PROPOSAL FOR THE ADDITION TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES AND THE MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN OF LEVETIRACETAM FOR THE TREATMENT OF ADULTS AND CHILDREN WITH FOCAL ONSET AND/OR GENERALIZED ONSET EPILEPSY

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None of the contributors have conflicts of interests to declare.

Contents

1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION

This submission advocates the addition of levetiracetam as an individual medicine to the core list of the EML and EMLc for the treatment of focal onset and generalized onset epilepsy.

Levetiracetam is now a well-established anti-seizure medication that is listed as a mainstay treatment for epilepsy in multiple guidelines, perhaps most notably the 2022 National Institute of Health and Care Excellence guideline on epilepsies in children, young people and adults (1). Levetiracetam has specific advantages above current EML anti-seizure medications, including few drug-drug interactions, no long-term side effects, good tolerability in older people and the safest teratogenic profile of all anti-seizure medications (ASMs;(2)).

As such, levetiracetam would prove a vital and useful addition to the current ASMs listed on the EML (carbamazepine, lamotrigine, phenobarbital, phenytoin, valproic acid/sodium valproate) providing an effective first line treatment in epilepsy, particularly in women and girls of childbearing potential, older people and those on complex treatment regimes. Levetiracetam has also been shown to be effective for status epilepticus that does not respond to benzodiazepines and it is proposed that levetiracetam is added to the current medications listed for treating benzodiazepine-refractory status epilepticus (phenobarbital, valproic acid/sodium valproate).

2. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

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3. OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

International League Against Epilepsy (AS is a member of the ILAE Commission on epilepsy in older people and a member of the ILAE Standards and Practice Council; HC is current president of the ILAE).

Letters of support are provided in Appendix VIII.

4. KEY INFORMATION FOR THE PROPOSED MEDICINE

International non-proprietary name (INN)	Levetiracetam	
Anatomical therapeutic chemical (ATC) code	N03AX14	
Dosage form(s) and strength(s)	Tablets immediate-release (250mg, 500mg, 750mg, 1g), oral solution (100mg/mL), injectable solution (5mg/mL, 10mg/mL, 15mg/mL, 100mg/mL)	
Indication(s): ICD11 codes	**8A60** Epilepsy due to structural or metabolic conditions or diseases **8A61** Genetic or presumed genetic syndromes primarily expressed as epilepsy **8A62** Epileptic encephalopathies **8A64** Single seizure due to remote causes * **8A66** Status epilepticus	**8A68** Types of seizures **8A68.0** Focal unaware seizure **8A68.1** Absence seizures, atypical **8A68.2** Absence seizures, typical **8A68.3** Focal aware seizure **8A68.4** Generalized tonic-clonic seizure **8A68.5** Generalized myoclonic seizure **8A68.6** Generalized tonic seizure **8A68.7** Generalized atonic seizure **8A68.Y** Other specified type of seizure **8A68.Z** Type of seizure, unspecified

*__8A64__ Single seizure due to remote causes: An unprovoked seizure occurring in a patient with no history of antecedent seizures but with abnormalities of brain development or a potentially responsible clinical condition (metabolic, structural, toxic). The temporal relationship with the CNS insult is beyond the interval estimated for the occurrence of acute symptomatic seizures. The CNS insult may be static or progressive.

5. PROPOSAL FOR AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS / THERAPEUTIC GROUP.

The submission relates to the individual listing of levetiracetam under section 5 anticonvulsants/antiepileptics. Other ASMs are listed on the WHO Model List of Essential Medicines (EML) i.e. carbamazepine, diazepam, lamotrigine, phenobarbital, phenytoin, valproic acid/valproate. Levetiracetam has a different and novel mode of action (binds to synaptic vesicle protein 2A; (3)) and is proposed here as an addition to the pharmacological armamentarium to help treat people with seizures.

6. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

Epilepsy, a disorder characterized by spontaneous unprovoked seizures, is one of the most common serious neurological conditions and affects over 50 million people worldwide.(4) Seizures may start in one part of the brain (focal epilepsy) or in both hemispheres simultaneously.(5) Both types of epilepsy can associate with risk of injury, head injury and mortality. Approximately 70% of people can achieve seizure freedom with appropriately selected ASMs.(6) Whilst older ASMs can be effective in controlling seizures, these can

i) associate with long term side effects (phenobarbital, carbamazepine, valproate, phenytoin)
ii) slow cognition (phenobarbital)
iii) have complex drug-drug interactions (phenobarbital, carbamazepine, phenytoin)
iv) be potently teratogenic (valproate)

As such it is vital that newer treatments, which are of equal efficacy to older ASMs but have much better side effect profiles, are included on the EML and made accessible to all people with epilepsy. Whilst lamotrigine is now included, this medication is not suitable in all circumstances, can associate with skin rash for 1 in 30 people, may have its metabolism affected by estrogen containing oral contraceptives/hormone replacement therapies, and is not a medication that can be utilized in emergency settings.

