6.10 CANNABIDIOL, Oral liquid 100 mg per mL, 100 mL, Epidyolex®, Jazz Pharmaceuticals ANZ Pty Ltd

1 Purpose of Submission

1.1 The Category 3 submission requested a change to the restriction level of PBS-listed cannabidiol (Epidyolex®) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), from Authority Required (Telephone/online PBS Authorities system) to Authority Required (STREAMLINED). The submission also sought amendments to the current PBS restrictions, proposing two options:

- Option 1: Change the clinical criterion requiring an electroencephalogram (EEG) to confirm the diagnosis of LGS, allowing for EEG confirmation where possible.
- Option 2: In addition to the change proposed in Option 1, remove the following requirements from the clinical criteria:
  - The requirement for the patient to have an EEG that showed a pattern of slow (less than 3.0 hertz) spike-and-wave discharges with generalised paroxysmal fast activity (sleep recording should be obtained where it is possible);
  - The restriction limiting seizure classification to generalised seizures only.
  - The requirement for seizure frequency and type, specifically at least two drop seizures (atonic, tonic, or tonic-clonic) per week; and
  - The requirement that cannabidiol be used as adjunctive therapy with at least two other antiseizure medication (AEDs) for continuing treatment.

  Additionally, Option 2 includes the following amendments to the current restrictions:
  - An amendment to the treatment criteria to allow prescribing by a paediatrician without the need for consultation with a neurologist, and continuation of therapy by a general practitioner in consultation with a paediatrician.
  - Removal of the prescribing instruction that tonic seizures must have been recorded on video-EEG or have been clearly observed and reported by a witness.

2 Background

2.1 Cannabidiol is currently listed on the PBS as a General Schedule Authority Required (Telephone/online PBS Authorities system) listing for seizures of the LGS.

2.2 Cannabidiol is also currently listed on the PBS as a General Schedule Authority Required (Telephone/online PBS Authorities system) listing for the treatment of severe myoclonic epilepsy in infancy (Dravet syndrome). The submission did not propose any amendments to the existing PBS listing for this indication.

Registration status

2.3 Cannabidiol was TGA registered on 21 September 2020 for use as adjunctive therapy of seizures associated with LGS or Dravet syndrome for patients 2 years of age or older. The TGA approved product information (PI) indicates that cannabidiol should be initiated and supervised by a neurologist.

Previous PBAC consideration

2.4 Cannabidiol has previously been considered for this indication by the PBAC on multiple occasions. In September 2022, the PBAC recommended 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 AEDs.

2.5 A summary of the key considerations from previous meetings, related to the PBS restrictions proposed for amendment, is presented in the table below.

Table 1: Summary of key considerations from previous meetings related to PBS restrictions

PBAC Meeting	PBS restriction	Previous PBAC consideration
July 2020	PBS restriction level of cannabidiol	Paragraph 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.
November 2020	Clinical criteria: • Patient must have a diagnosis of Lennox-Gastaut syndrome confirmed by an electroencephalogram (EEG) that showed a pattern of slow (less than 3.0 hertz) spike-and-wave discharges with generalised paroxysmal fast activity (sleep recording should be obtained where it is possible); and • Patient must have had at least two drop seizures (atonic, tonic or tonic-clonic) per week that are not adequately controlled with at least two other anti-epileptic drugs prior to initiating treatment with this medicine.	Paragraph 9.19: The PBAC noted the clinical advice that 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 criteria that appropriately identifies people with LGS.
March 2022		Paragraph 6.4: The Epilepsy Society of Australia (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. Paragraph 7.3: The PBAC noted the comments from the 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

