

Review of clinical guidelines and cost estimates for the use of AEDs for the treatment of epilepsy

Final Report

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EXECUTIVE SUMMARY

Levetiracetam and lamotrigine, both second-line medications for the treatment of epilepsy in Australia, are Pharmaceutical Benefits Scheme (PBS)-subsidised for epilepsy as Authority Required (STREAMLINED) listings if seizures fail to be satisfactorily controlled by other antiepileptic drugs (AEDs). Levetiracetam and lamotrigine are PBS-subsidised as first-line AEDs for women of childbearing potential due to the teratogenicity of current first-line AEDs such as valproate. The Pharmaceutical Benefits Advisory Committee (PBAC) recommended allowing women of childbearing potential with epilepsy to initiate treatment with these medications in September 2020.

At its September 2020 meeting, the PBAC requested that the Australian Government Department of Health and Aged Care (DoHAC) provide cost estimates for allowing levetiracetam and lamotrigine to be listed as first-line drugs for all people with epilepsy. The PBAC also requested the DoHAC to provide data on the utilisation of AEDs and any further evidence of the broader use of other second-line AEDs.

The aim of Part 1 of this report was to:

- Identify relevant key Australian and international clinical guidelines for the use of AEDs for the treatment of epilepsy (Research Question 1), and;
- Compare recommendations in the identified guidelines to the PBS restrictions and Therapeutic Goods Administration (TGA)-approved indications (Research Question 2).

The aim of Part 2 of this report was to:

- Estimate the cost to the PBS if the PBS restrictions for levetiracetam and lamotrigine were amended to allow their first-line use for epilepsy in the general Australian population (Research Question 3), and;
- Estimate how the first-line use of levetiracetam and lamotrigine in the general population will impact on the utilisation of the more expensive third-line AEDs (i.e., brivaracetam, perampanel, lacosamide, cannabidiol and stiripentol) (Research Question 4).

Part 1 Review of clinical guidelines

- Across the included guidelines, carbamazepine is commonly recommended as the first-line treatment for focal seizures and valproate for generalised seizures. However, for females who are of childbearing potential, lamotrigine or levetiracetam are recommended as alternatives to valproate.
- Two Australian guidelines recommended lamotrigine and levetiracetam as the first-line AED for the treatment of epilepsy. These recommendations were consistent with the recommendations in the majority of the international guidelines.
- The second-line AEDs recommended by the included Australian guidelines are similar to the TGA-approved and PBS-listed ones except for levetiracetam and lamotrigine. Two Australian local guidelines recommended lamotrigine and levetiracetam as the first-line AED for treatment of epilepsy. These local guidelines are generally a robust reflection of real-world practice, as they are reviewed and updated frequently by experts working in the field.

Part 2: Utilisation review and cost estimates

Part 2a: Utilisation review

Based on an analysis of PBS data from 2014-2023, the key findings were:

- 920,512 patients were supplied a PBS-listed AED between 2014 and 2023; 485,532 (53%) females and 434,790 (47%) males.
- 27,261,781 prescriptions for AEDs were supplied via the PBS between 2014-2023. Valproate was the most frequently supplied AED in 2014, accounting for 743,455 (31%) of all prescriptions. In 2023, valproate use had declined to 687,128 prescriptions (23%) and levetiracetam became the most dispensed AED with 849,522 prescriptions (28%). Lamotrigine was the third most frequently dispensed AED in 2023 with 566,345 (15%) prescriptions.
- 564,746 patients initiated on a PBS-listed AED between 2015 and 2023. The number of incident patients declined over time from 75,541 patients in 2015 to 55,776 patients in 2023.
- In 2023, women of childbearing potential (aged 15-49 years¹) were more than twice as likely to initiate AED treatment with lamotrigine or levetiracetam compared to men of the same age (Figure 7). Men aged 15-49 years more frequently initiated with valproate while women with lamotrigine.
- 27.3% of patients who were initiated on valproate or carbamazepine in the primary care setting had a recorded diagnosis of epilepsy based on POpulation Level Analysis & Reporting (POLAR) primary care data from 2018 to 2023.
- Approximately 15% of patients who initiated AED treatment were sequentially prescribed two or more different AEDs during the study period (2015-2023).
- The two most frequent drug sequences were from valproate to levetiracetam (n=4,373) and from levetiracetam to valproate (n=4,188).

Part 2b: Cost estimates

The [utilisation and cost model \(UCM\) workbook](#) was used to estimate changes in utilisation and the cost to the R/PBS if PBS restrictions for levetiracetam and lamotrigine were changed to allow their first-line use for epilepsy in the general Australian population (referred to as the “proposed listing”).

The key findings from the base-case analysis were:

- R/PBS utilisation of carbamazepine and valproate is expected to decrease by 69,043 prescriptions in 2025 and by 234,974 prescriptions in 2030.
- R/PBS utilisation of levetiracetam and lamotrigine is expected to increase by 64,045 prescriptions in 2025 and 219,360 prescriptions in 2030.
- The estimated net cost to the R/PBS as a result of the proposed listing is \$1,239,245 in 2025 increasing to \$4,398,303 in 2030. In total, this equates to \$16,873,770 over the 6-year period (2025-2030).

Sensitivity analyses were conducted to estimate how the proposed listing will impact on the utilisation of the more expensive third-line AEDs (i.e., brivaracetam, perampanel, lacosamide, cannabidiol and stiripentol). These analyses showed that:

- By increasing the substitution rate of valproate and carbamazepine from 10% in 2025 with an additional 10% each year up to 2030 (base-case) to 15%, the cost increased by 48%.
- By decreasing the substitution rate of valproate and carbamazepine from base-case to 5%, the cost decreased by 50%.

¹ Women of childbearing potential were defined in accordance with the World Health Organization (WHO) definition i.e., women aged 15-49 years. [https://www.who.int/data/gho/indicator-metadata-registry/imr-details/women-of-reproductive-age-\(15-49-years\)-population-\(thousands\)](https://www.who.int/data/gho/indicator-metadata-registry/imr-details/women-of-reproductive-age-(15-49-years)-population-(thousands)). Accessed 10 March 2025.

- By decreasing the substitution rate of valproate and carbamazepine liquid forms from base-case to 5%, the cost decreased by 68% and to 2.5% by 102% (i.e., the proposed listing has a lower cost than the current listing).
- By increasing the proportion of people with epilepsy from 27.3% of all people who initiate AED to 80%, decreased the cost by 79%.
- The flow-on effect to third-line AEDs is minimal. The increase in the net cost to the R/PBS from the base-case analysis (no flow-on effects) is 0.61% in the lowest cost scenario and 6.83% in the highest cost scenario.

BACKGROUND

In Australia, there are 22 anti-seizure medications¹ or antiepileptic drugs (AEDs) which are approved by the Therapeutic Goods Administration (TGA) and available through the Pharmaceutical Benefits Scheme (PBS) for epilepsy treatment. These AEDs can be categorised into three treatment phases - first-line, second-line and third-line. First-line AEDs include carbamazepine, ethosuximide, phenobarbital (phenobarbitone), phenytoin, primidone, sulthiame, valproate, clonazepam, and nitrazepam. Second-line AEDs include gabapentin, levetiracetam, tiagabine, zonisamide, lamotrigine, vigabatrin, oxcarbazepine, and topiramate; while third-line AEDs comprise brivaracetam, perampanel, lacosamide, cannabidiol, and stiripentol. Only six AEDs—carbamazepine, ethosuximide, phenytoin, primidone, sulthiame, and valproate—are unrestricted benefits on the PBS, with most AEDs requiring that specific criteria be met to receive the subsidy (Table 1). According to the clinical practice guidelines included in this report, monotherapy remains the primary approach to managing epilepsy, though combination therapy with additional AEDs may be required for some patients needing enhanced seizure control.

Levetiracetam and lamotrigine, both second-line medications for the treatment of epilepsy in Australia, are PBS-subsidised for epilepsy as Authority Required (STREAMLINED) listings if seizures fail to be satisfactorily controlled by other AEDs. Levetiracetam and lamotrigine are PBS-subsidised as first-line AEDs for women of childbearing potential due to the teratogenicity of current first-line AEDs such as valproate. The Pharmaceutical Benefits Advisory Committee (PBAC) recommended allowing women of childbearing potential with epilepsy to initiate treatment with these medications in September 2020. This recommendation was implemented in January 2021 and is consistent with several international clinical guidelines.

At its September 2020 meeting, the PBAC requested that the Australian Government Department of Health and Aged Care (DoHAC) provide cost estimates for allowing levetiracetam and lamotrigine to be listed as first-line drugs for all people with epilepsy. The PBAC also requested the DoHAC to provide data on the utilisation of AEDs and any further evidence on the broader use of other second-line AEDs. Many international guidelines recommend lamotrigine and levetiracetam as first-line treatments for epilepsy, which is also reflected in some Australian local hospital/general practice guidelines.

In September 2023, the Drug Utilisation Sub-Committee (DUSC) considered the ‘Utilisation analysis of PBS-listed AEDs in a cohort of epilepsy patients.’ The DUSC was also requested to advise the DoHAC on the development of the cost estimates to the PBS of allowing first-line use of levetiracetam and lamotrigine in the remaining population with epilepsy (i.e., males and females of all ages).

In April 2024, a contract was executed with the Centre for Medicine Use and Safety (CMUS), Monash University to:

- undertake a systematic literature review to identify relevant clinical guidelines for the use of AEDs for the treatment of epilepsy and compare these to the PBS restrictions and TGA-approved indications for these medicines, and;
- estimate the cost to the PBS of expanding the restrictions for the second-line AEDs levetiracetam and lamotrigine to allow their first-line use in the general Australian population with epilepsy.

Levetiracetam and lamotrigine are increasingly being used as initial drugs for epilepsy. For example, in Japan², Germany³, and Sweden⁴ more than 50-90% of adults with epilepsy have initiated treatment with levetiracetam or lamotrigine over the last 10 years.

TABLE 1 SUMMARY OF TGA-APPROVED EPILEPSY INDICATIONS AND PBS RESTRICTIONS*

Drug	TGA-approved epilepsy indication(s)	PBS-listed indication	Restriction level
First-line treatment			
Carbamazepine	Complex or simple partial seizures (with or without loss of consciousness), with or without secondary generalisation; Generalised tonic-clonic seizures; Mixed seizure patterns incorporating the above.	N/A	Unrestricted
Ethosuximide	Petit mal epilepsy	N/A	Unrestricted
Phenobarbital (phenobarbitone)	Epilepsy	Epilepsy	Restricted Benefit
Phenytoin	Generalised tonic-clonic (grand mal) and psychomotor seizures	N/A	Unrestricted
Primidone	Grand mal and psychomotor (temporal lobe) epilepsy: focal or Jacksonian seizures, myoclonic jerks and akinetic attacks.	N/A	Unrestricted
Sulthiame	Behavioural disorders associated with epilepsy; hyperkinetic behaviour; temporal lobe epilepsy; myoclonic seizures; grand mal attacks; Jacksonian seizures.	N/A	Unrestricted
Valproate	Primary generalised epilepsy (petit mal absences, various forms of myoclonic epilepsy and tonic-clonic grand mal seizures). Partial (focal) epilepsy either alone or as adjuvant therapy	N/A	Unrestricted
Clonazepam	<u>Tablets</u> : Most types of epilepsy in infants and children, especially absences (petit mal), myoclonic seizures and tonic clonic fits, whether due to primary generalised epilepsy, or to secondary generalisation of partial epilepsy. In adults all varieties of generalised epilepsy (including myoclonic, akinetic, tonic and tonic clonic seizures), and in partial epilepsy (including psychomotor seizures). <u>Injection</u> : Intravenous (IV) use, for status epilepticus.	Epilepsy	Restricted Benefit (for injection) Authority Required (other forms)
Nitrazepam	N/A	Myoclonic epilepsy Malignant neoplasia (late stage) Insomnia	Authority Required
Second-line treatment			
Gabapentin	Partial seizures, including secondarily generalised tonic-clonic seizures, initially as add-on therapy in adults and children aged 3 years and above who have not achieved adequate control with standard anti-epileptic medications	Partial epileptic seizures	Authority Required (STREAMLINED)

Drug	TGA-approved epilepsy indication(s)	PBS-listed indication	Restriction level
Levetiracetam	Epileptic patients aged 4 years and older, initially as add-on therapy, in the treatment of partial onset seizures with or without secondary generalisation; monotherapy in the treatment of partial onset seizures, with or without secondary generalisation, in patients from 16 years of age with newly diagnosed epilepsy; add-on therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy (JME); and add-on therapy in the treatment of primary generalized tonic-clonic seizures in adults and children from 4 years of age with idiopathic generalized epilepsy (IGE)	Partial epileptic seizures	Authority Required (STREAMLINED)
Tiagabine	Partial seizures, as add on therapy in patients who are not controlled satisfactorily with other antiepileptic drug(s)	Partial epileptic seizures	Authority Required (STREAMLINED)
Zonisamide	Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy who are intolerant to other agents or where other agents are contraindicated; adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation	Partial epileptic seizures	Authority Required (STREAMLINED)
Lamotrigine	Partial and generalised seizures in adults and children	Epileptic seizures	Authority Required (STREAMLINED)
Vigabatrin	Treatment of epilepsy which is not satisfactorily controlled by other antiepileptic drugs	Epileptic seizures	Authority Required (STREAMLINED)
Oxcarbazepine	Monotherapy or adjunctive therapy for the treatment of partial seizures and generalised tonic-clonic seizures, in adults and children	Seizures	Authority Required (STREAMLINED)
Topiramate	Adults and children, 2 years and over: monotherapy in patients with newly diagnosed epilepsy; for conversion to monotherapy in patients with epilepsy; add-on therapy in partial onset seizures (with or without secondary generalised seizures), primary generalised tonic-clonic seizures or drop attacks associated with Lennox-Gastaut syndrome	Seizures Migraines Item codes with both indications, seizure indication will be identified using authority codes (e.g. for PBS item code 13969F, authority code 5516 for seizure	Authority Required (STREAMLINED)

Drug	TGA-approved epilepsy indication(s)	PBS-listed indication	Restriction level
		will be included and 5325 for migraine excluded)	
Third-line treatment			
Brivaracetam	Add-on therapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 4 years of age with epilepsy	Intractable partial epileptic seizures	Authority Required (STREAMLINED)
Perampanel	Adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients from 4 years of age with epilepsy; adjunctive treatment of primary generalised tonic-clonic seizures in patients from 7 years of age with idiopathic generalised epilepsy.	Intractable partial epileptic seizures ¹ Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures ²	Authority Required (STREAMLINED)
Lacosamide	Monotherapy in the treatment of partial seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older; add-on therapy in the treatment of partial seizures with or without secondary generalisation in patients with epilepsy aged 4 years and older; add-on therapy in the treatment of primary generalised tonic-clonic seizures in patients with idiopathic generalised epilepsy aged 4 years and older.	Intractable partial epileptic seizures Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures	Authority Required (STREAMLINED)
Cannabidiol	Adjunctive therapy of seizures associated with Lennox Gastaut syndrome (LGS) or Dravet syndrome (DS) for patients 2 years of age and older.	Severe myoclonic epilepsy in infancy (Dravet syndrome)	Authority Required
Stiripentol	Adjunctive treatment of generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) in patients whose seizures are not adequately controlled with a benzodiazepine (usually clobazam) and valproate.	Severe myoclonic epilepsy in infancy (Dravet syndrome)	Authority Required (STREAMLINED)

See appendix table 1 for full details.

Please note that the TGA-approved epilepsy indications include older terminology that has been updated since publication. Partial seizures refer to focal seizures; secondarily generalised seizures refer to focal to bilateral tonic-clonic seizures;

OBJECTIVES

There were two parts to this review and the objectives were:

Part 1: Review of clinical guidelines

- To conduct a search of peer reviewed literature and a systematic search of the grey literature to identify relevant key Australian and international clinical guidelines for the use of AEDs for the treatment of epilepsy (Research Question 1), and;
- To compare recommendations in the guidelines identified in Research Question 1 to PBS restrictions and TGA-approved indications (Research Question 2).

Part 2: Utilisation review and cost estimates

- To estimate the cost to the PBS of expanding the restrictions for the second-line AEDs levetiracetam and lamotrigine to allow their first-line use in the general Australian population with epilepsy (Research Question 3), and;
- To model how the first-line use of levetiracetam and lamotrigine in the general population will impact on the utilisation of the more expensive third-line AEDs (i.e., brivaracetam, perampanel, lacosamide, cannabidiol and stiripentol) (Research Question 4).

PART 1: REVIEW OF CLINICAL GUIDELINES

Methodology

The “PICAR” framework⁵ was used to guide the review of clinical guideline eligibility criteria (Table 2). For the purpose of this review, a clinical guideline was defined according to the Institute of Medicine as “statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.”⁶ The exclusion criteria for clinical guidelines were also included in Table 2.

TABLE 2 PICAR STATEMENT

PICAR Framework	Eligibility Criteria
Population	People with epilepsy or seizures (all types)
Intervention	Any AEDs
Comparison	Any comparator or comparison
Attributes	National (Australia) or international clinical guidelines published between 2014-2024
Recommendation characteristics	Include recommendations on the use of AEDs for the treatment of epilepsy (e.g. first/ second/ third line) that are informed by an evidence-based approach
* Exclusion criteria	<ul style="list-style-type: none"> Females of childbearing potential (this subgroup has already been included in the current PBS-subsidised indication) Acute seizures or status epilepticus Management with non-oral AEDs No recommendations made for first/ second/ third line monotherapy (or similar) AEDs for treatment of epilepsy

AED = Antiepileptic drugs.

Identification of clinical guidelines

The project team identified eight key accessible international clinical guidelines for epilepsy (i.e. from Canada, Finland, Germany, Japan, New Zealand, Sweden, United Kingdom and United States) through their professional networks and search of peer-reviewed and grey literature performed by entering each country AND epilepsy AND “society OR organisation” AND guideline. Guidelines from Hong Kong, Scotland and the International League Against Epilepsy (ILAE, global epilepsy authority) were also included alongside the original eight guidelines.

Not all Australian clinical guidelines are published in peer-reviewed journals or available via academic databases. Hence, with the guidance of a specialist librarian at Monash University, a member of the project team conducted a search of the grey literature sources for existing and relevant clinical guidelines in Australia.

Search strategy for grey literature

The grey literature search involved using relevant grey sources available via the website of Monash University’s Library, customised Google searches, targeted searches at specific websites, and consultation with experts.

Consultation with 14 experts across Australia (ACT, NSW, NT, QLD, SA, TAS, VIC and WA), either via email or telephone were completed between May-June 2024. Online searches were conducted between July 7-10, 2024. Sources that were searched through the website of Monash University’s Library included Informit, Web of Science, Scopus, ProQuest One Academic, Clinical Practice Guidelines Portal- Australia (no longer active), Guidelines International Network (GIN) International Guidelines Library, National Guideline Clearinghouse, and TRIP database (advanced search feature was not available).

A set of search terms was identified and used for the online literature searches. The search terms encompassed three concepts i.e. clinical guidelines, epilepsy, and antiepileptic drugs (Table 3). Simplified terms, Boolean operators (AND or OR), and truncations were used in the searches as appropriate.

TABLE 3 SEARCH TERMS

Concept	Search terms
Clinical guidelines	guideline* OR recommendation* OR standard* OR best practice* OR guidance OR protocol OR management
Epilepsy	epilep* OR seizure* OR convulsion* OR fit*
Antiepileptic	antiepileptic* OR anti-epileptic* OR antiseizure* OR anti-seizure* OR anticonvulsant* OR anti-convulsant*

The grey literature searches were limited to Australia with publication year between 2014 and 2024. For customised Google searches, the first 100 results were reviewed, using the title and short text underneath⁷ or by clicking the link to scan the contents if necessary. In addition, targeted Google searches were conducted to identify relevant organisations or websites which potentially publish the guidelines of interest. Date of search, search strategy and terms used, number of search results, number of results screened, potentially relevant guidelines together with the organisation name and URL were recorded in a Word document template.

The project team also attempted to identify relevant guidelines in Australia via a) their professional networks; b) contacting the Pharmacy Department (or Medicines Information Services, if available) of major Australian health services through email or telephone; and c) professional organisations such as the Society of Hospital Pharmacists of Australia ([SHPA], Advanced Pharmacy Australia [AdPha] from 8/2024) and the Epilepsy Society of Australia.

The shortlisted clinical guidelines were screened and excluded if they did not meet the eligibility criteria outlined in the PICAR statement. For the Australian and international clinical guidelines (except for the Finnish, German and Swedish guidelines) that were included, two members of the project team independently extracted relevant data based on the PICAR statement. Discrepancies were discussed with a third reviewer. The quality of the included international clinical guidelines (except for the Finnish, German and Swedish guideline) was also assessed independently by two members of the project team using the Appraisal of Clinical Guidelines for Research and Evaluation Instrument version 2 (AGREE II) tool.⁸ Data extraction and assessment with the AGREE II tool for the non-English guidelines (i.e. the Finnish, German and Swedish guidelines) were completed by only one reviewer due to the lack of Finnish, Swedish and German speakers in the investigator team.

The clinical guidelines included in this review were then compared to PBS restrictions and TGA-approved indications for AEDs. We specifically compared:

- The recommended first-line AEDs in each guideline to current PBS restrictions and the TGA-approved indications
- The recommended second-line AEDs in each guideline to current PBS restrictions and the TGA-approved indications
- The recommended third-line AEDs in the guidelines to current PBS restrictions and the TGA-approved indications, and
- The specific population groups within each guideline that recommendations and restrictions apply to.

Results

Four relevant Australian clinical guidelines were identified through grey literature search; two were identified through targeted searches on specific websites, and two were obtained through the consultation with the experts (Table 4). Excluded clinical guidelines were mainly related to the management of acute seizures or status epilepticus (Appendix Table 2).

The included Australian clinical guidelines provided recommendations on first- and second-line AEDs for different seizure/ epilepsy types (Appendix Table 3). None of the Australian guidelines provided recommendations on third-line AEDs.

TABLE 4 FOUR AUSTRALIAN CLINICAL GUIDELINES FOR EPILEPSY INCLUDED IN THIS REVIEW

Source(s)	Guideline name	Publication year
Therapeutic Guidelines	Neurology- Epilepsy and seizures ⁹	2017 (amended 2023)
Australian Medicines Handbook	Neurological Drugs- Antiepileptics- Epilepsy ¹⁰	2024
Melbourne Health, Department of Neurology- Division of Neurosciences (Victoria)	Management of First Seizure & Epilepsy in Adults ¹¹	2019
Community Health Pathways- for GPs (Tasmania)	Anti-Epileptic Drugs (AEDs) ¹²	2021

Eleven key international clinical guidelines for epilepsy were included in this review (Table 5). The additional three international guidelines (Hong Kong, Scotland, and ILAE) were included due to the small number of relevant Australian clinical guidelines. The project team decided to include the ILAE's evidence review of AEDs from 2013 (which was outside the publication year range determined for this review) given its relevance to this review. No international clinical guidelines were purposively excluded. The included guidelines were identified with a targeted search of specific countries' clinical guidelines or guidelines already known to the project team.

Not all international clinical guidelines provide recommendations on first-, second- and third-line AEDs for the treatment of different seizure/ epilepsy types (Appendix Table 4). Different clinical guidelines use different terminology in their order of recommendations. For the purpose of this review, "alternative to first-line," "initial monotherapy," "drug of choice" and "should be considered" are all considered as first-line AED recommendations. The UK guidelines (the NICE guideline) is the only one which provides clear recommendation on third-line AEDs.

TABLE 5 ELEVEN INTERNATIONAL CLINICAL GUIDELINES FOR EPILEPSY INCLUDED IN THIS REVIEW

Country	Guideline name	Publication year
Canada (Ontario)	Clinical Guidelines for the Management of Epilepsy in Adults and Children ¹³	2020
Finland	Epilepsiat (aikuiset) [Epilepsies (adults)] ¹⁴	2020
Germany	Erster epileptischer Anfall und Epilepsien im Erwachsenenalter [First epileptic seizure and epilepsy in adulthood] ¹⁵	2023
Hong Kong	An update of the Hong Kong Epilepsy Guideline: consensus statement on the use of AEDs in Hong Kong ¹⁶	2017 (original version 2009 ¹⁷)
International League Against Epilepsy (ILAE)	Updated ILAE evidence review of AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes ¹⁸	2013 (original version in 2006 ¹⁹)
Japan	Clinical Practice Guidelines for Epilepsy ²⁰	2018
New Zealand	Epilepsy Guidelines & Pathways for Children & Young People ²¹	2022
Scotland	Diagnosis and Management of Epilepsy in Adults. SIGN Guideline ²²	2018
Sweden	Läkemedelsbehandling av epilepsi – bakgrundsdocumentation [Swedish Practice Guidelines for Monotherapy in Epilepsy] ²³	2019
United Kingdom	Epilepsies in Children, Young People and Adults. NICE Guideline ²⁴	2022
United States	Practice Guideline Update Summary: Efficacy and tolerability of the new AEDs I: Treatment of new-onset epilepsy ²⁵	2018

AED = antiepileptic drugs, ILAE = International League Against Epilepsy (global epilepsy authority), NICE = National Institute for Health and Care Excellence, SIGN = Scottish Intercollegiate Guidelines Network.

The quality of the eleven international guidelines included were assessed using the AGREE II tool (Table 6). For the purposes of this review, Domain 3- Rigour of development and Domain 4- Clarity of presentation were prioritised over the remaining domains as they were deemed more relevant to this project. The median AGREE II scores for Domain 3- Rigour of development was 69% (17-95%) and for Domain 4- Clarity of presentation was 94% (61-100%). The overall AGREE II assessment score (based on Domain 3 and Domain 4 only) for the included international guidelines ranged from 2 to 7 on a 7-point scale (1– strongly disagree to 7–strongly agree). The guidelines from the United Kingdom, Scotland, and Japan achieved the highest overall AGREE II assessment scores (based on Domain 3 and 4).

A broad range of terminology is used in the included clinical guidelines to describe different seizure/ epilepsy types and their recommendations. To allow more streamlined comparisons of the guideline recommendations, the project team has categorised different seizure/ epilepsy types into four major groups (focal, generalised, mixed, and undetermined/ unknown seizures) (Table 7).

TABLE 6 INTERNATIONAL GUIDELINES: ASSESSMENT USING THE APPRAISAL OF CLINICAL GUIDELINES FOR RESEARCH AND EVALUATION INSTRUMENT VERSION 2 (AGREE II) TOOL

Guidelines/ Domains ^a	Canada 2020	Finland 2020	Germany ^b 2023	Hong Kong 2017	ILAE 2013	Japan 2018	New Zealand 2022	Scotland 2018	Sweden ^b 2019	United Kingdom 2022	United States 2018
Domain 1: Scope and Purpose	94%	78%	100%	83%	81%	83%	94%	100%	44%	94%	100%
Domain 2: Stakeholder Involvement	56%	56%	100%	42%	33%	50%	36%	94%	39%	94%	22%
Domain 3: Rigour of development	17%	54%	69%	72%	69%	79%	18%	89%	65%	95%	75%
Domain 4: Clarity of presentation	89%	100%	94%	69%	83%	94%	94%	75%	100%	100%	61%
Domain 5: Applicability	4%	42%	83%	13%	8%	35%	50%	38%	33%	88%	17%
Domain 6: Editorial independence	29%	100%	50%	25%	79%	71%	25%	79%	17%	71%	100%

^a High quality guidelines are those with six domain scores that are all more than 70%. Those domain scores highlighted in green are with scores of more than 70%. For the purposes of this review, domain 3 and domain 4 are prioritised when determining the overall assessment score for each guideline.

^b AGREE II assessment for the non-English guidelines (Finland, Germany and Sweden) was completed by one reviewer.