Levetiracetam is a very well established medication and offers unique benefits that warrant its inclusion as a tablet and injection formulation on the EML. These include:

i) effective in both focal onset and generalized onset epilepsies
ii) no adverse effect on cognition
iii) no known long term side effects
iv) minimal drug-drug interactions; no interaction with contraception or hormone replacement therapy
v) effective across all ages, as intravenous formulation, in the emergency treatment of generalized tonic clonic status epilepticus (prolonged convulsive seizures that associate with significant risk)
vi) parenteral preparation can be used in people with symptomatic seizures in patients with comorbid liver /cardiac conditions as well as in people with epilepsy who are unable to take oral preparations
vii) effective in older people with minimal risk
viii) safety in pregnancy with no increased risk above the background risk of teratogenicity in the general population.

Inclusion of levetiracetam on the EML would therefore fundamentally shift epilepsy care globally so that all people, especially more vulnerable groups such as older people with seizures and women /girls of child-bearing potential who have epilepsy, can access an easy to titrate, well-tolerated and highly effective ASM.

7. TREATMENT DETAILS

Recommendations in existing WHO guidelines

In the forthcoming update of the WHO Mental Health Gap Action Programme (mhGAP) Guideline, the Guidelines Development Group has approved the following recommendations:

- Monotherapy with lamotrigine or levetiracetam, or valproic acid (sodium valproate), should be offered as first line treatment for generalized-onset seizures and focal-onset seizures in men/boys and women/girls who are not of childbearing potential.

- In women and girls of childbearing potential with generalized onset seizures, lamotrigine or levetiracetam should be offered as first line monotherapy.

- In adults with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, either intravenous fosphenytoin/phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproic acid should be considered with appropriate monitoring.

- In children with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, intravenous fosphenytoin /phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproate, should be considered with appropriate monitoring

It is expected that these recommendations will be approved by the WHO Guidelines Review Committee and published in 2023.

Recommendations in other current clinical guidelines

Examples of recent guidelines and recommendations already including levetiracetam as main choice for seizure control among people with epilepsy

Guideline	Year	Reference	Levetiracetam role
NICE Guidance – UK (1)	2022	https://www.nice.org.uk/guidance/ng217/evidence/e-monotherapy-for-generalised-tonicclonic-and-focal-onset-seizures-pdf-398366282814	"In general, lamotrigine and levetiracetam were more effective than other ASMs for 'time to treatment failure' for people with focal seizures." „For people with generalised tonic-clonic seizures no ASMs were more effective than sodium valproate for 'time to treatment failure' although there was no difference between sodium valproate, lamotrigine and levetiracetam." „For focal seizures there was high quality evidence that lamotrigine and levetiracetam were most effective in increasing the time to treatment withdrawal and in particular time to withdrawal due to adverse events, suggesting they were better tolerated and more

			effective than other options.“ „Overall the results of the NMAs suggested that lamotrigine and levetiracetam were the most effective first line monotherapy treatments for focal seizures.“ “In the absence of lamotrigine, levetiracetam becomes the least costly and most health improving.”
Ontario Clinical Guidelines for the Management of Epilepsy in Adults and Children (7)	2020	https://clinictocommunity.ca/wp-content/uploads/2021/01/ManagementGuidelines_Nov2020.pdf	Levetiracetam suggested as first-line antiseizure medication in adults and children with focal or generalized seizures
Recommendations for the treatment of epilepsy in adult and pediatric patients in Belgium: 2020 update (8)	2020	https://link.springer.com/article/10.1007/s13760-020-01488-y	Levetiracetam suggested as first-line antiseizure medication in adults and children with focal or generalized seizures
Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy (9)	2018	https://journals.sagepub.com/doi/full/10.5698/1535-7597.18.4.260	Levetiracetam suggested as class B medication in adults with new-onset focal epilepsy
Provincial guidelines for the management of epilepsy in adults and children (10)	2015	https://epilepsyontario.org/wp-content/uploads/2015/03/Provincial-Guidelines-for-the-Management-of-Epilepsy-in-Adults-and-Children_Janurary-20151.pdf	Indicated as an option for adults and children with focal and generalized seizures; indicated as safest medication, together with lamotrigine, during pregnancy.