PBAC Meeting	PBS restriction	Previous PBAC consideration
		at trial entry and considered it may be appropriate to also include this in the restriction criteria.
March 2022	Clinical criteria: Patient must have (as an initiating patient)/have had (as a continuing patient) more than one type of generalised seizures	The PBAC had previously noted the advice of the ESA that the definition for 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 (paragraph 6.3, PSD, July 2020 PBAC meeting). In the March 2022 resubmission, the sponsor proposed the clinical criterion: "Patient must have (as an initiating patient)/have had (as a continuing patient) more than one type of generalised seizure, including drop seizures (atonic, tonic, or tonic-clonic), that are not adequately controlled with at least two other antiseizure medication."
September 2022	Clinical criteria: The treatment must be as adjunctive therapy to at least two other antiseizure medication.	Paragraph 9.5: The PBAC reiterated its previous advice (see paragraph 5.7, PSD, July 2022 PBAC meeting) that the clinical criteria 'The treatment must be in combination with at least one anti-epileptic drug' should be amended to 'The treatment must be as adjunctive therapy to at least two other antiseizure medication', to be consistent with the clinical data for LGS and the current PBS listing for cannabidiol for DS.
July 2020	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.	Paragraph 6.3: The PBAC noted the advice of the ESA 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.
March 2022		November 2020, paragraph 9.11 for DS: 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. Paragraph 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 In March 2022, 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 3.3). The PBAC had previously advised that initial prescribing should be limited to neurologists, and that pediatricians and general practitioners, in addition to neurologists, could also continue treatment, but only in consultation with a neurologist (paragraph 9.11, PSD, November 2020 meeting).
July 2022	Prescribing Instructions: Tonic seizures must have been recorded on video-EEG or have been clearly observed and reported by a witness.	Paragraph 5.7: The PBAC considered the following changes to the draft restriction criteria proposed in the resubmission were required. The proposed changes included the addition of Prescribing Instruction: "Tonic seizures must have been recorded on video-EEG or have been clearly observed and reported by a witness." (Refer to comments from the ESA, paragraph 6.4. PSD, March 2022 PBAC meeting).

Source: Compiled during the evaluation, referencing the cannabidiol PSDs from July 2020, November 2020, March 2022, July 2022, and September 2022.

Abbreviations: DS = Dravet syndrome; EEG = electroencephalogram; Hz = hertz; LGS = Lennox-Gastaut syndrome; PSD = Public Summary Document; ESA = Epilepsy Society of Australia

3 Requested listing

3.1 The submission requested the following changes to the existing listing (PBS item code: 13277T), as outlined below. The submission's proposed additions are shown in bold text, and deletions are indicated with strikethrough.

Amend existing listing as follows:

Option 1*:

<table>
<tr><th colspan="2">MEDICINAL PRODUCT
medicinal product pack</th><th>PBS item code</th><th>Max. qty packs</th><th>Max. qty units</th><th>№.of Rpts</th><th>Available brands</th></tr>
<tr><td colspan="7">CANNABIDIOL</td></tr>
<tr><td colspan="2">cannabidiol 100 mg/mL oral liquid, 100 mL</td><td>13277T</td><td>1</td><td>1</td><td>5</td><td>Epidyolex</td></tr>
<tr><td colspan="7"></td></tr>
<tr><td colspan="7">Restriction Summary 14047/ Treatment of Concept: 14047</td></tr>
<tr><td rowspan="3">Concept ID
(for internal Dept. use)</td><td colspan="6">Category / Program: ☒ GENERAL - General Schedule (Code GE)</td></tr>
<tr><td colspan="6">Prescriber type: ☒Medical Practitioners</td></tr>
<tr><td colspan="6">Restriction type:
☒Authority Required (Streamlined)
☒~~Authority Required (telephone/online PBS Authorities system)~~</td></tr>
<tr><td rowspan="4">Prescribing rule level</td><td></td><td colspan="5">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.</td></tr>
<tr><td></td><td colspan="5">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.</td></tr>
<tr><td></td><td colspan="5">Administrative Advice: No increase in the maximum number of repeats may be authorised.</td></tr>
<tr><td></td><td colspan="5">Administrative Advice: Special Pricing Arrangements apply.</td></tr>
<tr><td colspan="2"></td><td colspan="5">Indication: Seizures of the Lennox-Gastaut syndrome</td></tr>
<tr><td colspan="2"></td><td colspan="5">Clinical criteria:</td></tr>
<tr><td colspan="2"></td><td colspan="5">Patient must have a diagnosis of Lennox-Gastaut syndrome. Where possible, the diagnosis should be confirmed by an electroencephalogram (EEG) that showed a pattern of slow (less than 3.0 hertz) spike-and-wave discharges with generalised paroxysmal fast activity (sleep recording should be obtained where it is possible)</td></tr>
</table>

*As the only change in Option 1 is to amend the EEG criterion, the full restriction has not been populated here.

