costs of concomitant AEDs, or costs of monitoring plasma levels of other AEDs. Included costs were based on MBS items and NHCDC costs. |
| Treatment discontinuation | Table 8: Assumed 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. | The revised model assumed continued treatment in all patients with ≥ 25% reduction in seizures. If patients remain in the <25% reduction in seizure frequency health state for 3 cycles, they were assumed to discontinue treatment. This was consistent with the ESC preferred assumptions for the stiripentol model (Table 10, stiripentol PSD March 2020). |
| Utilities | Paragraph 6.43: The vignettes used to derive the nominated utility values were not provided. It is likely that the utility values were overestimated, and this potentially favoured cannabidiol. | The revised model used utility values sourced from Verdian 2008. |
| Carer disutilities | Paragraph 6.48: 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. | The resubmission maintained that carers' quality of life should be considered in an economic analysis. Base case results with and without carer utilities were presented. |
| Hospitalisations | Paragraph 6.23: No statistically significant difference in rates of hospitalisation were observed in the trials, which was inconsistent with the assumption that cannabidiol would reduce epilepsy-related hospitalisations in the modelled economic evaluations. | The resubmission argued analyses of hospitalisations could not be conducted and it is reasonable to expect that reduced seizure frequency will translate to reduced frequency of hospitalisations. Costs of hospitalisation associated with seizure were included in the model. The ICER increased by 7% when hospitalisation costs were excluded. |

Source: Table 3-1, p14-18 of the resubmission.
AEs = adverse events; AEDs = anti-epileptic drugs; DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome; NHCDC = National Hospital Cost Data Collection; VBA = visual basic for applications

6.21 The key change to the economic model was the change in health states - reduction in number from 25 to 6 and use of health states based on percentage reduction in drop seizure frequency instead of number of seizures and numbers of days without drop seizures, shortening of the time horizon to 5 years from the 30 years used originally, and use of utility values from Verdian 2008. The table below provides a summary of the key components of the revised economic model.

**Table 8: Key components of the revised economic evaluation**

| Component | Description | Comments |
|---|---|---|
| Type of analysis | Cost-utility analysis. | As used in the July 2020 model, which was appropriate. |
| Outcomes | Quality-adjusted life years (QALYs). | As used in the July 2020 model, which was appropriate. |
| Time horizon | 5 years | On the basis of advice from ESC (para 6.50 of the July 2020 PSD). |
| Methods used to generate results | Cohort expected value analysis using a Markov model. | As per the July 2020 model. |
| Health states | Six health states:<br>i) 75% - 100% reduction in drop seizures<br>ii) 50% - < 75% reduction in drop seizures<br>iii) 25% - < 50% reduction in drop seizures<br>iv) < 25% reduction in drop seizures<br>v) Discontinued treatment (cannabidiol arm only)<br>vi) Death: Absorbing state | The reduction in health states was consistent with advice from the ESC (para 6.50 of the July 2020 PSD), |
| Cycle length | 28 days, with half cycle correction | Appropriate. |
| Transition probabilities | Sourced from patient-level data from GWPCARE3, GWPCARE4 and GWPCARE5, based on 20 mg/kg/day group. | |
| Utility values | Verdian 2008; carer disutilities were based on a vignette study. | Use of values from Verdian 2008 was on the basis of advice from ESC (para 6.50 of the July 2020 PSD). The stiripentol model of March 2020 also used utility values from Verdian 2008. |
| Costs | Drug cost based on assumed 15 mg/kg/day. Hospitalisation costs remain included. | Use of 15 mg/kg/day was not consistent with source of the clinical data used in the model. No costs for concomitant AEDs were included. |

Source: Table 3-2, p19 of the resubmission.
AEDs = anti-epileptic drugs; PSD = public summary document