1) Dose – tablet formulation

Adults and pregnant women: max. 3000mg/d
Infants and Children > 6 and up to 12 years of age (from 50kg weight): max. 3000mg/d

Elderly (based on Creatinine-Clearance ml/min/1,73m^2

>80 ml/min/1,73 m^2: 500 to 1500mg twice daily
50-79 ml/min/1,73 m^2: 500 to 1000mg twice daily
30-49 ml/min/1,73 m^2: 200 to 750mg twice daily
<30 ml/min/1,73 m^2: 250 to 500mg twice daily

2) Dose intravenous formulation

Intravenous Levetiracetam is available as 5 ml ampoule containing 500mg (100mg/ml) of levetiracetam. It should be diluted in 100ml of Ringer Lactate, 5% dextrose or normal saline and given over 15 minutes. The dosage is 40-60mg/kg up to a maximum of 4500mg.

Literature search, quality assessment and subgroup analysis can be found in Appendix III. Briefly, existing systematic reviews were identified by conducting searches in the following bibliographic databases: PubMed, Embase, Cochrane Register of Studies (CRS Web), ClinicalTrials.gov, The World Health Organization International Clinical Trials Registry Platform (ICTRP). Databases were searched for systematic reviews reporting on efficacy and safety of antiseizure medications. The term antiseizure medications (ASM) has been adopted and will replace the term antiepileptic drug in this application given the drugs considered are expected to prevent seizures rather than to prevent the development of epilepsy. (11) We restricted results to systematic reviews and meta-analyses, including network meta-analysis as the highest level of evidence. (12) The period of the searches covered from 1 January 2000 until 22 April 2022.

Quality assessment: The quality of the included systematic reviews was assessed with the AMSTAR quality appraisal tool 2. Three independent researchers (MR, AH, AS) applied the AMSTAR-2 checklist to the included studies, and any disagreements were resolved by consensus. The certainty of the evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations), and using a CiNeMA (Certainty in Network Meta-Analysis (13)) approach in case of network meta-analysis. When available, we extracted the original assessments from the meta-analysis and network meta-analysis. Further details on quality assessment can be found in Appendix III.

Analysis of subgroups or subsets

As optimal ASM choice depends on seizure semiology, we a priori defined to report the outcomes separately for focal onset seizures (focal seizures with/without awareness, focal to bilateral tonic clonic) and generalized onset seizures (with or without other generalized seizure types such as myoclonus or absence seizures).

8. Summary of available evidence for comparative effectiveness

Key messages

Efficacy in seizure control was reported as time to remission rates, while tolerability was reported as time to adverse events.

For focal onset seizures, network meta-analysis allowed comparison of levetiracetam with carbamazepine and lamotrigine, the antiseizure medication considered as first choice in focal epilepsy. (14)

For generalized onset seizures, network meta-analysis allowed comparison of levetiracetam with valproic acid, the antiseizure medications considered as first choice in generalized epilepsy.

In people with focal onset seizures:

- There was high certainty evidence that levetiracetam was as effective (time to remission rates) as lamotrigine and carbamazepine (levetiracetam vs lamotrigine: 2 randomized controlled studies, n=902, hazard ratio (HR)=1.01 (0.87 to 1.18); levetiracetam vs carbamazepine: 3 studies, n=1567, HR=1.08 (0.94-1.24));
- There was high certainty evidence that levetiracetam has lower rates of adverse events (time to adverse events) compared to carbamazepine (3 studies, n=1567, HR=0.65 (0.47 to 0.90)), and similar rates of