3.2 The evaluation noted that the EEG criterion for the diagnosis of LGS was added in the March 2022 resubmission, following advice from the PBAC that an EEG is the most definitive diagnostic measure for LGS (see Table 1). The proposed request is to make EEG confirmation of LGS diagnosis optional, which would effectively remove this diagnostic requirement for identifying patients with epilepsy who have a diagnosis of LGS.

3.3 The evaluation also noted that the phrase "where possible" would introduce considerable ambiguity and could lead to confusion among prescribers regarding its intended application.

3.4 The pre-PBAC response stated that formal consultation with a group of adult and paediatric epilepsy specialist physicians was conducted, and they supported the submission. The pre-PBAC response reiterated the limitations in obtaining an EEG

when services are not available in rural or remote areas. The submission aimed to reduce the stress on LGS families trying to meet EEG requirements.

For more detail on PBAC's view, see section 5 PBAC outcome.

Option 2:

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	13277T	1	1	5	Epidyolex
Restriction Summary 14047/ Treatment of Concept: 14047					
Category / Program: ☒ GENERAL - General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒**Authority Required (Streamlined)** ☒~~Authority Required (telephone/online PBS Authorities system)~~					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: 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 (sleep recording should be obtained where it is possible)~~ **Where possible, the diagnosis should be confirmed by an electroencephalogram (EEG).**					
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 had ~~at least two drop~~ seizures ~~(atonic, tonic or tonic-clonic) per week~~ that are not adequately controlled with at least two other antiseizure medication prior to initiating treatment with this medicine					
AND					
Clinical criteria:					
The treatment must be as adjunctive therapy, **at initiation,** to at least two other anti-epileptic drugs					
Treatment criteria:					
Must be treated by a prescriber who is either (i) a neurologist, **or** (ii) a **paediatrician** if treatment is being initiated; or					
Must be treated by a prescriber who is either (i) a neurologist, **or** (ii) a **paediatrician** 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 either (I) a neurologist**, or** (ii) a **paediatrician** if treatment is being continued					

Prescribing Instructions: ~~Tonic seizures must have been recorded on video-EEG or have been clearly observed and reported by a witness.~~
Prescribing Instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.

3.5 The evaluation noted that the proposed changes to the restriction criteria were not consistent with the TGA-approved PI, which specifies the use of cannabidiol as adjunctive therapy in patients with LGS, to be initiated and supervised by a neurologist. The proposed amendments would allow initiation and continuation by a paediatrician without consultation with a neurologist and enable continued use of cannabidiol without the requirement for concomitant AEDs. In the criterion: 'The treatment must be as adjunctive therapy, *at initiation*, to at least two other anti-epileptic drugs', The Secretariat proposed removing "at least two" rather than adding "at initiation," to ensure cannabidiol use as an add-on therapy with any number of concomitant AEDs, consistent with clinical trial data, TGA registration, and clinical practice.

3.6 Furthermore, the evaluation noted that the proposed restriction criteria were not closely aligned with the clinical trial evidence. In the trials (see Table 2), patients were required to have two or more drop seizures per week during a 28-day baseline period that were inadequately controlled on at least one AED. Patients were also required to have an EEG that showed a pattern of slow (< 3.0 Hz) spike-and-wave complexes. The primary endpoint in these trials was the percentage change from baseline in drop seizure frequency per 28 days during the treatment period, where drop seizures were defined as atonic, tonic, or tonic-clonic seizures that led or could have led to a fall or injury. Key secondary endpoints included the proportion of patients achieving at least a 50% reduction in drop seizure frequency (Refer to the Clinical Trials section in the PI).