TABLE 7 CATEGORISATION OF DIFFERENT SEIZURE/ EPILEPSY TYPES FOR COMPARISON OF THE CLINICAL GUIDELINE RECOMMENDATIONS

Focal seizures/ Focal epilepsy	Generalised seizures	Mixed seizures	Undetermined/ Unknown seizures
<ul style="list-style-type: none"> • complex or simple partial seizures • complex or simple partial seizures (with or without loss of consciousness), with or without secondary generalisation • focal-onset seizures (with or without secondary generalisation to tonic-clonic seizures) • focal seizures with or without evolution to bilateral tonic-clonic seizures • psychomotor seizures • temporal lobe epilepsy • Jacksonian seizures • benign epilepsy of childhood with centrotemporal spikes • self-limited epilepsy with centrotemporal spikes • benign epilepsy with occipital paroxysms • Landau-Kleffner syndrome 	<ul style="list-style-type: none"> • generalised tonic-clonic seizures or grand mal • genetic generalised epilepsy • idiopathic generalized epilepsy (IGE) • myoclonic seizures • tonic seizures • atonic seizures or akinetic attacks • clonic seizures • bilateral tonic-clonic seizures • absence seizures or petit mal • epilepsy with myoclonic-atonic seizures (EMAS), myoclonic-astatic epilepsy (MAE) or Doose Syndrome 	<ul style="list-style-type: none"> • mixed seizure patterns • myoclonic jerks • severe myoclonic epilepsy of infancy (SMEI) or myoclonic epilepsy in infancy or Dravet syndrome • infantile spasms • Lennox-Gastaut syndrome 	<ul style="list-style-type: none"> • childhood- or adolescence-onset epilepsy with undetermined seizure type • seizures where generalised or focal onset is unclear • unclassified epilepsy

Table 8 provides an overview of AEDs for the treatment of epilepsy, comparing the current TGA-approved and PBS-listed indications with the included Australian and international clinical guidelines. Table 8 presents the recommendations from different clinical guidelines for each of the AED approved by the TGA and listed on the PBS. The recommendations made by each included clinical guideline are detailed in Appendix Table 3 and 4.

TABLE 8 OVERVIEW OF AEDS FOR THE TREATMENT OF EPILEPSY: CURRENT TGA-APPROVED AND PBS-LISTED VERSUS AUSTRALIAN/ INTERNATIONAL CLINICAL GUIDELINES INCLUDED

	First-line					Second-line				Third-line ^c / Others				Adjuvant/ Add-on															
<i>F, focal seizures or focal epilepsies; G, generalised seizures; M, mixed seizures; U, undetermined or unknown (focal or generalised) seizures; E, epilepsy (details not specified)</i> <i>NOTE: For further details on each of the recommendation, please refer to Table 9; and Appendix Table 3 and 4</i>																													
Guideline	Carbamazepine	Ethosuximide	Phenobarbital	Phenytoin	Primidone	Sulthiame	Valproate	Clonazepam	Nitrazepam	Gabapentin	Levetiracetam	Tiagabine	Zonisamide	Lamotrigine	Vigabatrin	Oxcarbazepine	Topiramate	Brivaracetam	Perampanel	Lacosamide	Cannabidiol	Stiripentol	Clobazam	Pregabalin	Eslicarbazepine	Rufinamide	Retigabine	Piracetam	Cenobamate
TGA-approved ^a and PBS-listed ^b	F, G, M	G	E	F, G	F, G, M	F, G	F ^d , G	F, G	G	F ^e	F ^d , G ^e	F ^e	F ^d	F, G	E	F ^d , G ^d	F ^f , F ^e , G ^e , M ^e	F ^e	F ^e , G ^e	F ^d , G ^e	M ^e	G ^e							
Therapeutic Guidelines Limited; 2017 (amended 2023) [Ref 9]	F	G					G, M, U																						
			F	F			F, G			F	F, G, U	F	F	F, G, M, U		F	F, U		F	F			F, U	F					
																	G, M						G, M						
Australian Medicines Handbook Pty Ltd; 2024 [Ref 10]	F	G					G																						
	G		F, G	F, G			F, M	G, M		F	F, G	F	F	F, G	M	F, G	F, G			F			F, G	F					
Melbourne Health, Department of Neurology- Division of Neurosciences (Victoria); 2019 [Ref 11]	F	G					G				F			F															
	G			F, G			F	G		F	G		F	G		F	F, G	F	F	F			F, G	F					
Community Health Pathways- for GPs	F	G					G				F, G			F, G															

F, focal seizures or focal epilepsies; G, generalised seizures; M, mixed seizures; U, undetermined or unknown (focal or generalised) seizures; E, epilepsy (details not specified)

NOTE: For further details on each of the recommendation, please refer to Table 9; and Appendix Table 3 and 4

Guideline	Carbamazepine	Ethosuximide	Phenobarbital	Phenytoin	Primidone	Sulthiame	Valproate	Clonazepam	Nitrazepam	Gabapentin	Levetiracetam	Tiagabine	Zonisamide	Lamotrigine	Vigabatrin	Oxcarbazepine	Topiramate	Brivaracetam	Perampanel	Lacosamide	Cannabidiol	Stiripentol	Clobazam	Pregabalin	Eslicarbazepine	Rufinamide	Retigabine	Piracetam	Cenobamate	
(Tasmania); 2021 [Ref 12]																F	F, G													
Canada (Ontario); March 2020 [Ref 13]	F	G	F, G	F			F, G, M			F	F, G			F, G	M	F	F, G, M		G					F, G		F	M			
			F					G			G		G				G, M						G	F						
	F	G	G	F	G		F, G			F	F, G			F, G, M		F	F, G, M	F	F, G, M			M	F, G, M		F	M				
Finland; 2020 [Ref 14]	F						F ^B , G			F ^B	F, G ^B		F ^B	F ^B , G ^B		F	F ^B , G ^B			F ^B					F ^B					
			F	F											F													F		
										F	F	F	F	F			F	F	F	F			F, G	F	F					
Germany; 2023 [Ref 15]							G							F																
										F	F, G			G						F										
Hong Kong; 2017 (original version in 2009) [Ref 16, 17]	F, G	G		F, G			F, G, M	G, M			F, G			F, G, M	M	F	F, G, M							G, M						
		M					M	G, M		F	F, G, M			G		G	F, G, M							F, G, M	F				G	
			F, G, M	G	F, G			F, G	M					G																
International League Against Epilepsy (ILAE); 2013 (original version in 2006) [Ref 18, 19]	F, G	G	F, G	F, G	F	F	F, G	F		F, G	F, G		F	F, G	F, G	F, G	F, G							F						

Guideline	Carbamazepine	Ethosuximide	Phenobarbital	Phenytoin	Primidone	Sulthiame	Valproate	Clonazepam	Nitrazepam	Gabapentin	Levetiracetam	Tiagabine	Zonisamide	Lamotrigine	Vigabatrin	Oxcarbazepine	Topiramate	Brivaracetam	Perampanel	Lacosamide	Cannabidiol	Stiripentol	Clobazam	Pregabalin	Eslicarbazepine	Rufinamide	Retigabine	Piracetam	Cenobamate
Japan; 2018 [Ref 20]	F, U	G					G, U	G		F	F, G, U		F, U	F, G, U			F, G												
			F, G	F, G			F	F		F	G		G	G			G		F, G	F			F, G						G
New Zealand; 2022 [Ref 21]	F	G					G				F, G			F, G									G						
											G			G															
Scotland; 2018 [Ref 22]	F ^B						G, U			F	F ^B , G ^B , U			F, G ^B , U			G ^B , U												
	F	G, U					F, G			F	F, G		F	F, G		F	F, G		F	F				F					
Sweden; 2019 [Ref 23]	F	G					G				F, G		F ^B	F, G		F ^B	G ^B				F ^B				F ^B				
United Kingdom; 2022 [Ref 24]		G					G, M				F, G			F	M														
	F						G, M		M		G, M		F	G, M		F	M												
		G ^c	G ^c			F ^c		G ^c			G ^c		G ^c	G ^c			G ^c	G ^c	G ^c	F ^c			G ^c			G ^c		G ^c	
	F	G	F, G	F	G	F	F, G, M	G	M		F, G, M	F	F, G	F, G, M	F	F	F, G, M	F, G	F, G	F, G	M	M	G, M	F	F	G, M		G	F
United States; 2018 [Ref 25]		G					G							F ^h , U ^h															
										F ⁱ , U ⁱ	F ⁱ , U ⁱ		F ⁱ , U ⁱ	G															

^a Per the Product Information (PI) accessed from the [TGA website](#) on 3 March 2023

^b Source: Extracted from PBS.gov.au on 29 August 2023

^c Recommended as third-line AEDs (instead of 'Others') in the guidelines

^d Either as monotherapy or as adjuvant therapy (TGA-approved epilepsy indication^a)

^e As adjuvant or add-on therapy (TGA-approved epilepsy indication^a)

^f As monotherapy (TGA-approved epilepsy indication^a)

^g Alternative to first-line AEDs as per the guidelines; and the alternative AED is considered as equivalent to first line AED in this project

^h This AED should be considered as per the guideline; and this is considered as equivalent to first line AED in this project

ⁱ This AED may be considered as per the guideline; and this is considered as equivalent to second line AED in this project

TABLE 9 RECOMMENDATIONS OF AEDS FOR THE TREATMENT OF EPILEPSY: CURRENT TGA-APPROVED AND PBS-LISTED INDICATIONS VERSUS RECOMMENDATIONS FROM THE INCLUDED AUSTRALIAN/ INTERNATIONAL CLINICAL GUIDELINES

Recommendations from included Australian/ international clinical guidelines							
AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
First-line treatment ^{a,b}							
Carbamazepine	Complex or simple partial seizures (with or without loss of consciousness), with or without secondary generalisation; GTCS; Mixed seizure patterns incorporating the above.	N/A	<u>Focal seizures</u> <ul style="list-style-type: none">• TG (Aus)- adults & children• AMH (Aus)• MH (Aus)- adults, with/ without secondary generalisation to tonic-clonic seizures• CHP (Aus)• CA- adults & children; benign epilepsy of childhood with centrotemporal spikes• FI- adults^d• HK- adolescents & adults, with/ without secondary generalisation; benign epilepsy with centrotemporal spikes or occipital paroxysms• ILAE- adults^d, elderly^d & children^d; children with benign childhood epilepsy with centro-temporal spikes^d• JP- adults, elderly (≥65 years without complications or co-morbidities)• NZ- children & young people• SCT- adults^{d,k}• SE- adults & children <u>Generalised seizures</u> <ul style="list-style-type: none">• HK- adolescents & adults with GTCS• ILAE- adults^d & children^d with GTCS <u>Undetermined seizures</u> <ul style="list-style-type: none">• JP- childhood/ adolescence-onset^e	<u>Focal seizures</u> <ul style="list-style-type: none">• UK- with/ without evolution to bilateral tonic-clonic seizures; self-limited epilepsy with centrotemporal spikes <u>Generalised seizures</u> <ul style="list-style-type: none">• AMH (Aus)- GTCS• MH (Aus)- adults with GTCS		<u>Focal seizures</u> <ul style="list-style-type: none">• CA- adults• SCT- adults^d• UK- with/ without evolution to bilateral tonic-clonic seizures (1st line add-on)	<u>Focal seizures</u> <ul style="list-style-type: none">• DE- adults (not as initial monotherapy)• HK- Landau-Kleffner syndrome <u>Generalised seizures</u> <ul style="list-style-type: none">• CA- adults with GTCS (if there are AS or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected); children with GTCS or AS; myoclonic (including juvenile myoclonic epilepsy)• HK- adolescents & adults with AS; myoclonic/ tonic/ atonic seizure; childhood/ juvenile absence epilepsy; juvenile myoclonic epilepsy; myoclonic astatic epilepsy• JP- adults with new-onset AS^e, myoclonic/ tonic/ atonic seizures^e <u>Mixed seizures</u> <ul style="list-style-type: none">• CA- Dravet syndrome; Lennox-Gastaut Syndrome• HK- infantile spasms; SMEI; Lennox-Gastaut syndrome

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
							Undetermined seizures • JP- childhood/ adolescence-onset ^e
Ethosuximide	Petit mal epilepsy	N/A	<u>Generalised seizures</u> <ul style="list-style-type: none"> • TG (Aus)- childhood & juvenile AS • AMH (Aus)- AS • MH (Aus)- AS • CHP (Aus)- AS • CA- children with AS • HK- adolescents & adults with AS; childhood/ juvenile absence epilepsy • ILAE- children with AS^d • JP- adults with new-onset AS • NZ- AS • SE- children with AS • UK- AS • US- childhood absence epilepsy 	<u>Mixed seizures</u> <ul style="list-style-type: none"> • HK- Lennox-Gastaut syndrome 	<u>Generalised seizures</u> <ul style="list-style-type: none"> • UK- epilepsy with myoclonic-atonic seizures (Doose syndrome)^c 	<u>Generalised seizures</u> <ul style="list-style-type: none"> • CA- children with AS • SCT- adults with genetic generalised epilepsy^d • UK- epilepsy with myoclonic-atonic seizures (Doose syndrome) <u>Undetermined seizures</u> <ul style="list-style-type: none"> • SCT- adults^d 	
Phenobarbital (phenobarbitone)	Epilepsy	Epilepsy	<u>Focal seizures</u> <ul style="list-style-type: none"> • CA- children • ILAE- adults & children^d <u>Generalised seizures</u> <ul style="list-style-type: none"> • CA- children with GTCS • ILAE- adults & children with GTCS^d 	<u>Focal seizures</u> <ul style="list-style-type: none"> • TG (Aus)- children • AMH (Aus) • JP- adults <u>Generalised seizures</u> <ul style="list-style-type: none"> • AMH (Aus)- GTCS; myoclonic seizures • JP- adults with new-onset tonic-clonic/ clonic seizure or myoclonic seizure 	<u>Focal seizures</u> <ul style="list-style-type: none"> • CA- adults • FI- adults^f • HK- adolescents & adults with/without secondary generalisation <u>Generalised seizures</u> <ul style="list-style-type: none"> • HK- adolescents & adults with primary GTCS, tonic or atonic seizure • UK- myoclonic seizures^c <u>Mixed seizures</u> <ul style="list-style-type: none"> • HK- SMEI 	<u>Focal seizures</u> <ul style="list-style-type: none"> • UK- with/ without evolution to bilateral tonic-clonic seizures (3rd line add-on) <u>Generalised seizures</u> <ul style="list-style-type: none"> • CA- adults with GTCS • UK- GTCS (2nd line add-on); myoclonic seizures 	

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
Phenytoin	Generalised tonic-clonic (grand mal) and psychomotor seizures	N/A	Focal seizures <ul style="list-style-type: none"> CA- adults HK- adolescents & adults with/ without secondary generalisation ILAE- adults & children^d Generalised seizures <ul style="list-style-type: none"> HK- adolescents & adults with primary GTCS ILAE- adults & children with GTCS^d 	Focal seizures <ul style="list-style-type: none"> TG (Aus)- adults & children AMH (Aus) MH (Aus)- adults with/ without secondary generalisation to tonic-clonic seizures JP- adults with new-onset Generalised seizures <ul style="list-style-type: none"> AMH (Aus)- GTCS MH (Aus)- adults with GTCS JP- adults with new-onset tonic-clonic/ clonic seizure^e 	Focal seizures <ul style="list-style-type: none"> FI- adults^f Generalised seizures <ul style="list-style-type: none"> HK- adolescents & adults with tonic seizure 	Focal seizures <ul style="list-style-type: none"> CA- adults UK- with/ without evolution to bilateral tonic-clonic seizures (3rd line add-on) 	Generalised seizures <ul style="list-style-type: none"> CA- adults with GTCS (with AS or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected); children with GTCS or AS; myoclonic (including juvenile myoclonic epilepsy) HK- adolescents & adults with atonic seizure; childhood or juvenile absence epilepsy; juvenile myoclonic epilepsy JP- adults with new-onset AS^e or new-onset tonic-clonic/ clonic seizure or myoclonic seizure^e Mixed seizures <ul style="list-style-type: none"> CA- Dravet syndrome
Primidone	Grand mal and psychomotor (temporal lobe) epilepsy: focal or Jacksonian seizures, myoclonic jerks and akinetic attacks.	N/A	Focal seizures <ul style="list-style-type: none"> ILAE- adults^d 		Focal seizures <ul style="list-style-type: none"> HK- adolescents & adults with/ without secondary generalisation Generalised seizures <ul style="list-style-type: none"> HK- adolescents & adults with primary GTCS, tonic or atonic seizure 	Generalised seizures <ul style="list-style-type: none"> CA- adults with GTCS UK- GTCS (2nd line add-on) 	
Sulthiame	Behavioural disorders associated with epilepsy; hyperkinetic behaviour; temporal lobe epilepsy;	N/A	Focal seizures		Focal seizures <ul style="list-style-type: none"> UK- self-limited epilepsy with 	Focal seizures <ul style="list-style-type: none"> UK- self-limited epilepsy with 	

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
	myoclonic seizures; grand mal attacks; Jacksonian seizures.		<ul style="list-style-type: none"> • ILAE- children with benign childhood epilepsy with centro-temporal spikes^d 		centrotemporal spikes ^c	centrotemporal spikes	
Valproate	Primary generalised epilepsy (petit mal absences, various forms of myoclonic epilepsy and tonic-clonic grand mal seizures). Partial (focal) epilepsy either alone or as adjuvant therapy	N/A	<p>Focal seizures</p> <ul style="list-style-type: none"> • CA- adults & children; benign epilepsy of childhood with centrotemporal spikes • FI- adults^{d,i,k} • HK- adolescents & adults with with/ without secondary generalisation; benign epilepsy with centrotemporal spikes or occipital paroxysms; Landau-Kleffner syndrome • ILAE- adults, elderly & children^d; children with benign childhood epilepsy with centro-temporal spikes^d <p>Generalised seizures</p> <ul style="list-style-type: none"> • TG (Aus)- juvenile myoclonic epilepsy^g; other symptomatic generalised epilepsies^h • AMH (Aus)- GTCS; AS; myoclonic seizures • MH (Aus)- Adults with GTCS; AS (with tonic-clonic); myoclonic seizures • CHP (Aus)ⁱ • CA- adults & children with GTCS; children with AS; myoclonic (including juvenile myoclonic epilepsy) • FI- adultsⁱ • DE- adults with genetic generalised seizuresⁱ • HK- adolescents & adults with primary GTCS, or AS, or myoclonic/ tonic/ atonic seizure; childhood or juvenile absence 	<p>Focal seizures</p> <ul style="list-style-type: none"> • TG (Aus)- adults & children • AMH (Aus) • MH (Aus)- adults with/ without secondary generalisation to tonic-clonic seizures • JP- adults with new-onset <p>Generalised seizures</p> <ul style="list-style-type: none"> • TG (Aus)- childhood & juvenile ASⁱ • UK- ASⁱ <p>Mixed seizures</p> <ul style="list-style-type: none"> • AMH (Aus)- infantile spasms • HK- infantile spasms • UK- infantile spasms syndrome 		<p>Focal seizures</p> <ul style="list-style-type: none"> • CA- adults • SCT- adults^d • UK- with/ without evolution to bilateral tonic-clonic seizuresⁱ (2nd line add-on) <p>Generalised seizures</p> <ul style="list-style-type: none"> • CA- adults with GTCS; children with AS; myoclonic (including juvenile myoclonic epilepsy) • SCT- adults with genetic generalised epilepsy^d • UK- GTCS (1st line add-on)ⁱ; ASⁱ <p>Mixed seizures</p> <ul style="list-style-type: none"> • UK- infantile spasms syndrome 	<p>Focal seizures</p> <ul style="list-style-type: none"> • DE- adults (not as initial monotherapy)

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
			epilepsy; juvenile myoclonic epilepsy; MAE <ul style="list-style-type: none"> • ILAE- adults & children with GTCS^d; children with AS^d; juvenile myoclonic epilepsy^d • JP- adults with new-onset tonic-clonic/ clonic seizureⁱ or AS or myoclonic/ tonic/ atonic seizure; elderly-onset (≥65 years) • NZ- AS (boys with high risk of GTCS); GTCS^j; myoclonic/ tonic/ atonic seizures^j • SCT- adults with genetic generalised epilepsy^d • SE- adults & children with GTCS; children with AS^k • UK- GTCS^j; myoclonic^l/ tonic^l/ atonic^l seizures; idiopathic generalised epilepsies^l; EMAS (Doose syndrome)^m • US- childhood absence epilepsy <p>Mixed seizures</p> <ul style="list-style-type: none"> • TG (Aus)- Lennox-Gastaut syndrome^h • CA- Dravet syndrome; Lennox-Gastaut Syndrome • HK- SMEI; Lennox-Gastaut syndrome • UK- Dravet Syndrome^m; Lennox-Gastaut Syndrome^m <p>Undetermined seizures</p> <ul style="list-style-type: none"> • TG (Aus)- adults & children with tonic-clonic seizures where generalised or focal onset is unclear^g • JP- childhood- or adolescence-onset epilepsy with undetermined seizure type (partial or generalized) 				

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
			<ul style="list-style-type: none"> SCT- adults^d 				
Clonazepam	<p><u>Tablets</u>: Most types of epilepsy in infants and children, especially absences (petit mal), myoclonic seizures and tonic clonic fits, whether due to primary generalised epilepsy, or to secondary generalisation of partial epilepsy. In adults all varieties of generalised epilepsy (including myoclonic, akinetic, tonic and tonic clonic seizures), and in partial epilepsy (including psychomotor seizures).</p> <p><u>Injection</u>: Intravenous (IV) use, for status epilepticus.</p>	Epilepsy	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> ILAE- adults & children^d <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> HK- MAE JP- adults with new-onset myoclonic seizure <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> HK- SMEI 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> JP- adults with new-onset <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> AMH (Aus)- AS; myoclonic seizures MH (Aus)- AS HK- adolescents & adults with AS; myoclonic/ tonic/ atonic seizure; juvenile myoclonic epilepsy <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> AMH (Aus)- infantile spasms HK- infantile spasms; Lennox-Gastaut syndrome 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> HK- adolescents & adults with/ without secondary generalisation <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> CA- children with AS; myoclonic (including juvenile myoclonic epilepsy) HK- adolescents & adults with primary GTCS UK: Myoclonic seizures^c 	<p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> UK- myoclonic seizures 	
Nitrazepam	N/A	Myoclonic epilepsy Malignant neoplasia (late stage) Insomnia		<p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> UK- infantile spasms syndrome 	<p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> HK- infantile spasms 	<p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> UK- infantile spasms syndrome 	
Second-line treatment ^{a,b}							
Gabapentin	Partial seizures, including secondarily generalised tonic-clonic seizures, initially as add-on therapy in adults and children aged 3 years and above who have not achieved adequate control with standard anti-epileptic medications	Partial epileptic seizures	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> CA- benign epilepsy of childhood with centrottemporal spikes FI- adults^{d,k} ILAE- adults including elderly^d; children with benign childhood epilepsy with centro-temporal spikes^d JP- elderly-onset (≥65 years) SCT- elderly^d 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> TG (Aus)- adults & children AMH (Aus) MH (Aus)- adults with/ without secondary generalisation to tonic-clonic seizures 		<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> CA- adults FI- adults^d SCT- adults including elderly^d 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> DE- adults (not as initial monotherapy) <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> CA- adults with GTCS (with AS or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected); children

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
			<u>Generalised seizures</u> <ul style="list-style-type: none"> ILAE- adults with GTCS^d 	<ul style="list-style-type: none"> DE- adults (for ≥65 years) HK- adolescents & adults with/ without secondary generalisation JP- adults with new-onset US- elderly (≥60 years) with new-onset (may be considered)^d <u>Undetermined seizures</u> <ul style="list-style-type: none"> US- elderly (≥60 years) with new-onset unclassified tonic-clonic seizures (may be considered)^d 			with AS; myoclonic (including juvenile myoclonic epilepsy) <ul style="list-style-type: none"> HK- adolescents & adults with AS or myoclonic seizure; childhood or juvenile absence epilepsy; juvenile myoclonic epilepsy JP- adults with new-onset AS^e, new-onset myoclonic^e /tonic^e/ atonic^e seizure <u>Mixed seizures</u> <ul style="list-style-type: none"> CA- Dravet syndrome; Lennox-Gastaut Syndrome
Levetiracetam	Epileptic patients aged 4 years and older, initially as add-on therapy, in the treatment of partial onset seizures with or without secondary generalisation; monotherapy in the treatment of partial onset seizures, with or without secondary generalisation, in patients from 16 years of age with newly diagnosed epilepsy; add-on therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy (JME); and add-on therapy in the treatment of primary generalized tonic-clonic seizures in adults and children from 4 years of age with idiopathic generalized epilepsy (IGE)	Partial epileptic seizures	<u>Focal seizures</u> <ul style="list-style-type: none"> MH (Aus)- adults with/ without secondary generalisation to tonic-clonic seizures CHP (Aus) CA- adults; benign epilepsy of childhood with centrotemporal spikes FI- adults^d HK- adolescents & adults with/ without secondary generalisation ILAE- adults^d; children with benign childhood epilepsy with centro-temporal spikes^d JP- Adults with new-onset; elderly-onset (≥65 years) NZ SCT- adults^{d,k} including elderly^d SE- adults, elderly & children 	<u>Focal seizures</u> <ul style="list-style-type: none"> TG (Aus)- adults & children with focal seizures AMH (Aus)ⁿ DE- adults HK- benign epilepsy with centrotemporal spikes or occipital paroxysms; Landau-Kleffner syndrome US- adults with new-onset^d <u>Generalised seizures</u> <ul style="list-style-type: none"> TG (Aus)- juvenile myoclonic epilepsy AMH (Aus)- GTCSⁿ; myoclonic seizures 	<u>Generalised seizures</u> <ul style="list-style-type: none"> CA- children with AS UK- AS^c 	<u>Focal seizures</u> <ul style="list-style-type: none"> CA- adults & children FI- adults^d SCT- adults^d UK- with/ without evolution to bilateral tonic-clonic seizures (1st line add-on) <u>Generalised seizures</u> <ul style="list-style-type: none"> CA- adults with GTCS; myoclonic (including juvenile myoclonic epilepsy) SCT- adults with genetic generalised epilepsy^d UK- GTCS (1st line add-on); AS; myoclonic seizuresⁿ; 	

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
			<ul style="list-style-type: none"> • UK- with or without evolution to bilateral tonic-clonic seizures; self-limited epilepsy with centrottemporal spikes <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • CHP (Aus) • CA- adults & children with GTCS; myoclonic (including juvenile myoclonic epilepsy) • FI- adults^k • HK- adolescents & adults with myoclonic seizure • ILAE- adults with GTCS^d • JP- elderly-onset (≥65 years) • NZ- GTCS (girls > 10 years & child < 3 years); myoclonic, tonic or atonic seizures (girls > 10 years) • SCT- adults with genetic generalised epilepsy^{d,k} • SE- adults & children with GTCS • UK- EMAS (Dooose syndrome) <p><u>Undetermined seizures</u></p> <ul style="list-style-type: none"> • JP- childhood- or adolescence-onset epilepsy with undetermined seizure type (partial or generalized) • SCT: adults with unclassified epilepsy^{d,n} 	<ul style="list-style-type: none"> • MH (Aus)- adults with GTCS; AS; myoclonic seizures • DE- adults with genetic generalised seizures • HK- adolescents & adults with primary GTCS or tonic/ atonic seizure; childhood or juvenile absence epilepsy; juvenile myoclonic epilepsy; MAE • JP- adults with new-onset tonic-clonic/ clonic/ myoclonic/ tonic/ atonic seizure • NZ- AS^p • UK- GTCSⁿ; myoclonic seizuresⁿ; idiopathic generalised epilepsiesⁿ <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • HK- SMEI; Lennox-Gastaut syndrome • UK- infantile spasms syndrome <p><u>Undetermined seizures</u></p> <ul style="list-style-type: none"> • TG (Aus)- adults & children with tonic-clonic seizures where generalised or focal onset is unclear^o • US- adults with new-onset unclassified tonic-clonic seizures (may be considered)^d 		<p>idiopathic generalised epilepsiesⁿ</p> <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • UK- Dravet Syndrome (3rd line add-on); infantile spasms syndrome (2nd line add-on) 	