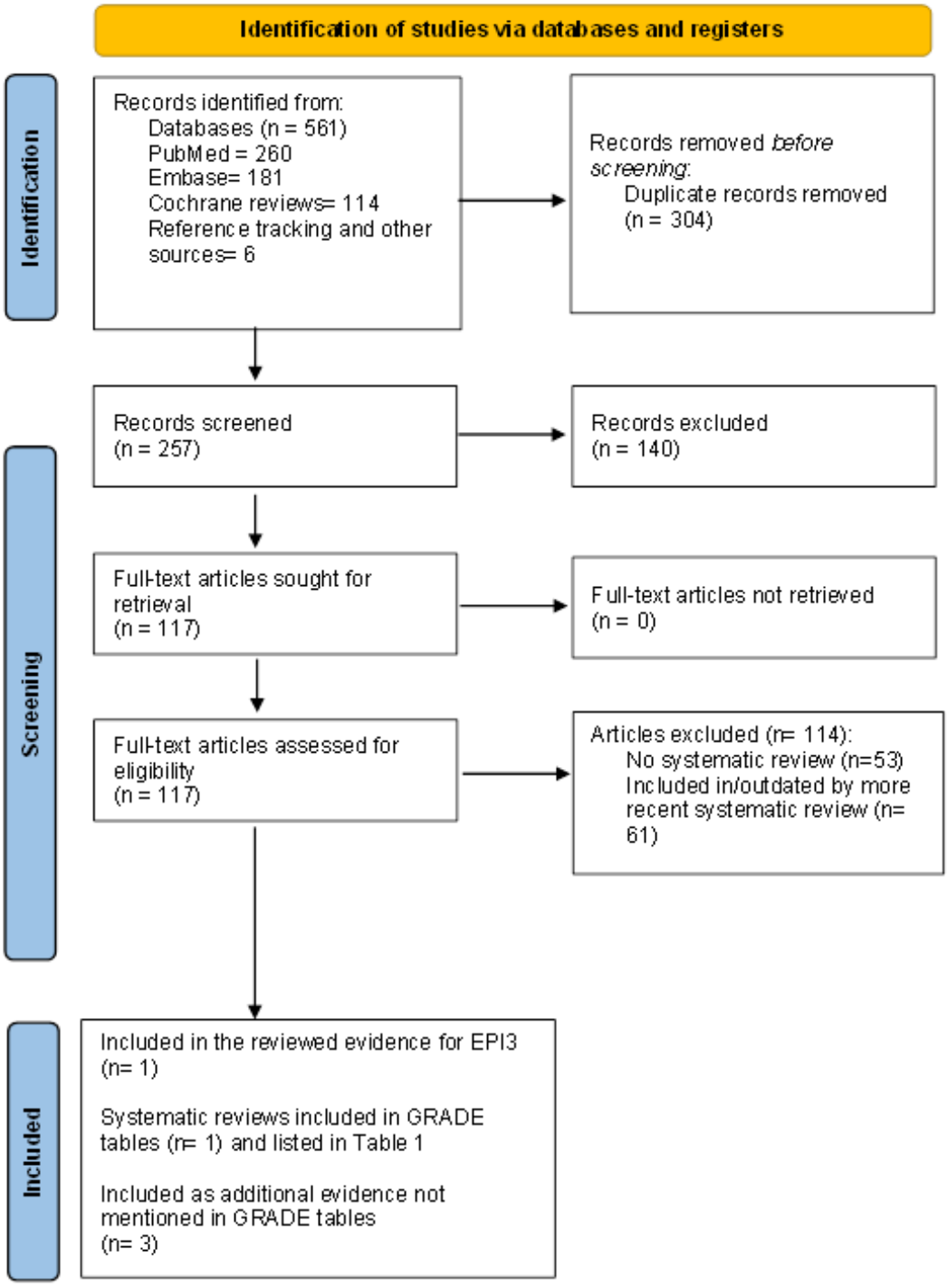
adverse events (time to adverse events) compared to lamotrigine (2 studies, n=902, HR=1.16 (0.81 to 1.66)).

In people with generalized-onset seizures:

- There was high certainty of evidence that levetiracetam had similar efficacy (time to remission rates) compared to valproic acid (2 randomized controlled studies, n=1032, HR=0.99 (0.82 to 1.20);
- There was high certainty of evidence that levetiracetam had similar tolerability (time to adverse events) compared to valproic acid (2 randomized controlled studies, n=1032, HR=1.21 (0.66 to 2.21)

Results

1-Results from search strategy:



2-Key systematic reviews and network meta-analyses identified by the search process and evidence synthesis

First author, journal, year	Population	Interventions and comparisons	Outcomes of interest for the application	Design	Number of studies included (primary outcome)	Number of participants included (primary outcome)	Included in GRADE Tables
Nevitt et al., 2022 (14)	Adults and children with focal or generalized epilepsy	carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide, eslicarbazepine acetate, lacosamide comparison one another via network meta-analysis	Efficacy (time to remission); tolerability (time to adverse events)	Individual patient data network meta-analysis of randomized controlled trials	39	14789	YES
Kanner et al., 2018 (9)	Adults with new onset epilepsy	Any antiseizure medication tested in a RCT	Efficacy and tolerability	Practice guideline	NA	NA	no (practice guideline)
Leone et al., 2021 (15)	Adults and children with first unprovoked seizure	Any antiseizure medication tested in RCT	Efficacy and tolerability	Individual patient data network meta-analysis of randomized controlled trials	6	1634	no (not focused on epilepsy but just first unprovoked seizure)

Nevitt et al., (14) conducted an individual patient data network meta-analysis of the efficacy and tolerability of antiseizure medications in children and adults with focal or generalized epilepsy. Carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide, eslicarbazepine acetate, lacosamide were compared for time to seizure remission (efficacy) and time to adverse events (tolerability) when used as monotherapy in children and adults with focal onset seizures (simple focal, complex focal or secondary generalized) or generalized tonic-clonic seizures with or without other generalized seizure types. The analysis included 14789 records from 39 randomized controlled trials, with certainty of evidence profiles elaborated according to CiNeMA approach. For focal onset seizure carbamazepine and lamotrigine were taken as comparators, while for generalized onset seizure valproic acid was used as comparator.

