

**7.07 CANNABIDIOL,
Oral liquid 100 mg per mL, 100mL,
Epidyolex[®],
Chiesi Australia Pty Ltd.**

1 Purpose of resubmission

- 1.1 The early re-entry resubmission requested a General Schedule Authority Required listing for the adjunctive treatment of seizures in patients with Lennox-Gastaut syndrome (LGS) aged 2 years and older.

2 Background

- 2.1 At the March 2022 meeting, the PBAC did not recommend the listing of cannabidiol for the treatment of seizures associated with 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 (ICER) was high and uncertain at the requested price.
- 2.2 The PBAC considered the outstanding issues for cannabidiol could be resolved in a simple early re-entry resubmission if the following issues were addressed (paragraph 7.11, cannabidiol Public Summary Document (PSD) March 2022 PBAC meeting):
- provide revised restriction criteria;
 - propose a price reduction to achieve an ICER less than \$45,000 to < \$55,000 per QALY (excluding carer utilities) with revised economic model assumptions;
 - provide revised financial estimates incorporating the new price; and
 - propose an RSA with expenditure caps that reflect the revised financial estimates.
- 2.3 The resubmission addressed the issues raised by PBAC as summarised in Table 1.

Table 1: Summary of key matters to be addressed

Matter of concern	PBAC comments (paragraph references to cannabidiol Minutes, March 2022 PBAC meeting)	July 2022 resubmission
Restriction criteria	<p>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 Epilepsy Society of Australia. 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 (paragraph 7.3).</p>	<p>The resubmission proposed revised restriction criteria as requested.</p>
Cost effectiveness	<p>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) (paragraph 7.9).</p> <p>The PBAC requested 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 (paragraph 7.11)</p>	<p>The resubmission reduced the effective ex-manufacturer price from \$■■■■ to \$■■■■ (a ■■■■% reduction). The resubmission stated that the price proposed is the lowest price viable for this indication from a commercial perspective.</p> <p>The resubmission did not accept all economic model respecifications (as discussed below).</p> <p>ICER using the base case economic model from the previous submission: \$55,000 to < \$75,000 excluding carer utilities and \$45,000 to < \$55,000 including carer utilities.</p> <p>ICER using PBAC respecified economic model (per paragraph 7.9): \$75,000 to < \$95,000 excluding carer utilities and \$55,000 to < \$75,000 including carer utilities.</p>
Financial estimates	<p>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 (paragraph 7.10).</p> <p>The PBAC requested revised financial estimates incorporating the new price (paragraph 7.11).</p>	<p>Revised financial estimates reflect reduced price.</p> <p>Revised financial estimates reflect an average dose of 15 mg/kg/day (rather than 17 mg/kg/day per the PBAC's respecified base case for the economic model), which was conservative in the context of estimating an RSA cap.</p>
Risk sharing arrangement	<p>The PBAC advised a risk share arrangement (RSA) to manage the outstanding uncertainty regarding the dose likely to be used in clinical practice would be required (paragraph 7.10).</p> <p>The PBAC requested an RSA with expenditure caps that reflect the revised financial estimates (paragraph 7.11)</p>	<p>The resubmission proposed a ■■■■% rebate on expenditure above the financials caps.</p>

ICER incremental cost effectiveness ratio; LGS Lennox-Gastaut syndrome; PBAC Pharmaceutical Benefits Advisory Committee; QALY quality adjusted life year; RSA risk sharing arrangement.

Source: Pages 4-12 of the resubmission; Section 7, cannabidiol Minutes, March 2022 PBAC Meeting).

3 Requested listing

3.1 The resubmission accepted the amendments to the restriction proposed by the PBAC in March 2022 which were:

- remove population criteria related to age; and
- provide an improved definition of LGS, consistent with that proposed by the Epilepsy Society of Australia (ESA). 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 (paragraph 7.3, cannabidiol PSD, March 2022 PBAC Meeting).

3.2 The restriction proposed in the resubmission is outlined below. Changes to the previous restriction proposed by the sponsor are in bold, changes proposed by the Secretariat are in italics and strikethrough.