3.7 The pre-PBAC response stated that the health professionals group emphasised the importance of utilising cannabidiol as an adjunctive option for reducing seizures and increasing seizure-free periods for patients. The pre-PBAC response also reiterated that seizure types in patients with LGS are not limited to generalised seizures, as most patients also experience focal seizures.

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

4.2 The PBAC noted and welcomed the input from health care professionals (11), a medical organisation (1), and consumer groups (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits associated

with cannabidiol, including improved seizure control, better sleep quality, and enhanced mood and behaviour in patients with LGS. Cannabidiol is generally considered to be well tolerated, with fewer side effects and drug interactions compared to other AEDs. The comments also emphasised the importance of access to cannabidiol as an adjunctive treatment, particularly for its role in reducing seizure frequency and increasing seizure-free periods. Overall, these benefits were seen as contributing to improved quality of life, reduced hospital admissions, and a lower risk of seizure-related injuries and complications. Concerns were raised regarding the current PBS restriction, specifically the requirement for defined EEG criteria in patients with LGS. Practical challenges include limited access to EEG services in rural and remote areas, the evolving nature of EEG patterns in LGS, and difficulties in obtaining historical or repeated EEGs, especially in adults with intellectual and behavioural impairments. Additionally, the specified EEG features may not consistently appear or be captured in short recordings, further limiting access to treatment. In the comments, health care professionals (mainly neurologists and epileptologists) supported the proposed amendments to the cannabidiol listing and the streamlined authority process, considering diagnosis by an epilepsy specialist sufficient without mandatory EEG documentation to improve equity of access for patients with LGS.

4.3 Epilepsy Action Australia and the Epilepsy Foundation provided input supporting amendments to the PBS restrictions for cannabidiol. Their comments highlighted barriers to accessing EEGs and specialist care, particularly in rural and remote areas, and emphasised the need to allow paediatricians to prescribe cannabidiol and to amend EEG requirements where testing is not feasible, to improve equitable access, reduce financial burden, and ensure timely treatment for eligible patients.

4.4 The National Paediatric Medicines Forum (NPMF) provided input in support of amending the PBS restrictions for cannabidiol, including lowering the restriction level to Authority Required (STREAMLINED), amending clinical criteria to ease EEG requirements, and allowing paediatricians to prescribe the medication for continuing treatment. The NPMF highlighted challenges in accessing EEG services, particularly in rural areas, the burden on families due to hospital constraints, and emphasised the importance of equitable access, the need to maintain treatment continuity, and the significant impact of cannabidiol in improving quality of life for patients with LGS, who often require complex, multi-drug regimens.

Clinical trials

4.5 Two randomised, double-blind, placebo-controlled studies (GWPCARE3 and GWPCARE4) were presented in the previous submissions to demonstrate the efficacy and safety of cannabidiol as an adjunctive treatment for seizures associated with LGS in children and adults. In both studies, 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 (paragraph 3.4, Public Summary Document (PSD), July 2020 PBAC meeting).

Table 2: Trials presented in the previous resubmissions

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 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 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 *The Lancet* 2018: 391(10125): 1085-1096

Source: Table 3, March 2022 cannabidiol PSD.

4.6 The submission did not present any new clinical evidence in support of the proposed amendments to the current restriction criteria.

Rationale for the proposed changes

4.7 The submission claimed that the current PBS restrictions for cannabidiol in the LGS indication delay or prevent patient access to the medicine, based on formal feedback from epilepsy specialist physicians. However, the evaluation noted that the submission did not include details about the clinicians who provided this feedback, the number of clinicians involved, or the specific concerns they raised regarding the restrictions. In its pre-PBAC response, the sponsor subsequently provided some information about the epilepsy specialist physicians who were consulted for their input.

Administrative burden

4.8 The submission claimed that the lower-than-expected usage of cannabidiol for the treatment of seizures associated with LGS is partly due to the current restriction level, which requires authority approval through the telephone or online PBS Authorities system. The submission stated that this approval process imposes an administrative burden on prescribers and, therefore, requested that the authority level be changed from Authority Required (Telephone/online PBS Authorities system) to Authority Required (STREAMLINED).