6.22 A summary of the key drivers of the economic model is provided in the table below.

**Table 9: Key drivers of the model**

| Description | Method/Value | Impact<br>Base case: $[redacted][1]/QALY gained |
|---|---|---|
| Cannabidiol dose | The 15 mg/kg/day dose used in the model was not consistent with the source of the clinical data used. | High, favours cannabidiol. Increasing the cannabidiol dose to 20 mg/kg/day increased the ICER by 34%, to $[redacted][2]/ QALY. |
| Utilities | Sourced from Verdian 2008 as suggested by the ESC. | High, largely favours cannabidiol. Altering the source of utility values changed the ICER to a range of $[redacted][3] to $[redacted][4]/ QALY. |
| Transition probabilities | Assumed that all transitions following Cycle 20 (approximately 1.5 years of the 5-year model) would not change. | Likely favours cannabidiol but cannot be tested given the model structure. |

Source: Section 3.4 to Section 3.6, p27-38 of the resubmission.
*The redacted values correspond to the following ranges:*
[1] *$75,000 to < $95,000*
[2] *$95,000 to < $115,000*
[3] *$55,000 to < $75,000*
[4] *$135,000 to < $155,000*

6.23 Further detail on the dose issue and a description of additional issues with the model are provided below:

- Only patients that were assigned to receive 20 mg/kg/day in the trials were included in the calculation of transition probabilities in the cannabidiol arm of the model. This was inconsistent with the dose used in the model (15 mg/kg/day), and therefore drug costs calculated in the model will underestimate the cost required to achieve the calculated outcomes.
- To determine the dose used in the model, individual patient data (IPD) was used to calculate the amount of drug required for each patient based on their weight. The amount of drug was calculated for each patient in the trial assuming they were treated with 10 mg/kg/day or 20 mg/kg/day. The ESC noted that using this methodology the dose was based on an average patient weight of 43.3 kg (across a range of 10.8 kg to 140.2 kg) with approximately 30% of patients over 18 years of age. The ESC considered this approach was reasonable and the patients in the trial were likely to reflect the average treated patient population.
- The model did not include the cost of concomitant AEDs. These have been included in published models (e.g. Neuberger 2020), as well as the July 2020 model. While it can be assumed costs for concomitant AEDs would be the same across the two treatment groups and therefore not impact the incremental cost, overall drug cost in the model would be underestimated.

6.24 The resubmission did not provide a stepped economic evaluation. Results of the economic evaluation are in the table below.

**Table 10: Results of the economic evaluation**

| Component | Cannabidiol | Placebo | Increment |
|---|---|---|---|
| **Modelled evaluation – 5 year time horizon (discounted)** | | | |
| Costs ($) | | | |
| QALY - patient | 0.613 | 0.137 | 0.476 |
| QALY - carer | -1.153 | -1.324 | 0.172 |
| QALY – including carer disutilities | -0.540 | -1.187 | 0.648 |
| **Incremental cost/QALY gained (base case) excluding carer disutilities** ($) | | | [1] |
| Incremental cost/QALY gained including carer disutilities ($) | | | [2] |
| Incremental cost/QALY gained excluding carer disutilities July 2020 ($) | | | [3] |
| Incremental cost/QALY gained including carer disutilities July 2020 ($) | | | [2] |

Source: Table 3-10, p39 of the resubmission; Table 12, 5.03.COM.23.
QALY = quality adjusted life year
Blue shading indicates data presented in the July 2020 submission.
*The redacted values correspond to the following ranges:*
[1] *$75,000 to < $95,000*
[2] *$55,000 to < $75,000*
[3] *$155,000 to < $255,000*

6.25 The base case ICER, excluding carer disutilities, was $75,000 to < $95,000/ QALY. When carer disutilities are included, it reduced to $55,000 to < $75,000/ QALY. The ICERs are less than those presented for the July 2020 submission, and which the PBAC considered unreliable (paragraphs 7.7 and 11.21, cannabidiol PSD, July 2020 PBAC meeting).

6.26 As noted above, the model was inconsistent with its use of transition probabilities based on a 20 mg/kg/day dose, but application of costing based on 15 mg/kg/day.

When drug cost is based on a 20 mg/kg/day dose, the ICER increased to over $95,000 to < $115,000/ QALY (see sensitivity analyses below for detail). The ESC considered the most appropriate approach for the economic model was to ensure that there was consistency in the dose used to derive both the health state transition probabilities and costs.