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
Tiagabine	Partial seizures, as add on therapy in patients who are not controlled satisfactorily with other antiepileptic drug(s)	Partial epileptic seizures		Focal seizures <ul style="list-style-type: none"> • TG (Aus)- adults & children • AMH (Aus) 		Focal seizures <ul style="list-style-type: none"> • FI- adults^d • UK- with/ without evolution to bilateral tonic-clonic seizures (3rd line add-on) 	Generalised seizures <ul style="list-style-type: none"> • CA- children with AS Mixed seizures <ul style="list-style-type: none"> • CA- Dravet syndrome; Lennox-Gastaut Syndrome
Zonisamide	Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy who are intolerant to other agents or where other agents are contraindicated; adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation	Partial epileptic seizures	Focal seizures <ul style="list-style-type: none"> • FI- adults^{d,k} • ILAE- adults & children^d • JP- adults with new-onset • SE- adults^t Undetermined seizures <ul style="list-style-type: none"> • JP- childhood- or adolescence-onset epilepsy with undetermined seizure type (partial or generalised) 	Focal seizures <ul style="list-style-type: none"> • TG (Aus)- adults & children • AMH (Aus) • MH (Aus)- adults with or without secondary generalisation to tonic-clonic seizures • UK- with/ without evolution to bilateral tonic-clonic seizures; self-limited epilepsy with centrotemporal spikes • US- adults with new-onset (may be considered)^d Generalised seizures <ul style="list-style-type: none"> • JP- adults with new-onset tonic-clonic/ clonic seizure Undetermined seizures <ul style="list-style-type: none"> • US- adults with new-onset unclassified tonic-clonic seizures (may be considered)^d 	Generalised seizures <ul style="list-style-type: none"> • CA- children with AS; myoclonic (including juvenile myoclonic epilepsy) • UK- myoclonic seizures^c; EMAS (Dooze syndrome)^c 	Focal seizures <ul style="list-style-type: none"> • FI- adults^d • SCT- adults^d • UK- with/ without evolution to bilateral tonic-clonic seizures (1st line add-on) Generalised seizures <ul style="list-style-type: none"> • UK- GTCS (2nd line add-on); myoclonic seizures; EMAS (Dooze syndrome) 	
Lamotrigine	Partial and generalised seizures in adults and children	Epileptic seizures	Focal seizures	Focal seizures	Generalised seizures	Focal seizures <ul style="list-style-type: none"> • CA- elderly 	Mixed seizures <ul style="list-style-type: none"> • CA- Dravet syndrome

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
			<ul style="list-style-type: none"> • MH (Aus)- adults with/ without secondary generalisation to tonic-clonic seizures • CHP (Aus) • CA- adults • FI- adults^{d,k} • DE- adults • HK- adolescents & adults with/ without secondary generalisation; benign epilepsy with centrottemporal spikes or occipital paroxysms; Landau-Kleffner syndrome • ILAE- Adults, elderly & children^d • JP- adults with new-onset; elderly-onset (≥65 years) • NZ • SCT- adults & elderly^d • SE- adults, elderly & children • UK- with/ without evolution to bilateral tonic-clonic seizures; self-limited epilepsy with centrottemporal spikes • US- adults & elderly (≥60 years) with new-onset (should be considered)^d <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • CHP (Aus) • CA- adults & children with GTCS; children with AS; myoclonic (including juvenile myoclonic epilepsy) • FI- adults^k • HK- adolescents & adults with primary GTCS, AS, tonic/ atonic seizure; childhood or juvenile absence epilepsy • ILAE- adults with GTCS^d; children with AS^d • JP- elderly-onset (≥65 years) 	<ul style="list-style-type: none"> • TG (Aus)- adults & children • AMH (Aus)ⁿ <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • TG (Aus)- juvenile myoclonic epilepsy; other symptomatic generalised epilepsies (with Valproate) • AMH (Aus)- GTCSⁿ; AS • MH (Aus)- adults with GTCS; AS; myoclonic seizures • DE- adults with genetic generalised seizures • HK- Juvenile myoclonic epilepsy; MAE • JP- adults with new-onset tonic-clonic/ clonic/ tonic/ atonic seizure; adults with new-onset AS • NZ- AS^p • UK- GTCSⁿ; tonic or atonic seizuresⁿ; idiopathic generalised epilepsiesⁿ • US- childhood absence epilepsy <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • TG (Aus)- Lennox-Gastaut syndrome (with Valproate) 	<ul style="list-style-type: none"> • HK- adolescents & adults with myoclonic seizure • UK- myoclonic seizures^c; AS^c 	<ul style="list-style-type: none"> • FI- adults^d • SCT- adults^d • UK- with/ without evolution to bilateral tonic-clonic seizures (1st line add-on) <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • CA- adults with GTCS; children with AS; myoclonic (including juvenile myoclonic epilepsy) • SCT- adults with genetic generalised epilepsy^d • UK- GTCS (1st line add-on); AS; myoclonic seizures; tonic or atonic seizures; idiopathic generalised epilepsies <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • CA- Lennox-Gastaut Syndrome • UK- Lennox-Gastaut Syndrome 	<ul style="list-style-type: none"> • HK- SMEI

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
			<ul style="list-style-type: none"> • NZ- AS (girls with high risk of GTCS who are > 10 years or younger girls likely to require treatment beyond 10 years of age); GTCS (girls > 10 years and child < 3 years) • SCT- adults with genetic generalised epilepsy^{d,k} • SE- adults & children with GTCS <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • HK- Lennox-Gastaut syndrome <p><u>Undetermined seizures</u></p> <ul style="list-style-type: none"> • JP- childhood- or adolescence-onset epilepsy with undetermined seizure type (partial or generalized)^e • SCT- adults^d • US- adults & elderly (≥60 years) with new-onset unclassified tonic-clonic seizures (should be considered)^d 	<ul style="list-style-type: none"> • UK- Lennox-Gastaut Syndrome <p><u>Undetermined seizures</u></p> <ul style="list-style-type: none"> • TG (Aus)- adults & children with tonic-clonic seizures where generalised or focal onset is unclear 			
Vigabatrin	Treatment of epilepsy which is not satisfactorily controlled by other antiepileptic drugs	Epileptic seizures	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • ILAE- adults & children^d <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • ILAE- adults with GTCS^d <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • CA- infantile spasms • HK- infantile spasms (with tuberous sclerosis) • UK- infantile spasms syndrome 	<p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • AMH (Aus)- infantile spasms (if no safer alternative) 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • FI- adults^f 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • UK- with/ without evolution to bilateral tonic-clonic seizures (3rd line add-on) 	<p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • CA- children with AS <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • CA- Dravet syndrome; Lennox-Gastaut Syndrome
Oxcarbazepine	Monotherapy or adjunctive therapy for the treatment of partial seizures and generalised tonic-clonic seizures, in adults and children	Seizures	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • CA- adults & children; benign epilepsy of childhood with centrotemporal spikes • FI- adults^d 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • TG (Aus)- adults & children • AMH (Aus) 		<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • CA- adults • SCT- adults^d • UK- with/ without evolution to bilateral 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • HK- Landau-Kleffner syndrome <p><u>Generalised seizures</u></p>

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
			<ul style="list-style-type: none"> • HK- adolescents & adults with/ without secondary generalisation; benign epilepsy with centrottemporal spikes or occipital paroxysms • ILAE- adults & children; children with benign childhood epilepsy with centrottemporal spikes^d • SE- children^k <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • ILAE- adults & children with GTCS^d 	<ul style="list-style-type: none"> • MH (Aus)- adults with with/ without secondary generalisation to tonic-clonic seizures • CHP (Aus) • UK- with/ without evolution to bilateral tonic-clonic seizures; self-limited epilepsy with centrottemporal spikes <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • AMH (Aus)- GTCS • HK- adolescents & adults with primary GTCS 		tonic-clonic seizures (1 st line add-on)	<ul style="list-style-type: none"> • CA- adults with GTCS (with AS or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected); children with AS; myoclonic (including juvenile myoclonic epilepsy) • HK- adolescents & adults with AS, myoclonic/ tonic/ atonic seizure; childhood or juvenile absence epilepsy; juvenile myoclonic epilepsy; MAE <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • CA- Dravet syndrome; Lennox-Gastaut Syndrome • HK- infantile spasms; SMEI; Lennox-Gastaut syndrome
Topiramate	Adults and children, 2 years and over: monotherapy in patients with newly diagnosed epilepsy; for conversion to monotherapy in patients with epilepsy; add-on therapy in partial onset seizures (with or without secondary generalised seizures), primary generalised tonic-clonic seizures or drop attacks associated with Lennox-Gastaut syndrome	Seizures Migraines Item codes with both indications, seizure indication will be identified using authority codes (e.g. for PBS item code 13969F, authority code 5516 for	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • CA- adults & children • FI- adults^{d,k} • HK- adolescents & adults with/ without secondary generalisation • ILAE- adults, elderly & children^d • JP- adults with new-onset <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • CA- children with GTCS; myoclonic (including juvenile myoclonic epilepsy) • FI- adults^k • HK- adolescents & adults with primary GTCS; MAE 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • TG (Aus)- adults & children • AMH (Aus) • MH (Aus)- adults with/ without secondary generalisation to tonic-clonic seizures • CHP (Aus) • HK- benign epilepsy with centrottemporal spikes or occipital paroxysms; Landau-Kleffner syndrome 	<p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • TG (Aus)- symptomatic generalised epilepsies • CA- children with AS • UK- myoclonic/ tonic/ atonic seizures^c; idiopathic generalised epilepsies^c; EMAS (Doose syndrome)^c <p><u>Mixed seizures</u></p> <ul style="list-style-type: none"> • TG (Aus)- Lennox-Gastaut syndrome 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • CA- adults • FI- adults^d • SCT- adults^d • UK- with/ without evolution to bilateral tonic-clonic seizures (1st line add-on) <p><u>Generalised seizures</u></p> <ul style="list-style-type: none"> • CA- adults with GTCS; myoclonic (including juvenile myoclonic epilepsy) 	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • DE- adults (not as initial monotherapy)

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
		seizure will be included and 5325 for migraine excluded)	<ul style="list-style-type: none"> ILAE- adults & children with GTCS^d; juvenile myoclonic epilepsy^d JP- elderly-onset (≥65 years) SCT- adults with genetic generalised epilepsy^{d,k} SE- children with GTCS^k <p>Mixed seizures</p> <ul style="list-style-type: none"> CA- Dravet syndrome HK- SMEI; Lennox-Gastaut syndrome <p>Undetermined seizures</p> <ul style="list-style-type: none"> SCT- adults^d 	<p>Generalised seizures</p> <ul style="list-style-type: none"> AMH (Aus)- GTCS MH (Aus)- adults with GTCS CHP (Aus) HK- adolescents & adults with AS, myoclonic/ tonic/ atonic seizure; childhood or juvenile absence epilepsy; juvenile myoclonic epilepsy JP- adults with new-onset tonic-clonic/ clonic/ myoclonic/ tonic/ atonic seizure <p>Mixed seizures</p> <ul style="list-style-type: none"> HK- infantile spasms UK- Infantile spasms syndrome <p>Undetermined seizures</p> <ul style="list-style-type: none"> TG (Aus)- adults & children with tonic-clonic seizures where generalised or focal onset is unclear 	<ul style="list-style-type: none"> CA- infantile spasms 	<ul style="list-style-type: none"> SCT- adults with genetic generalised epilepsy^d UK- GTCS (1st line add-on); myoclonic/ tonic/ atonic seizures; idiopathic generalised epilepsies; EMAS (Doose syndrome) <p>Mixed seizures</p> <ul style="list-style-type: none"> CA- Lennox-Gastaut Syndrome UK- Dravet Syndrome (3rd line add-on); Lennox-Gastaut Syndrome (3rd line add-on); infantile spasms syndrome 	
Third-line treatment^{a,b}							
Brivaracetam	Add-on therapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 4 years of age with epilepsy	Intractable partial epileptic seizures		<p>Focal seizures</p> <ul style="list-style-type: none"> MH (Aus)- adults with or without secondary generalisation to tonic-clonic seizures 	<p>Generalised seizures</p> <ul style="list-style-type: none"> UK- Myoclonic seizures^c 	<p>Focal seizures</p> <ul style="list-style-type: none"> CA- adults & children FI- adults^d UK- with/ without evolution to bilateral tonic-clonic seizures (2nd line add-on) <p>Generalised seizures</p>	

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
						<ul style="list-style-type: none"> UK- GTCS (2nd line add-on); myoclonic seizures 	
Perampanel	Adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients from 4 years of age with epilepsy; adjunctive treatment of primary generalised tonic-clonic seizures in patients from 7 years of age with idiopathic generalised epilepsy.	Intractable partial epileptic seizures ¹ Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures ²	<u>Generalised seizures</u> <ul style="list-style-type: none"> CA- adults with GTCS 	<u>Focal seizures</u> <ul style="list-style-type: none"> TG (Aus)- adults MH (Aus)- adults with/ without secondary generalisation to tonic-clonic seizures JP- adults with new-onset <u>Generalised seizures</u> <ul style="list-style-type: none"> JP- adults with new-onset tonic-clonic/ clonic seizure 	<u>Generalised seizures</u> <ul style="list-style-type: none"> UK- idiopathic generalised epilepsies^c 	<u>Focal seizures</u> <ul style="list-style-type: none"> CA- adults FI- adults^d SCT- adults^d UK- with/ without evolution to bilateral tonic-clonic seizures (2nd line add-on) <u>Generalised seizures</u> <ul style="list-style-type: none"> CA- adults with GTCS; myoclonic (including juvenile myoclonic epilepsy) UK- GTCS (1st line add-on); idiopathic generalised epilepsies <u>Mixed seizures</u> <ul style="list-style-type: none"> CA- Lennox-Gastaut Syndrome 	
Lacosamide	Monotherapy in the treatment of partial seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older; add-on therapy in the treatment of partial seizures with or without secondary generalisation in patients with epilepsy aged 4 years and older; add-on therapy in the treatment of primary generalised tonic-clonic seizures in patients with idiopathic generalised epilepsy aged 4 years and older.	Intractable partial epileptic seizures ¹ Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures ²	<u>Focal seizures</u> <ul style="list-style-type: none"> FI- adults^{d,k} SE- adults^k 	<u>Focal seizures</u> <ul style="list-style-type: none"> TG (Aus)- adults AMH (Aus) MH (Aus)- adults with/ without secondary generalisation to tonic-clonic seizures DE- adults JP- adults with new-onset 	<u>Focal seizures</u> <ul style="list-style-type: none"> UK- with/ without evolution to bilateral tonic-clonic seizures^c 	<u>Focal seizures</u> <ul style="list-style-type: none"> FI- adults^d SCT- adults^d UK- with/ without evolution to bilateral tonic-clonic seizures (1st line add-on) <u>Generalised seizures</u> <ul style="list-style-type: none"> UK- GTCS (2nd line add-on) 	
Cannabidiol	Adjunctive therapy of seizures associated with Lennox Gastaut	Severe myoclonic				<u>Mixed seizures</u>	

AEDs	TGA-approved epilepsy indication(s) ^a	PBS-listed indication ^b	Recommendations from included Australian/ international clinical guidelines				
			1 st line	2 nd line	3 rd line ^c / Others	Adjunctive/ Add-on	To avoid/ Do not offer
	syndrome (LGS) or Dravet syndrome (DS) for patients 2 years of age and older.	epilepsy in infancy (Dravet syndrome)				<ul style="list-style-type: none"> • UK- Dravet Syndrome (2nd line add-on with clobazam if >2yo); Lennox-Gastaut Syndrome (3rd line add-on with clobazam if >2yo) 	
Stiripentol	Adjunctive treatment of generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) in patients whose seizures are not adequately controlled with a benzodiazepine (usually clobazam) and valproate.	Severe myoclonic epilepsy in infancy (Dravet syndrome)				<u>Mixed seizures</u> <ul style="list-style-type: none"> • CA- Dravet syndrome • UK- Dravet Syndrome (1st line add-on with clobazam) 	

AEDs, antiepileptic drugs; **AMH (Aus)**, Australian Medicines Handbook Pty Ltd 2024 Neurological Drugs- Antiepileptics- Epilepsy [Ref 10]; **AS**, absence seizures; **CA**, Canada (Ontario) March 2020 Clinical Guidelines for the Management of Epilepsy in Adults and Children [Ref 13]; **CHP (Aus)**, Community Health Pathways for GPs (Tasmania) 2021 Anti-Epileptic Drugs (AEDs) [Ref 12]; **DE**, Germany 2023 Erster epileptischer Anfall und Epilepsien im Erwachsenenalter [First epileptic seizure and epilepsy in adulthood] [Ref 15]; **EMAS**, epilepsy with myoclonic-atonic seizures; **FI**, Finland 2020 Epilepsiat (aikuiset) [Epilepsies (adults)] [Ref 14]; **GTCS**, generalised tonic-clonic seizures; **HK**, Hong Kong 2017 (original version in 2009) The Hong Kong Epilepsy Guideline [Ref 16, 17]; **ILAE**, International League Against Epilepsy (ILAE) 2013 (original version in 2006) Updated ILAE evidence review of AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes [Ref 18, 19]; **JP**, Japan 2018 Clinical Practice Guidelines for Epilepsy [Ref 20]; **MAE**, myoclonic-astatic epilepsy; **MH (Aus)**, Melbourne Health's Department of Neurology- Division of Neurosciences (Victoria) 2019 Management of First Seizure & Epilepsy in Adults [Ref 11]; **NZ**, New Zealand 2022 Epilepsy Guidelines & Pathways for Children & Young People [Ref 21]; **PBS**, Pharmaceutical Benefits Scheme; **SCT**, Scotland 2018 Diagnosis and management of epilepsy in adults. SIGN guideline [Ref 22]; **SE**, Sweden 2019 Swedish practice guidelines for monotherapy in epilepsy [Ref 23]; **SMEI**, severe myoclonic epilepsy of infancy; **TG (Aus)**, Therapeutic Guidelines Limited 2017 (amended 2023) Neurology- Epilepsy and seizures [Ref 9]; **TGA**, Therapeutic Goods Administration; **UK**, United Kingdom 2022 Epilepsies in children, young people and adults. NICE guideline [Ref 24]; **US**, United States 2018 Practice guideline update: Efficacy and tolerability of the new AEDs I: Treatment of new-onset epilepsy [Ref 25]

^a Per the Product Information (PI) accessed from the [TGA website](#) on 3 March 2023

^b Source: Extracted from PBS.gov.au on 29 August 2023

^c Recommended as third-line AEDs (instead of 'Others') in the guidelines

^d Details on level of evidence or grade of recommendation are provided in the respective guidelines or refer to Appendix Table 3 and 4

^e AEDs that should be used with caution in this indication, details are provided in the respective guidelines

^f In special situations (allergies, other medications are not effective)

^g Avoid in females of childbearing potential who do not have reliable contraception

^h Use with caution in females of childbearing potential who do not have reliable contraception

ⁱ Avoid in females of childbearing potential

^j For males and girls < 10 years of age who are not likely to require AED treatment after 10 years of age

^k Alternative to first-line AEDs as per the guidelines; and the alternative AED is considered as equivalent to first line AED in this project

^l For boys, men, girls <10 years of age and who are unlikely to need AED treatment when they are old enough to have children, and women who are unable to have children

^m Use with caution in women and girls

ⁿ May be first-line AED in females of child-bearing potential

^o First-line AED in females of childbearing potential who do not have reliable contraception

^p When ethosuximide and valproate are unsuitable, ineffective or not tolerated

First-line AEDs

The TGA-approved and PBS-listed first-line AEDs include carbamazepine, ethosuximide, phenobarbital (phenobarbitone), phenytoin, primidone, sulthiame, valproate, clonazepam and nitrazepam (Table 9).

The first-line AEDs recommended by the Australian guidelines, identified in our search, are in-line with the TGA-approved and PBS-listed indications. The specific recommendations are to use carbamazepine for the treatment of focal seizures, valproate for generalised seizures except for females of childbearing potential, and ethosuximide for absence seizures (Table 8). Phenobarbital, phenytoin, primidone, sulthiame, clonazepam and nitrazepam are not recommended as first-line AEDs in the included Australian guidelines. Phenobarbital, phenytoin and clonazepam are recommended as second-line AEDs in at least one of the four included Australian guidelines. There is no first- or second-line recommendation made for primidone, sulthiame and nitrazepam in the included Australian guidelines.

Carbamazepine, valproate and ethosuximide are also listed as first-line AEDs in over half of the included international guidelines (Canada, Hong Kong, ILAE, Japan, New Zealand and Sweden; Table 8). The ILAE guidelines has the most similar first-line AEDs (except for nitrazepam) to the TGA-approved and PBS-listed recommendations. Two other international guidelines (Canada and Hong Kong) have also listed phenobarbital and/or phenytoin as first-line AEDs. The remaining TGA-approved and PBS-listed first-line AEDs, are generally recommended as either second-line, “others” or adjunctive/ add-on therapy in the included international guidelines (Table 8 and 9).

Second-line AEDs

The TGA-approved and PBS-listed second-line AEDs are gabapentin, levetiracetam, tiagabine, zonisamide, lamotrigine, vigabatrin, oxcarbazepine and topiramate.

The second-line AEDs recommended by the included Australian guidelines are similar to the TGA-approved and PBS-listed ones except for levetiracetam and lamotrigine. The Therapeutic Guidelines and Australian Medicines Handbook are consistent with the current PBAC recommendations i.e. to use lamotrigine and levetiracetam as a second-line AEDs. However, two other included Australian guidelines (one from a Victorian major tertiary referral teaching hospital and the other from a Tasmanian non-governmental primary health care organisation) have recommended using either lamotrigine and/or levetiracetam as a first-line AED in adults with focal and/or generalised seizures (Table 7 and 8).

Some of the TGA-approved and PBS-listed second-line AEDs are recommended as first-line AEDs in the included international guidelines (Table 8). In the ILAE guidelines all the TGA-approved and PBS-listed second-line AEDs (except for tiagabine) are recommended as first-line AEDs for treatment of certain seizure types. Of the eleven international guidelines included, all (100%) recommended lamotrigine, and nine (82%; excluding Germany and the US) recommended levetiracetam as first-line AEDs for certain types of focal seizures. (Table 8 and 9). Eight guidelines (73%; except for Germany, UK and US) have recommended lamotrigine and nine (82%; except for Germany and US) recommended levetiracetam as a first-line AED for certain types of generalised seizures.

Third-line AEDs

The TGA-approved and PBS-listed third-line AEDs are brivaracetam, perampanel, lacosamide, cannabidiol and stiripentol.

Some of these TGA-approved and PBS-listed third-line AEDs are recommended as first- or second-line AEDs, or adjunctive/ add-on therapy in the included Australian and international guidelines (Table 8). Three out of the four Australian guidelines identified recommend brivaracetam,

perampanel and/or lacosamide as the second-line AEDs for treatment of focal seizures. Among the international guidelines identified, the Canadian guidelines recommend perampanel and the Finnish together with the Swedish guidelines recommend lacosamide as a first-line AED for the treatment of certain types of generalised and focal seizures, respectively. The Japanese guidelines recommend perampanel and lacosamide as second-line AEDs for the treatment of focal and/or generalised seizures.

Only one of the included clinical guidelines i.e. the UK guidelines has clearly specified the recommendations for third-line AEDs. The UK guidelines recommend brivaracetam, perampanel and lacosamide as third-line AEDs. The other included guidelines use 'adjunctive' or 'others' after the first- and second-line AEDs in their recommendations. 'Adjunctive' is considered as adjuvant or add-on therapy in this review; whereas 'others' are grouped together with third-line AEDs during data extraction.

Other AEDs

There are other AEDs which are not TGA-approved and PBS-listed for the treatment of epilepsy but are recommended in the included Australian or international guidelines (Table 8). These include clobazam, pregabalin, eslicarbazepine, rufinamide, retigabine, piracetam and cenobamate. Clobazam and pregabalin are second- or "others" AEDs in three of the four Australian guidelines for the treatment of focal, generalised, mixed or undetermined/ unknown seizures (Table 8).

Clobazam and rufinamide are approved by the TGA as an adjunctive therapy for certain types of epilepsy but they are not PBS-listed. Pregabalin is approved by the TGA for the treatment of neuropathic pain in adults and as an adjunctive therapy in adults with partial seizures with or without secondary generalisation; however, pregabalin is only PBS-listed for the treatment of neuropathic pain (that is refractory to other drugs). Eslicarbazepine, retigabine, piracetam and cenobamate are not approved by the TGA nor listed on the PBS for any indication.

Population groups

Most of the included Australian and international guidelines provide recommendations for the treatment of epilepsy across different population groups (namely children, young people, adults, and the elderly) except for five guidelines (Appendix Table 3 and 4). One of the Australian guidelines (i.e. the one from a Victorian major tertiary referral teaching hospital) and three of the international guidelines (Finland, Germany and Scotland) only provide AED recommendations for the adult population, whereas the New Zealand guidelines only provide recommendations for children and young people with epilepsy.

Discussion

Our consultation with the Australian experts suggested the majority of public hospitals use the Therapeutic Guidelines, Australian Medicines Handbook, UpToDate®, international guidelines, current literature, the neurologist's guidance or individual clinician's judgement for chronic management of epilepsy in their daily practice.

There are similarities and differences among the AED recommendations made by the included Australian and international clinical guidelines when compared to the current PBS restrictions and the TGA-approved indications. A commonality among the included guidelines is that most recommend carbamazepine as the first-line AED for treating focal seizures and valproate for generalised seizures. However, for females of childbearing potential, lamotrigine or levetiracetam is recommended as an alternative to valproate.

There have been recent concerns about a possible higher risk of neurodevelopmental disorders (e.g. intellectual disability, autism spectrum disorders, attention deficit hyperactivity disorder and others) in children born to men treated with valproate.²⁶⁻²⁸ Prescribers are encouraged to inform their male patients of this potential risk, discuss the need to consider effective contraception with treatment or consider alternative treatment options.^{26, 27}

The second-line AEDs recommended by the included Australian guidelines are similar to the TGA-approved and PBS-listed ones except for levetiracetam and lamotrigine. Two Australian local guidelines recommended lamotrigine and levetiracetam as the first-line AED for treatment of epilepsy. Local guidelines are generally a robust reflection of real-world practice, as they are reviewed and updated frequently by experts working in the field. These recommendations were consistent with the recommendations in the majority of the international guidelines.

The use of levetiracetam and lamotrigine for the initial treatment of epilepsy has increased globally. For example, a Swedish nationwide study which analysed the choice of AED in patients who initiated epilepsy treatment using monotherapy found that the most evident changes were levetiracetam use increased from 10% in 2010 to 55% in 2022 whilst carbamazepine or valproate use decreased during this period from 35% to 5% and 20% to 5%, respectively.³ The use of lamotrigine remained unchanged (20%).³ The selection of initial monotherapy varied across age group with patients aged 16-40 years twice as likely as other age groups to use lamotrigine, and with increasing age (>65 years) levetiracetam was the preferred option.³

There are several reasons that many guidelines now recommend levetiracetam and lamotrigine as first line treatment, and that these AEDs are now used increasingly often as first-line treatment in real-world practice. This is likely due to their increased tolerability compared to other AEDs, and their long-term safety profile.^{29,30}

UpToDate® is an online collection of clinical practice guidelines, written and regularly revised by global experts, that draw on the available evidence to assist clinicians with clinical decision making.³¹ It is available in >190 countries and accessed by >1.9 million clinicians worldwide. UpToDate® recommends the use of lamotrigine and levetiracetam, alongside carbamazepine, as an option for focal seizures, and recommends valproate for generalised seizures.³²

None of the included Australia and international guidelines provide clear recommendations on third-line AEDs except for the UK guidelines (NICE guidelines). Some of the TGA-approved and PBS-listed third-line AEDs are recommended as first- or second-line AEDs, or adjunctive/ add-on therapy in the included Australian and international guidelines. Among the TGA-approved and PBS-listed third-line AEDs, brivaracetam, perampanel and/or lacosamide are still recommended by most of the included Australian and international guidelines. Two international guidelines recommended stiripentol as adjuvant therapy for Dravet Syndrome, and one of these also recommended cannabidiol as adjuvant therapy for both Dravet and Lennox-Gastaut Syndrome. The remaining guidelines included in this review pre-date these indications for cannabidiol, or else are general epilepsy guidelines which do not specifically discuss management of these particular development and epileptic encephalopathies.