4.9 In its previous consideration of cannabidiol for the treatment of DS and LGS, the PBAC advised that an Authority Required (Telephone/Online), Section 85 (General Schedule) listing was appropriate (paragraphs 3.7 and 9.8, PSDs, July and November 2020 PBAC meetings). In the March 2022 resubmission, the proposed restriction level for LGS was consistent with that approved for DS: Authority Required (Telephone/Online).

4.10 The evaluation noted that the PBAC had previously acknowledged the potential for cannabidiol to be used outside the intended population, other than as adjunctive therapy in combination with other AEDs for LGS, and that the submission did not propose any changes to the current restriction level for DS.

Inequitable access to cannabidiol

4.11 The submission stated that consultation with epilepsy specialist physicians and the Epilepsy Society of Australia (ESA) has highlighted that the current restriction criteria contribute to inequitable access to cannabidiol, particularly for adult patients and those living in rural and remote areas. This inequity is attributed to:

- the unavailability of EEG services in rural and remote areas.
- difficulties in obtaining EEG in adults with LGS due to behavioural, cognitive, and physical comorbidities.
- the inability to detect the specified EEG features in adult patients due to the well-documented evolution of LGS EEG patterns with age, and
- difficulties in accessing historical medical records containing previously performed and reported EEGs, or the need to repeat an EEG.

4.12 The submission proposed two options to address inequitable access to cannabidiol, which arises from limitations associated with EEG (particularly in rural and remote areas and adult patients with LGS) or the unavailability of EEG records, as outlined in paragraph 4.11: Option 1, to remove the requirement for an EEG to confirm the diagnosis of LGS, and Option 2, to remove the requirement for an EEG showing a pattern of slow (less than 3.0 hertz) spike-and-wave discharges with generalised paroxysmal fast activity. The submission stated that Option 2 was based on input from epilepsy specialist physicians indicating that such EEG features may not be present in adults. The submission claimed that LGS progresses with age, leading to changes in seizure patterns and EEG features. For example, the submission stated that while children and adolescents typically exhibit 1.5–2.5 hertz slow spike-wave discharges during wakefulness and generalised paroxysmal fast activity during sleep, these patterns become less prominent or may even disappear in adulthood. Subsequently, many adults (after the age of 16 years) no longer display the typical slow spike-wave discharges required for access to cannabidiol.

4.13 However, the PBAC had previously noted clinical advice that LGS is a heterogeneous condition, often inconsistently defined in clinical practice, and that EEG is the most definitive diagnostic measure for LGS. Further, the ESA stated that it would be appropriate to require patients to have an electroclinical diagnosis of LGS confirmed by a neurologist with expertise in epilepsy and include typical EEG features of LGS in the clinical criteria. As such, the PBAC considered it appropriate to include a specific definition of LGS in the restriction criteria to clearly identify patients with LGS (paragraph 9.19, PSD, November 2020 PBAC meeting).

4.14 The submission argued that, as no other country with registration and reimbursement requires EEG as a criterion for accessing cannabidiol and given that PBS restrictions for other AEDs used in the treatment of LGS do not specify EEG requirements, seizure type, or frequency in the clinical criteria, similar criteria should therefore be applied to the cannabidiol listing. The evaluation could not verify whether other jurisdictions impose the requirement for an EEG as a diagnostic measure for LGS to access government-funded cannabidiol. Topiramate and cannabidiol are explicitly TGA-approved as add-on therapies for LGS in Australia. Topiramate is currently PBS-listed as a General Schedule Authority Required (STREAMLINED) listing for LGS when seizures are not satisfactorily controlled by other AEDs.

4.15 The submission indicated that, should an EEG no longer be required to confirm a diagnosis of LGS under the updated restriction, the prescribing instruction "Tonic seizures must have been recorded on video-EEG or have been clearly observed and reported by a witness" would be redundant. The submission therefore requested the removal of this prescribing instruction under Option 2.

Clinical terms for seizure types and frequency.