6.27 The PSCR stated the use of outcomes and health state transition probabilities based on the 20 mg/kg/day dose was reasonable, given the limitations with the GWPCARE trial designs in terms of dose regimens and argued the use of outcomes based on the 10mg/kg/day arm of the trials would not reflect the benefit of a dosing regimen which allows titration up to 20 mg/kg/day in practice. Furthermore, the PSCR stated the assumption of 15 mg/kg/day dosing in the economic model was reasonable and argued it was unreasonable to require a 20 mg/kg/day dose to be used in the economic model (despite deriving outcomes from that dosage arm of the trials), as such an assumption implies all patients will receive the maximum allowable dose. The PSCR noted sensitivity analyses (i) limiting the examination of cost-effectiveness to those treated with a cannabidiol dose of 10 mg/kg/day in the GWPCARE 3 trial and (ii) examining cost-effectiveness for all patients treated with cannabidiol regardless of dose administered in the GWPCARE3 and GWPCARE4 trials increased by ICER by 4.6% and 1.5%, respectively. The ESC noted using transition probabilities regardless of dose resulted in an ICER of $75,000 to < $95,000/ QALY, assuming a drug cost based on a dose of 15 mg/kg/day. The ESC noted using transition probabilities regardless of dose and a drug cost based on 70% (i.e., 162/235) of patients being treated with 20 mg/kg/day resulted in an ICER of $75,000 to < $95,000/ QALY.

6.28 The results of key sensitivity analyses are summarised below. The resubmission maintained that carers' quality of life should be considered in an economic analysis and therefore all results presented by the resubmission included carer disutilities. As the base case should exclude carer disutilities, as stated previously (paragraph 6.48, cannabidiol PSD, July 2020), results for those analyses are included below. The ESC again acknowledged the significant impact of LGS on caregiver's quality of life, however considered it was not appropriate to include this utility in the base case.

**Table 11: Sensitivity analyses**

| Analyses | Base case: excluding carer disutilities | | | Including carer disutilities | | |
|---|---|---|---|---|---|---|
| | Incremental cost ($) | Incremental QALY | ICER ($) | Incremental cost ($) | Incremental QALY | ICER ($) |
| **Base case** | [redacted] | **0.476** | [redacted][1] | [redacted] | **0.648** | [redacted][7] |
| Time horizon (base case: 5 years) | | | | | | |
| 4 cycles (trial-based analysis) | [redacted] | 0.032 | [redacted][2] | [redacted] | 0.044 | [redacted][2] |
| 3 years | | 0.377 | [redacted][1] | | 0.513 | [redacted][7] |
| 10 years | | 0.542 | [redacted][1] | | 0.738 | [redacted][7] |
| 1 year | | 0.152 | [redacted][3] | | 0.208 | [redacted][1] |
| Discount rate (base case: [redacted]%) | | | | | | |
| [redacted]% | [redacted] | 0.521 | [redacted][1] | [redacted] | 0.709 | [redacted][7] |
| [redacted]% | | 0.489 | [redacted][1] | | 0.665 | [redacted][7] |
| Cannabidiol dose (base case: 15 mg/kg/day) | | | | | | |
| 10 mg/kg/day | [redacted] | 0.476 | [redacted][4] | [redacted] | 0.648 | [redacted][8] |
| 20 mg/kg/day | | 0.476 | [redacted][5] | | 0.648 | [redacted][1] |
| Hospitalisation costs (base case: included) | | | | | | |
| Excluded | [redacted] | 0.476 | [redacted][1] | [redacted] | 0.648 | [redacted][7] |
| Utility weight (base case: EQ-5D from Verdian 2008) | | | | | | |
| TTO from Verdian 2008 | [redacted] | 0.244 | [redacted][6] | [redacted] | 0.416 | [redacted][1] |
| VAS from Verdian 2008 | | 0.561 | [redacted][7] | | 0.733 | [redacted][4] |
| Stiripentol model | | 0.360 | [redacted][5] | | 0.532 | [redacted][7] |
| Cannabidiol dose (base case: 15 mg/kg/day) and utility weight (base case: EQ-5D from Verdian 2008) | | | | | | |
| 20 mg/kg/day and TTO from Verdian 2008 | [redacted] | 0.244 | [redacted][2] | [redacted] | 0.416 | [redacted][3] |
| 20 mg/kg/day and VAS from Verdian 2008 | | 0.561 | [redacted][1] | | 0.733 | [redacted][7] |
| 20 mg/kg/day and stiripentol model | | 0.360 | [redacted][6] | | 0.532 | [redacted][1] |
| Source of transition probabilities (base case: 20 mg/kg/day group) | | | | | | |
| 10 mg/kg/day group (drug cost assuming 15 mg/ kg/day) | [redacted] | 0.510 | [redacted][1] | [redacted] | 0.693 | [redacted][7] |
| 10 mg/kg/day and 20 mg/kg/day[a] (drug cost assuming 15 mg/ kg/day) | | 0.486 | [redacted][1] | | 0.661 | [redacted][7] |
| 10 mg/kg/day and 20 mg/kg/day and drug cost assuming 70% of patients treated with 20 mg/kg/ day | | 0.486 | [redacted][1] | | 0.661 | [redacted][7] |