PART 2: UTILISATION REVIEW AND COST ESTIMATES

As noted above (p11), the objectives of Part 2 of this report were to:

- Estimate the cost to the PBS of expanding the restrictions for the second-line AEDs levetiracetam and lamotrigine to allow their first-line use in the general Australian population with epilepsy (referred to as the “proposed listing”) (Research Question 3).
- To model how the first-line use of levetiracetam and lamotrigine in the general population will impact on the utilisation of the more expensive third-line AEDs (i.e., brivaracetam, perampanel, lacosamide, cannabidiol and stiripentol) (Research Question 4).

PART 2A: UTILISATION REVIEW

For Part 2a, a utilisation review of PBS-listed AEDs was undertaken based on historical PBS data from 2014-2023. The purpose of Part 2a is to provide the PBAC with additional data on the utilisation of AEDs and any further evidence on the broader use of other second-line AEDs as requested by the committee in September 2020. The utilisation review presented in this report is intended as a supplement to the ‘Utilisation analysis of PBS-listed AEDs in a cohort of epilepsy patients’ that was considered by the DUSC in September 2023.

Methodology

For Part 2a we analysed PBS data from 2014 to 2023 provided by the DoHAC. We conducted analyses for all people who initiated on a PBS-listed AED (refer to Appendix Table 1 for a list of PBS-listed AEDs). We acknowledge that not all people who initiate on an AED have an epilepsy diagnosis, as some of these medicines are used to treat conditions such as bipolar disorder. The following PBS dispensing data was excluded from the utilisation review:

- all dispensings for nitrazepam and gabapentin where the PBS item code was not for epilepsy;
- all dispensings for topiramate where the authority code was specific to migraine, and;
- all dispensings for carbamazepine where the PBS item code was for dentist prescribing.

We did not exclude any valproate or carbamazepine dispensings (except for the carbamazepine item codes for dentist prescribing) even though these drugs may be used to treat mood disorders or trigeminal neuralgia. This was because inspection of first-time AED dispensing data suggested that the number of valproate and carbamazepine prescriptions dispensed were within the range expected for an AED recommended as a ‘first-line’ treatment in national (e.g., Therapeutic Guidelines) and international guidelines. This approach was also consistent with the clinical experience of the neurologists on the investigation team. We augmented analyses of PBS dispensing data by reviewing POpulation Level Analysis & Reporting (POLAR) primary care data for people who initiate AEDs with and without an epilepsy diagnosis (Xia et al 2024).³³ These primary care data were predominately from Victoria and New South Wales.

In order to investigate how PBS-listed AEDs are used concomitantly and to determine the extent of monotherapy versus combination therapy, a drug sequence analysis was conducted. The drug sequence analysis was also used to inform the flow-on effects from levetiracetam and lamotrigine to the third-line AEDs (brivaracetam, perampanel, lacosamide, cannabidiol and stiripentol) that may result from the proposed listing.

The number of patients incident to a PBS-listed AED was estimated by identifying each patient's first AED dispensing between 2015-2023 and using 2014 as a 12-month lookback window to ensure no prior AED use. All national and international guidelines reviewed for this report recommended initiating with only one AED for new-onset epilepsy. Therefore, people who were dispensed two different AEDs concurrently as part of their first treatment episode were excluded from the analysis, as these cases were deemed to be unusual and/or complex presentations, and outside the scope of this report. The number of prevalent patients to each AED was estimated for the years 2014-2023. If a patient had one or more prescriptions supplied for a particular AED within a calendar year, they were considered prevalent to that AED. All PBS data were analysed using SAS statistical software.

Results

Patient demographics

920,512 people were dispensed an AED between 2014 and 2023 (Table 10). This included 485,532 (53%) females and 434,790 (47%) males. 48,373 people were aged 0-14 years, 380,814 were aged 15-49 years, and 491,135 were aged 50 years and over.

TABLE 10 COHORT CHARACTERISTICS

Age group	Sex	N
0-14*	Females	21,465
	Males	26,908
	Total	48,373
15-49*	Females	201,127
	Males	179,687
	Total	380,814
50 and over*	Females	262,940
	Males	228,195
	Total	491,135
Total		920,512

*Excluding people with missing data (total n=190)

Prescription utilisation trends

After removing duplicate dispensings, there were 27,261,781 AED prescriptions dispensed via the PBS between 2014-2023. Valproate was the most frequently dispensed AED with 7,265,539 prescriptions (27%). Levetiracetam and lamotrigine were the second and third most frequently dispensed AEDs, with 6,272,933 (23%) and 4,699,289 (17%) prescriptions dispensed, respectively. General practitioners prescribed 85% of all prescriptions for PBS-listed AEDs, followed by neurologists (7%), psychiatrists (3%), paediatricians (2%) and internists (1%).

The number of prescriptions dispensed for PBS-listed AEDs increased from 2,387,740 in 2014 to 3,045,526 in 2023 (an increase of 28%) (Figure 1).

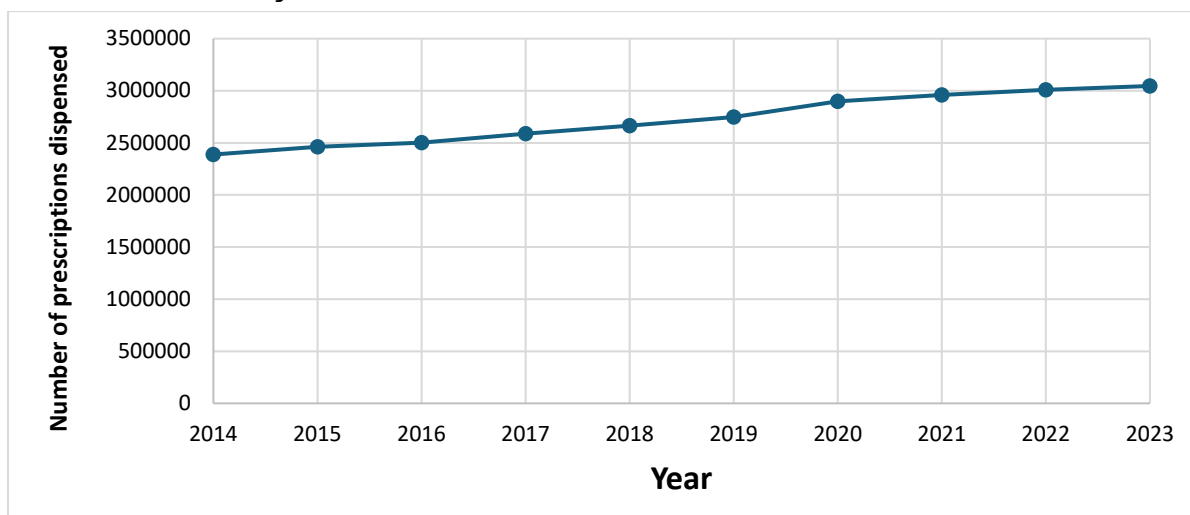


FIGURE 1 NUMBER OF PRESCRIPTIONS DISPENSED FOR PBS-LISTED AEDS (2014-2023)

Females aged 50 years and over had the highest number of AEDs dispensed, followed by males aged 50 years and over, females aged 15-49, and males aged 15-49. There was an increase in the number of AEDs dispensed among all adult groups over time. Children had the lowest number of AEDs dispensed and the dispensing was stable for children over the study period.

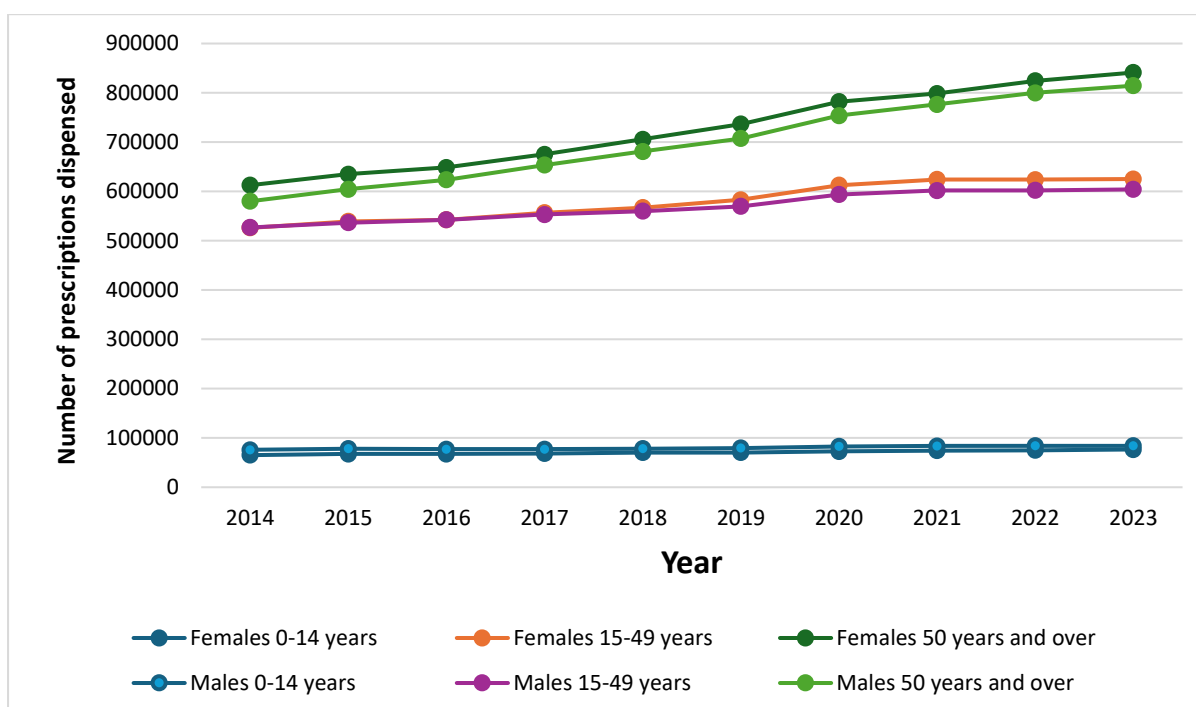


FIGURE 2 NUMBER OF PRESCRIPTIONS DISPENSED FOR PBS-LISTED AEDS BY SEX AND AGE (2014-2023)

The number of valproate prescriptions dispensed declined from 743,455 (31%) prescriptions in 2014, to 687,128 (23%) prescriptions in 2023 (Figure 3). The number of prescriptions dispensed for levetiracetam increased from 405,682 (17%) to 849,552 (28%), and for lamotrigine from 368,176 (15%) to 566,345 (19%) between 2014 to 2023.

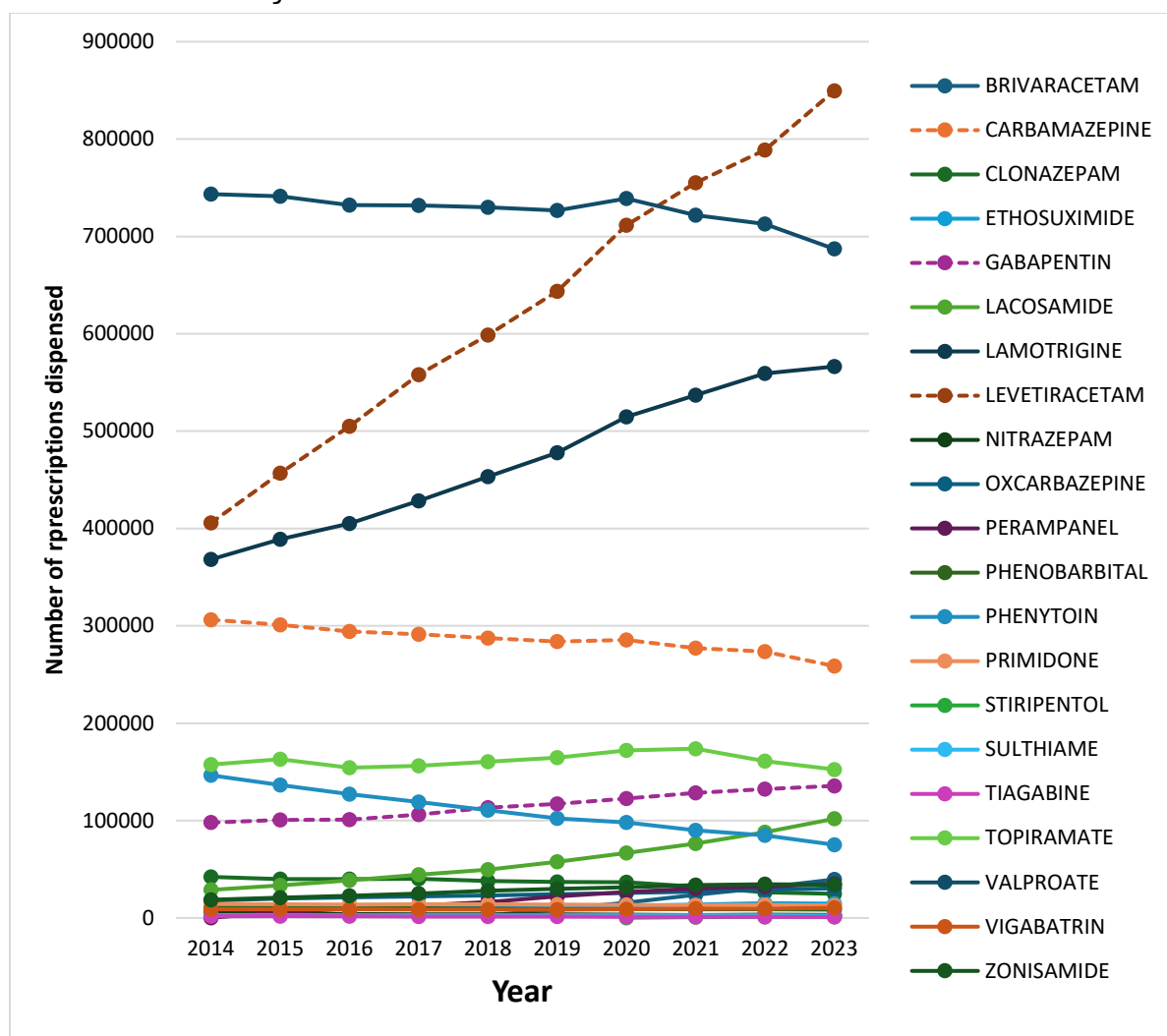


FIGURE 3 NUMBER OF PRESCRIPTIONS DISPENSED FOR PBS-LISTED AEDS BY DRUG (2014-2023)

Patient utilisation trends

Incident (initiating) patients

As shown in Figure 4, the number of patients incident to a PBS-listed AED declined from 75,541 in 2015 to 55,776 in 2023. The total number of incident patients over that time was 564,746.

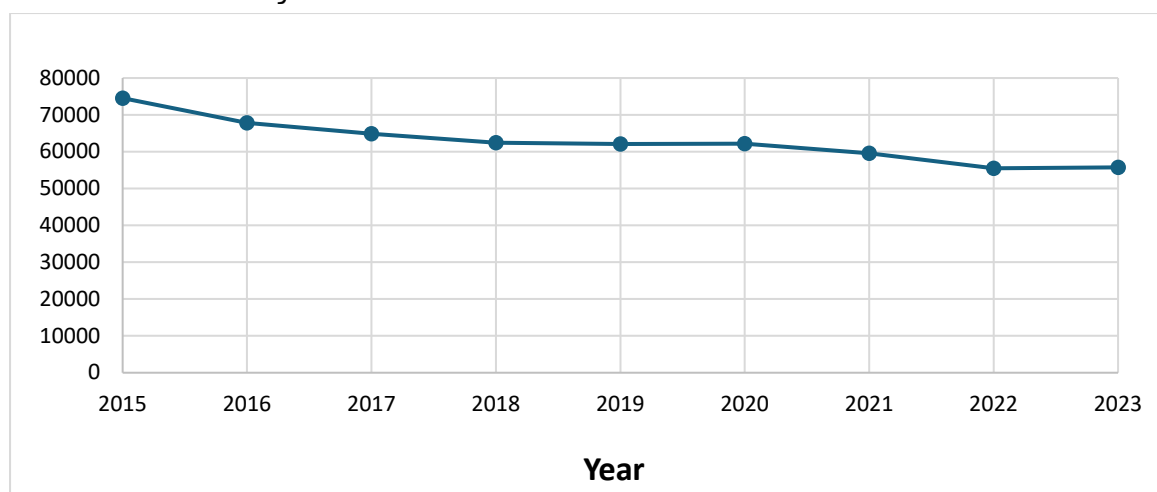


FIGURE 4 PATIENTS INCIDENT TO A PBS-LISTED AED (2015-2023)

The number of patients incident to a PBS-listed AED was highest among females aged 50 years and over, followed by males aged 50 years and over. The number of incident patients was lowest among children, and this was similar among girls and boys. There was a decline in incidence among all males and females aged 15-49 years, and 50 years and over.

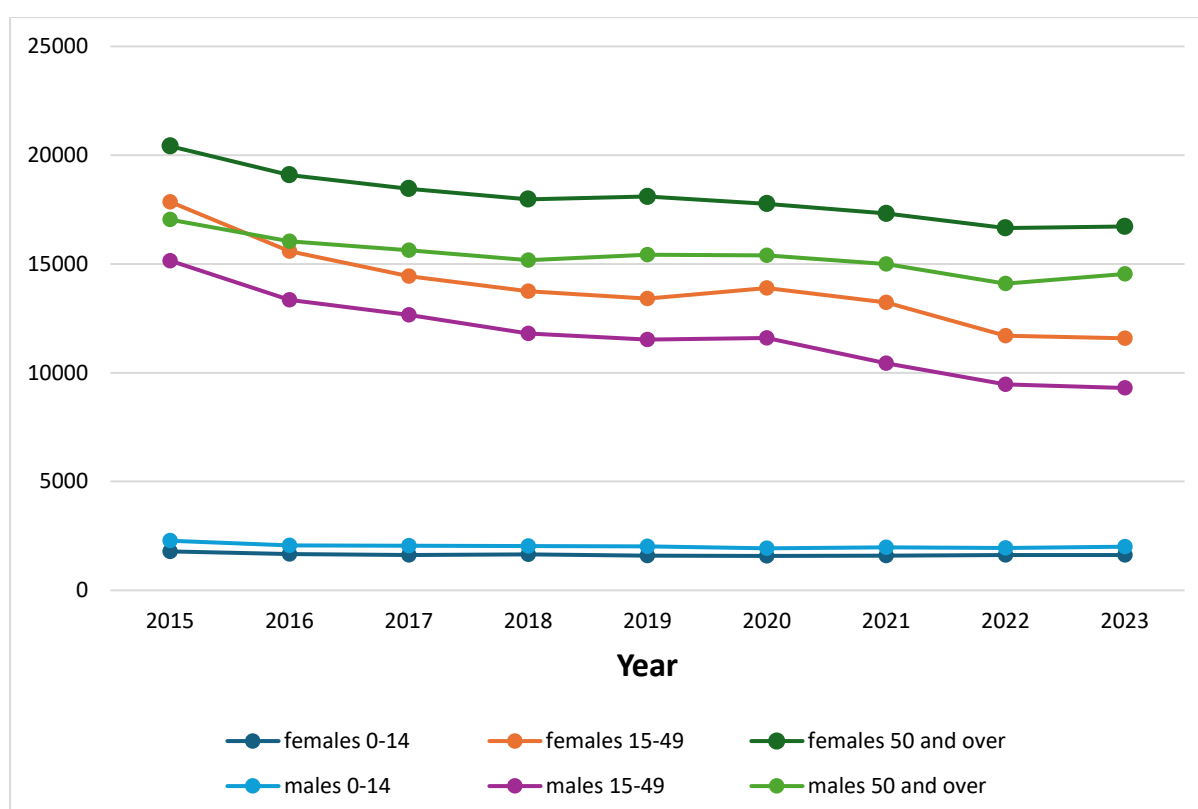


FIGURE 5 NUMBER OF PATIENTS INITIATING PBS-LISTED AED TREATMENT BY AGE AND SEX (2015-2023)

The number of patients initiating AED treatment was highest for valproate, but it declined steeply from 32,307 patients (43% of all AED initiations) in 2015 to 14,760 patients (27% of all AED initiations) in 2023 (Figure 6). The number of patients initiating levetiracetam as their first AED

almost doubled from 7,529 in 2015 (10% of all initiating patients) to 12,516 in 2023 (22% of all initiating patients).

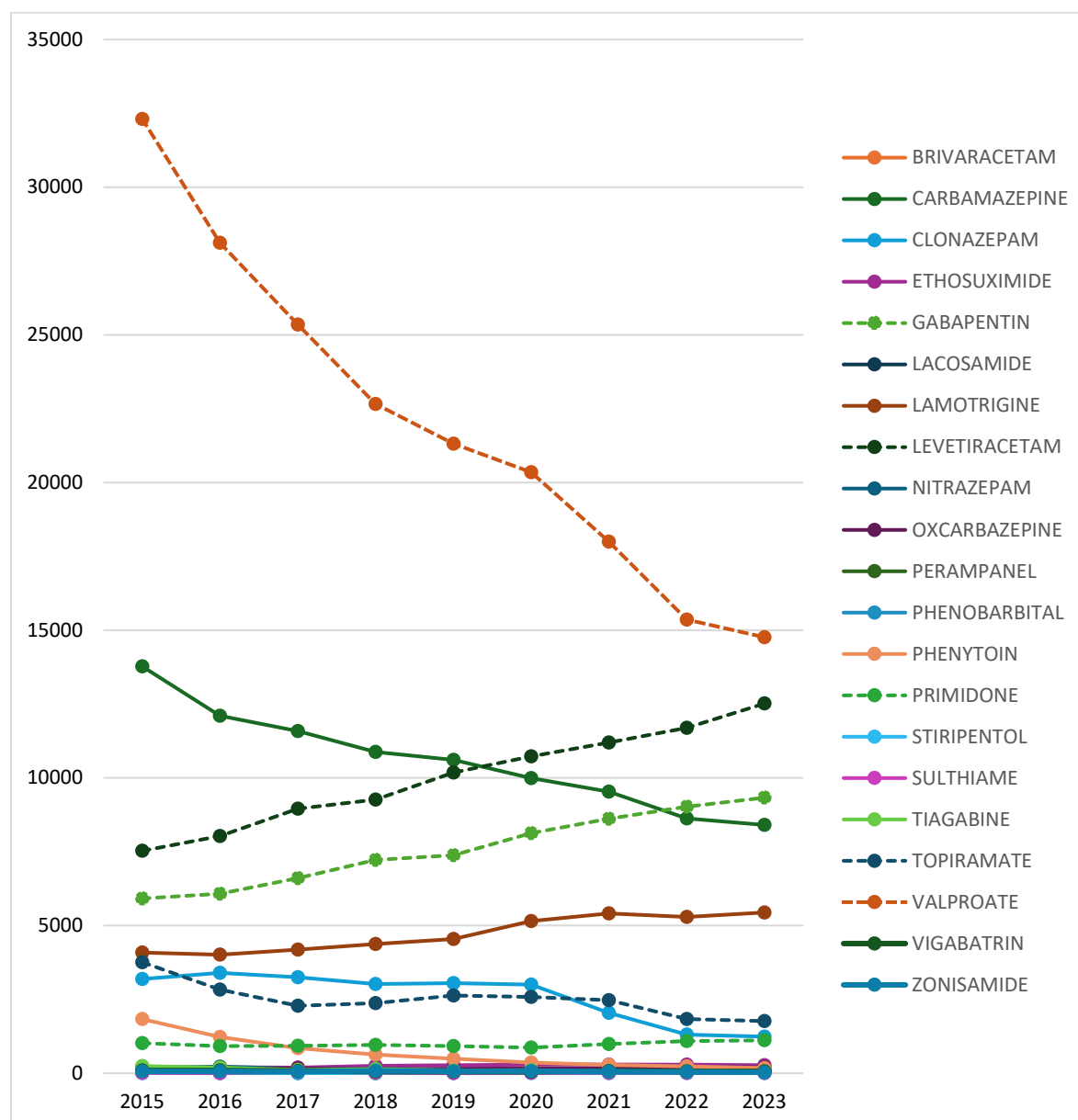


FIGURE 6 NUMBER OF PATIENTS INITIATING PBS-LISTED AED TREATMENT BY DRUG (2015-2023)

PBS data from 2023 showed that women of childbearing potential (aged 15-49 years) were more than twice as likely to be initiated on lamotrigine or levetiracetam compared to men of the same age (Figure 7). Men aged 15-49 years most frequently initiated with valproate while women with lamotrigine.

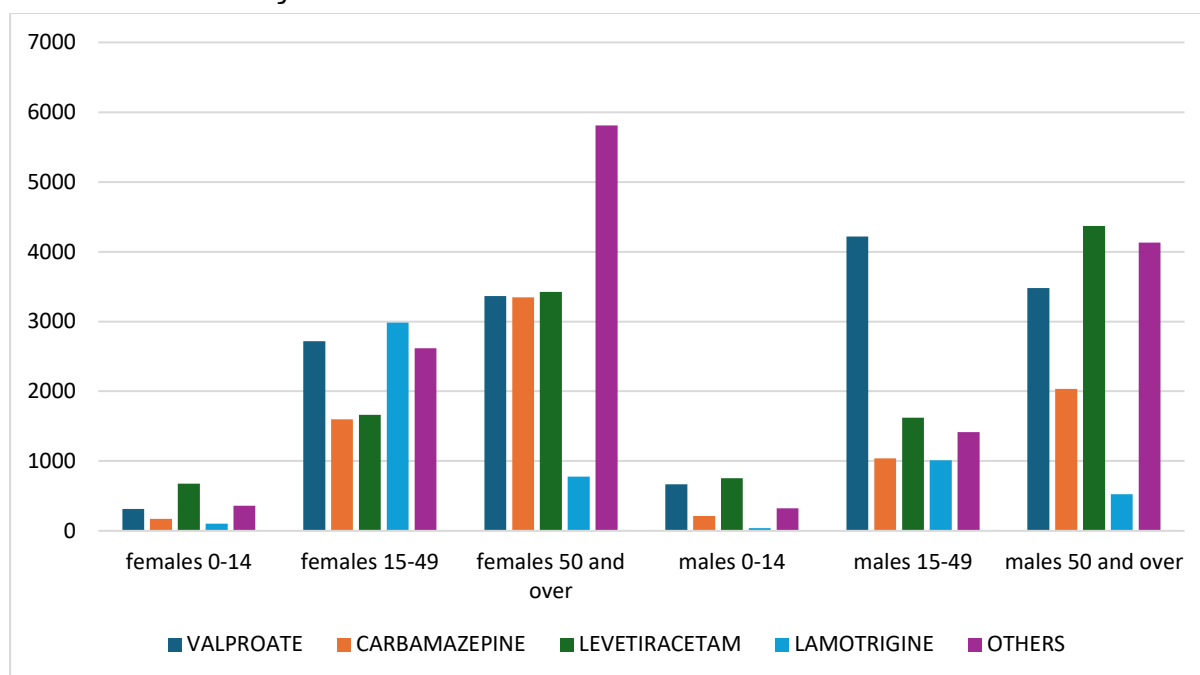


FIGURE 7 NUMBER OF PATIENTS INITIATING PBS-LISTED AED TREATMENT BY AGE AND SEX (2023)

Prevalent patients

There were 920,512 patients prevalent to one or more AEDs between 2014-2023 (i.e. at least one dispensing per year). The number of prevalent patients increased from 326,885 in 2014 to 355,334 in 2023 (Figure 8).