Name, Restriction, Redavb Manner of administration and form	Max. qty packs	Max. qty units	No. of Rpts	DPMQ	Proprietary Name and Manufacturer	
CANNABIDIOL cannabidiol 100 mg/mL oral liquid, 100 mL	1	1	5	Published: \$1,533.93 Effective: \$ [REDACTED]	Epidyolex®	Chiesi Australia Pty Ltd
Category / Program: GENERAL – General Schedule (Code GE)						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency						
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 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: No increase in the maximum number of repeats may be authorised.						
Administrative Advice: Special Pricing Arrangements apply.						
Indication: Seizures of the Lennox-Gastaut syndrome						
Clinical criteria: Patient must have a diagnosis of Lennox-Gastaut syndrome confirmed by an electroencephalogram (EEG) that showed a pattern of slow (less than 3.0 hertz) spike-and-wave discharges with generalised paroxysmal fast activity (where it is possible to obtain a sleep recording) (sleep recording should be obtained where it is possible)						
AND						
Clinical criteria: Patient must have (as an initiating patient)/have had (as a continuing patient) more than one type of generalised seizures						
AND						

Clinical criteria:
Patient must have at least two drop seizures (atonic, tonic or tonic-clonic) per week that are not adequately controlled with at least two other anti-epileptic drugs. Tonic seizures must have been recorded on video-EEG or been clearly observed and reported by a witness.
AND
Clinical criteria:
The treatment must be as adjunctive therapy to at least one other anti-epileptic drug. <i>The treatment must be in combination with at least one anti-epileptic drug.</i>
Treatment criteria:
Must be treated by a neurologist if treatment is being initiated; or
Must be treated by a neurologist if treatment is being continued or re-initiated; or
Must be treated by a paediatrician in consultation with a neurologist if treatment is being continued; or
Must be treated by a general practitioner in consultation with a neurologist if treatment is being continued.
Prescribing Instructions: <i>Tonic seizures must have been recorded on video-EEG or have been clearly observed and reported by a witness.</i>
Prescribing Instructions: <i>Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records</i>

- 3.3 The population criteria ‘Patient must be 2 years of age or older’ has been removed from the proposed restriction criteria as recommended by the PBAC.
- 3.4 The Secretariat recalled the PBAC had previously recommended the listing for DS change from in combination with one anti-epileptic drug to in combination with two anti-epileptic drug (paragraph 11.9, cannabidiol PSD, July 2020 PBAC meeting). The Secretariat noted approximately 95% of patients in both the LGS and DS trials were on at least two anti-epileptic drugs (refer to relevant section in Product Information document) and that it may be appropriate for consistent clinical criteria with regards to the number of anti-epileptic drugs to be used in combination with cannabidiol. The PBAC agreed with the Secretariat and considered it would be appropriate for clinical criteria should be consistent with the DS clinical criteria.
- 3.5 The resubmission proposed a reduction to the current published dispensed price for maximum quantity (DPMQ) for cannabidiol from \$2,006.43 to \$1,533.93 per 100 mL bottle.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

4.3 Clinical data was not presented in this early re-entry resubmission.

Clinical claim

4.4 The PBAC recalled its previously expressed view that the claim that cannabidiol was of superior comparative effectiveness and inferior comparative safety compared to the nominated comparator (standard care) was reasonable (paragraph 6.19, cannabidiol PSD, March 2022 PBAC meeting).

Economic analysis

4.5 In March 2022, “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” (paragraph 7.9, cannabidiol Minutes, March 2022 PBAC Meeting). The PBAC further considered that a simple resubmission using the early re-entry pathway should “propose a price reduction to achieve an ICER less than \$45,000 to < \$55,000 per QALY (excluding carer utilities)” with aforementioned revisions to the assumptions applied in the economic model (paragraph 7.11, cannabidiol Minutes, March 2022 PBAC Meeting).

4.6 As outlined in Table 2, the resubmission presented the results of the economic model using the parameters specified by the PBAC in March 2022 (per paragraphs 7.9 and 7.11, cannabidiol Minutes, March 2022 PBAC Meeting), and using the base case from the previous submission. As an early re-entry submission, the changes to the economic model have not been evaluated.

Table 2: Results of economic model

	Excluding carer disutilities			Including carer disutilities		
	Δ cost	Δ QALY	ICER	Δ cost	Δ QALY	ICER
PBAC respecified base case – price from previous submission ^a	\$█ ¹	0.486	\$█ ³	\$█ ¹	0.661	\$█ ⁴
PBAC respecified base case ^a applying resubmission’s lower price	\$█ ¹	0.486	\$█ ³	\$█ ¹	0.661	\$█ ⁴
Base case from previous submission applying resubmission’s lower price ^b	\$█ ²	0.476	\$█ ⁴	\$█ ²	0.648	\$█ ⁵

ICER incremental cost effectiveness ratio; PBAC Pharmaceutical Benefits Advisory Committee; QALY quality adjusted life year

Source: Table 2 of the resubmission

^a Applied transition probabilities from the 10 mg/kg/day and 20 mg/kg/day arms of the GWPCARE trials and assumed an average dose of 17 mg/kg/day dose of cannabidiol (based on an assumption that 70% of patients would be treated with 20 mg/kg/day and the remainder treated with 10 mg/kg/day) ^b Transition probabilities based on a 20 mg/kg/day dose but application of costing based on 15 mg/kg/day.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$25,000 to < \$35,000