Source: Source: Table 3-11, p41 of the resubmission.
LGS = Lennox-Gastaut syndrome; TTO = time trade off; VAS = visual analogue scale
[a] ~70% of patients (162/235) treated with 20 mg/kg/day
*The redacted values correspond to the following ranges:*
[1] *$75,000 to < $95,000*
[2] *$155,000 to < $255,000*
[3] *$115,000 to < $135,000*
[4] *$45,000 to < $55,000*
[5] *$95,000 to < $115,000*
[6] *$135,000 to < $155,000*
[7] *$55,000 to < $75,000*
[8] *$35,000 to < $45,000*

6.29 The model was sensitive to cannabidiol dose and the utility values used (see table below for utilities). Increasing the cannabidiol dose to 20 mg/kg/day increased the ICER by 34%, to $95,000 to < $115,000/ QALY without carer utilities and

$75,000 to < $95,000/ QALY with carer utilities. The pre-PBAC response stated the impact of varying the source of transition probabilities was relatively small and argued this was not unexpected given the treatment effect of cannabidiol, which was similar regardless of whether a 10 mg/kg/day or 20 mg/kg/day dose was administered, given patients are able to titrate dose.

**Table 12: Utility values sourced from Verdian 2008 and the March 2020 stiripentol model**

| Health state | Verdian 2008 | | | Stiripentol March 2020 |
|---|---|---|---|---|
| | EQ-5D (base case) | TTO | VAS | |
| 75% to 100% reduction in drop seizure frequency | 0.596 | 0.699 | 0.677 | 0.648 |
| 50% to <75% reduction in drop seizure frequency | 0.500 | 0.605 | 0.556 | 0.553 |
| 25% to <50% reduction in drop seizure frequency | 0.100 | 0.461 | 0.414 | 0.281 |
| <25% reduction in drop seizure frequency | 0.02 | 0.393 | 0.02 | 0.207 |
| Discontinued treatment | 0.02 | 0.393 | 0.02 | 0.207 |

Source: Table 3-6, p35 of the submission; worksheet 'Model inputs' of the Excel workbook 'Bilinks to model – Epidyolex (cannabidiol) – LGS-PBAC meeting Mar 2022'.
TTO = time trade off; VAS = visual analogue scale

6.30 The ESC considered the utility values used in the base case model were appropriate (Verdian 2008, as suggested by ESC in July 2020) but noted the ICER is highly sensitive to the use of other utility values. Altering the source of utility values changed the ICER to a range of $55,000 to < $75,000 to $115,000 to < $135,000/ QALY, depending on the alternate source used. When the dose and utility changes were combined, the ICER ranged from $75,000 to < $95,000/ QALY to $155,000 to < $255,000/ QALY. The PBAC considered that, while the model was sensitive to the source of utility values, overall, it agreed with the ESC that the utilities used in the base case model were reasonable.