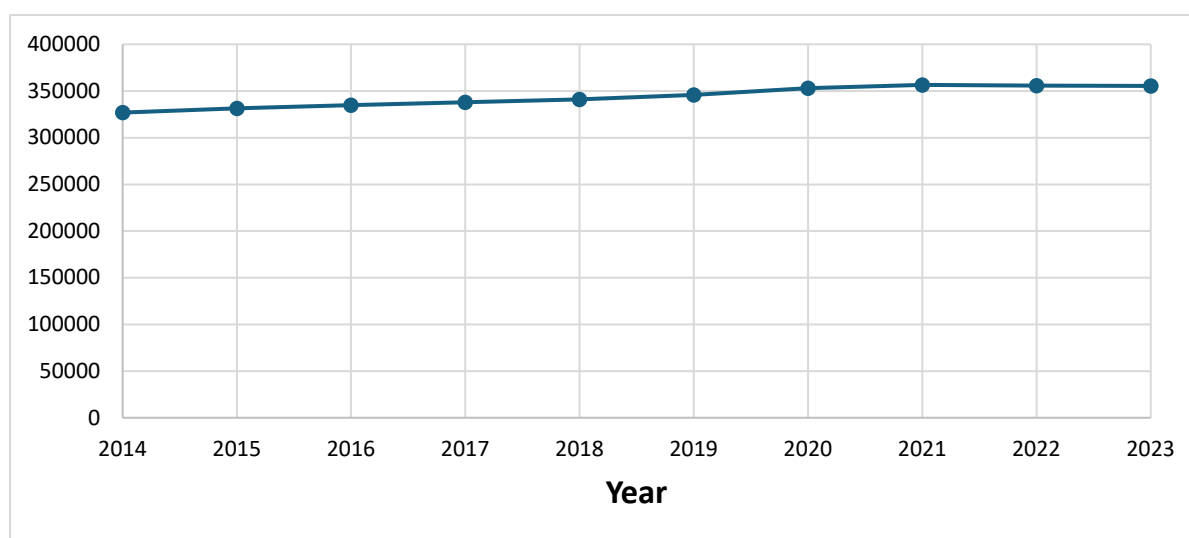


FIGURE 8 NUMBER OF PATIENTS PREVALENT TO A PBS-LISTED AED (2014-2023)

The number of patients prevalent to a PBS-listed AED was highest among females aged 50 years and over (n=107,618 in 2023), followed by males 50 years and over (n=98,088), (Figure 9). There were 66,896 females and 66,427 males prevalent to a PBS-listed AED who were aged 15-49 years. The number of prevalent patients was lowest amongst children aged 0-14 years of age (<9,000 in each sex group). The prevalence increased among women and men aged 50 years and over. The number of prevalent patients remained stable among females and males aged 15-49 years, and among children.

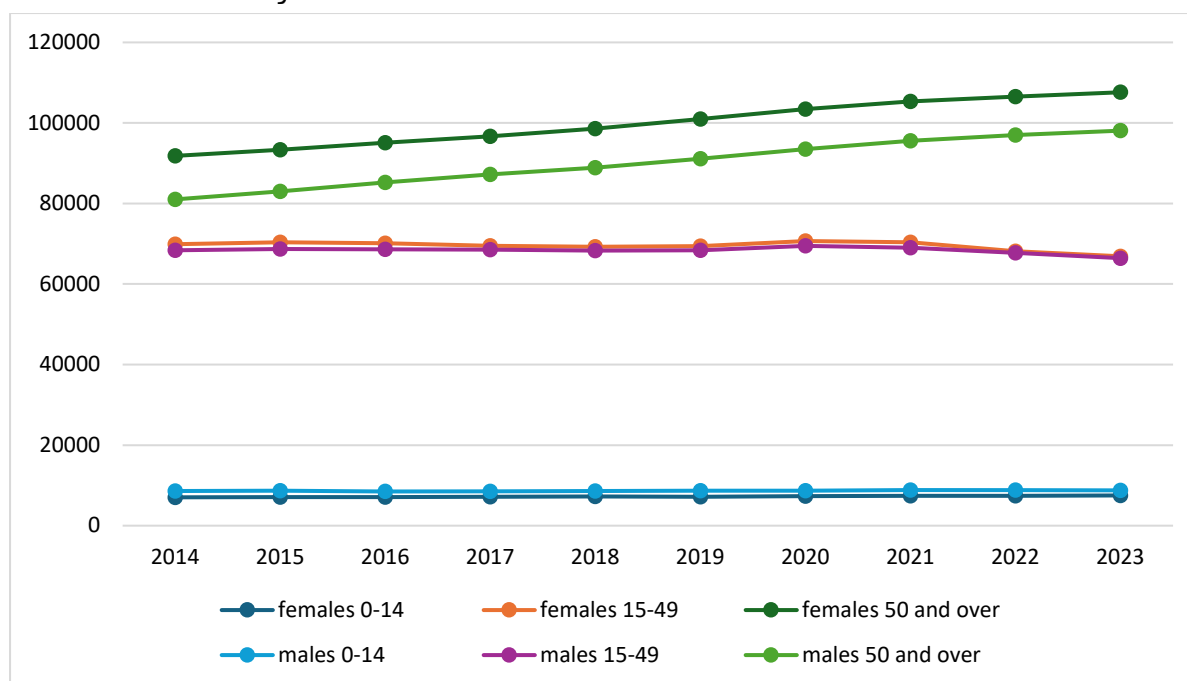


FIGURE 9 NUMBER OF PATIENTS PREVALENT TO A PBS-LISTED AED BY AGE AND SEX (2014-2023)

Valproate was the most prevalent AED each year over the study period (Figure 10). However, the number of patients prevalent to valproate declined over time from 161,183 people (49% of all prevalent patients) in 2014 to 140,192 people (39 % of all prevalent patients) in 2023. Prevalent patients to carbamazepine declined from 76,656 (23%) in 2014 to 65,207 (18%) in 2023.

Prevalent patients to levetiracetam doubled from 40,550 (12% of all prevalent patients) in 2014 to 81,983 (23% of all prevalent patients) in 2023. Over the same period lamotrigine prevalence increased from 34,639 (11%) patients to 57,504 patients (16%).

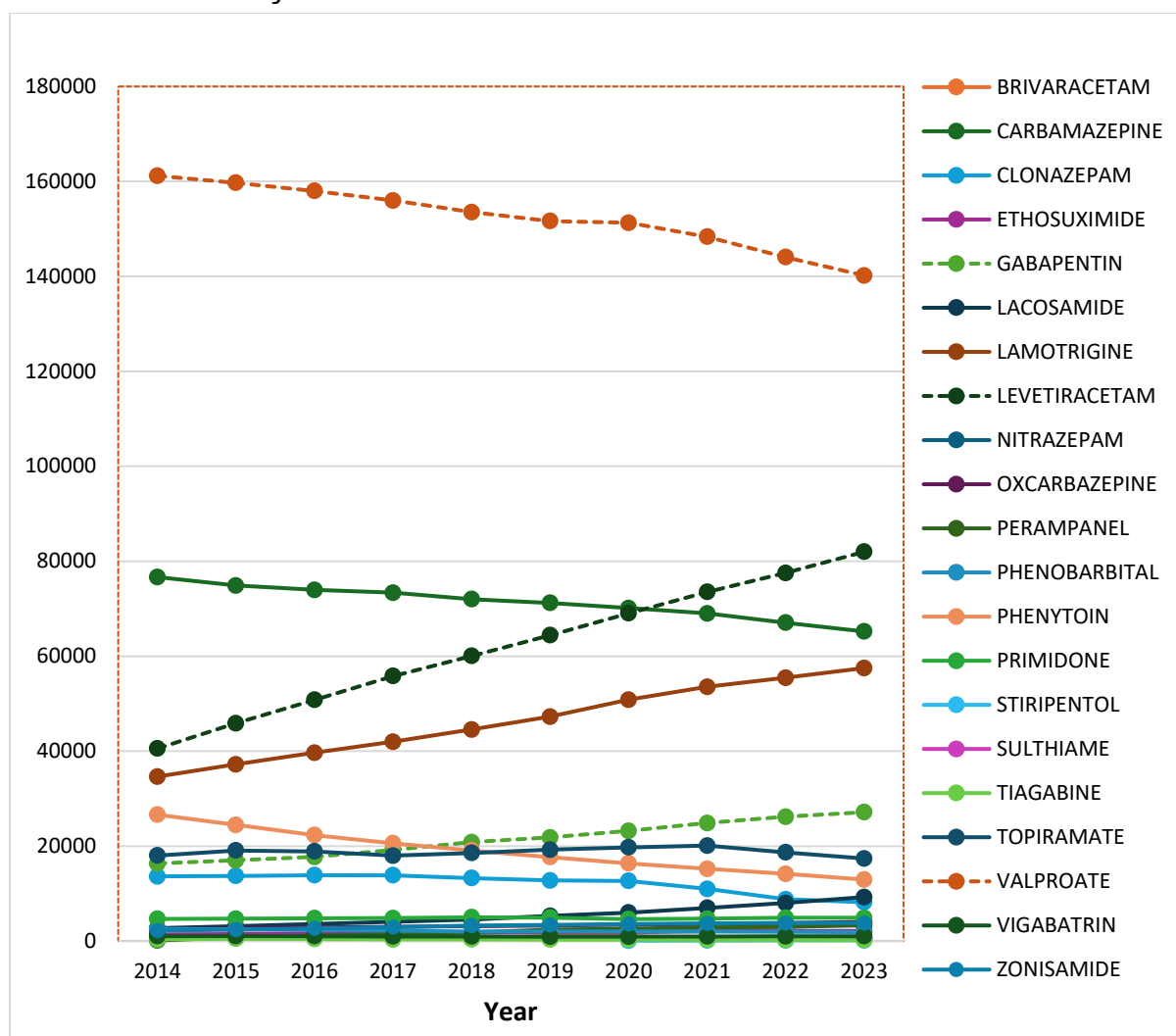


FIGURE 10 NUMBER OF PATIENTS PREVALENT TO A PBS-LISTED AED BY DRUG (2014-2023)

Drug initiation sequence analysis

Overall, 484,780 patients (85.8%) who initiated AED received only one type of AED during the study period (Table 11), while 79,966 (14.4%) received two or more different AEDs. Only 3.4% of patients received more than two different AEDs.

TABLE 11 THE NUMBER OF DRUG INITIATIONS BY NUMBER OF PATIENTS

Number of initiations	N (%)
1	484,780 (85.8)
2	60,743 (10.8)
3 or more	19,223 (3.4)

Table 12 shows the sequence of AED initiation. The two most frequent sequences (change or add-on) were from valproate to levetiracetam (n=4,373) and from levetiracetam to valproate (n=4,188) followed by valproate to lamotrigine (n=3,372) and levetiracetam to lamotrigine (n=2,552). N.B. Sequences of AED initiations with 100 or more patients are reported in table 12.

TABLE 12 DRUG INITIATION SEQUENCES IN PATIENTS WHO INITIATE ON MORE THAN ONE PBS-LISTED AED

Drug1	Drug2	Drug3	N
VALPROATE	LEVETIRACETAM	-	4373
LEVETIRACETAM	VALPROATE	-	4188
VALPROATE	LAMOTRIGINE	-	3372
LEVETIRACETAM	LAMOTRIGINE	-	2552
VALPROATE	CARBAMAZEPINE	-	2223
CARBAMAZEPINE	VALPROATE	-	1991
CARBAMAZEPINE	LEVETIRACETAM	-	1844
LEVETIRACETAM	CLONAZEPAM	-	1675
LEVETIRACETAM	CARBAMAZEPINE	-	1353
LAMOTRIGINE	VALPROATE	-	1323
VALPROATE	CLONAZEPAM	-	1136
CARBAMAZEPINE	GABAPENTIN	-	899
VALPROATE	GABAPENTIN	-	784
LAMOTRIGINE	LEVETIRACETAM	-	769
CARBAMAZEPINE	LAMOTRIGINE	-	754
PHENYTOIN	LEVETIRACETAM	-	723
LEVETIRACETAM	LACOSAMIDE	-	717
VALPROATE	TOPIRAMATE	-	681
GABAPENTIN	VALPROATE	-	633
GABAPENTIN	CARBAMAZEPINE	-	577
VALPROATE	LEVETIRACETAM	LAMOTRIGINE	539
LEVETIRACETAM	VALPROATE	LAMOTRIGINE	457
TOPIRAMATE	VALPROATE	-	433
LEVETIRACETAM	GABAPENTIN	-	426
LEVETIRACETAM	TOPIRAMATE	-	396
ETHOSUXIMIDE	VALPROATE	-	355
LEVETIRACETAM	PHENYTOIN	-	346
LEVETIRACETAM	OXCARBAZEPINE	-	330
CARBAMAZEPINE	LEVETIRACETAM	VALPROATE	311
CARBAMAZEPINE	OXCARBAZEPINE	-	309
VALPROATE	LAMOTRIGINE	LEVETIRACETAM	306
CARBAMAZEPINE	LEVETIRACETAM	LAMOTRIGINE	274
LAMOTRIGINE	TOPIRAMATE	-	263
VALPROATE	CARBAMAZEPINE	LEVETIRACETAM	261
LEVETIRACETAM	BRIVARACETAM	-	256
GABAPENTIN	LEVETIRACETAM	-	251
VALPROATE	LEVETIRACETAM	CARBAMAZEPINE	250
LEVETIRACETAM	LAMOTRIGINE	VALPROATE	247
CLONAZEPAM	VALPROATE	-	246
PHENYTOIN	VALPROATE	-	244
LAMOTRIGINE	CARBAMAZEPINE	-	242
CARBAMAZEPINE	VALPROATE	LEVETIRACETAM	227
VALPROATE	ETHOSUXIMIDE	-	222
LEVETIRACETAM	VALPROATE	CLONAZEPAM	222
LAMOTRIGINE	GABAPENTIN	-	221
TOPIRAMATE	LAMOTRIGINE	-	220
LEVETIRACETAM	VALPROATE	CARBAMAZEPINE	218
CLONAZEPAM	LEVETIRACETAM	-	213
LEVETIRACETAM	VALPROATE	LACOSAMIDE	208

LEVETIRACETAM	CARBAMAZEPINE	VALPROATE	203
CARBAMAZEPINE	CLONAZEPAM	-	195
CARBAMAZEPINE	TOPIRAMATE	-	195
LEVETIRACETAM	CARBAMAZEPINE	LAMOTRIGINE	191
GABAPENTIN	CLONAZEPAM	-	180
VALPROATE	LEVETIRACETAM	CLONAZEPAM	179
TOPIRAMATE	GABAPENTIN	-	171
CARBAMAZEPINE	PHENYTOIN	-	152
GABAPENTIN	LAMOTRIGINE	-	152
TOPIRAMATE	LEVETIRACETAM	-	150
VALPROATE	LEVETIRACETAM	TOPIRAMATE	150
VALPROATE	LEVETIRACETAM	LACOSAMIDE	143
GABAPENTIN	TOPIRAMATE	-	137
ETHOSUXIMIDE	VALPROATE	LAMOTRIGINE	136
CARBAMAZEPINE	VALPROATE	LAMOTRIGINE	135
LEVETIRACETAM	VALPROATE	TOPIRAMATE	134
VALPROATE	LACOSAMIDE	-	132
LEVETIRACETAM	CARBAMAZEPINE	LACOSAMIDE	131
LEVETIRACETAM	LAMOTRIGINE	LACOSAMIDE	131
LAMOTRIGINE	CLONAZEPAM	-	129
VALPROATE	CARBAMAZEPINE	LAMOTRIGINE	129
VALPROATE	PHENYTOIN	-	127
TOPIRAMATE	CARBAMAZEPINE	-	119
LEVETIRACETAM	CLONAZEPAM	VALPROATE	115
VALPROATE	LAMOTRIGINE	CARBAMAZEPINE	110
VALPROATE	ETHOSUXIMIDE	LAMOTRIGINE	108
LEVETIRACETAM	LACOSAMIDE	VALPROATE	106
LEVETIRACETAM	ZONISAMIDE	-	104
PRIMIDONE	GABAPENTIN	-	103
LEVETIRACETAM	PHENYTOIN	VALPROATE	102
CARBAMAZEPINE	LAMOTRIGINE	LEVETIRACETAM	100

Primary care prescribing data

Australian primary care data was sourced from Xia et al 2024.³³ This study used data from 2018 to 2023 from the POLAR primary care database. These data show the proportion of people with a recorded epilepsy or seizure diagnosis at the time of AED initiation (Table 13). The data were reported by sex and age (14-49 years and 50 years and over) groups. The percentage of people with a recorded epilepsy diagnosis among those who initiated on AED treatment was used to inform the calculations in the UCM Workbook (see Table 14).

TABLE 13 PROPORTION OF PEOPLE WITH AN EPILEPSY DIAGNOSIS AT AED INITIATION IN PRIMARY CARE

		Men	Men	Women	Women	
		14-49 years	≥50 years	14-49 years	≥50 years	Total
Topiramate	Total	1,156	825	4,974	2,960	9,915
	Epilepsy	131 (11.3)	81 (9.82)	283 (5.69)	157 (5.30)	652 (6.6)
Carbamazepine	Total	1,661	1,757	1,046	2,272	6,736
	Epilepsy	434 (26.1)	559 (31.8)	332 (31.7)	516 (22.7)	1,841 (27.3)
Valproate	Total	3,470	3,042	2,319	3,011	11,842
	Epilepsy	1,202 (34.6)	810 (26.6)	555 (23.9)	669 (22.2)	3,236 (27.3)
Levetiracetam	Total	980	2,161	1,104	1,700	5,945
	Epilepsy	687 (70.1)	1,040 (48.1)	830 (75.2)	790 (46.5)	3,347 (56.3)
Lamotrigine	Total	1,381	769	3,310	1,156	6,616
	Epilepsy	377 (27.3)	231 (30.0)	660 (19.9)	274 (23.7)	1,542 (23.3)
Gabapentin	Total	10,037	27,683	12,153	41,644	91,517
	Epilepsy	129 (1.29)	211 (0.76)	148 (1.22)	297 (0.71)	785 (0.86)

PART 2B: COST ESTIMATES

Part 2b of this report aims to:

- Estimate the cost to the PBS of expanding the restrictions for the second-line AEDs levetiracetam and lamotrigine to allow their first-line use in the general Australian population with epilepsy (referred to as the “proposed listing”) (Research Question 3).
- To model how the first-line use of levetiracetam and lamotrigine in the general population will impact on the utilisation of the more expensive third-line AEDs (i.e., brivaracetam, perampanel, lacosamide, cannabidiol and stiripentol) (Research Question 4).

Methodology

The primary market share approach was used to estimate the cost to the PBS if levetiracetam and lamotrigine were recommended for first-line use in the general Australian population with epilepsy (referred to as the “proposed listing”). Carbamazepine and valproate are the most commonly used first-line AEDs for epilepsy based on Australian guidelines. Therefore, it was assumed in the financial modelling that the proposed listing would lead to a partial displacement of these medicines by levetiracetam and lamotrigine. The number of prescriptions dispensed via the PBS between 2014-2023 for levetiracetam, lamotrigine, valproate and carbamazepine were used to inform the projections and modelling.

The [utilisation and cost model \(UCM\) workbook](#) was used to estimate the following as a result of the proposed listing:

- the change in PBS use of the first-line AEDs, valproate and carbamazepine, over the forward estimates period (2025-2030);
- the change in PBS use of levetiracetam and lamotrigine from 2025-2030;
- the increased uptake of the third-line AEDs from 2025-2030;
- the cost to the R/PBS as a result of the above changes from 2025-2030.

The forecasting was conducted using MS Excel. The market forecasting was estimated based on historical PBS data (2014-2023), using linear regression models for valproate, carbamazepine, levetiracetam and lamotrigine.

The inputs and assumptions used to inform the financial modelling are summarised in Table 14.

TABLE 14 INPUTS AND ASSUMPTIONS USED TO INFORM THE FINANCIAL MODELLING

Assumption/input	Value used in the base-case	Value used in sensitivity analyses	Rationale
Replacement rate for all dosage forms	10% of valproate and carbamazepine prescriptions would be replaced by levetiracetam and lamotrigine in year 1 (2025), increasing by 10% per year thereafter (i.e. 10% in 2025, 20% in 2026, 30% in 2027 and so on).	5% or 15% of valproate and carbamazepine prescriptions would be replaced by levetiracetam and lamotrigine in year 1 (2025), increasing by 5 or 15% per year thereafter.	Based on our PBS data analysis on AED dispensings and consultation with the neurologists on the investigation team.
Replacement rate for liquid dosage forms	10% of valproate and carbamazepine prescriptions would be replaced by levetiracetam and lamotrigine in year 1 (2025), increasing by 10% per year thereafter (i.e. 10% in 2025, 20% in 2026, 30% in 2027 and so on).	2.5% or 5% of valproate and carbamazepine prescriptions would be replaced by levetiracetam and lamotrigine in year 1 (2025), increasing by 2.5 or 5% per year thereafter.	Based on the advice of the neurologists on the investigation team, lower rates of replacement are expected for liquid forms relative to the tablet forms. Patients requiring liquid forms are often unique cases where changes to treatment regimens are typically avoided.
Replacement ratio of levetiracetam : lamotrigine	60/40 in 2025 (i.e. 60% of valproate and carbamazepine scripts will be replaced by levetiracetam, and 40% by lamotrigine), with levetiracetam increasing by 1%-unit and lamotrigine decreasing by 1%-unit annually thereafter.	N/A	PBS data from 2014-2023 shows that the ratio of levetiracetam to lamotrigine prescriptions (60/40 in 2014) has changed over time with levetiracetam prescriptions increasing by 0-2%-units per year relative to lamotrigine.
Proportion of patients who initiate on carbamazepine or valproate for epilepsy vs. other indications	27.3% for both valproate and carbamazepine.	Due to possibility of under-reporting, a proportion of 37.3%, 50%, 60%, and 80% were tested in sensitivity analyses.	POLAR primary care data (Xia et al 2024)*
Replacement with lamotrigine 5mg and 25mg tablets	No replacement	5mg and 25mg lamotrigine tablets each replace 2.5% of valproate 100mg and carbamazepine 100 mg prescriptions each year	The base-case model did not include lamotrigine 5mg and 25mg tablets due to their low script equivalence values. Based on the advice of

		to account for a small number of initiations with these low doses.	the neurologists on the investigation team, these strengths can be used at the start of treatment for dose up-titration.
Flow-on effect to current third-line AEDs	No flow-on considered	Flow-on to third-line AEDs was modelled using 'highest cost' and 'lowest cost' scenarios. In the highest cost scenario, flow-on is assumed from the lowest cost second-line AED to the highest cost third-line AED. In the lowest cost scenario flow-on is assumed from the highest cost second-line AED to the lowest cost third-line AED.	The flow-on effect to third-line AEDs was modelled based on PBS data from 2014 to 2023, that showed a 2.2% flow-on rate. We assumed that flow-on was a replacement rather than an add-on treatment.

* See Table 13 above.

**the proportion of lamotrigine and levetiracetam initiators (as first AED) who transition to a third-line AED within the first 12 months. Data for cannabidiol was not available, and only one person transitioned to stiripentol. The modelling is, therefore, based on perampanel, lacosamide and brivaracetam only.

***In the lowest cost scenario, all flow-on will be from the highest cost lamotrigine/levetiracetam listing to the lowest cost third-line listing. In the highest cost scenario, all flow-on will be from the lowest cost lamotrigine/levetiracetam listing to the highest cost third-line listing. Oral liquid was excluded from being selected as the highest cost product due to their lower use and much higher cost than the tablet formulations.

Results

Estimated change in utilisation resulting from the proposed listing

The number of dispensings that would be affected by the increased uptake of lamotrigine and levetiracetam are presented in Table 15. In total, the number of R/PBS scripts for valproate and carbamazepine would decrease by 69,043 in 2025 and by 234,974 in 2030.

TABLE 15 ESTIMATED REDUCTION OF SCRIPTS FOR VALPROATE AND CARBAMAZEPINE BETWEEN 2025 AND 2030 (BASE-CASE ANALYSIS)

	2025	2026	2027	2028	2029	2030
<i>PBS script volumes</i>						
Valproate Tablet 100mg	-3,144	-4,649	-6,111	-7,529	-8,902	-10,231
Valproate Tablet 200mg	-13,200	-19,533	-25,687	-31,665	-37,463	-43,083
Valproate Tablet 500mg	-17,346	-25,890	-34,349	-42,721	-51,007	-59,208
Valproate Oral solution 200mg/5ml	-17,215	-26,156	-35,320	-44,706	-54,314	-64,144
Carbamazepine Oral liquid 100mg/5ml	-3,901	-5,748	-7,525	-9,232	-10,871	-12,440
Carbamazepine Tablet 100mg	-2,435	-3,688	-4,966	-6,267	-7,593	-8,943
Carbamazepine Tablet 200mg	-3,893	-5,531	-6,963	-8,191	-9,211	-10,028
Carbamazepine Tablet 200mg (CR)	-3,845	-5,714	-7,549	-9,349	-11,113	-12,844
Carbamazepine Tablet 400mg (CR)	-3,034	-4,544	-6,050	-7,551	-9,049	-10,541
Total PBS	-68,012	-101,453	-134,518	-167,210	-199,524	-231,462
<i>RPBS script volumes</i>						
Valproate Tablet 100mg	-48	-71	-93	-114	-135	-155
Valproate Tablet 200mg	-200	-296	-390	-480	-568	-654
Valproate Tablet 500mg	-263	-393	-521	-648	-774	-898
Valproate Oral solution 200mg/5ml	-261	-397	-536	-678	-824	-973
Carbamazepine Oral liquid 100mg/5ml	-59	-87	-114	-140	-165	-189
Carbamazepine Tablet 100mg	-37	-56	-75	-95	-115	-136
Carbamazepine Tablet 200mg	-59	-84	-106	-124	-140	-152
Carbamazepine Tablet 200mg (CR)	-58	-87	-115	-142	-169	-195
Carbamazepine Tablet 400mg (CR)	-46	-69	-92	-115	-137	-160
Total RPBS	-1,031	-1,540	-2,042	-2,536	-3,027	-3,512
Total R/PBS	-69,043	-102,993	-136,560	-169,746	-202,551	-234,974

The number of scripts for levetiracetam and lamotrigine that would replace the scripts for carbamazepine and valproate was estimated using the defined daily doses of medications published by the WHO,³⁴ the strength of the medication and the maximum quantity per script using the following formula:

$$\text{script equivalence} = \text{maximum quantity} / (\text{DDD [mg]} / \text{strength [mg]})$$

TABLE 16 DEFINED DAILY DOSES (DDD) AND SCRIPT EQUIVALENCES

Medication	Formulation	Strength (mg)	Pack size	Max quantity	DDD (mg)	Script equivalence*
Valproate	Tablet	100	100	200	1500	13.33
	Tablet	200	100	200	1500	26.67
	Tablet	500	100	200	1500	66.67
	Oral liquid	200mg/5ml	60 (300ml)	120 (2x300ml)	1500	16.00
Carbamazepine	Oral liquid	100mg/5ml	60 (300ml)	60 (300ml)	1000	6.00
	Tablet	100	100	200	1000	20.00
	Tablet	200	100	200	1000	40.00
	Tablet (CR)	200	200	200	1000	40.00
	Tablet (CR)	400	200	200	1000	80.00
Lamotrigine	Tablet	5	56	56	300	0.933
	Tablet	25	56	56	300	4.67
	Tablet	50	56	56	300	9.33
	Tablet	100	56	56	300	18.67
	Tablet	200	56	56	300	37.33
Levetiracetam	Tablet	250	60	60	1500	10.00
	Tablet	500	60	60	1500	20.00
	Tablet	1000	60	60	1500	40.00
	Oral liquid	100mg/ml	300 (300mg)	300 (300mg)	1500	20.00
Lacosamide**	Tablet	100mg	56	56	1000	5.60
Perampanel**	Tablet	8mg	28	28	8	28

*Calculation of script equivalence: maximum quantity / (DDD [mg]/strength [mg])

** Used only in sensitivity analyses to estimate the flow-on effect to third-line medications (highest vs. lowest cost scenarios)

Table 17 shows the estimated increase in the number of lamotrigine and levetiracetam scripts as a result of the proposed listing. The estimated increase in R/PBS scripts for levetiracetam and lamotrigine in the base-case analysis ranges increases from 64,045 in 2025 to 219,360 in 2030.