Network meta-analysis showed **high-certainty evidence that levetiracetam was as effective (time to remission rates) as lamotrigine and carbamazepine for focal onset seizures** (levetiracetam vs lamotrigine: 2 randomized controlled studies, n=902, hazard ratio (HR)=1.01 (95% CI 0.87 to 1.18); levetiracetam vs carbamazepine: 3 studies, n=1567, HR=1.08 (95% CI 0.94-1.24)) (Table 1).

Network meta-analysis showed **high-certainty of evidence that levetiracetam had lower rates of adverse events (time to adverse events) compared to carbamazepine** (3 studies, n=1567, HR=0.65 (95% CI 0.47 to 0.90)), **and similar rates of adverse events (time to adverse events) compared to lamotrigine** (2 studies, n=902, HR=1.16 (95% CI 0.81 to 1.66)) (Table 1).

Network meta-analysis showed **high-certainty of evidence that levetiracetam as effective (time to remission rates) and safe (time to adverse events) compared to valproic acid for generalized onset seizures** (2 studies, n=1032, HR=0.99 (95% CI 0.82 to 1.20)) (Table 1, see also appendix for further details on network meta-analysis results).

The most commonly reported adverse events across all ASMs were drowsiness/fatigue, headache or migraine, gastrointestinal disturbances, dizziness/faintness and rash or skin disorders.

Table 1. Summary of results from Nevitt et al. (14), readapted

Seizure type	Quality assessment				Summary of findings				Importance
					Direct evidence	Network meta-analysis			
	Intervention	Comparator	No of studies	Participants	Estimate HR (95%CI)	Estimate HR (95%CI)	Direct evidence	Certainty of the evidence	
Time to remission (Efficacy)									
Focal seizure	Levetiracetam	Carbamazepine	3	1567	1.09 (0.92 to 1.29); I2 = 0%	1.08 (0.94 to 1.24)	22.30%	⊕⊕⊕⊕ HIGH	CRITICAL
Focal seizure	Levetiracetam	Lamotrigine	2	902	1.02 (0.86 to 1.20); I2 = 0%	1.01 (0.87 to 1.18)	23.60%	⊕⊕⊕⊕ HIGH	CRITICAL
Generalized seizure	Levetiracetam	Sodium valproate	2	1032	1.10 (0.59 to 2.04); I2: 55%	0.99 (0.82 to 1.20)	53.20%	⊕⊕⊕⊕ HIGH	CRITICAL
Time to adverse events (Tolerability)									
Focal seizure	Levetiracetam	Carbamazepine	3	1567	0.60 (0.47 to 0.77); I2 = 35%	0.65 (0.47 to 0.90)	28.80%	⊕⊕⊕⊕ HIGH	CRITICAL
Focal seizure	Levetiracetam	Lamotrigine	2	902	0.84 (0.60 to 1.19); I2 =32%	1.16 (0.81 to 1.66)	14.6%	⊕⊕⊕⊕ HIGH	CRITICAL
Generalized seizure	Levetiracetam	Sodium valproate	2	1032	0.79 (0.19 to 3.39); I2 =0%	1.21 (0.66 to 2.21)	14.7%	⊕⊕⊕⊕ HIGH	CRITICAL

Summary of studies not included in evidence synthesis

Kanner et al (9) reported an update on American Academy of Neurology/American Epilepsy Society guidelines on treatment of adults with new-onset epilepsy. They systematically searched records up to November 2015 to update the previous guidelines, dating back to 2004. Several second-generation antiseizure medications were considered to be effective for new-onset focal epilepsy. As final recommendations, Kanner and colleagues highlighted that lamotrigine, levetiracetam and zonisamide are the antiseizure medications that may be preferred to decrease seizure frequency in adults with new-onset focal epilepsy.

Leone et al (15) reported on the indications to start an antiseizure medication treatment after a first seizure. No specific data on efficacy and safety of levetiracetam was investigated.

Additional details are provided in the Appendix

Among papers not reaching final stages according to specified criteria, a narrative review from **Kanner et al (16)** covered optimal antiseizure medication choice in adults with epilepsy. Among 26 US Food and Drug Administration–approved medications for epilepsy, 24 were considered to have similar antiseizure efficacy for focal epilepsy and 9 have similar efficacy for generalized epilepsy. The authors stressed the concept that antiseizure medication choice must be selected based on the seizure and epilepsy types, the epilepsy syndrome, and the adverse effects associated with the drug. Levetiracetam, together with lamotrigine, was suggested as a first-line option for both focal onset and generalized onset seizures, with particular regard to women and girls of childbearing potential given the low teratogenic risk.

Assessment of applicability of the available evidence across diverse populations and settings

Regarding seizure semiology, results from the network meta-analysis from Nevitt and colleagues are reported according to focal or generalized onset seizure type. (14) This reinforces the efficacy and safety of levetiracetam in both seizure type.