4.16 The submission proposed removing the term "generalised" from the criterion: "Patient must have (as an initiating patient)/have had (as a continuing patient) more than one type of generalised seizure." The submission argued that the current wording is clinically inaccurate, as seizure types in patients with LGS are not limited to generalised seizures. While generalised seizures, such as tonic, atonic, and atypical absence seizures, are characteristic features of LGS, many patients also experience focal seizures.

4.17 The submission further argued that limiting the seizure types and frequency in the initiation criterion to "at least two drop seizures (atonic, tonic, or tonic-clonic) per week" is excessively restrictive. As noted in paragraph 4.16, while atonic, tonic, and tonic-clonic seizures are common in patients with LGS, the condition is characterised by multiple seizure types, including myoclonic, atypical absence, and focal seizures. Seizure frequency can also fluctuate naturally, with some patients experiencing clusters in one week and fewer in another. The PBAC had previously noted that clinical trials of cannabidiol required patients to have at least two drop seizures per week at baseline and considered it appropriate to reflect this in the restriction criteria (Table 1). The evaluation noted that the PBS listing was based on these trials, which demonstrated the efficacy of cannabidiol on drop seizures in LGS (paragraph 3.6).

Adjunctive therapy

4.18 The submission requested the addition of "at initiation" to the clinical criterion: "The treatment must be as adjunctive therapy to at least two other antiseizure medication". This amendment is intended to require that cannabidiol be used with two concomitant AEDs only at the initiation of treatment, with this requirement not applying to continuing therapy.

4.19 The submission noted input from epilepsy specialists indicating that patients who initially achieve seizure control with cannabidiol and two AEDs may later discontinue one AED while maintaining seizure control. Under the current restriction, such patients would become ineligible for continued PBS-subsidised treatment. However, the submission did not provide evidence demonstrating that cannabidiol combined with a single AED offers comparable clinical benefit to its use with two AEDs. The evaluation noted that the proposed criterion could allow continued treatment with cannabidiol even in the absence of any concomitant AEDs, potentially resulting in a small increase in the eligible population. The evaluation also notes the TGA-approved indication for cannabidiol is as adjunctive therapy (paragraph 2.3), without specifying a required number of concomitant AEDs for ongoing treatment.

Treatment criteria

4.20 The submission requested amending the treatment criteria to allow prescribing by a paediatrician without neurologist consultation, and continuation by a general practitioner in consultation with a paediatrician. This request was based on the limited availability of paediatric neurologists in rural areas (e.g., Queensland) where general paediatricians are often responsible for managing patients with LGS. In March 2022, the restriction in the resubmission was modelled on that approved for DS, where 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 (see Table 1).

Economic analysis

4.21 No economic analysis was provided, as the submission stated that the proposed changes to the PBS restrictions would not impact the cost-effectiveness of cannabidiol.

Estimated PBS usage and financial implications

4.22 The submission presented a comparison between the actual utilisation (measured by the number of bottles dispensed) and the net financial impact against those estimated in the July 2022 PBAC submission (see Table 3). It claimed that current usage represents only 18% of the projected number of bottles expected to be dispensed, and 23% of the estimated financial impact during the first year of listing (June 2023 to May 2024). The evaluation noted that the submission did not reference the revised utilisation and financial estimates from the September 2022 PBAC submission.

4.23 The submission claimed that the proposed changes to the PBS restrictions would not affect the intended population or alter the existing recommendation, as there were no changes to the clinical, economic, or financial information most recently relied upon by the PBAC. However, the evaluation noted that, should the requested amendments to the PBS restrictions be recommended, it would remain uncertain whether cannabidiol might be used outside the intended population. Further, some proposed changes explicitly broaden the eligible population (e.g. removing the

requirement for two concomitant AEDs in continuing therapy or making certain diagnostic criteria optional or unnecessary). This could lead to use in populations for whom cost-effectiveness has not been established. The submission did not provide evidence supporting cost-effectiveness in these proposed scenarios and instead relied on clinician feedback, without supplying direct supporting evidence.