TABLE 17 ESTIMATED INCREASE OF SCRIPTS FOR LAMOTRIGINE AND LEVETIRACETAM BETWEEN 2025-2030 (BASE-CASE ANALYSIS)

	Estimated dispensing volumes					
AED	2025	2026	2027	2028	2029	2030
PBS						
Lamotrigine Tablet 5mg	0	0	0	0	0	0
Lamotrigine Tablet 25mg	0	0	0	0	0	0
Lamotrigine Tablet 50mg	1,341	1,950	2,519	3,048	3,538	3,989
Lamotrigine Tablet 100mg	5,164	7,413	9,450	11,282	12,916	14,359
Lamotrigine Tablet 200mg	4,467	6,504	8,412	10,193	11,847	13,378
Levetiracetam Tablet 250mg	2,151	3,246	4,374	5,523	6,692	7,882
Levetiracetam Tablet 500mg	8,283	12,345	16,416	20,453	24,447	28,392
Levetiracetam Tablet 1g	7,173	10,844	14,629	18,497	22,447	26,475
Levetiracetam Oral solution 100mg/ml	34,510	51,834	69,207	86,626	104,092	121,605
Total	63,089	94,137	125,007	155,623	185,980	216,080
RPBS*						
Lamotrigine Tablet 5mg	0	0	0	0	0	0
Lamotrigine Tablet 25mg	0	0	0	0	0	0
Lamotrigine Tablet 50mg	20	30	38	46	54	61
Lamotrigine Tablet 100mg	112	144	171	196	218	112
Lamotrigine Tablet 200mg	99	128	155	180	203	99
Levetiracetam Tablet 250mg	49	66	84	101	120	49
Levetiracetam Tablet 500mg	187	249	310	371	431	187
Levetiracetam Tablet 1g	109	165	222	281	341	402
Levetiracetam Oral solution 100mg/ml	523	786	1,050	1,314	1,579	1,846
Total	956	1,428	1,897	2,360	2,822	3,279
PBS and RPBS total	64,045	95,565	126,904	157,983	188,802	219,360

*The proportion of RPBS dispensings were estimated using publicly available dispensing data – see Appendix Table 5.

Estimated financial impact resulting from the proposed listing

Table 18 shows the dispensed price for maximum quantity (DPMQ) applied in the financial estimates for each PBS item code. The DPMQs were sourced from the PBS website.³⁵

TABLE 18 DPMQS APPLIED IN THE FINANCIAL ESTIMATES

Resource item	DPMQ	Source
Valproate		PBS items
Tablet, crushable, 100 mg	\$35.71	2294R
Tablet (enteric coated) 200 mg	\$24.49	2289L
Tablet (enteric coated) 500 mg	\$34.87	2290M
Oral liquid 200 mg per 5 mL, 300 mL	\$42.29	2293Q, 2295T
Carbamazepine		PBS items
Oral suspension 100 mg per 5 mL, 300 mL	\$26.44	2427R
Tablet 100 mg	\$23.89	2422L
Tablet 200 mg	\$30.89	1706T
Tablet 200 mg (controlled release)	\$31.24	2426Q
Tablet 400 mg (controlled release)	\$47.25	2431Y
Lamotrigine		PBS items
Tablet 5mg	\$19.78	8063J
Tablet 25mg	\$17.76	2848X
Tablet 50mg	\$19.35	2849Y
Tablet 100mg	\$23.28	2850B
Tablet 200mg	\$29.96	2851C
Levetiracetam		PBS items
Tablet 1 g	\$41.16	8656N
Tablet 250 mg	\$23.08	8654L
Tablet 500 mg	\$29.49	8655M
Oral solution 100 mg per mL, 300 mL	\$78.10	9169N
Lacosamide		PBS items
Tablet 100mg	\$ 84.72	9335H
Perampanel	\$ 303.63	PBS items
Tablet 8mg		10160R, 11429M

DPMQ = dispensed price for maximum quantity

In Table 19, we present the financial impact (excluding carbamazepine and valproate cost offsets) of expanding the PBS restrictions for levetiracetam and lamotrigine to allow their first-line use in the general Australian population with epilepsy. In the base-case analysis, the estimated cost to the R/PBS is \$2,637,357 in 2025, increasing to \$9,233,763 in 2030. In total, this equates to a cost to the R/PBS of \$35.6 million over the 6-year period (2025-2030) excluding cost offsets. When including the cost offsets the net costs to R/PBS increases from \$1,239,245 in 2025 to \$4,398,303 in 2030; totalling \$16.9 million over the 6-year period (Table 20).

TABLE 19 COST TO THE R/PBS OF THE PROPOSED LISTING EXCLUDING COST OFFSETS (BASE-CASE)

	2025	2026	2027	2028	2029	2030	Total
Cost to PBS	\$3,466,432	\$5,191,779	\$6,916,132	\$8,637,381	\$10,355,338	\$12,070,107	\$46,637,169
Less co-payments	-\$876,797	-\$1,308,309	-\$1,737,333	-\$2,162,826	-\$2,584,727	-\$3,003,062	-\$11,673,054
Net cost to PBS	\$2,589,635	\$3,883,469	\$5,178,799	\$6,474,554	\$7,770,611	\$9,067,045	\$34,964,113
Cost to RPBS	\$52,521	\$78,747	\$104,918	\$130,988	\$157,118	\$183,177	\$707,469
Less co-payments	-\$4,799	-\$7,169	-\$9,521	-\$11,846	-\$14,163	-\$16,459	-\$63,957
Net cost to RPBS	\$47,722	\$71,579	\$95,396	\$119,142	\$142,954	\$166,718	\$643,511
Net cost to R/PBS	\$2,637,357	\$3,955,048	\$5,274,196	\$6,593,696	\$7,913,566	\$9,233,763	\$35,607,626

TABLE 20 ADDITIONAL NET COST TO THE R/PBS OF THE PROPOSED LISTING INCLUDING COST OFFSETS (BASE-CASE)

	2025	2026	2027	2028	2029	2030	Total
New listing	\$2,589,635	\$3,883,469	\$5,178,799	\$6,474,554	\$7,770,611	\$9,067,045	\$34,964,113
Changed listing	-\$1,368,215	-\$2,047,460	-\$2,723,524	-\$3,396,414	-\$4,066,052	-\$4,732,483	-\$18,334,148
Net cost to PBS	\$1,221,420	\$1,836,010	\$2,455,275	\$3,078,140	\$3,704,559	\$4,334,562	\$16,629,966
New listing	\$47,722	\$71,579	\$95,396	\$119,142	\$142,954	\$166,718	\$643,511
Changed listing	-\$29,897	-\$44,759	-\$59,477	-\$74,036	-\$88,561	-\$102,978	-\$399,708
Net cost to RPBS	\$17,825	\$26,820	\$35,919	\$45,105	\$54,393	\$63,740	\$243,802
Net cost to R/PBS	\$1,239,245	\$1,862,830	\$2,491,195	\$3,123,245	\$3,758,952	\$4,398,303	\$16,873,770

Sensitivity analyses

In the sensitivity analysis with a 15% replacement rate of valproate and carbamazepine prescriptions to levetiracetam or lamotrigine prescriptions, the total net cost to the R/PBS is \$24,996,509 over the period of 2025-2030; a 48% increase from the base-case analysis (Table 21). With a 5% replacement rate, the total estimated net costs to the R/PBS are \$8,436,889 from 2025-2030; a 50% decrease from the base-case analysis.

Decreasing the replacement rate of valproate and carbamazepine oral liquid with levetiracetam oral liquid decreases the estimated net costs by 68% (5% replacement) and 102% (2.5% replacement) over the 2025-2030 period (Table 21). This means that the net cost in this scenario is lower than the cost of the current listing. Increasing the proportion of people with epilepsy from 27.3% to 37.3%, 50%, 60% and to 80% results in increasingly lower net costs compared to the base-case analysis (from 13% to 79% decrease). Other sensitivity analyses resulted in minimal change (5% or less) to the base-case analysis.

TABLE 21 ADDITIONAL NET COST TO THE R/PBS OF THE PROPOSED LISTING (SENSITIVITY ANALYSES)

	2025	2026	2027	2028	2029	2030	Total	% change
Substitution rate 10% in the first year, increasing by 10% each additional year (base-case analysis)								
Net cost to PBS	\$1,221,420	\$1,836,010	\$2,455,275	\$3,078,140	\$3,704,559	\$4,334,562	\$16,629,966	
Net cost to RPBS	\$17,825	\$26,820	\$35,919	\$45,105	\$54,393	\$63,740	\$243,802	
Net cost to R/PBS	\$1,239,245	\$1,862,830	\$2,491,195	\$3,123,245	\$3,758,952	\$4,398,303	\$16,873,770	0%
Sensitivity analysis 1) Substitution rate 15% per year, increasing by 15% each additional year [base-case analysis: 10%]								
Net cost to PBS	\$1,832,016	\$2,753,911	\$3,682,897	\$4,617,201	\$5,556,953	\$6,192,213	\$24,635,191	
Net cost to RPBS	\$26,862	\$40,351	\$53,900	\$67,665	\$81,459	\$91,083	\$361,320	
Net cost to R/PBS	\$1,858,878	\$2,794,261	\$3,736,796	\$4,684,865	\$5,638,413	\$6,283,296	\$24,996,509	48.14%
Sensitivity analysis 2) Substitution rate 5% per year, increasing by 5% each additional year [base-case analysis: 10%]								
Net cost to PBS	\$610,595	\$917,901	\$1,227,634	\$1,539,057	\$1,852,390	\$2,167,353	\$8,314,931	
Net cost to RPBS	\$9,037	\$13,531	\$17,963	\$22,565	\$27,072	\$31,790	\$121,958	

Net cost to R/PBS	\$619,632	\$931,432	\$1,245,597	\$1,561,622	\$1,879,462	\$2,199,143	\$8,436,889	-50.00%
Sensitivity analysis 3) Substitution rate 10% per year for tablet forms and 5% for liquid forms, increasing by 10% and 5%, respectively each additional year [base-case analysis: 10% for all forms]								
Net cost to PBS	\$382,351	\$579,352	\$782,255	\$989,886	\$1,202,403	\$1,419,580	\$5,355,827	
Net cost to RPBS	\$4,358	\$6,515	\$8,775	\$11,237	\$13,692	\$16,373	\$60,950	
Net cost to R/PBS	\$386,709	\$585,866	\$791,031	\$1,001,123	\$1,216,094	\$1,435,954	\$5,416,777	-67.90%
Sensitivity analysis 4) Substitution rate 10% per year for tablet forms and 2.5% for liquid forms, increasing by 10% and 2.5%, respectively each additional year [base-case analysis: 10% for all forms]								
Net cost to PBS	-\$37,032	-\$48,903	-\$54,355	-\$54,266	-\$48,776	-\$37,959	-\$281,292	
Net cost to RPBS	-\$2,540	-\$3,722	-\$4,686	-\$5,671	-\$6,548	-\$7,253	-\$30,420	
Net cost to R/PBS	-\$39,572	-\$52,625	-\$59,041	-\$59,937	-\$55,324	-\$45,213	-\$311,711	-101.85%
Sensitivity analysis 5) Lamotrigine 5mg and 25mg to each replace 2.5% of all substitution of valproate 100mg and carbamazepine 100mg each year [base-case analysis: no substitution for lamotrigine 5mg and 25mg strengths]								
Net cost to PBS	\$1,220,719	\$1,842,231	\$2,463,521	\$3,088,386	\$3,716,781	\$4,348,735	\$16,680,372	
Net cost to RPBS	\$17,798	\$26,927	\$36,061	\$45,281	\$54,603	\$63,983	\$244,654	
Net cost to R/PBS	\$1,238,518	\$1,869,158	\$2,499,582	\$3,133,667	\$3,771,383	\$4,412,718	\$16,925,026	0.30%
Sensitivity analysis 6) Epilepsy diagnosis among people prescribed valproate or carbamazepine in primary care is 37.33% [base-case analysis: 27.33%]								
Net cost to PBS	\$1,054,404	\$1,588,205	\$2,129,284	\$2,676,204	\$3,228,853	\$3,787,296	\$14,464,246	
Net cost to RPBS	\$14,373	\$21,735	\$29,247	\$36,841	\$44,620	\$52,473	\$199,289	
Net cost to R/PBS	\$1,068,777	\$1,609,940	\$2,158,531	\$2,713,045	\$3,273,473	\$3,839,769	\$14,663,535	-13.10%
Sensitivity analysis 7) Epilepsy diagnosis among people prescribed valproate or carbamazepine in primary care is 50% [base-case analysis: 27.33%]								
Net cost to PBS	\$842,740	\$1,274,218	\$1,716,250	\$2,166,906	\$2,626,085	\$3,093,831	\$11,720,030	
Net cost to RPBS	\$10,022	\$15,255	\$20,718	\$26,337	\$32,177	\$38,162	\$142,671	
Net cost to R/PBS	\$852,762	\$1,289,472	\$1,736,968	\$2,193,243	\$2,658,262	\$3,131,993	\$11,862,701	-29.70%
Sensitivity analysis 8) Epilepsy diagnosis among people prescribed valproate or carbamazepine in primary care is 60% [base-case analysis: 27.33%]								
Net cost to PBS	\$675,719	\$1,026,397	\$1,390,275	\$1,764,970	\$2,150,399	\$2,546,566	\$9,554,326	
Net cost to RPBS	\$6,577	\$10,187	\$14,027	\$18,072	\$22,376	\$26,888	\$98,128	
Net cost to R/PBS	\$682,296	\$1,036,584	\$1,404,302	\$1,783,043	\$2,172,775	\$2,573,454	\$9,652,454	-42.80%
Sensitivity analysis 9) Epilepsy diagnosis among people prescribed valproate or carbamazepine in primary care is 80% [base-case analysis: 27.33%]								
Net cost to PBS	\$341,661	\$530,852	\$738,378	\$961,126	\$1,199,037	\$1,452,043	\$5,223,097	
Net cost to RPBS	-\$296	-\$67	\$573	\$1,521	\$2,765	\$4,340	\$8,836	
Net cost to R/PBS	\$341,365	\$530,785	\$738,951	\$962,647	\$1,201,802	\$1,456,383	\$5,231,932	-79.07
Sensitivity analysis 10) Flow-on effect to third-line – the least expensive scenario [base-case analysis: no flow-on effect to third-line]								
Net cost to PBS	\$1,215,654	\$1,826,588	\$2,441,623	\$3,059,676	\$3,680,707	\$4,304,712	\$16,528,960	

Net cost to RPBS	\$17,700	\$26,620	\$35,620	\$44,706	\$53,869	\$63,091	\$241,606	
Net cost to R/PBS	\$1,233,355	\$1,853,208	\$2,477,243	\$3,104,382	\$3,734,576	\$4,367,803	\$16,770,567	-0.61%
Sensitivity analysis 11) Flow-on effect to third-line – the most expensive scenario [base-case analysis: no flow-on effect to third-line]								
Net cost to PBS	\$1,321,957	\$1,991,756	\$2,668,284	\$3,349,593	\$3,704,559	\$4,723,231	\$17,759,380	
Net cost to RPBS	\$19,544	\$29,398	\$39,357	\$49,402	\$59,549	\$69,755	\$267,005	
Net cost to R/PBS	\$1,341,500	\$2,021,154	\$2,707,641	\$3,398,995	\$3,764,108	\$4,792,986	\$18,026,384	6.83%

Flow-on impact of the proposed listing to the utilisation of the third-line AEDs

Based on the analyses using the lowest cost (from levetiracetam 1g to lacosamide 100mg) and highest cost (from lamotrigine 50mg to perampanel 8mg) scenarios, the flow-on effect to third-line AEDs is minimal. Compared to the base-case model, the net cost to R/PBS decreases by 0.61% in the lowest cost scenario and increases by 6.83% in the highest cost scenario (Table 21).

DISCUSSION

This Australia-wide longitudinal analysis shows AED dispensing trends over a 10-year period from 2014–2023. Levetiracetam and lamotrigine were the second and third most frequently dispensed AEDs after valproate in 2014. The proportion of patients dispensed levetiracetam and lamotrigine increased over time. In 2023, levetiracetam was the most frequently dispensed AED. The most common AED treatment sequences involved switching from valproate to either lamotrigine or levetiracetam.

This apparent preference towards levetiracetam and lamotrigine was accompanied by a steep decline in valproate dispensing. These dispensing patterns were likely informed by changes to international guidelines that urge caution around valproate use due to long-term adverse cardiovascular, metabolic, and skeletal effects, and its clear teratogenicity risks for women of childbearing potential. Our data show that females aged 15–49 were more than twice as likely to initiate on PBS-listed lamotrigine or levetiracetam than males of the same age. Males most often initiated with valproate irrespective of the emerging evidence of neurodevelopmental disorders in children born to fathers using valproate.⁶ Globally, there is a move away from the enzyme inducing AEDs (e.g., valproate, carbamazepine) towards the non-enzyme inducing AEDs in clinical practice (e.g., levetiracetam, lamotrigine) due to lower tolerability, increased metabolic and bone health adverse effects, and increased drug-drug interactions experienced with enzyme inducing AEDs.

When comparing the PBS dispensing data to the POLAR primary care data between males and females aged 15–49, we found some discrepancies. In the POLAR data, among men almost half of the included AED initiations for epilepsy diagnosis were for lamotrigine, while this proportion was 24% for women (Table 13). In contrast, in the dispensing data, 12% of AED initiations were with lamotrigine among men, and 27% among women (Figure 7). This discrepancy was less prominent in levetiracetam initiations. Discrepancy in lamotrigine initiation implies that there are men who receive lamotrigine via private (non-PBS) prescriptions. With the available data, it is not possible to say with certainty, what this proportion would be. This will potentially cause inequity in access to lamotrigine among people with epilepsy. This will particularly affect patients with a concession card or First Nations People eligible for the PBS Closing the Gap program which aims to improve access to affordable medications.

POLAR primary care data were reviewed to estimate the proportion of people who initiated an AED who had a recorded diagnosis of epilepsy. The purpose of this was to help estimate how many people that were dispensed valproate or carbamazepine would transition to levetiracetam or lamotrigine for the treatment of epilepsy. Analysis of primary care data found that just over a quarter of people prescribed valproate or carbamazepine had a recorded epilepsy diagnosis (27.3%). This estimate appeared low so we conducted a sensitivity analysis to test a proportion of 37.3%, 50%, 60% and 80%. We also reviewed recent data from the United Kingdom regarding epilepsy diagnosis in women of childbearing potential prescribed valproate.³⁶ The UK data shows that 50-60% of females aged 15-49 who were prescribed valproate had an epilepsy diagnosis.

We found a 25% decline in the incidence of AED use between 2015 to 2023. This is despite no evidence indicating that the incidence of epilepsy in Australia is declining. The decline in the incidence of AED use can be explained by two reasons. Firstly, we included each person only once in the analysis with at least a 12-month look-back period. This means that AED initiators at the start of the study period had an opportunity to be included even if they had an AED dispensed just before the 12-month look-back period. However, they were not included again even after another 12-month look-back window. Those who were incident patients later in the study period, by default, were not incident patients earlier in the period. As AEDs are long-term medications, our definition would most likely underestimate AED incidence at the end of the study period if it is used for another indication. The second reason may be that there is an increase in dispensing of private AED prescriptions which is not captured in PBS data

We found that the proportion of patients incident to valproate or carbamazepine declined over the study period, whilst the proportion of patients incident to levetiracetam and lamotrigine increased. This means that levetiracetam and lamotrigine are likely already replacing valproate and carbamazepine as first-line AEDs.

Based on our analyses, the flow-on effect from levetiracetam and lamotrigine as the first AED to more expensive lacosamide or brivaracetam has been modest to date. We estimated that the change in the net cost to the R/PBS due to flow-on effect will be minimal. Neurologists on the investigation team have indicated that patients would usually trial a first-line AED or another second-line AED first, before progressing to treatment with a third-line AED.

Our estimates show that there would be a considerable increase in levetiracetam liquid dispensing. This is because we used the same assumption of 10% substitution of carbamazepine and valproate oral liquid as we did for the tablet forms. At the moment levetiracetam liquid is not frequently prescribed and there is no liquid form of lamotrigine available. However, based on our experts' opinion, people who are on valproate or carbamazepine liquid would be unlikely to switch to levetiracetam or lamotrigine. Most patients on the liquid forms are people with a disability or with swallowing difficulty and therefore clinicians may be reluctant to change a stable current treatment to a new one, even if available.

Easing the restrictions for the second-line AEDs, levetiracetam and lamotrigine, is expected to result in an additional net cost to the R/PBS of \$1,239,245 in 2025, increasing to \$4,398,303 in 2030 (a total of \$16,873,770 between 2025-2030) per the base-case analysis. These costs changed from a 50% reduction to a 50% increase in sensitivity analyses where substitution rates are varied. Lowering the substitution of liquid forms to 2.5% lowered the cost further by 102% (proposed listing has lower cost than current listing). The costs also changed when the proportion of people with epilepsy varied (13% reduction from base case of 27.3% to 37.7%, and 79% reduction from base case to 80%). Other sensitivity analyses had minimal impact on cost.

There are several limitations to these analyses. First, the number of people dispensed AEDs in Australia based on PBS data (i.e., 350,000 in 2023) outweighs the estimated number of people living with epilepsy in Australia (prevalence estimates vary from 160,000 to 250,000 in 2023). This suggests that several AEDs (e.g., topiramate, gabapentin) were also prescribed for disorders such as migraine and chronic neuropathic pain. This is also supported by the analysis of the POLAR primary care data, which showed that only 6.6% of topiramate initiators and 1% of gabapentin initiators have an epilepsy diagnosis recorded. Second, the PBS dispensing data includes subsidised but not private dispensing. Even with the availability of the POLAR primary care data, it remains unclear how many people were dispensed AEDs for epilepsy outside of the PBS.

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APPENDICES

APPENDIX TABLE 1: LIST OF ANTIEPILEPTIC DRUGS APPROVED BY THE THERAPEUTIC GOODS ADMINISTRATION (TGA) AND LISTED ON THE PHARMACUTICAL BENEFITS SCHEME (PBS)

Drug	TGA-approved epilepsy indication(s)	PBS Item codes	PBS-listed indication	Restriction level	Restriction criteria
First-line treatment					
Carbamazepine	Complex or simple partial seizures (with or without loss of consciousness), with or without secondary generalisation; Generalised tonic-clonic seizures; Mixed seizure patterns incorporating the above.	01706T 01708X 01724R 01755J 02419H 02422L 02426Q 02427R 02431Y 05037D 05038E 05039F 05040G 05041H 13918M 14050L 14051M	N/A	Unrestricted	N/A
Ethosuximide	Petit mal epilepsy	01413J 01414K 11703Y 13127X 14014N	N/A	Unrestricted	N/A
Phenobarbital (phenobarbitone)	Epilepsy	01850J (epilepsy) 01853M (epilepsy) 02138M (epilepsy)	Epilepsy	Restricted Benefit	N/A
Phenytoin	Generalised tonic-clonic (grand mal) and psychomotor seizures	01249R 01873N 01874P 02692Q 13841L 13894G 13972J	N/A	Unrestricted	N/A

Drug	TGA-approved epilepsy indication(s)	PBS Item codes	PBS-listed indication	Restriction level	Restriction criteria
		14015P			
Primidone	Grand mal and psychomotor (temporal lobe) epilepsy: focal or Jacksonian seizures, myoclonic jerks and akinetic attacks.	01939C 11883K	N/A	Unrestricted	N/A
Sulthiame	Behavioural disorders associated with epilepsy; hyperkinetic behaviour; temporal lobe epilepsy; myoclonic seizures; grand mal attacks; Jacksonian seizures.	02099L 02100M 13916K 14016Q	N/A	Unrestricted	N/A
Valproate	Primary generalised epilepsy (petit mal absences, various forms of myoclonic epilepsy and tonic-clonic grand mal seizures). Partial (focal) epilepsy either alone or as adjuvant therapy	02031X 02032Y 02033B 02289L 02290M 02293Q 02294R 02295T 13840K 13917L 13950F 13973K 14017R	N/A	Unrestricted	N/A
Clonazepam	<u>Tablets</u> : Most types of epilepsy in infants and children, especially absences (petit mal), myoclonic seizures and tonic clonic fits, whether due to primary generalised epilepsy, or to secondary generalisation of partial epilepsy. In adults all varieties of generalised epilepsy (including myoclonic, akinetic, tonic and tonic clonic seizures), and in partial epilepsy (including psychomotor seizures). <u>Injection</u> : Intravenous (IV) use, for status epilepticus.	01805B (epilepsy) 01806C (epilepsy) 01807D (epilepsy) 01808E (epilepsy) 11559J (epilepsy) 05340C 05341D 05342E	Epilepsy	Restricted Benefit (for injection) Authority Required (other forms)	The condition must be neurologically proven.
Nitrazepam	N/A	ATC=N05 02732T (epilepsy)	Myoclonic epilepsy Malignant neoplasia (late stage) Insomnia	Authority Required	N/A
Second-line treatment					

Drug	TGA-approved epilepsy indication(s)	PBS Item codes	PBS-listed indication	Restriction level	Restriction criteria
Gabapentin	Partial seizures, including secondarily generalised tonic-clonic seizures, initially as add-on therapy in adults and children aged 3 years and above who have not achieved adequate control with standard anti-epileptic medications	01834M (epilepsy) 01835N (epilepsy) 08389M (epilepsy) 08505P (epilepsy) 08559L (epilepsy)	Partial epileptic seizures	Authority Required (STREAMLINED)	The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs.
Levetiracetam	Epileptic patients aged 4 years and older, initially as add-on therapy, in the treatment of partial onset seizures with or without secondary generalisation; monotherapy in the treatment of partial onset seizures, with or without secondary generalisation, in patients from 16 years of age with newly diagnosed epilepsy; add-on therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy (JME); and add-on therapy in the treatment of primary generalized tonic-clonic seizures in adults and children from 4 years of age with idiopathic generalized epilepsy (IGE)	08654L (epilepsy) 08655M (epilepsy) 08656N (epilepsy) 09169N (epilepsy) 13937M (epilepsy) 13992K (epilepsy) 13993L (epilepsy) 14034P (epilepsy) 09708Y 09709B 09710C 09724T 09725W 09726X	Partial epileptic seizures	Authority Required (STREAMLINED)	The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs; OR Patient must be a woman of childbearing potential, <u>AND</u> The treatment must not be given concomitantly with brivaracetam, except for cross titration.
Tiagabine	Partial seizures, as add on therapy in patients who are not controlled satisfactorily with other antiepileptic drug(s)	08221Q (epilepsy) 08222R (epilepsy) 08223T (epilepsy) 13892E (epilepsy) 13893F (epilepsy) 13947C (epilepsy)	Partial epileptic seizures	Authority Required (STREAMLINED)	The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs.
Zonisamide	Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy who are intolerant to other agents or where other agents are contraindicated; adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation	09388D (epilepsy) 09389E (epilepsy) 09390F (epilepsy) 13853D (epilepsy) 13854E (epilepsy) 13988F (epilepsy)	Partial epileptic seizures	Authority Required (STREAMLINED)	The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs.
Lamotrigine	Partial and generalised seizures in adults and children	02848X (epilepsy) 02849Y (epilepsy) 02850B (epilepsy) 02851C (epilepsy) 08063J (epilepsy) 13842M (epilepsy) 13843N (epilepsy) 13975M (epilepsy) 14047H (epilepsy)	Epileptic seizures	Authority Required (STREAMLINED)	The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs; OR Patient must be a woman of childbearing potential.