Regarding age, sensitivity analysis results adjusted for age were reported in the individual patient data network meta-analysis by Nevitt et al., (14) to have estimates similar to those displayed in main results, further supporting the robustness of their findings. Overall, age range for their network meta-analysis was 1-95 years old, with 4/39 studies providing individual-patient data including people aged 15 or lower, and 35/39 studies including people older than 15 years. (14)

In the SANAD II (Standard and New Anti-epileptic Drug II) study, an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial, levetiracetam was compared to valproic acid for the treatment of generalized and unclassified epilepsy. (17) Although levetiracetam did not reach the non-inferiority margins defined vs valproate, it did assocaite with similar propbability of 12-month remission compared to valproate in the long-term and is considered non-inferior to valproate for generalised epilepsy. (17)

Special Circumstances:

- Women and girls of child-bearing potential

Very specific risks arise in females with epilepsy that need to be considered across the lifespan. (18) It is important that ASMs have limited interactions with contraception/HRT and that medications with limited teratogenic risk are available. (19) Enzyme inducing medications (carbamazepine, phenytoin, phenobarbital) can interfere with the oral contraceptive and render it less effective. Oestrogen containing oral contraceptives can lower lamotrigine levels. Levetiracetam does not interact with oral contraception thereby giving it a specific advantage for women who are taking oral contraceptives.

Levetiracetam is also the ASM with the best overall safety in pregnancy. (2, 19) Levetiracetam is not thought to substantially increase teratogenic risk above that seen in the general population. By contrast, sodium valproate increases the risk of structural anomolies (for example spina bifida, cleft lip, cleft palate, cardiac anomolies) up to around 10% and women taking valproate through pregnancy have an approximately 30-40% risk that their offspring will have neurodevelopmental anomolies (autism, learning disabilitiies (2)). It is vital, therefore, that women and girls have ASMs available that are effective and do not associate with such risk.

- Older people

Levetiracetam has previously been reported as effective in reducing seizure frequency in older adults aged>65. (20) In that study, 76.9% of patients were found to have at least a 50% reduction in seizure frequency, with only 19.2% experiencing an adverse event leading to discontinuation. (20)

Levetiracetam is not an enzyme-inducing ASM. The reduced drug-drug interactions are particulalry important in older people who may be on poly-therapy. Levetiracetam also does not have an adverse impact on bone health, giving it additional advantages over carbamazepine, phenytoin, phenobarbital and valproate.

- Specific ethinc populations

Many ASMs associate with skin rashes including carbamazepine, lamotrigine and phenytoin. Associated with the HLA-B*1502 allele, though, there is a marked increase in the risk of severe skin rashes with carbamazepine and phenytoin for people of, for example, Han Chinese origin. (21) There is often cross-reactivity between ASMs with similar modes of action and therefore having levetriacetam available on the EML offers a medication that is substantially less likely to associate with rash, even in those who have experienced dermatological reactions with one of the other ASMs.

- Status epilepticus

Status epilepticus is defined, for convulsive seizures, as a seizure lasting more than five minutes. It is a condition that associates with significant risk of morbidity and mortality. Expedient management is essential. Whilst it has

been established that benzodizaepines (diazepam, lorazepam) are the first line treatment in status epilepticus, the choice of second line treatment should benzodiazepines not stop the seizure has been uncertain. (22)

Two recent studies have helped clarify things (please also see Appendix IV):

a) The Established Status Epilepticus Treatment Trial (ESETT) enrolled 384 adult participants and randomised them to receive levetiracetam, fosphenytoin or valproate. Efficacy and incidence of adverse events were similar for all three agents. (23)
b) The EcLiPSE trial randomly assigned 1432 children aged 6 months to 18 years to receive either phenytoin or levetiracetam for benzodiazepine refractory status epilepticus. (24) Levetiracetam was not found to be significantly superior to phenytoin for status epilepticus which is in accordance with the ConSEPT study.(25) However, the EcLIPSE investgigators concluded that the ease of administration of levetiracetam meant that it could be an appropriate treatment for benzodiazepine-refractory status epilepticus.(25) To contextualise this, administration of phenytoin requires cardiac monitoring and, therefore, there may be some specific advantages in resource poor settings to have levetiracetam available to treat status epilepticus.

In conclusion, therefore, although levetiracetam is not necessarily more effective than either phenytoin or valproate in treating established status epilepticus, there would be advantages in clinicians having access to levetriacetam as a treatment option for this condition.

9. REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF COMPARATIVE SAFETY

A comprehensive list of potential side effects of levetiracetam is listed in the Appendix II.

