Levetiracetam

Essential medicine status

Section: 5. Medicines for neurological disorders > 5.1. Antiseizure medicines

EMLc | ATC codes: N03AX14

Indication	Epilepsy or seizures ICD11 code: 8A6Z
INN	Levetiracetam
Medicine type	Chemical agent
List type	Core (EML) (EMLc)
Formulations	Oral > Liquid: 100 mg per mL Oral > Solid > tablet: 250 mg ; 500 mg ; 750 mg ; 1000 mg
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Levetiracetam
DrugBank	Levetiracetam

Expert Committee recommendation

The Expert Committee recognized that epilepsy is a common, serious neurological condition with a significant disease burden, affecting millions of people around the world. The Committee acknowledged that treatment strategies for people with epilepsy need to be individualized considering multiple factors including, but not limited to, seizure type, co-morbidities, adverse event profile, concomitant medication use, pregnancy and patient preferences. The Committee also noted that three quarters of people living with epilepsy in low-income countries do not get the treatment they need, increasing their risk of dying prematurely and condemning many to a life of stigma. The Committee noted the high-certainty evidence presented in the application that levetiracetam was as effective as alternative EML-listed antiseizure medicines for focal-onset seizures and generalized-onset seizures. The Committee also noted that levetiracetam is an effective treatment option for use in adults and children in the treatment of status epilepticus that does not respond to treatment with benzodiazepines. The Committee also noted the high-certainty evidence presented for safety, which indicates that levetiracetam has similar or greater acceptability and tolerability than alternative antiseizure medicines. Importantly, the Committee noted that the risks of congenital malformation and neurodevelopmental disorders in infants and children exposed to levetiracetam (and lamotrigine) in utero are similar to those of placebo, while other antiseizure medicines currently included on the Model Lists have a significant risk of inducing congenital malformations and neurodevelopmental disorders. Carbamazepine, phenobarbital and valproic acid are associated with chronic and severe teratogenic effects, the most common of which are congenital heart disease, cleft lip/palate, and urogenital and neural tube defects. Therefore, levetiracetam and lamotrigine are preferred antiseizure medications for use in women and girls of childbearing potential. The Committee noted that levetiracetam (and lamotrigine) will be recommended in the updated WHO mhGAP guidelines as first-line treatment options for women and girls of childbearing potential with generalized-onset seizures. Based on these considerations, the Expert Committee recommended the inclusion of oral levetiracetam on the core list of the EML and EMLc for the treatment of focal- and generalized- onset seizures in adults and children. The Committee also recommended the inclusion of intravenous levetiracetam on the complementary list of the EML and EMLc for the treatment of benzodiazepine-refractory status

epilepticus in adults and children. Additionally, the Committee recommended that the section title in the Model Lists be updated from “anticonvulsants/antiepileptics” to “antiseizure medicines”.

Background

Levetiracetam has not previously been evaluated for inclusion on the Model Lists. The EML currently lists 10 antiseizure medicines: carbamazepine, diazepam, ethosuximide, lamotrigine, lorazepam, magnesium sulfate, midazolam, phenobarbital, phenytoin, and valproic acid. With the exception of magnesium sulfate (which is listed for use only in eclampsia and severe pre-eclampsia), the same medicines are also included on the EMLc. These medicines are intended to treat generalized and partial epilepsy, mostly as first-line therapies.

Public health relevance

The public health relevance of effective and safe treatments for epilepsy is well established. Epilepsy, a disorder characterized by spontaneous unprovoked seizures, is one of the most common serious neurological conditions and affects more than 50 million people worldwide (1). Seizures may start in one part of the brain (focal epilepsy) or in both hemispheres simultaneously (2). Both types of epilepsy are associated with risk of injury, head injury and death. About 70% of people can achieve freedom from seizures with appropriately selected antiseizure medicines (3). While older antiseizure medicines can be effective in controlling seizures, they can be associated with long-term side-effects (phenobarbital, carbamazepine, valproic acid, phenytoin) and slow cognition (phenobarbital), can have complex drug–drug interactions (phenobarbital, carbamazepine, phenytoin) and can be teratogenic (valproic acid). Lamotrigine, a newer antiseizure medicine, can cause skin rash in 1 in 30 people, may have its metabolism affected by estrogen-containing oral contraceptives/hormone replacement therapies, and is not a medicine that can be used in emergency settings. Treatment strategies for epilepsy should be individualized according to the seizure type, co-prescribed medications and co-morbidities, the person’s lifestyle, and the preferences of the person and their family and/or caregivers. Levetiracetam is a well established medicine in the pharmacological armamentarium for epilepsy treatment, and offers the following benefits: • effective in both focal-onset and generalized-onset epilepsies; • no adverse effects on cognition; • no known long-term side-effects; • minimal drug–drug interactions; no interaction with contraception or hormone replacement therapy; • effective in all ages; • can be used intravenously in the emergency treatment of generalized tonic-clonic status epilepticus (prolonged convulsive seizures associated with significant risk); • parenteral preparation available that can be used in people with symptomatic seizures, people with co-morbid liver/cardiac conditions and people with epilepsy who are unable to take oral preparations; • effective in older people with lower risk of adverse events; • safe in pregnancy with no increased risk above the background risk of teratogenicity in the general population. Levetiracetam is particularly beneficial for more vulnerable groups such as older people with seizures and women/girls of childbearing potential who have epilepsy.