Drug	TGA-approved epilepsy indication(s)	PBS Item codes	PBS-listed indication	Restriction level	Restriction criteria
		14052N (epilepsy)			
Vigabatrin	Treatment of epilepsy which is not satisfactorily controlled by other antiepileptic drugs	02667J (epilepsy) 02668K (epilepsy) 13919N (epilepsy) 13974L (epilepsy)	Epileptic seizures	Authority Required (STREAMLINED)	The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs.
Oxcarbazepine	Monotherapy or adjunctive therapy for the treatment of partial seizures and generalised tonic-clonic seizures, in adults and children	08584T (seizures) 08585W (seizures) 08586X (seizures) 08588B (seizures) 13935K (seizures) 13936L (seizures) 14033N (seizures)	Seizures	Authority Required (STREAMLINED)	Patient must have partial epileptic seizures; OR Patient must have primary generalised tonic-clonic seizures, <u>AND</u> The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs.
Topiramate	Adults and children, 2 years and over: monotherapy in patients with newly diagnosed epilepsy; for conversion to monotherapy in patients with epilepsy; add-on therapy in partial onset seizures (with or without secondary generalised seizures), primary generalised tonic-clonic seizures or drop attacks associated with Lennox-Gastaut syndrome	08166T (seizures) 08371N (seizures) 08372P (seizures) 08520K (seizures) 13878K (seizures) 13905W (seizures) 14009H (seizures) 14063E (seizures) 08163P (seizures&migraine) 08164Q (seizures&migraine) 08165R (seizures&migraine) 13913G (seizures&migraine) 13969F (seizures&migraine) 14008G (seizures&migraine)	Seizures Migraines Item codes with both indications, seizure indication will be identified using authority codes (e.g. for PBS item code 13969F, authority code 5516 for seizure will be included and 5325 for migraine excluded)	Authority Required (STREAMLINED)	Patient must have partial epileptic seizures; OR Patient must have primary generalised tonic-clonic seizures; OR Patient must have seizures of the Lennox-Gastaut syndrome, <u>AND</u> The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs.
Third-line treatment					

Drug	TGA-approved epilepsy indication(s)	PBS Item codes	PBS-listed indication	Restriction level	Restriction criteria
Brivaracetam	Add-on therapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 4 years of age with epilepsy	11327E (epilepsy) 11328F (epilepsy) 11334M (epilepsy) 11338R (epilepsy) 11339T (epilepsy) 11349H (epilepsy) 11350J (epilepsy) 11356Q (epilepsy) 11357R (epilepsy) 11358T (epilepsy) 09701N 09702P 09703Q 09704R 09705T 09706W 09707X 09717K 09718L 09719M 09720N 09721P 09722Q 09723R	Intractable partial epileptic seizures	Authority Required (STREAMLINED)	Must be treated by a neurologist (for initiation) The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, <u>AND</u> The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents, <u>AND</u> The treatment must not be given concomitantly with levetiracetam, except for cross titration.

Drug	TGA-approved epilepsy indication(s)	PBS Item codes	PBS-listed indication	Restriction level	Restriction criteria
Perampanel	Adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients from 4 years of age with epilepsy; adjunctive treatment of primary generalised tonic-clonic seizures in patients from 7 years of age with idiopathic generalised epilepsy.	10151G (epilepsy) 10157N (epilepsy) 10159Q (epilepsy) 10160R (epilepsy) 10162W (epilepsy) 10163X (epilepsy) 11407J (epilepsy) 11409L (epilepsy) 11418Y (epilepsy) 11428L (epilepsy) 11429M (epilepsy) 11436X (epilepsy) 13864Q (epilepsy) 13865R (epilepsy) 13914H (epilepsy) 13915J (epilepsy) 13948D (epilepsy) 13970G (epilepsy) 13971H (epilepsy) 14010J (epilepsy) 14012L (epilepsy) 14046G (epilepsy)	Intractable partial epileptic seizures ¹ Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures ²	Authority Required (STREAMLINED)	¹ The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, <u>AND</u> The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents. Must be treated by a neurologist (for initiation). ² Must be treated by a neurologist. The condition must have failed to be controlled satisfactorily by at least two anti-epileptic drugs, <u>AND</u> The treatment must be in combination with at least one PBS-subsidised anti-epileptic drug. Patient must be aged 12 years or older.

Drug	TGA-approved epilepsy indication(s)	PBS Item codes	PBS-listed indication	Restriction level	Restriction criteria
Lacosamide	Monotherapy in the treatment of partial seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older; add-on therapy in the treatment of partial seizures with or without secondary generalisation in patients with epilepsy aged 4 years and older; add-on therapy in the treatment of primary generalised tonic-clonic seizures in patients with idiopathic generalised epilepsy aged 4 years and older.	08982R (epilepsy) 09333F (epilepsy) 09334G (epilepsy) 09335H (epilepsy) 09336J (epilepsy) 09337K (epilepsy) 09338L (epilepsy) 10293R (epilepsy) 11694L (epilepsy) 12626M (epilepsy) 12627N (epilepsy) 12628P (epilepsy) 12633X (epilepsy) 12634Y (epilepsy) 12649R (epilepsy) 12658F (epilepsy) 13838H (epilepsy) 13839J (epilepsy) 13867W (epilepsy) 13949E (epilepsy) 13951G (epilepsy) 14011K (epilepsy) 14013M (epilepsy) 14048J (epilepsy) 14049K (epilepsy) 14053P (epilepsy)	Intractable partial epileptic seizures ¹ Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures ²	Authority Required (STEAMLINED)	¹ Must be treated by a neurologist (for initiation). The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, <u>AND</u> The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents. ² Must be treated by a neurologist; OR Must be treated by a paediatrician. <u>AND</u> Must be treated by an eligible practitioner type who has consulted at least one of the above mentioned specialist types, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion. The condition must have failed to be controlled satisfactorily by at least two anti-epileptic drugs prior to when the drug is/was first commenced, <u>AND</u> The treatment must be (for initiating treatment)/have been (for continuing treatment) in combination with at least one PBS-subsidised anti-epileptic drug at the time the drug is/was first commenced.
Cannabidiol	Adjunctive therapy of seizures associated with Lennox Gastaut syndrome (LGS) or Dravet syndrome (DS) for patients 2 years of age and older.	12467E (epilepsy) 13277T (epilepsy)	Severe myoclonic epilepsy in infancy (Dravet syndrome)	Authority Required	Patient must have (as an initiating patient)/have had (as a continuing patient), generalised tonic-clonic seizures or generalised clonic seizures that are not adequately

Drug	TGA-approved epilepsy indication(s)	PBS Item codes	PBS-listed indication	Restriction level	Restriction criteria
					<p>controlled with at least two other anti-epileptic drugs, <u>AND</u> The treatment must be as adjunctive therapy to at least two other anti-epileptic drugs. 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.</p>
Stiripentol	Adjunctive treatment of generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) in patients whose seizures are not adequately controlled with a benzodiazepine (usually clobazam) and valproate.	12088F (epilepsy) 12103B (epilepsy) 12106E (epilepsy) 12107F (epilepsy)	Severe myoclonic epilepsy in infancy (Dravet syndrome)	Authority Required (STREAMLINED)	<p>Patient must have (as an initiating patient)/have had (as a continuing patient), generalised tonic-clonic seizures or generalised clonic seizures that are not adequately controlled with at least two other anti-epileptic drugs, <u>AND</u> The treatment must be as adjunctive therapy to at least two other anti-epileptic drugs. 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.</p>

*Modified form Department of Health and Aged Care: Request for Quotation (RFQ) – SON3352211: Review of clinical guidelines and cost estimates for the use of anti-epileptic drugs (AEDs) for the treatment of epilepsy.

** Item codes with Authority requirement, where the indication is not seizures or epilepsy, will be excluded.

APPENDIX TABLE 2. GREY LITERATURE SEARCH RESULTS FOR IDENTIFYING AUSTRALIAN CLINICAL GUIDELINES

Source(s)	Result(s) or Guideline/ Document name	Included (I) or Excluded (E)	Exclusion reason, if applicable
Strategy 1. Targeted website browsing/ searching^a			
Royal Australian College of General Practitioners (RACGP)	None from the clinical guidelines' resources	-	-
National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines Portal	None- this site is no longer active	-	-
Therapeutic Guidelines Limited	<ul style="list-style-type: none"> Neurology- Epilepsy and seizures 	I	-
Australian Medicines Handbook Pty Ltd	<ul style="list-style-type: none"> Neurological Drugs- Antiepileptics- Epilepsy 	I	-
Australian Institute of Health and Welfare (AIHW)	<ul style="list-style-type: none"> Epilepsy in Australia 	E	Web report
The Epilepsy Society of Australia (ESA)	<ul style="list-style-type: none"> Suicidality and AEDs Generic AEDs AEDs and Bone Health HLA testing for SJS Valproate and Women – September 2020 Valproate and Women checklist – Example Epilepsy and childbearing – September 2020 VEEG Guidelines – November 2013 	E E E E E E E E	ESA position statements and guidelines

	<ul style="list-style-type: none"> • <i>ESA Social Media Policy – June 2021</i> • <i>Expert advice for prescribing cannabis medicines for patients with epilepsy—drawn from the Australian clinical experience</i> • <i>Continuous Electroencephalography Monitoring in the Intensive Care Unit</i> • <i>ESA Statement on the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA)</i> 	E E E E	
The Royal Children’s Hospital Melbourne	<ul style="list-style-type: none"> • <i>Febrile seizure</i> • <i>Afebrile seizures</i> 	E E	Acute management of seizures
Association of Neurophysiology Scientists of Australia Inc	None is relevant	-	-
Epilepsy Foundation	None is relevant	-	-
Strategy 2. Grey literature database search^a			
Informit	None is relevant	-	-
Web of Science	<ul style="list-style-type: none"> • <i>Algorithm for the treatment of status epilepticus: an Australian perspective</i> • <i>The management of epilepsy in children and adults</i> • <i>New-onset epilepsy in the elderly</i> • <i>Management of epilepsy in older adults: A critical review by the ILAE Task Force on Epilepsy in the elderly</i> • <i>The pharmacological treatment of epilepsy: recent advances and future perspectives</i> 	E E E E E	Personal viewpoint on acute management of seizures Review only Review only Review only Treatment overview
Scopus	<ul style="list-style-type: none"> • <i>Treatment of seizures in the neonate: Guidelines and consensus-based recommendations—Special report from the ILAE Task Force on Neonatal Seizures</i> 	E	Special report on neonatal seizures

ProQuest One Academic	None is relevant	-	-
National Guideline Clearinghouse	None- 502 error, this site could not be accessed	-	-
Guidelines International Network (GIN) International Guidelines Library	None from Australia is identified	-	-
TRIP database ^b	<ul style="list-style-type: none"> <i>Status epilepticus – Emergency management in children (2023)</i> 	E	Acute management of seizures
Strategy 3. Search engine searching^a			
Google	<ul style="list-style-type: none"> <i>Guideline: Neonatal seizures (Queensland Health 2022)</i> <i>Epilepsy in adults (AFP 2014)</i> <i>Seizures in Children SA Paediatric Clinical Practice Guideline</i> <i>The management of epilepsy in children and adults (MJA 2018)</i> <i>Seizures and Status Epilepticus – Management (The Sydney Children’s Hospitals Network 2021)</i> <i>Seizures in Pregnancy (SA Health 2014)</i> <i>Infantile Spasms (RCH 2020)</i> <i>Epilepsy in adults (Reprinted from AFP 2014)</i> <i>Seizures – Adult ECAT Protocols (NSW Government 2023)</i> <i>First afebrile seizure – Emergency management in children (Queensland Health 2024)</i> <i>Epilepsy in Pregnancy (WA King Edward Memorial Hospital 2023)</i> <i>Seizure - First presentation (WA Perth Children’s Hospital 2023)</i> <i>Guideline: Neonatal seizures (Queensland Health 2022)</i> 	E E E E E E E E E E E E	Acute management of seizures Narrative review only Acute management of seizures Narrative review only Acute management of seizures Acute management of seizures Not PBS indication-related Narrative review only Acute management of seizures Acute management of seizures Did not meet PICAR eligibility criteria Did not meet PICAR eligibility criteria Acute management of seizures

	<ul style="list-style-type: none"> • <i>Clinical Practice Guidelines: Neurological/ Seizures (Queensland Ambulance Service 2020)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Clinical Practice Guidelines: Afebrile seizures (RCH 2020)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Clinical Practice Guidelines: Febrile seizures (RCH 2020)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Febrile seizure – Emergency management in children (Queensland Health 2023)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Epilepsy in Australia (Australian Institute of Health and Welfare, AIHW 2022)</i> 	E	Web report
	<ul style="list-style-type: none"> • <i>Status epilepticus – Emergency management in children (Queensland Health)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Status Epilepticus (Perth Children’s Hospital)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Febrile convulsions (Perth Children’s Hospital)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Seizure Management for Children > 1 Month of Age - NETS (NSW Health)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Epilepsy and pregnancy management (SA Health)</i> 	E	Did not meet PICAR eligibility criteria
	<ul style="list-style-type: none"> • <i>Management of seizures occurring in the context of harmful drinking Clinical Guideline (SA Health 2023)</i> 	E	Did not meet PICAR eligibility criteria
	<ul style="list-style-type: none"> • <i>Guideline Supplement: Neonatal seizures (Queensland Health 2022)</i> 	E	Did not meet PICAR eligibility criteria
	<ul style="list-style-type: none"> • <i>Seizure - Medication (WA Perth Children’s Hospital)</i> 	E	Medication protocol for Emergency Department
	<ul style="list-style-type: none"> • <i>Seizures in the neonate (Safer Care Victoria)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Seizures: Neonatal (WA Child and Adolescent Health Service)</i> 	E	Acute management of seizures
	<ul style="list-style-type: none"> • <i>Seizures – NETS (WA Child and Adolescent Health Service)</i> 	E	Acute management of seizures
		E	Acute management of seizures

	<ul style="list-style-type: none"> <i>Clinical Practice Guidelines: Infantile spasms (RCH 2020)</i> 	E	
Strategy 4. Contact knowledge experts^c			
Personal communication (neurologist) VIC- Melbourne Health- Royal Melbourne Hospital	<ul style="list-style-type: none"> <i>First Seizure</i> <i>Status Epilepticus</i> <i>Management of First Seizure & Epilepsy in Adults</i> 	E E I	Acute management of seizures Acute management of seizures -
Personal communication (neurologist) VIC- St Vincent's Hospital	No relevant institution-generated guidelines	-	-
Drug Information Services, Pharmacy Department VIC- Alfred Health	<ul style="list-style-type: none"> <i>Status Epilepticus Management in Adults</i> <i>Antiepileptics in Traumatic Brain Injury</i> 	E E	Acute management of seizures Acute management of seizures
Drug Information Services, Pharmacy Department VIC- Austin Health	No relevant institution-generated guidelines	-	-
Drug Information Services, Pharmacy Department VIC- Eastern Health	Unable to ascertain	-	-
Drug Information Services, Pharmacy Department VIC- Monash Health	No relevant institution-generated guidelines	-	-
Education, Development & Research, Pharmacy Department VIC- Northern Health	No relevant institution-generated guidelines	-	-
Pharmacy Department VIC- Peninsula Health	<ul style="list-style-type: none"> <i>Status Epilepticus Management for Adults</i> 	E	Acute management of seizures
Pharmacy Department VIC- Western Health	<ul style="list-style-type: none"> <i>Neonatal Seizure Management</i> 	E	Acute management of seizures
Personal communication (neurologist)	No relevant institution-generated guidelines	-	-

VIC- Royal Children's Hospital			
Drug Information Services, Pharmacy Department NSW- Central Sydney- Royal Prince Alfred Hospital	Unable to ascertain	-	-
Pharmacy Department NSW- Gosford Hospital	Unable to ascertain	-	-
Drug Information Services, Pharmacy Department NSW- Northern Sydney- Royal North Shore Hospital	<ul style="list-style-type: none"> <i>Seizure Management for Adult Patients – NSLHD</i> 	E	Acute management of seizures
Drug Information Services, Pharmacy Department NSW- Southeastern Sydney- St George Hospital	No relevant institution-generated guidelines	-	-
Personal communication (neurologist) NSW- Southeastern Sydney Local Health District	No relevant institution-generated guidelines	-	-
Pharmacy Department NSW- Southwestern Sydney- Liverpool Hospital	Unable to ascertain	-	-
Drug Information Services, Pharmacy Department NSW- Western Sydney- Westmead Hospital	No relevant institution-generated guidelines	-	-
Personal communication (neurologist) NSW- Western Sydney Local Health District	No relevant institution-generated guidelines	-	-

Personal communication (neurologist) NSW- Sydney's Children's Hospitals Network	<ul style="list-style-type: none"> <i>PENNSW- Medications: Lamotrigine</i> <i>PENNSW- Medications: Levetiracetam</i> 	E E	Did not meet PICAR eligibility criteria
Pharmacy Department/ Personal communication (neurologist) ACT- Canberra Hospital	<ul style="list-style-type: none"> <i>Canberra Health Services Clinical Guideline: Afebrile Seizures – Paediatrics (Infants, Children and Adolescents – Not Neonates)</i> <i>Canberra Health Services Clinical Guideline: Febrile Seizures – Paediatrics (Infants, Children and Adolescents)</i> 	E E	Acute management of seizures Acute management of seizures
Pharmacy Department ACT- Calvary Public Hospital	No relevant institution-generated guidelines	-	-
Pharmacy Department/ Personal communication (neurologist) NT- Royal Darwin Hospital	<ul style="list-style-type: none"> <i>Status Epilepticus in Adults and Children RDH PRH ED Guideline</i> <i>Seizures Management RDH ICU Medical Guideline</i> 	E E	Acute management of seizures Acute management of seizures
Personal communication (neurologist) NT- Alice Spring Hospital	<ul style="list-style-type: none"> <i>Remote Primary Health Care Manuals</i> 	E	Did not meet PICAR eligibility criteria
Drug Information Services, Pharmacy Department QLD- Mater Hospital Brisbane	<ul style="list-style-type: none"> <i>Seizure management in the Epilepsy Monitoring Unit – South Brisbane procedure</i> 	E	Acute management of seizures
Drug Information Services, Pharmacy Department/ Personal communication (neurologist) QLD- Royal Brisbane and Women's Hospital	No relevant institution-generated guidelines	-	-
Personal communication (neurologist) QLD- Sunshine Coast Hospital	No relevant institution-generated guidelines	-	-
Drug and Therapeutics Information Service (DATIS); GP Plus Marion	No relevant institution-generated guidelines	-	-

SA- SA Health			
SA Pharmacy Medicines Information Service SA- Women's and Children's Hospital	<ul style="list-style-type: none"> <i>Epilepsy and Pregnancy Management</i> <i>Seizures in pregnancy</i> <i>Seizures in Children SA Paediatric Clinical Practice Guideline</i> 	E E E	Did not meet PICAR eligibility criteria Acute management of seizures
Personal communication (neurologist) SA- Flinders Medical Centre	No relevant institution-generated guidelines	-	-
Tasmanian Medicines Information Centre TAS- Royal Hobart Hospital	No relevant institution-generated guidelines	-	-
Personal communication (neurologist) TAS- Tasmania Health Pathways (Community setting for GPs)	<ul style="list-style-type: none"> <i>First Seizure in Adults</i> <i>Epilepsy in Women and Pregnancy</i> <i>Anti-Epileptic Drugs (AEDs)</i> 	E E I	Did not meet PICAR eligibility criteria
Drug Information Services, Pharmacy Department/ Personal communication (neurologist) WA- Fiona Stanley Hospital	<ul style="list-style-type: none"> <i>Adult Seizure Management</i> <i>Seizure Management in Emergency Department</i> <i>Epilepsy in Pregnancy- use guidelines from King Edward Memorial Hospital (see below)</i> <i>Seizures: Neonatal- use guideline from CAHS (see below)</i> 	E E	Acute management of seizures Acute management of seizures
Drug Information Services, Pharmacy Department/ Personal communication (neurologist) WA- Royal Perth Hospital	<ul style="list-style-type: none"> <i>Seizure Management Guidelines</i> 	E	Acute management of seizures
WA- King Edward Memorial Hospital	<ul style="list-style-type: none"> <i>Epilepsy in Pregnancy</i> 	E	Did not meet PICAR eligibility criteria
WA- The Child and Adolescent Health Service (CAHS)	<ul style="list-style-type: none"> <i>Seizures: Neonatal</i> 	E	Acute management of seizures
Personal communication (neurologist)	No relevant institution-generated guidelines	-	-

WA- Perth Children's Hospital			
Personal communication (neurologist) WA- Sir Charles Gairdner Hospital	No relevant institution-generated guidelines	-	-

VIC, Victoria; NSW, New South Wales; ACT, Australian Capital Territory; NT, Northern Territory; QLD, Queensland; SA, South Australia; TAS, Tasmania; GPs, General Practitioners; WA, Western Australia

^a The search was conducted between July 7-10, 2024.

^b Monash Library's subscription does not allow Advanced search feature and has no access to the results on guidelines.

^c Project team's professional network, Pharmacy Department (or Medicines Information Services, if available) of major Australian health services, and professional organisations were contacted through email or telephone between May and June 2024.

APPENDIX TABLE 3. AUSTRALIAN GUIDELINES: DATA EXTRACTION

Guideline name	Population	Intervention	Comparison	Attributes	Recommendation characteristics
Neurology-Epilepsy and seizures [Ref 9]	Children and adults (including females of childbearing potential) with epilepsy	Anti-epileptic drugs (AEDs) *Antiepileptic therapy should start with a single drug. If seizures are not controlled by the first AED, a second drug is added. If	-	Therapeutic Guidelines Limited; published November 2017 (Amended June 2023)	<p><u>Adults and children with tonic-clonic seizures where generalised or focal (partial) onset is unclear</u></p> <ul style="list-style-type: none"> 1st line: Valproate (avoid in females of childbearing potential who do not have reliable contraception) 2nd line: Levetiracetam (1st line females of childbearing potential who do not have reliable contraception), Lamotrigine, Topiramate, Clobazam <p><u>Adults with focal seizures</u></p> <ul style="list-style-type: none"> 1st line: Carbamazepine 2nd line: Clobazam, Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Perampanel, Phenytoin, Pregabalin, Valproate, Tiagabine, Topiramate, Zonisamide <p><u>Children with focal seizures</u></p>

		<p>combined therapy is effective, the first drug may be gradually withdrawn to find out if monotherapy with the second drug is effective. However, many patients prefer to continue combination therapy rather than risk the seizures returning. If combination therapy is not effective, one of the drugs is withdrawn gradually and replaced by a third drug.</p>			<ul style="list-style-type: none"> • 1st line: Carbamazepine • 2nd line: Clobazam, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenobarbital (Phenobarbitone), Phenytoin, Valproate, Tiagabine, Topiramate, Zonisamide <p><u>Childhood and juvenile absence seizures</u></p> <ul style="list-style-type: none"> • 1st line: Ethosuximide • 2nd line: Valproate (avoid in girls of childbearing potential if possible) <p><u>Juvenile myoclonic epilepsy</u></p> <ul style="list-style-type: none"> • 1st line: Valproate (avoid in young females of childbearing potential who do not have reliable contraception if possible) • 2nd line: Levetiracetam, Lamotrigine <p><u>Lennox-Gastaut syndrome and other symptomatic generalised epilepsies</u></p> <ul style="list-style-type: none"> • 1st line: Valproate (consider the relative harms and benefits, and the probability of pregnancy before use in females of childbearing potential who do not have reliable contraception) • 2nd line: Valproate with Lamotrigine • Others: Clobazam, Topiramate
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Neurological Drugs-Antiepileptics-Epilepsy [Ref 10]	Children and adults (including females of childbearing potential) with epilepsy	Anti-epileptic drugs (AEDs) *Start treatment with 1 first-line drug only. Increase the dose gradually, especially for Carbamazepine and Lamotrigine. Exhaust all reasonable options for monotherapy before considering long-term treatment with >1 drug. Although evidence for the most appropriate combinations is lacking, a reasonable	-	Australian Medicines Handbook Pty Ltd; January 2024	<p><u>Focal seizures</u></p> <ul style="list-style-type: none"> • 1st line: Carbamazepine • 2nd line: Lamotrigine^a, Clobazam, Gabapentin, Lacosamide, Levetiracetam^a, Oxcarbazepine, Phenobarbital, Phenytoin, Pregabalin, Tiagabine, Topiramate, Valproate, Zonisamide <p><u>Generalised tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • 1st line: Valproate • 2nd line: Carbamazepine^b, Clobazam, Lamotrigine^a, Levetiracetam^a, Oxcarbazepine^b, Phenobarbital, Phenytoin^b, Topiramate <p><u>Absence seizures</u></p> <ul style="list-style-type: none"> • 1st line: Ethosuximide^c, Valproate • 2nd line: Clobazam, Clonazepam, Lamotrigine <p><u>Myoclonic seizures</u></p> <ul style="list-style-type: none"> • 1st line: Valproate • 2nd line: Clobazam, Clonazepam, Levetiracetam, Phenobarbital <p><u>Infantile spasms</u></p> <ul style="list-style-type: none"> • 1st line: Prednisolone, Tetracosactide • 2nd line: Vigabatrin^d, Clonazepam, Valproate <p>^a May be first line in females of child-bearing potential</p> <p>^b Do not use if juvenile myoclonic epilepsy is suspected (often presents with a tonic-clonic seizure) as it may be ineffective or worsen seizures</p>
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		approach is to combine drugs with differing mechanisms of action. Before changing drug treatment, check compliance, dose (maximal with minimal adverse effects), and diagnosis.			<p>^c Does not prevent generalised tonic-clonic seizures which often coexist in juvenile absence epilepsy</p> <p>^d Use only if no safer alternative</p> <p>NOTE: Lamotrigine may be used in adults as monotherapy in focal (partial) and generalised seizures and it appears to be as effective as carbamazepine. It is also used as adjunctive treatment. Its use is limited by risk of severe adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Levetiracetam is mainly used as adjunctive treatment but may also be used as monotherapy.</p>
Management of First Seizure & Epilepsy in Adults [Ref 11]	Adults (including females of childbearing potential) with epilepsy	Anti-epileptic drugs (AEDs)	-	Victoria; May 2019 Melbourne Health, Department of Neurology- Division of Neurosciences	<p><u>Focal-onset seizures (with or without secondary generalisation to tonic-clonic seizures)</u></p> <ul style="list-style-type: none"> 1st line: Carbamazepine, Lamotrigine, Levetiracetam 2nd line: (One or more, in alphabetical order) Brivaracetam, Clobazam, Gabapentin, Lacosamide, Oxcarbazepine, Phenytoin, Pregabalin, Perampanel, Valproate, Topiramate, Zonisamide <p><u>Generalised Tonic-clonic seizures</u></p> <ul style="list-style-type: none"> 1st line: Valproate (except women of childbearing potential) 2nd line: Lamotrigine^a, Levetiracetam, Topiramate, Carbamazepine, Phenytoin, Clobazam <p><u>Absence seizures</u></p>

					<ul style="list-style-type: none"> • 1st line: Valproate (absence and tonic-clonic), Ethosuximide (absence only) • 2nd line: Lamotrigine, Levetiracetam, Clonazepam, Clobazam <p>Myoclonic seizures</p> <ul style="list-style-type: none"> • 1st line: Valproate • 2nd line: Lamotrigine, Levetiracetam, Clobazam <p>^a Lamotrigine could aggravate myoclonic seizures.</p>
Anti-Epileptic Drugs (AEDs) [Ref 12]	Children and adults (including females of childbearing potential) with epilepsy	Anti-epileptic drugs (AEDs)	-	Tasmania; last updated 9/8/2021 Community Health Pathways (for GPs)	<p>Generalised seizures</p> <ul style="list-style-type: none"> • 1st line: Valproate (avoid in women of childbearing age), Lamotrigine^b, Levetiracetam • 2nd line: Topiramate <p>Focal seizures</p> <ul style="list-style-type: none"> • 1st line: Carbamazepine, Lamotrigine, Levetiracetam • 2nd line: Oxcarbazepine, Topiramate <p>Absence epilepsies</p> <ul style="list-style-type: none"> • 1st line: Ethosuximide <p>^b Lamotrigine may worsen myoclonic seizures</p>

APPENDIX TABLE 4: INTERNATIONAL GUIDELINES: DATA EXTRACTION

Guideline name	Population	Intervention	Comparison	Attributes	Recommendation characteristics
Clinical Guidelines for the Management of Epilepsy in Adults and Children [Ref 13]	Children, young people and adults (including females of childbearing potential) with epilepsy	Anti-epileptic drugs (AEDs) *To start with monotherapy with 1 st line AED and if unsuccessful, use another AED or add-on adjunctive treatment	Any of the AEDs	Canada (Ontario); March 2020 Critical Care Services Ontario (CCSO) and EpLink – The Epilepsy Research Program of the Ontario Brain Institute	<p>Adults with focal seizures</p> <ul style="list-style-type: none"> 1st line: Carbamazepine, Eslicarbazepine, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenytoin, Topiramate, Valproic acid Adjunctive: Brivaracetam, Carbamazepine, Clobazam, Eslicarbazepine, Gabapentin, Lamotrigine (for elderly), Levetiracetam, Oxcarbazepine, Perampanel, Phenytoin, Topiramate, Valproic acid Others: Phenobarbital, Pregabalin <p>Adults with generalised tonic-clonic seizures</p> <ul style="list-style-type: none"> 1st line: Clobazam, Lamotrigine, Levetiracetam, Perampanel, Valproic acid Adjunctive: Clobazam, Lamotrigine, Levetiracetam, Perampanel, Phenobarbital, Primidone, Topiramate, Valproic acid Do not offer (if there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected): Carbamazepine, Gabapentin, Oxcarbazepine, Phenytoin, Pregabalin <p>Children with focal seizures</p> <ul style="list-style-type: none"> 1st line: Carbamazepine, Clobazam, Oxcarbazepine, Phenobarbital, Topiramate, Valproic acid Adjunctive: Brivaracetam, Levetiracetam <p>Children with generalised tonic-clonic seizures</p> <ul style="list-style-type: none"> 1st line: Lamotrigine, Levetiracetam, Phenobarbital, Topiramate, Valproic acid

					<ul style="list-style-type: none"> • Adjunctive: Clobazam • Do not offer (may precipitate or aggravate generalised tonic-clonic seizures): Carbamazepine, Phenytoin <p><u>Children with absence seizures</u></p> <ul style="list-style-type: none"> • 1st line: Ethosuximide, Valproic acid, Lamotrigine • Adjunctive: Ethosuximide, Lamotrigine, Valproic acid • Others: Clobazam, Clonazepam, Levetiracetam, Topiramate, Zonisamide • Do not offer: Carbamazepine, Gabapentin, Oxcarbazepine, Phenytoin, Pregabalin, Tiagabine, Vigabatrin <p><u>Benign epilepsy of childhood with centrotemporal spikes</u></p> <ul style="list-style-type: none"> • 1st line: Carbamazepine, Valproic acid, Gabapentin, Clobazam, Levetiracetam, Oxcarbazepine <p><u>Myoclonic (including Juvenile Myoclonic Epilepsy)</u></p> <ul style="list-style-type: none"> • 1st line: Lamotrigine, Levetiracetam, Topiramate, Valproic acid • Adjunctive: Lamotrigine, Levetiracetam, Perampanel, Topiramate, Valproic acid • Others: Clobazam, Clonazepam, Zonisamide • Do not offer: Carbamazepine, Gabapentin, Oxcarbazepine, Phenytoin, Pregabalin <p><u>Infantile spasms</u></p> <ul style="list-style-type: none"> • 1st line: Vigabatrin, Steroids • Others: Topiramate, Ketogenic diet <p><u>Dravet Syndrome</u></p>
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Epilepsiat (aikuiset) [Epilepsies (adults)] [Ref 14]	Adults (from adolescence) with epilepsy	Anti-epileptic drugs (AEDs)	Any of the AEDs	Finland; 2020 Finnish Medical Society Duodecim and the Finnish Neurological Association	<p><u>Adults with focal seizures</u></p> <ul style="list-style-type: none"> • 1st line: Oxcarbazepine, Carbamazepine or Levetiracetam (Level A evidence) • Alternative (equivalent to 1st line): Eslicarbazepine (Level B evidence), Lacosamide (B), Lamotrigine (B), Topiramate (A), Valproate (A), Gabapentin (B) or Zonisamide (B) <p>*Pregabalin not recommended for first-line treatment (B)</p> <ul style="list-style-type: none"> • Add-on medication: Brivaracetam (A), Eslicarbazepine, Gabapentin, Clobazam, Lacosamide, Lamotrigine, Levetiracetam, Perampanel (A), Pregabalin, Tiagabine (A), Topiramate (A) or Zonisamide. • In special situations (allergies, other medications are not effective): Phenytoin, Phenobarbital, Retigabine or Vigabatrin.