The network meta-analysis by Nevitt and colleagues (14) on antiseizure medications in people with focal or generalized onset seizures provides data both on the "acceptability" of treatments (i.e., all-cause treatment discontinuation, which is generally considered a pragmatic proxy of the balance between desirable and undesirable effects of medications) and "tolerability" (i.e., adverse events). The analysis on acceptability shows that levetiracetam is as acceptable as valproate in generalized onset seizure, as acceptable as lamotrigine in focal onset seizure, and more acceptable than carbamazepine in focal onset seizure (Table 2). The analysis on tolerability shows that levetiracetam is better tolerated than carbamazepine in focal onset seizures (high quality of evidence), and that has similar tolerability compared to lamotrigine and valproate. Please refer to appendix for the full set of evidence tables.

Special consideration should be given to harms and toxicity in women and girls of childbearing potential. A systematic review and meta-analysis from Veroniki and colleagues (19) compared the risk of congenital malformations and prenatal outcomes of antiseizure medications in infants and children exposed to antiseizure medications in utero. The authors included 96 studies for an overall sample size of 58461 patients. Levetiracetam and lamotrigine emerged as the only antiseizure medications with risks similar to those of placebo, therefore suggesting the preferential use of lamotrigine and levetiracetam among women and girls of childbearing potential. (19) This has shaped the Guideline Development Group's recent approval of the mhGAP guideline recommendation that:

- "In women and girls of childbearing potential with generalized onset seizures, lamotrigine or levetiracetam should be offered as first line monotherapy"

Such results were also taken into account in the guidelines for treatment of people with epilepsy from the National Institute for Health and Care Excellence (NICE). In the latest 2022 version of NICE guideline, levetiracetam and lamotrigine are proposed as first-line medications, with particular regard to women and children of childbearing potential in light of their low teratogenic risk and tolerability profile. (1)

Table 2. Acceptability of treatment with levetiracetam as compared with carbamazepine, lamotrigine and valproate (Nevitt et al., (14); readapted)

Outcome	Quality assessment				Summary of findings				Importance
					Direct evidence	Network meta-analysis			
Time to treatment failure (for)	Intervention	Comparator	No of studies	Participants	Estimate HR (95%CI)	Estimate HR (95%CI)	Direct evidence	Certainty of the evidence	
vs carbamazepine in focal onset seizure									
Any reason	Levetiracetam	Carbamazepine	3	1567	0.85 (0.71 to 1.01); I2 = 50%	0.80 (0.69 to 0.93)	15.8%	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events	Levetiracetam	Carbamazepine	3	1567	0.60 (0.47 to 0.77); I2 = 35%	0.65 (0.47 to 0.90)	28.8%	⊕⊕⊕⊕ HIGH	CRITICAL
Lack of efficacy	Levetiracetam	Carbamazepine	2	1032	1.44 (0.98 to 2.12); I2: 0%	1.07 (0.78 to 1.45)	23%	⊕⊕⊕⊕ HIGH	CRITICAL
vs lamotrigine in focal onset seizure									
Any reason	Levetiracetam	Lamotrigine	2	902	0.87 (0.71 to 1.07); I2 = 0%	1.01 (0.86 to 1.20)	23.3%	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events	Levetiracetam	Lamotrigine	2	902	0.84 (0.60 to 1.19); I2 =32%	1.16 (0.81 to 1.66)	14.6%	⊕⊕⊕⊕ HIGH	CRITICAL
Lack of efficacy	Levetiracetam	Lamotrigine	2	902	0.83 (0.57 to 1.21); I2 =3%	1.05 (0.76 to 1.46)	30.9%	⊕⊕⊕⊕ HIGH	CRITICAL
vs valproate in generalized onset seizure									
Any reason	Levetiracetam	Valproate	2	1032	1.46 (0.63 to 3.38); I2=0%	1.13 (0.89 to 1.42)	17.8%	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events	Levetiracetam	Valproate	2	1032	0.79 (0.19 to 3.39); I2=0%	1.21 (0.66 to 2.21)	14.7%	⊕⊕⊕⊕ HIGH	CRITICAL
Lack of efficacy	Levetiracetam	Valproate	2	1032	3.02 (0.43 to 21.1); I2=0%	1.25 (0.81 to 1.93	14.7%	⊕⊕⊕⊕ HIGH	CRITICAL

10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS

Summary of studies included in the economic evidence review

We identified one study reporting cost-effectiveness data (SANAD-II trial (17)) and the 2022 NICE guideline on treatment of people with epilepsy (1) also reports a cost-effectiveness analysis. The SANAD-II trial provides an economic evaluation conducted alongside a RCT involving 990 people comparing ASMs for people with newly diagnosed focal epilepsy. The RCT was conducted at 65 centres across the UK between 2013 and 2017 with costs reported for the 2019/20 cost year and compared levetiracetam and zonisamide to lamotrigine. The study reports outcomes in terms of QALYs calculated from participant completed EuroQol-5 Dimension (EQ-5D) questionnaires scored using the UK tariff. The study took an NHS & personal social services (PSS) perspective.