4.24 The submission stated that the observed under-utilisation, relative to PBAC-accepted estimates, was due to PBS restrictions that unnecessarily limit patient access and contribute to therapeutic inequality. However, the submission did not provide evidence to support the claim that the restrictions are the primary driver of under-utilisation. The submission also did not consider other potential contributing factors, such as uncertainty in the original estimates, changes in prescriber behaviour, or the real-world adverse event profile. Additionally, the submission did not include a sensitivity analysis or modelling to assess the extent to which the proposed changes are expected to improve access within the eligible population.

Table 3: Comparison of actual use and financial implications against estimates in the July 2022 submission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
July 2022 resubmission						
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of bottles	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][7]	$[redacted][6]
Actual PBS usage data provided in the submission (note: Year 2 is not a full year)						
Extent of use						
Number of bottles dispensed	[redacted][1]	[redacted][1]	N/A			
Net financial implications						
Net cost to PBS/RPBS	$[redacted][5]	$[redacted][5]	N/A			

Abbreviations: MBS = Medical Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; PSD = Public Summary Document; N/A = not available

Source: Table 3 of the cannabidiol July 2022 PSD; Table 1.4-1 of the submission

Note: Year 1: June 2023 to May 2024; Year 2: June 2024 and January 2025

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *10,000 to < 20,000*

[3] *20,000 to < 30,000*

[4] *30,000 to < 40,000*

[5] *$10 million to < $20 million*

[6] *$20 million to < $30 million*

[7] *$30 million to < $40 million*

Risk-sharing arrangements

4.25 The submission did not propose any changes to the existing RSA.

5 PBAC Outcome

5.1 The PBAC recommended amending the restriction level of cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), from Authority Required (Telephone/online PBS Authorities system) to Authority Required (STREAMLINED).

5.2 The PBAC also recommended the following amendments to the current PBS criteria for cannabidiol in the LGS indication, as proposed in Option 2 of the submission:

- Change the mandatory requirement for an electroencephalogram (EEG) to confirm the diagnosis of LGS, allowing for EEG confirmation where possible.
- Remove the specific EEG feature requirement of slow (less than 3.0 hertz) spike-and-wave discharges with generalised paroxysmal fast activity (sleep recording should be obtained where it is possible).
- Remove the requirement for seizure classification to be limited to generalised seizures for both initial and continuing treatment.

- Remove the requirement for seizure frequency and type: "at least two drop seizures (atonic, tonic, or tonic-clonic) per week".
- Remove the requirement for "at least two" other antiseizure medication, allowing ongoing cannabidiol use with one or more concomitant AEDs.
- Amend the treatment criteria to allow prescribing by a paediatrician without the need for consultation with a neurologist, and continuation of therapy by a general practitioner in consultation with a paediatrician;
- Remove the prescribing instruction that "tonic seizures must have been recorded on video-EEG or have been clearly observed and reported by a witness."

5.3 The PBAC noted input from health professionals, primarily neurologists and epileptologists involved in the management of patients with LGS, who emphasised the clinical need for cannabidiol as an adjunctive therapy. The comments highlighted the therapeutic benefits of cannabidiol in reducing seizure frequency, hospital admissions, and the risk of seizure-related injuries and complications, which contributes to an overall improvement in the quality of life for patients and their families. The PBAC also noted input from the National Paediatric Medicines Forum (NPMF) and consumer groups supporting amendments to the current PBS restrictions. In particular, the comments expressed support for removing the requirement for defined EEG criteria, reflecting the limited availability of EEG services, especially in rural and remote areas, and the variability of EEG features observed in adult patients. Additionally, the comments supported the inclusion of paediatricians as eligible prescribers to ensure equitable and timely access to cannabidiol for patients with LGS.

5.4 The PBAC noted the submission's claim that the current PBS restrictions delay or prevent access to cannabidiol for patients with LGS, based on feedback from epilepsy specialist physicians and utilisation data since its listing for LGS. The data showed that actual utilisation (bottles dispensed) accounted for only 18% of the projected number of bottles expected to be dispensed, and 23% of the estimated financial impact during the first year of listing (June 2023 to May 2024).