					<u>Adults with generalised seizures</u> <ul style="list-style-type: none"> • 1st line: Valproate (restrictions for women who are in childbearing age – use Lamotrigine or Levetiracetam instead) • Alternative (equivalent to 1st line): Lamotrigine, Levetiracetam, Topiramate • Add-on medicine: Clobazam
Erster epileptischer Anfall und Epilepsien im Erwachsenenalter [First epileptic seizure and epilepsy in adulthood] [Ref 15]	Adults with epilepsy	Anti-epileptic drugs (AEDs) *Start with monotherapy and if unsuccessful, switch to alternative AED as monotherapy before considering dual therapy.	Any of the AEDs	Germany; 2023 German Society for Neurology in cooperation with the German Society for Epileptology	<u>Adults with focal seizures</u> <ul style="list-style-type: none"> • 1st line: Lamotrigine • 2nd line: Lacosamide or Levetiracetam; Gabapentin (another option for ≥65 years) • Carbamazepine, Gabapentin, Topiramate, and Valproate should not be used as initial monotherapy. <u>Adults with genetic generalised seizures</u> <ul style="list-style-type: none"> • 1st line: Valproate (not for women of childbearing age) • 2nd line: Lamotrigine or Levetiracetam <p>*Also included recommendations for AEDs in pregnancy and breastfeeding, people with intellectual disability- not extracted here.</p>
An update of the Hong Kong Epilepsy Guideline: consensus statement on the use of	Children, adolescents and adults with epilepsy	Anti-epileptic drugs (AEDs)	Any of the AEDs	Hong Kong; 2017 (original version in 2009) The Hong Kong Epilepsy Society (HKES)	<u>Adolescents and adults with primary generalised tonic-clonic seizure (modified from NICE)</u> <ul style="list-style-type: none"> • 1st line: Valproate, Carbamazepine, Phenytoin, Lamotrigine, Topiramate • 2nd line: Clobazam, Levetiracetam, Oxcarbazepine • Others: Primidone, Clonazepam, Phenobarbital

AEDs in Hong Kong [Ref 16, 17]					<p><u>Adolescents and adults with absence seizure (modified from NICE)</u></p> <ul style="list-style-type: none"> • 1st line: Ethosuximide, Valproate, Lamotrigine • 2nd line: Clobazam, Clonazepam, Topiramate • Drugs to be avoided: Carbamazepine, Gabapentin, Pregabalin, Oxcarbazepine <p><u>Adolescents and adults with myoclonic seizure (modified from NICE)</u></p> <ul style="list-style-type: none"> • 1st line: Valproate, Levetiracetam • 2nd line: Clobazam, Clonazepam, Piracetam, Topiramate • Others: Lamotrigine • Drugs to be avoided: Carbamazepine, Gabapentin, Pregabalin, Oxcarbazepine <p><u>Adolescents and adults with tonic seizure (modified from NICE)</u></p> <ul style="list-style-type: none"> • 1st line: Valproate, Lamotrigine • 2nd line: Clobazam, Clonazepam, Topiramate, Levetiracetam • Others: Primidone, Phenobarbital, Phenytoin • Drugs to be avoided: Carbamazepine, Oxcarbazepine <p><u>Adolescents and adults with atonic seizure (modified from NICE)</u></p> <ul style="list-style-type: none"> • 1st line: Valproate, Lamotrigine • 2nd line: Clobazam, Clonazepam, Levetiracetam, Topiramate • Others: Primidone, Phenobarbital • Drugs to be avoided: Carbamazepine, Oxcarbazepine, Phenytoin <p><u>Adolescents and adults with focal seizure- with/without secondary generalisation (modified from NICE)</u></p>
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					<p><u>Severe myoclonic epilepsy of infancy</u></p> <ul style="list-style-type: none"> • 1st line: Clobazam, Clonazepam, Valproate, Topiramate • 2nd line: Levetiracetam • Others: Phenobarbital • Drugs to be avoided: Carbamazepine, Lamotrigine, Oxcarbazepine <p><u>Lennox-Gastaut syndrome</u></p> <ul style="list-style-type: none"> • 1st line: Lamotrigine, Valproate, Topiramate • 2nd line: Clobazam, Clonazepam, Ethosuximide, Levetiracetam • Drugs to be avoided: Carbamazepine, Oxcarbazepine <p><u>Landau-Kleffner syndrome</u></p> <ul style="list-style-type: none"> • 1st line: Lamotrigine, Valproate, Steroids • 2nd line: Levetiracetam, Topiramate • Drugs to be avoided: Carbamazepine, Oxcarbazepine <p><u>Myoclonic astatic epilepsy</u></p> <ul style="list-style-type: none"> • 1st line: Clobazam, Clonazepam, Valproate, Topiramate • 2nd line: Lamotrigine, Levetiracetam • Drugs to be avoided: Carbamazepine, Oxcarbazepine
Updated ILAE evidence review of AED efficacy and effectiveness as initial monotherapy for epileptic	Children, adults and elderly with epilepsy	Anti-epileptic drugs (AEDs)	Any of the AEDs	International League Against Epilepsy (ILAE); 2013 (original version in 2006)	<p><u>Adults with partial onset seizures</u></p> <ul style="list-style-type: none"> • Initial monotherapy: Carbamazepine, Levetiracetam, Phenytoin, and Zonisamide (level A evidence); Valproate (level B); Gabapentin, Lamotrigine, Oxcarbazepine, Phenobarbital, Topiramate, and Vigabatrin (level C); Clonazepam and Primidone (level D) <p><u>Children with partial-onset seizures</u></p>

seizures and syndromes [Ref 18, 19]					<ul style="list-style-type: none"> • Initial monotherapy: Oxcarbazepine (level A); Carbamazepine, Phenobarbital, Phenytoin, Topiramate, Valproate, and Vigabatrin (level C); Clobazam, Clonazepam, Lamotrigine, and Zonisamide (level D) <p><u>Elderly adults with partial-onset seizures</u></p> <ul style="list-style-type: none"> • Initial monotherapy: Gabapentin and Lamotrigine (level A); Carbamazepine (level C); Topiramate and Valproate (level D) <p><u>Adults with generalized onset tonic–clonic seizures</u></p> <ul style="list-style-type: none"> • Initial monotherapy: Carbamazepine, Lamotrigine, Oxcarbazepine, Phenobarbital, Phenytoin, Topiramate, and Valproate (level C); Gabapentin, Levetiracetam, and Vigabatrin (level D) <p><u>Children with generalized-onset tonic–clonic seizures</u></p> <ul style="list-style-type: none"> • Initial monotherapy: Carbamazepine, Phenobarbital, Phenytoin, Topiramate, and Valproate (level C); Oxcarbazepine (level D) <p><u>Children with absence seizures</u></p> <ul style="list-style-type: none"> • Initial monotherapy: Ethosuximide and Valproate (level A); Lamotrigine (level C) • No conclusion can be made about Levetiracetam’s efficacy/effectiveness for absence seizures. <p><u>Children with benign childhood epilepsy with centro-temporal spikes (BECTS)</u></p> <ul style="list-style-type: none"> • Initial monotherapy: Carbamazepine and Valproate (level C); Gabapentin, Levetiracetam, Oxcarbazepine, and Sulthiame (level D) <p><u>Juvenile myoclonic epilepsy</u></p> <ul style="list-style-type: none"> • Initial monotherapy: Topiramate and Valproate (level D) <p>Note: Level of Evidence:</p>
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					A = efficacious or effective as initial monotherapy B = probably efficacious or effective as initial monotherapy C = possibly efficacious or effective as initial monotherapy D = potentially efficacious or effective as initial monotherapy
Clinical Practice Guidelines for Epilepsy [Ref 20]	Children, young people, adults and elderly with epilepsy	Anti-epileptic drugs (AEDs)	Any of the AEDs	Japan; 2018 Japanese Society of Neurology in collaboration with the Japan Epilepsy Society, the Japan Neurosurgical Society, the Japan Society of Child Neurology, and the Japanese Society of Neurological Therapeutics	<p><u>Adults with new-onset partial seizure</u></p> <ul style="list-style-type: none"> • 1st line: Carbamazepine, Lamotrigine, Levetiracetam, Zonisamide, Topiramate • 2nd line: Phenytoin, Valproate, Clobazam, Clonazepam, Phenobarbital, Gabapentin, Lacosamide and Perampanel <p><u>Adults with new-onset tonic-clonic/ clonic seizure</u></p> <ul style="list-style-type: none"> • 1st line: Valproate (excluding women of child-bearing potential) • 2nd line: Lamotrigine, Levetiracetam, Topiramate, Zonisamide, Clobazam, Phenobarbital, Phenytoin, and Perampanel • Drugs that should be used with caution: Phenytoin <p><u>Adults with new-onset absence seizure</u></p> <ul style="list-style-type: none"> • 1st line: Valproate, Ethosuximide • 2nd line: Lamotrigine • Drugs that should be used with caution: Carbamazepine, Gabapentin, Phenytoin <p><u>Adults with new-onset myoclonic seizure</u></p> <ul style="list-style-type: none"> • 1st line: Valproate, Clonazepam • 2nd line: Levetiracetam, Topiramate, Piracetam, Phenobarbital, Clobazam

					<ul style="list-style-type: none"> • Drugs that should be used with caution: Carbamazepine, Gabapentin, Phenytoin <p><u>Adults with new-onset tonic/ atonic seizure</u></p> <ul style="list-style-type: none"> • 1st line: Valproate • 2nd line: Lamotrigine, Levetiracetam, Topiramate • Drugs that should be used with caution: Carbamazepine, Gabapentin <p><u>Elderly-onset (≥65 years) partial (focal) seizures</u></p> <ul style="list-style-type: none"> • Recommended (without complications or co-morbidities): Carbamazepine, Lamotrigine, Levetiracetam, Gabapentin • Recommended (with complications or co-morbidities): Levetiracetam, Lamotrigine, Gabapentin <p><u>Elderly-onset (≥65 years) generalised seizures</u></p> <ul style="list-style-type: none"> • Recommended: Lamotrigine, Valproate, Levetiracetam, Topiramate <p><u>Childhood- or adolescence-onset epilepsy with undetermined seizure type (partial or generalized)</u></p> <ul style="list-style-type: none"> • 1st line: Valproate, Carbamazepine, Zonisamide, Levetiracetam, Lamotrigine • Drugs to be used with caution: Carbamazepine (could exacerbate generalised seizures other than generalised tonic-clonic seizure), Lamotrigine (requires strict adherence to the package insert for dosage and administration, and it takes a long time to up-titrate to the effective dosage) <p><u>Recurrent seizures for childhood/ adolescent partial seizures treated with Carbamazepine</u></p> <ul style="list-style-type: none"> • Recommended: Zonisamide, Lamotrigine, Levetiracetam, Clobazam, Topiramate, Valproate, Gabapentin
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					<p><u>Recurrent seizures for childhood/ adolescent generalised seizures treated with Valproate</u></p> <ul style="list-style-type: none"> • <u>Generalised tonic-clinic seizure</u>- Recommended: Lamotrigine, Carbamazepine, Oxcarbazepine, Clobazam, Levetiracetam, Topiramate (avoid Carbamazepine and Oxcarbazepine if absence seizures and myoclonic seizures co-exist) • <u>Absence seizure</u>- 1st line: Ethosuximide; 2nd line: Lamotrigine • <u>Juvenile myoclonic seizure</u>- Recommended: Levetiracetam, Lamotrigine, Topiramate • <u>Myoclonic seizure complicating other epilepsies</u> - Recommended: Clonazepam, Clobazam <p>*Also included recommendations from NICE guideline (2012) for different seizure type and epileptic syndrome in the guidelines.</p>
<p>Epilepsy Guidelines & Pathways for Children & Young People [Ref 21]</p>	Children and young people with epilepsy	Anti-epileptic drugs (AEDs)	Any of the AEDs	<p>New Zealand; 2022 Paediatric Society of New Zealand and Epilepsy New Zealand</p>	<p>*Based on seizure types and epilepsy types</p> <p><u>Absence seizures</u></p> <ul style="list-style-type: none"> • 1st line: Ethosuximide, Valproate (for boys with a high risk of generalised tonic-clonic seizures), Lamotrigine (for girls with a high risk of generalised tonic-clonic seizures who are > 10 years or younger girls likely to require treatment beyond 10 years of age) • Alternatives if Ethosuximide and Valproate are unsuitable, ineffective or not tolerated: Lamotrigine, Levetiracetam <p><u>Generalised tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • 1st line: Valproate (males and girls < 10 years of age who are not likely to require ASM treatment after 10 years of age), Lamotrigine or Levetiracetam (girls > 10 years and child < 3 years), Clobazam (children < 3 years) <p><u>Myoclonic, tonic or atonic seizures</u></p>

					<ul style="list-style-type: none"> • 1st line: Valproate (males and girls < 10 years of age who are not likely to require ASM treatment after 10 years of age), Clobazam, Levetiracetam (girls older than 10 years) <p><u>Focal epilepsy and focal seizures</u></p> <ul style="list-style-type: none"> • 1st line: Carbamazepine, Levetiracetam, Lamotrigine <p>*Based on epilepsy syndrome</p> <p><u>Childhood absence epilepsy</u></p> <ul style="list-style-type: none"> • 1st line: Ethosuximide • 2nd line: Valproate, Lamotrigine <p><u>Juvenile absence epilepsy</u></p> <ul style="list-style-type: none"> • 1st line: Valproate for males; Lamotrigine or Levetiracetam for females • 2nd line: Lamotrigine or Levetiracetam <p><u>Juvenile myoclonic epilepsy</u></p> <ul style="list-style-type: none"> • 1st line: Valproate for males; Lamotrigine or Levetiracetam for females • 2nd line: Lamotrigine or Levetiracetam <p><u>Other genetic generalised epilepsies</u></p> <ul style="list-style-type: none"> • 1st line: Valproate for males and females <10 years; Lamotrigine or Levetiracetam for females >10 years • 2nd line: Lamotrigine or Levetiracetam <p><u>Focal epilepsy</u></p> <ul style="list-style-type: none"> • 1st line: Lamotrigine, Levetiracetam, Carbamazepine <p><u>Dravet Syndrome</u></p>
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Diagnosis and management of epilepsy in adults. SIGN guideline [Ref 22]	Adults (including the elderly) with epilepsy	Anti-epileptic drugs (AEDs)	Any of the AEDs	Scotland; 2018 Scottish Intercollegiate Guidelines Network	<p><u>Adults with focal onset seizures</u></p> <ul style="list-style-type: none"> • Drug of choice: Lamotrigine (grade A recommendation) • Alternatives: Carbamazepine, Levetiracetam (grade A recommendation) • Adjunctive: Carbamazepine, Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Perampanel, Pregabalin, Topiramate, Valproate, Zonisamide (grade A recommendation) <p><u>Adults with genetic generalised epilepsy or unclassified epilepsy</u></p> <ul style="list-style-type: none"> • Drug of choice: Valproate (grade A recommendation) • Alternatives: Lamotrigine, Topiramate (grade A recommendation); For women of childbearing age- Lamotrigine or Levetiracetam (grade D recommendation) • Adjunctive (generalised): Lamotrigine, Levetiracetam, Ethosuximide, Valproate, Topiramate (grade A recommendation) <p><u>Elderly with focal onset seizures</u></p> <ul style="list-style-type: none"> • Drug of choice: Lamotrigine or possibly Levetiracetam (grade B recommendation) • Alternative/ Adjunctive: Gabapentin (grade C recommendation)

					<p>Note: Grades of Recommendations:</p> <p>A = At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</p> <p>B = A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</p> <p>C = A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</p> <p>D = Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</p>
<p>Läkemedelsbehandling av epilepsi – bakgrundsdokumentation [Swedish practice guidelines for monotherapy in epilepsy]</p> <p>[Ref 23]</p>	Children, adults and elderly with epilepsy	Anti-epileptic drugs (AEDs)	Any of the AEDs	Sweden; 2019 Swedish Medical Products Agency	<p><u>Focal onset seizures in children</u></p> <ul style="list-style-type: none"> • 1st line: Carbamazepine, Lamotrigine, Levetiracetam • Alternative: Oxcarbazepine <p><u>Focal onset seizures in adults</u></p> <ul style="list-style-type: none"> • 1st line: Carbamazepine, Lamotrigine, Levetiracetam • Alternative: Eslicarbazepine, Lacosamide, Zonisamide <p><u>Focal onset seizures in elderly</u></p> <ul style="list-style-type: none"> • 1st line: Lamotrigine, Levetiracetam <p><u>Children with generalised tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • 1st line: Lamotrigine, Levetiracetam, Valproate • Alternative: Topiramate

					<p><u>Children with absence epilepsy</u></p> <ul style="list-style-type: none"> • 1st line: Ethosuximide • Alternative: Valproate <p><u>Adults with generalised tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • 1st line: Lamotrigine, Levetiracetam, Valproate
<p>Epilepsies in children, young people and adults. NICE guideline [Ref 24]</p>	<p>Children, young people and adults (including females of childbearing potential) with epilepsy</p>	<p>Anti-epileptic drugs (AEDs)</p> <p>*To start with monotherapy and if unsuccessful, use another AED as monotherapy. If monotherapy not successful, consider add-on adjunctive treatment</p>	<p>Any of the AEDs</p>	<p>United Kingdom; 2022 National Institute for Health and Care Excellence (NICE)</p>	<p><u>Focal seizures with or without evolution to bilateral tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • 1st line: Lamotrigine or Levetiracetam • 2nd line: Carbamazepine, Oxcarbazepine, Zonisamide • 3rd line: Lacosamide • 1st line add-on treatment: Carbamazepine, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Topiramate, Zonisamide • 2nd line add-on treatment: Brivaracetam, Cenobamate, Eslicarbazepine acetate, Perampanel, Pregabalin, Valproate (except in women and girls able to have children) • 3rd line add-on treatment: Phenobarbital, Phenytoin, Tiagabine, Vigabatrin <p><u>Generalised tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • 1st line: Valproate (boys, men, girls <10 years and who are unlikely to need treatment when they are old enough to have children, and women who are unable to have children) • 2nd line: Lamotrigine or Levetiracetam (1st line for women and girls able to have children) • 1st line add-on treatment: Clobazam, Lamotrigine, Levetiracetam, Perampanel, Valproate (except in women and girls able to have children), Topiramate

					<ul style="list-style-type: none"> • 2nd line add-on treatment: Brivaracetam, Lacosamide, Phenobarbital, Primidone, Zonisamide <p><u>Absence seizures (including childhood absence epilepsy)</u></p> <ul style="list-style-type: none"> • 1st line: Ethosuximide • 2nd line or add-on treatment: Valproate (boys of all ages, girls <10 years and who are unlikely to need treatment when they are old enough to have children, and women who are unable to have children) • 3rd line or add-on treatment: Lamotrigine, Levetiracetam <p><u>Myoclonic seizures</u></p> <ul style="list-style-type: none"> • 1st line: Valproate (boys, men, girls <10 years and who are unlikely to need treatment when they are old enough to have children, and women who are unable to have children) • 2nd line or add-on treatment: Levetiracetam (1st line for women and girls able to have children) • 3rd line or add-on treatment: Brivaracetam, Clobazam, Clonazepam, Lamotrigine, Phenobarbital, Piracetam, Topiramate, Zonisamide <p><u>Tonic or atonic seizures</u></p> <ul style="list-style-type: none"> • 1st line: Valproate (boys, men, girls <10 years and who are unlikely to need treatment when they are old enough to have children, and women who are unable to have children) • 2nd line or add-on treatment: Lamotrigine (1st line for women and girls able to have children) • 3rd line or add-on treatment: Clobazam, Rufinamide, Topiramate <p><u>Idiopathic generalised epilepsies</u></p>
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					<ul style="list-style-type: none"> • 1st line: Valproate (boys, men, girls <10 years and who are unlikely to need treatment when they are old enough to have children, and women who are unable to have children) • 2nd line or add-on treatment: Lamotrigine, Levetiracetam (1st line for women and girls able to have children) • 3rd line or add-on treatment: Perampanel, Topiramate <p><u>Dravet syndrome</u></p> <ul style="list-style-type: none"> • 1st line: Valproate (use with caution in women and girls) • 1st line add-on treatment: Stiripentol <u>and</u> Clobazam • 2nd line add-on treatment: Cannabidiol <u>and</u> Clobazam (if > 2 years old) • 3rd line add-on treatment: ketogenic diet, Levetiracetam, Topiramate • Last line: Potassium bromide (under specialist guidance) <p><u>Lennox-Gastaut Syndrome</u></p> <ul style="list-style-type: none"> • 1st line: Valproate (use with caution in women and girls) • 2nd line or add-on treatment: Lamotrigine • 3rd line add-on treatment: Cannabidiol <u>and</u> Clobazam (if > 2 years old), Clobazam, Rufinamide, Topiramate <p><u>Infantile spasms syndrome</u></p> <ul style="list-style-type: none"> • 1st line: High dose oral Prednisolone and Vigabatrin (if not due to tuberous sclerosis; consider Vigabatrin alone if due to tuberous sclerosis or the child is at high risk of steroid-related side effects) • 2nd line or add-on treatment: ketogenic diet, Levetiracetam, Nitrazepam, Valproate, Topiramate <p><u>Self-limited epilepsy with centrottemporal spikes</u></p>
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					<ul style="list-style-type: none"> • 1st line: Lamotrigine, Levetiracetam • 2nd line: Carbamazepine, Oxcarbazepine, Zonisamide • 3rd line or add-on treatment: Sulthiame (under specialist guidance) <p><u>Epilepsy with myoclonic-atonic seizures (Doose syndrome)</u></p> <ul style="list-style-type: none"> • 1st line: Levetiracetam, Valproate (use with caution in women and girls) • 2nd line or add-on treatment: ketogenic diet (under ketogenic diet team supervision) • 3rd line or add-on treatment: Clobazam, Ethosuximide, Topiramate, Zonisamide
Practice Guideline Update Summary: Efficacy and tolerability of the new AEDs I: Treatment of new-onset epilepsy [Ref 25]	Children, young people and adults with epilepsy	Anti-epileptic drugs (AEDs)	Any of the AEDs	United States; 2018 American Academy of Neurology and the American Epilepsy Society	<p><u>Adults with new-onset focal epilepsy or unclassified tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • Should be considered: Lamotrigine (Level B) • May be considered: Levetiracetam (Level C), Zonisamide (Level C) <p><u>Elderly (≥60 years) with new-onset focal epilepsy or unclassified tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • Should be considered: Lamotrigine (Level B) • May be considered: Gabapentin (Level C) <p><u>Children with new-onset focal epilepsy or unclassified tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • No recommendations made- only discussed about high-dose vs. low dose Topiramate <p><u>Adults and children with new-onset generalised epilepsy or unclassified generalised tonic-clonic seizures</u></p>

					<ul style="list-style-type: none"> • No recommendations made- insufficient evidence to compare efficacy of Lamotrigine and Topiramate with that of Valproate. <p><u>Adults and adolescents with new-onset focal, generalised epilepsy, or unclassified generalised tonic-clonic seizures</u></p> <ul style="list-style-type: none"> • No recommendations made- insufficient evidence to compare efficacy of Carbamazepine (controlled-release), Levetiracetam, and Valproate (extended-release). <p><u>Childhood absence epilepsy</u></p> <ul style="list-style-type: none"> • 1st line: Ethosuximide, Valproate • 2nd line: Lamotrigine
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APPENDIX TABLE 5: PROPORTION OF REPATRIATION PHARMACEUTICAL BENEFITS SCHEME DISPENSINGS OF ALL PBS DISPENSINGS

AED	Proportion of RPBS
Lamotrigine 5mg	0.016506
Lamotrigine 25mg	0.022353
Lamotrigine 50mg	0.020532
Lamotrigine 100mg	0.024134
Lamotrigine 200mg	0.015071
Levetiracetam 250mg	0.021767
Levetiracetam 500mg	0.017929
Levetiracetam 1g	0.008948
Levetiracetam oral liquid	0.003447
Valproate 100mg	0.020984
Valproate 200mg	0.014551
Valproate 500mg	0.00694
Valproate liquid	0.017547
Carbamazepine 100mg	0.00406
Carbamazepine 200mg	0.020247
Carbamazepine 200mg CR	0.012978
Carbamazepine 400mg CR	0.01441
Carbamazepine liquid	0.007586

Further information

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