The study shows lamotrigine to be cost saving and health improving in the base-case dominating the other options. At a £20,000 per QALY threshold lamotrigine has a greater than 99.9% probability of being the preferred option. This was the case in the adult subgroup analysis but not for people under the age of 16 (levetiracetam is cost saving and health improving when compared to lamotrigine). From the sensitivity analyses lamotrigine remained dominant apart from when QALYs were valued using the epilepsy specific NEWQOL-6D (levetiracetam becomes the preferred option at a £20,000 per QALY threshold). When complete cases only are used in the analysis where lamotrigine remains the preferred option but levetiracetam becomes cost saving.

Overall, the bespoke economic model suggests that whilst lamotrigine (which is already listed on the EML) is the most cost effective medication for focal epilepsy, levetiracetam is also a highly cost-effective option. (1) As has been illustrated, levetiracetam has specific advantages over lamotrigine including for women and girls of child bearing potential, those on polypharmacy and in the emergency setting. In these settings, one might expect a further cost advantage.

To contextualise actual costs, we here summarise costs of starting doses of ASMs already listed on the EML and levetiracetam

Data are first taken from UK as fully government funded National Health Service. Prices may therefore be lower than other high-income countries owing to bulk purchasing. Original brands are marked with an asterisk. Examples of generic pricing are also included. Data collated from https://bnf.nice.org.uk/. (26)

Levetiracetam, especially in generic formulation, is therefore a relatively cheap anti-seizure medication.

Name of drug	*Manufacturer*	*Dose*	*Number of doses*	*NHS indicative price*	*Drug tariff*
Carbamazepine (Tegretol)	Novartis Pharmaceuticals	200mg	84	£3.83	£3.83
Carbamazepine (Tegretol Prolonged release)	Novartis Pharmaceuticals	200mg	56	£5.20	£5.20
Carbamazepine	Crescent Pharma	200mg	84	£3.83	£3.83
Lamotrigine (Lamictal)	GlaxoSmtihKline*	25mg	56	£23.53	£1.33
Lamotrigine	Accord Healthcare	25mg	56	£2.64	£1.33
Levetiracetam (Keppra)	UCB Pharma Ltd*	250mg	60	£28.01	£1.90
Levetiracetam	Accord Healthcare	250mg	60	£2.51	£1.90
Phenytoin	Alliance Healthcare	300mg	28	£9.11	£9.11
Phenytoin	Flynn Pharma Limited	300mg	28	£9.11	£9.11
Phenobarbitone	Alliance Healthcare	30mg	28	£0.94	£0.94
Phenobarbitone	Teva UK Limited	30mg	28	£0.63	£0.94

It is quite difficult to obtain accurate costings for levetiracetam in other settings. Some examples are provided:

1. Healthline – The cost of epilepsy medications; generic levetiracetam estimated cost of $9 for 60 tablets of levetiracetam 500mg in the United States (healthline.com)
2. Nepali online pharmacies dispense levetiracetam for the equivalent of $8.32 for 60 tablets of levetiracetam 500mg (accessed through online search 4.12.22)
3. In 2019, the South African Department of Health estimated that the total annual cost of levetiracetam at a dose of 3000mg per day would cost R4,126.08 ($237.37 at current exchange rate; 27)

11. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS

Levetiracetam was granted US FDA-approval under the trade name 'Keppra' produced by UCB Pharma Inc, on 30th November 1999 (Application Number: 21-035). The immediate release tablet has been available as a generic drug in the US since 2008 and in the UK since 2011. An extended release version of levetiracetam exists, and this remains under patent until 2028. The current submission does not propose including prolonged release levetiracetam on the EML.

Levetiracetam, as illustrated, is now available in multiple generic forms. The generic forms in particular offer very competitive pricing compared to currently recommended medications on the EML. Addition of levetiracetam to the EML should help democratise access to levetiracetam therapy.

Pharmacopoieal standards

Example pharmacopoeial standards: results for levetiracetam:

(a) United States Pharmacopoeia:
(https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/levetiracetam_tablets.pdf)

(b) European Pharmacopoeia:

(https://www.ema.europa.eu/en/documents/scientific-discussion/keppra-epar-scientific-discussion_en.pdf)

(c) Japanese Pharmacopoeia:

(https://www.pmda.go.jp/files/000229077.pdf. Source: Japanese Pharmacopeia 17th Edition)

Levetiracetam is already listed on country specific EMLs in Albania, Algeria, Bahrain, Bhutan, Bulgaria, Czech Republic, Estonia, Iran, Iraq, Jordan, Latvia, Lithuania, Maldives, Mexico, Montenegro, Oman, Poland, Portugal, Romania, Russian Federation, Rwanda, Serbia, Seychelles, Slovakia, Sweden, Syrian Arab Republic, Thailand, The former Yugoslav Republic of Macedonia, Timor Leste, Viet Nam.

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