6.31 The ESC recalled the ICER previously accepted by the PBAC for stiripentol for DS was $35,000 to < $45,000 (Table 11, stiripentol PSD, March 2020 PBAC meeting). For stiripentol the PBAC acknowledged the issues raised by the ESC with respect to the economic model but noted the high clinical need in the rare and refractory population, and considered that the cost-effectiveness of stiripentol was acceptable (paragraph 7.8, stiripentol PSD, March 2020 PBAC meeting). The ESC considered that this may provide an appropriate frame of reference for the PBAC's consideration of cannabidiol for LGS.

## *Drug cost/patient/4 weeks*

6.32 The economic model applied an average cost of $[redacted] for one cycle (4 weeks). This was based on 50% of patients being dosed at 10 mg/kg/day and an associated cost of $[redacted] and the remaining 50% being dosed at 20 mg/kg/day with an associated cost of $[redacted]. These costs were calculated based on the average number of milliliters of cannabidiol required per 4 week period.

6.33 The financial estimates provided with the resubmission applied an average cost of $[redacted] per script which was assumed to last 4 weeks. This was based on 50% of patients being dosed at 10 mg/kg/day and an associated cost of $[redacted] and the remaining 50% being dosed at 20 mg/kg/day with an associated cost of $[redacted]. These costs were calculated

based on the average number of whole bottles required per 4 week period i.e. any drug remaining at the end of the 4 weeks was assumed to be discarded. This will not happen in practice and so the cost of the cannabidiol has been overestimated. The ESC noted the average cost per script was amended to $ (consistent with the economic model) in the PSCR. The ESC noted the PSCR reduced the average cost per script and still assumed 13.04 scripts per year, which may not be appropriate as this approach does not reflect the amount of medicine dispensed each script (i.e., whole bottles per script). The ESC noted the drug cost in the economics and financials assumed zero wastage i.e., patients use every mL in a bottle.

## *Estimated PBS usage & financial implications*

6.34 The July 2020 submission was not considered by DUSC and the resubmission was not considered by DUSC. The following table provides a summary of the issues raised by the ESC and PBAC in regard to the July 2020 financial estimates, and the approach taken by the resubmission.

**Table 13: Issues raised by ESC and PBAC regarding the July 2020 estimates**

| Parameter | ESC/PBAC comments (July 2020 PSD) | Resubmission |
|---|---|---|
| Incidence and prevalence | Table 12: The ESC noted the incidence and prevalence of LGS was based on a systematic review (Rosander 2015) but minimal detail regarding the review or associated publications were provided in the submission.<br>Paragraph 6.59: 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[2]. | The incidence and prevalence of epilepsy was estimated using a published systematic review (Fiest 2017) and validated using Essue 2011. The sponsor commissioned an analysis of a database of patients with epilepsy to identify the proportion of patients with epilepsy who have a diagnosis of LGS. |
| Proportion eligible | Table 12: Data sources were considered inappropriate and unreasonable to apply. | The sponsor commissioned an analysis of a video-EEG monitoring (VEM) database of patients with epilepsy who were assessed by VEM at 3 hospitals in Victoria between 1995 and 2015. There were 3,175 patients with epilepsy, and 455 were screened, and of these, 74 were identified as having LGS (2.33%). |
| Uptake | Table 12: Uptake rates of cannabidiol ranged from 48% in the first year of listing, increasing to 96% in Year 6 after listing. | Estimated uptake has been altered to 30% in Year 1 increasing to 80% in Year 6 |
| Continuation rates | Table 12: The estimated rates of continuation of patients achieving a ≥ 25% reduction in drop seizure frequency at 14 weeks were considered suggestive of a higher likely rate of continuation than assumed in the submission's estimates. | Patient-level data from the GWPCARE3, GWPCARE4 and GWPCARE5 studies were provided and analysed to permit calculation of year to year continuation rates. |

[2] The resubmission stated that the media release referenced by the PBAC did not provide a source for its estimate of patients with LGS and the source provided for this (https://www.health.vic.gov.au/healthvictoria/apr19/epilepsy.htm) now returns a '404 error message'.