5.5 The PBAC acknowledged concerns related to the requirement for an EEG to confirm LGS diagnosis under the current clinical criteria, including limited EEG services in rural and remote areas, which require severely disabled patients to travel long distances to metropolitan centres for testing, difficulties in meeting sleep/video EEG requirements in inpatient hospital settings due to bed shortages, challenges in obtaining EEGs in adult patients with behavioural, cognitive, and physical comorbidities, and issues accessing historical EEG reports. The PBAC recalled clinical advice that EEG is the most definitive diagnostic measure for LGS (paragraph 9.19, PSD, November 2020 PBAC meeting), and considered it appropriate to retain EEG confirmation as an optional criterion in the restriction to improve patient access to cannabidiol.

5.6 The PBAC advised that the proposed amendments in Option 2 to remove specific EEG features, seizure frequency and type, and the number of concomitant AEDs are reasonable, based on input from epilepsy specialist physicians. The PBAC also considered it appropriate to allow prescribing by a paediatrician for both initial and continuing treatment. In clinical practice, paediatric patients with LGS are often managed by paediatricians due to a shortage of trained neurologists, particularly in regional and rural areas.

5.7 The PBAC acknowledged input from health professionals and organisations supporting the proposed authority level amendment to reduce administrative burden. The PBAC noted that current utilisation of cannabidiol is lower than anticipated, that prescribers now have considerable experience with its use, and that the risk of prescribing to ineligible patients is low. Therefore, the PBAC considered a streamlined authority to be appropriate.

5.8 The PBAC noted the submission's estimate that the proposed changes would have no net financial impact. While the PBAC considered there is uncertainty regarding the extent of financial implications from the revised PBS restrictions, which may increase utilisation of cannabidiol, it is not expected to result in a substantial financial impact. The PBAC recommended that no revision to the existing financial estimates previously agreed for cannabidiol was required. The PBAC advised that it will closely monitor the usage of cannabidiol on the PBS and its financial impact.

5.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met, as its recommendation to amend the clinical criteria for cannabidiol for the treatment of seizures associated with LGS is not expected to address a high and urgent unmet clinical need.

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

Outcome:
Recommended

6 Recommended listing

6.1 Amend existing listing as follows:

Additions are in *italics* and deletions are in ~~strikethrough~~

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	13277T	1	1	5	Epidyolex
Amend Restriction Summary 14047/ Treatment of Concept: 14047					
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒~~Authority Required (telephone/online PBS Authorities system)~~ ☒*Authority Required (Streamlined) (New code)*				
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 (sleep recording should be obtained where it is possible)~~ *Patient must have a diagnosis of Lennox-Gastaut syndrome. The diagnosis should be confirmed by an electroencephalogram (EEG) where possible.*					
AND					
Clinical criteria:					
Patient must have (as an initiating patient)/have had (as a continuing patient) more than one type of ~~generalised~~ seizures *that are not adequately controlled with at least two other antiseizure medication prior to initiating treatment with this medicine.*					
~~**AND**~~					
~~**Clinical criteria:**~~					
~~Patient must have had seizures that are not adequately controlled with at least two other anti-epileptic drugs prior to initiating treatment with this medicine~~					
AND					
Clinical criteria:					
The treatment must be as adjunctive therapy to ~~at least two~~ other antiseizure medication					
Treatment criteria:					
Must be treated by ~~a neurologist~~ *a prescriber who is either (i) a neurologist, (ii) a paediatrician* if treatment is being initiated; or					
Must be treated by ~~a neurologist~~ *a prescriber who is either (i) a neurologist, (ii) a paediatrician* if treatment is being continued or re-initiated; or					
Must be treated by a general practitioner in consultation with ~~a neurologist~~ *either (I) a neurologist, (ii) a paediatrician* if treatment is being continued					
~~**Prescribing Instructions:**~~ ~~Tonic seizures must have been recorded on video-EEG or have been clearly observed and reported by a witness.~~					

Prescribing Instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.

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

7 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.

8 Sponsor's Comment

The sponsor had no comment.