³ \$75,000 to < \$95,000

⁴ \$55,000 to < \$75,000

⁵ \$45,000 to < \$55,000

- 4.7 The ICER was \$75,000 to < \$95,000 per QALY using the parameters specified by the PBAC in March 2022 (i.e. transition probabilities from the 10 mg/kg/day and 20 mg/kg/day treatment arms and a dose of 17 mg/kg/ day) and the resubmission's proposed 13% reduction to the effective ex-manufacturer price (EMP). The PBAC had previously considered that an ICER less than \$45,000 to < \$55,000 per QALY (excluding carer utilities) would be acceptable (paragraph 7.11, cannabidiol Minutes, March 2022 PBAC Meeting).
- 4.8 The resubmission acknowledged that the proposed price did not align with the PBAC's advice from March 2022 but stated that the price proposed in the resubmission is the lowest price viable for this indication from a commercial perspective. The resubmission stated that should the price not be acceptable, the sponsor will not be able to submit any further resubmissions for cannabidiol for the LGS indication, nor for other indications for which evidence is available or being developed (e.g., tuberous sclerosis complex) for the foreseeable future.
- 4.9 The resubmission reiterated its previous arguments (consistent with paragraph 6.27, cannabidiol Minutes, March 2022 PBAC Meeting) that it would not be appropriate to use transition probabilities from the 10 mg/kg/day treatment arm (which are based on fixed dose regimens from the GWPCARE trials) as it will underestimate the benefit of the proposed PBS dosing regimen which permits dose titration up to 20 mg/kg/day based on individual benefit and risk. The resubmission further argued that evidence for a dose-response effect is limited. In this context, the resubmission presented the base case from the previous submission (transition probabilities based on a 20 mg/kg/day dose but costs based on a 15 mg/kg/day dose) and the resubmission's lower price, which resulted in an ICER of \$55,000 to < \$75,000 per QALY (excluding carer utilities). The previous PBAC Minutes note that this inconsistent use of sources for outcome and costs will underestimate the cost required to achieve the calculated outcomes (paragraph 6.23, cannabidiol Minutes, March 2022 PBAC Meeting).
- 4.10 The resubmission further argued that:
- an average dose of 15 mg/kg/day aligns with real world evidence, whereas the average dose of 17 mg/kg/day in the PBAC's respecified base case was based on the trials and thus reflects the trial design. The resubmission proposed a risk sharing arrangement (RSA) based on an average dose of 15 mg/kg/day;
 - the model is conservative because a stopping rule was not applied while in practice it is likely that more patients than observed in the studies will discontinue treatment if they do not achieve a satisfactory treatment effect; and
 - the impact on carers should be taken into consideration, at least to some extent, when considering the cost-effectiveness of cannabidiol in patients with LGS given that the PBAC has previously acknowledged that the frequency of seizures has a considerable impact on carers' quality of life. When using the base case from the previous submission and including carer utilities and the resubmission's lower price, the ICER was \$45,000 to < \$55,000 per QALY.

Drug cost/patient/4 weeks

4.11 In the economic model, the estimated drug cost per patient was \$█ per four weeks based on an average dose of 17 mg/kg/day (per the PBAC’s respecified base case) or \$█ per four weeks based on an average dose of 15 mg/kg/day (as assumed in the financial estimates). This was based on an average body weight of 43.3 kg from the trials (previously considered appropriate by the ESC, paragraph 6.23, cannabidiol Minutes, March 2022 PBAC meeting).

Estimated PBS usage & financial implications

4.12 In March 2022, 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 and requested that the financial estimates be revised to incorporate the new price (paragraphs 7.10 and 7.11, cannabidiol Minutes, March 2022 PBAC Meeting).

4.13 The estimated utilisation and financial implications are outlined in Table 3. As an early re-entry submission, the changes to the financial estimates have not been evaluated.

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
July 2022 resubmission						
Number of patients treated ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts	█ ²	█ ³	█ ³	█ ³	█ ³	█ ³
Number of bottles	█ ³	█ ⁶	█ ⁸	█ ⁸	█ ⁸	█ ⁸
Total PBS/RPBS effective net expenditure ^b	\$█ ⁴	\$█ ⁷	\$█ ⁷	\$█ ⁷	\$█ ⁵	\$█ ⁷
March 2022 submission						
Number of patients treated ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number scripts	█ ²	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to PBS/RPBS effective net expenditure ^b	\$█ ⁴	\$█ ⁷	\$█ ⁷	\$█ ⁵	\$█ ⁵	\$█ ⁵
July 2020 submission						
Number treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number scripts	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Net cost to PBS/RPBS effective net expenditure ^b	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵

Source: Table 3 of the resubmission

^a Includes 86 patients that will transition to PBS-subsidised treatment.