| Parameter | ESC/PBAC comments (July 2020 PSD) | Resubmission |
|---|---|---|
| Extent of use | Paragraph 3.8: The PBAC noted the proposed maximum quantity for DS and LGS was based on patients receiving an average dose of 15 mg/kg/day which was not consistent with the 10 mg/kg/day dose assumed in the economic and financial models.<br>Paragraph 6.51: The cost per patient applied in the economic analysis was lower compared to the financial estimates, due to the economic model's use of median weights rather than mean weights, and the assumption in the model that some patients will discontinue treatment.<br><br>Table 12: The average number of bottles (1.29) per month assumed to be used by patients with LGS did not account for wastage and were considered an underestimate. | The revised financial analysis assumed a 15 mg/kg/day dose of cannabidiol, consistent with the dose assumed in the economic model. As in the economic model, dose was estimated based on the weight of patients in the clinical trials.<br>Discontinuation rates were sourced from the economic model. |
| Hospitalisations | Table 12: The incorporation of savings due to reduced hospitalisation was considered inappropriate because such savings may not be realised. | Cost offsets assuming a reduction in hospitalisations were not incorporated in the financial analysis. |

Source: Table 4-1, p42-44 of the resubmission.
DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome; PSD = public summary document; VEM = video EEG (electroencephalogram) monitoring.

6.35 The resubmission applied an epidemiological approach to estimate the incidence and prevalence of LGS in Australia. The table below summarises the inputs used for the financial estimates.

**Table 14: Data sources and parameter values applied in the utilisation and financial estimates**

| Component | Data source |
|---|---|
| **Epidemiology** | |
| Incidence and prevalence data | Literature: Fiest 2017 – systematic review and meta-analysis of studies reporting the incidence and prevalence of epilepsy. The review included 222 studies (197 on prevalence, 48 on incidence, 4 on both) published since 1985.<br>Lifetime prevalence of epilepsy: 7.60 per 1,000 persons (95% CI: 6.17, 9.38). The resubmission claimed this was supported by Essue 2011 and an estimate commissioned by the sponsor based on a 10% PBS sample.<br>Incidence of epilepsy: 61.44 per 100,00 person-years (95% CI: 50.75, 74.38), applied to an Australian population aged 2 to 18 years.<br>Patients having LGS: Commissioned analysis of VEM database in Victoria: 3,175 with epilepsy; 455 (14.3%) with focal/ multifocal generalised epilepsy or epileptic encephalopathies screened for potentially being diagnosed with LGS; medical records reviewed and N=74 of the 455 (16.3%) were identified as having LGS. Thus, overall, 2.33% of patients with epilepsy (74/3175) were diagnosed as having LGS. Estimate triangulated by a survey of 18 clinicians. |
| Eligible patients | Eligible under proposed PBS listing: Commissioned analysis of VEM database to identify those who would meet PBS criteria. Of the 55 patients who had sufficient medical detail available, N=35 (66%) met the PBS criteria. Estimate was triangulated by the clinician survey. |
| **Utilisation** | |
| Uptake and treatment | Sponsor assumption: Uptake: Year 1: 30%; Year 2: 35%; Year 3: 45%; Year 4: 60%; Year 5: 75%; Year 6: 80%<br>Discontinuation: The resubmission assumed patients would initiate and discontinue treatment at mid-year. The rates used were sourced from the economic model. Year 1: 55%; Year 2: 17%; Year 3: 8%; Year 4: 6%; Year 5+: 4%<br>The PSCR (pg. 4) acknowledged there was a discrepancy between the rates of discontinuation rates applied in the economic model and financial estimates and stated this was due to |

| Component | Data source |
|---|---|
| | discontinuation in the financial estimates being an aggregate of patients who died and discontinued, whereas in the economic model these were applied separately. Further, the PSCR also noted an error which impacts on this difference, specifically that the re-submission incorrectly utilised the Markov trace, applying a mortality ratio of 1 in the financial estimates, whereas a mortality ratio of 13.92 (from Autry 2010) was applied in the economic model. These errors were corrected in the updated estimates provided in the PSCR (updated in Table 15 below). |
| Treatment duration | Ongoing |
| Number of scripts | The resubmission assumed 2.2 bottles would be supplied per script and 13.04 scripts would be supplied per patient per year. This is likely to be an overestimate as it assumes patients discard any remaining supply after 4 weeks. The PSCR acknowledged this issue and provided updated estimates adjusting for supply lasting longer than 4 weeks (updated in Table 15 below). The ESC noted the methodology applied now assumed zero wastage i.e., patients use every mL in a bottle. |
| **Cost of medicines** | |
| Cannabidiol | Requested price: $[redacted]<br>Per script: $[redacted] assuming dose of 15 mg/kg/day. Revised to $[redacted] in PSCR. |

Source: Section 4.1.1, p46-54; Section 4.2.1, p55; Section 4.3, p57; Section 4.5, p57 of the resubmission.
LGS = Lennox-Gastaut syndrome; VEM = video EEG (electroencephalogram) monitoring

6.36 The estimated patient numbers, prescription numbers, bottle numbers and costs for the PBS listing of cannabidiol for LGS are provided below. The PSCR provided updated estimates which accounted for issues noted in Table 14 above.

**Table 15: Estimated use and financial implications (updated in PSCR)**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Estimated extent of use** | | | | | | |
| Number of patients treated[a] | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 |
| Patient-years of treatment[b] | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 |
| Number of scripts | [redacted]2 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| Number of bottles | [redacted]3 | [redacted]6 | [redacted]8 | [redacted]8 | [redacted]8 | [redacted]8 |
| **Estimated financial implications of cannabidiol for LGS** | | | | | | |
| Total PBS/RPBS effective net expenditure (excluding patient co-payments) | [redacted]4 | [redacted]7 | [redacted]7 | [redacted]5 | [redacted]5 | [redacted]5 |
| **Previous submission July 2020** | | | | | | |
| Number treated | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 |
| Number scripts | [redacted]2 | [redacted]2 | [redacted]2 | [redacted]2 | [redacted]2 | [redacted]2 |
| Net cost to PBS/RPBS | [redacted]5 | [redacted]5 | [redacted]5 | [redacted]5 | [redacted]5 | [redacted]5 |

[a] Includes 86 patients that will transition to PBS–subsidised treatment.
[b] Patient-years were calculated assuming patients initiating/discontinuing treatment received half a year of treatment (assume initiate/discontinue at mid-year) and patients continuing treatment receive a full year of treatment.
Source: Table 1 (pg. 5) of the Pre-Sub-Committee Response
*The redacted values correspond to the following ranges:*
*[1] 500 to < 5,000*
*[2] 5,000 to < 10,000*
*[3] 10,000 to < 20,000*
*[4] $10 million to < $20 million*
*[5] $30 million to < $40 million*
*[6] 20,000 to < 30,000*
*[7] $20 million to < $30 million*
*[8] 30,000 to < 40,000*

6.37 The net cost to the PBS/RPBS of listing cannabidiol for the treatment of LGS was estimated to be $30 million to < $40 million per year in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing.

6.38 The ESC noted the financial estimates were sensitive to the average dose and assuming that all patients are treated with 20 mg/kg/day, the estimated net cost to the PBS/RPBS increased to $200 million to < $300 million over the first 6 years of listing. The pre-PBAC response reiterated that the average dose used in the utilisation estimates of 15 mg/kg/day was reasonable and argued real-world evidence of cannabidiol use in drug-resistant epilepsies, including LGS, supported this conclusion.

### *Quality Use of Medicines*

6.39 The resubmission indicated the sponsor has a medical education program in place to ensure that prescribers receive appropriate education about cannabidiol prior to prescribing. The program provides education on the eligibility criteria for cannabidiol access, titration and dosing and management of AEs.

### *Financial Management – Risk Sharing Arrangements*

6.40 The resubmission did not propose a risk-sharing arrangement (RSA), but the sponsor indicated it was willing to enter into an RSA should the PBAC consider it necessary.