^b Excludes patient co-payments

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

4.14 The resubmission estimated a net cost to the PBS/RPBS of \$20 million to < \$30 million in Year 6, and \$100 million to < \$200 million in the first 6 years of listing.

- 4.15 Compared with the previous submission, the only change to the financial estimates was the inclusion of the lower price. The resubmission maintained the average dose per patient at 15 mg/kg/day (rather than 17 mg/kg/day per the PBAC's respecified base case for the economic model), which was conservative in the context of estimating an RSA cap.
- 4.16 The resubmission stated the estimated number of treated patients was aligned with the diagnostic criteria outlined by the ESA (refer to Table 13, cannabidiol Minutes, 2022 PBAC meeting for methodology) and the proposed patient numbers were appropriate.

Financial Management – Risk Sharing Arrangements

- 4.17 The PBAC previously advised that a RSA would be required to manage the outstanding uncertainty regarding the dose likely to be used in clinical practice (paragraph 7.10, cannabidiol Minutes, March 2022 PBAC Meeting).
- 4.18 The resubmission proposed a [REDACTED] % rebate on PBS expenditure that is in excess of the financial estimates outlined in Table 3. The resubmission proposed a [REDACTED] % rebate (rather than [REDACTED] %) as the resubmission considered there was uncertainty around patient numbers and the potential for use outside the requested indication, 'given that different definitions of LGS can be applied in clinical practice (e.g., where 'LGS-like' conditions are labelled LGS)'.
- 4.19 Further, the resubmission argued that a [REDACTED] % rebate would require that the sponsor rebate the wholesaler mark-ups, pharmacy mark-ups and dispensing fees (in addition to the ex-manufacturer cost of cannabidiol) which the resubmission stated would not be commercially feasible. The resubmission stated that having to rebate both the cost of the drug and the fees and mark-ups means that sponsor's total income upon reaching the nominated threshold does not plateau (which is a reasonable expectation) but, instead, total income begins to decline once the threshold is reached.

5 PBAC Outcome

- 5.1 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 unacceptably high at the price proposed in the resubmission.
- 5.2 The PBAC noted that no consumer comments were received in support of the resubmission but recalled comments supporting the availability of cannabidiol for LGS have been received previously (paragraph 6.2, cannabidiol PSD, March 2022 PBAC meeting).

- 5.3 The PBAC acknowledged LGS is a difficult condition to diagnose and treat but there are a number of other effective treatment options available and the benefit of cannabidiol was likely to be modest.
- 5.4 The PBAC noted the resubmission did not accept the economic model respecifications proposed by the PBAC at the March 2022 meeting. The PBAC noted the ICER using the respecified economic model was \$75,000 to < \$95,000 per QALY (excluding carer utilities) and using the base case economic model from the previous submission was \$55,000 to < \$75,000 per QALY (excluding carer utilities) (both using the resubmission's lower price). The PBAC recalled it had previously considered cannabidiol would be cost-effective for this population with an ICER less than \$45,000 to < \$55,000 per QALY (excluding carer utilities) and noted both economic models resulted in substantially higher ICERs. The PBAC considered cannabidiol was not cost effective at the price proposed in the resubmission.
- 5.5 The PBAC noted the base case economic model in the resubmission continued to apply transition probabilities from the 20 mg/kg/day arm of the clinical trials and treatment costs based on an average dose of 15 mg/kg/day. The PBAC considered this may be reasonable but it remained uncertain if the clinical outcomes in the 20 mg/ kg/ day treatment arm would be achieved at an average dose of 15 mg/ kg/ day in clinical practice. The PBAC acknowledged the fixed dose design of the clinical trials means this will remain unresolved.
- 5.6 The PBAC noted the estimated net cost to the PBS/ RPBS over the first 6 years of listing at the price proposed in the resubmission was \$100 million to < \$200 million. The PBAC considered the financial impact was substantial and, as acknowledged in the resubmission, there was uncertainty around patient numbers and the potential for use outside the proposed population. The PBAC noted the resubmission appropriately proposed an RSA with expenditure caps aligned with the financial estimates to manage the risk. However, the PBAC noted the resubmission proposed a 1% rebate on any expenditure over the caps and considered it was uncertain if this appropriately managed the significant financial risk to the Commonwealth.
- 5.7 The PBAC considered the following changes to the draft restriction criteria proposed in the resubmission were required:
- Amendments as proposed by the Secretariat in Section 2;
 - The clinical criteria 'The treatment must be in combination with at least one anti-epileptic drug' should be amended to 'The treatment must be in combination with at least two anti-epileptic drug', to be consistent with the clinical data for LGS and the current PBS listing for DS.
- 5.8 A resubmission may be lodged for consideration at any future PBAC meeting in accordance with lodgement timelines applicable to a standard re-entry pathway submission for that PBAC meeting.
- 5.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

6 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.

7 Sponsor's Comment

The sponsor had no comment.