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

## 7 PBAC Outcome

7.1 The PBAC did not recommend the listing of cannabidiol for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients who have not achieved adequate seizure control with at least two other anti-epileptic drugs (AEDs), as the incremental cost effectiveness ratio was high and uncertain at the requested price.

7.2 The PBAC noted patients and clinicians were supportive of the listing of cannabidiol for LGS and that the consumer comments highlighted the effectiveness of cannabidiol in reducing seizures associated with LGS and the prohibitive costs of accessing cannabidiol privately.

7.3 The PBAC noted the comments from the Epilepsy Society of Australia (ESA) regarding the importance of appropriately identifying patients with LGS in the restriction criteria. The PBAC advised the following changes to the restriction criteria for cannabidiol would be appropriate (i) remove population criteria related to age and (ii) an improved definition of LGS, consistent with that proposed by the ESA (refer to paragraph 6.4). The PBAC noted the clinical trials for cannabidiol required patients to have least 2 drop seizures per week at trial entry and considered it may be appropriate to also include this in the restriction criteria.

7.4 The PBAC noted the nominated comparator of standard care was unchanged in the resubmission and reaffirmed its view this was appropriate.

7.5 The PBAC noted no new clinical evidence was presented in the resubmission but results for some additional outcomes was provided. The PBAC noted that compared with placebo, an additional 8% of LGS patients treated with cannabidiol 10 mg/kg/day and an additional 16% to 22% of patients treated with 20 mg/kg/day achieved a 75% reduction in drop seizure frequency over 14 weeks. The PBAC considered that, consistent with its previous consideration, the evidence presented demonstrated cannabidiol is likely to be beneficial in some patients.

7.6 Noting no new evidence was presented in the resubmission, the PBAC reaffirmed its previous view that cannabidiol (plus standard care) is likely to be of inferior comparative safety to placebo (plus standard care).

7.7 The PBAC noted the key clinical trials used two fixed doses of cannabidiol (10 mg/kg/day and 20 mg/kg/day) whilst the requested listing (and TGA registration) allows for dose titration (up to 20 mg/kg/ day). The PBAC noted the dose likely to be used in clinical practice remained uncertain but considered dose escalation was likely to be limited by the tolerability of cannabidiol.

7.8 The PBAC considered the structure of the revised economic model provided in the resubmission was generally reliable for decision-making. The PBAC noted the model was inconsistent with its use of transition probabilities based on a 20 mg/kg/day dose but application of costing based on 15 mg/kg/day. The PBAC noted the economic model was sensitive to the cannabidiol dose and assuming a dose of 20 mg/kg/day, consistent with the transition probabilities used, increased the ICER from $75,000 to < $95,000/ QALY (excluding carer utilities) to $95,000 to < $115,000/ QALY (excluding carer utilities).

7.9 The PBAC noted using transition probabilities from the 10 mg/kg/day and 20 mg/kg/day treatment arms and a dose of 17 mg/kg/ day (assuming 70% of patients treated with 20 mg/kg/day consistent with the clinical trials) resulted in an ICER of $75,000 to < $95,000/ QALY (excluding carer utilities). The PBAC considered that, with these assumptions, the economic model provided a reasonable degree of certainty but that cannabidiol was not cost effective at the price proposed in the resubmission.

7.10 The PBAC considered the estimated number of patients likely to be treated with cannabidiol and the methodology for calculating the estimated cost of listing on the PBS were reasonable. The PBAC advised a risk share arrangement (RSA) to manage the outstanding uncertainty regarding the dose likely to be used in clinical practice (refer to paragraph 7.7) would be required.

7.11 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for cannabidiol using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- provide revised restriction criteria as outlined in paragraph 7.3;
- propose a price reduction to achieve an ICER less than $45,000 to < $55,000 per

QALY (excluding carer utilities) with the revised economic model assumptions outlined in paragraph 7.9;

- provide revised financial estimates incorporating the new price; and
- propose an RSA with expenditure caps that reflect the revised financial estimates.

7.12 The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**
Not recommended

# 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

Based on the discussions during the post-PBAC meeting, the sponsor decided to lodge a resubmission via the early re-entry pathway for the July 2022 PBAC meeting.