Benefits

The applicants conducted and presented the findings of a systematic literature review and network meta-analysis which summarized the evidence from recent meta-analyses comparing the effectiveness and safety of antiseizure medications in adults and children with epilepsy. The evidence synthesis included one Cochrane systematic review and network meta-analysis of individual patient data of the efficacy and tolerability of antiseizure medications in children and adults with focal or generalized epilepsy (4). Carbamazepine, phenytoin, valproic acid, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide, eslicarbazepine acetate and lacosamide were compared for time to seizure remission (efficacy) 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 14 789 records from 39 randomized trials, with certainty of evidence profiles elaborated according to confidence in network meta-analysis (CiNeMA) approach. For focal-onset seizures, carbamazepine and lamotrigine were taken as comparators, while for generalized-onset seizures valproic acid was used as the comparator, as these medicines are considered first-choice in the treatment of the respective epilepsy types. The network meta-analysis (4) showed high-certainty evidence that for focal-onset seizures, levetiracetam was as effective as lamotrigine (hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.87 to 1.18; two randomized controlled trials, 902 participants) and carbamazepine (HR 1.08, 95% CI 0.94 to 1.24; three studies, 1567 participants). The network meta-analysis also showed high-certainty evidence that for generalized-onset seizures, levetiracetam was as effective as valproic acid (HR 0.99, 95% CI 0.82 to 1.20; two randomized controlled trials, 1032 participants). The network meta-analysis

reported sensitivity analysis results adjusted for age, which showed similar estimates to those in the main results. Overall, the age range for the network meta-analysis was 1 to 95 years, with 4/39 studies providing individual patient data for people 15 years or younger, and 35/39 studies including people older than 15 years (4). An update was reported in 2018 of American Academy of Neurology/American Epilepsy Society guidelines on treatment of adults with new-onset epilepsy (5). The authors 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. The authors highlighted that lamotrigine, levetiracetam and zonisamide were the preferred antiseizure medications to decrease seizure frequency in adults with new-onset focal epilepsy. Another study reported on the indications to start an antiseizure medication treatment after a first seizure, but the efficacy and safety of levetiracetam were not investigated (6). A narrative review in 2022 covered optimal antiseizure medication choices in adults with epilepsy (7). Among 26 medications for epilepsy approved by the US Food and Drug Administration, 24 were considered to have similar antiseizure efficacy for focal epilepsy and nine had similar efficacy for generalized epilepsy. The authors stressed that the choice of antiseizure medication must be 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, particularly for women and girls of childbearing potential given the low teratogenic risk. The SANAD II study was a randomized, open-label, non-inferiority, phase IV trial which compared levetiracetam to valproic acid for treatment of generalized and unclassified epilepsy (8). Although levetiracetam did not reach the non-inferiority margins defined versus valproic acid, it was associated with a similar probability of 12-month remission compared with valproic acid in the long-term and is considered non-inferior to valproic acid for generalized epilepsy.

Harms

The Cochrane systematic review and network meta-analysis provided data on both acceptability of treatments (i.e. all-cause treatment discontinuation, generally considered a pragmatic proxy of the balance between desirable and undesirable effects) and tolerability (i.e. adverse events) (4). The network meta-analysis showed high-certainty evidence that: • for focal-onset seizures, levetiracetam had better acceptability (HR 0.80, 95% CI 0.69 to 0.93) and tolerability (HR 0.65, 95% CI 0.47 to 0.90) compared with carbamazepine (three studies, 1567 participants). • for focal-onset seizures, levetiracetam had similar acceptability (HR 1.01, 95% CI 0.86 to 1.20) and tolerability (HR 1.16, 95% CI 0.81 to 1.66) compared with lamotrigine (two studies, 902 participants). • for generalized-onset seizures, levetiracetam had similar acceptability (HR 1.13, 95% CI 0.89 to 1.42) and tolerability (HR 1.21, 95% CI 0.66 to 2.21) compared with valproic acid (two studies, 1032 participants). The most commonly reported adverse events across all antiseizure medicines were drowsiness/fatigue, headache or migraine, gastrointestinal disturbances, dizziness/faintness, and rash or skin disorders. A systematic review and meta-analysis of 96 studies (58 461 participants) evaluated the risk of congenital malformations and prenatal outcomes of antiseizure medications in infants and children exposed to antiseizure medications in utero (9). Levetiracetam and lamotrigine emerged as the only antiseizure medications with risks similar to placebo, suggesting the preferred use of lamotrigine and levetiracetam for women and girls of childbearing potential.

Cost / cost effectiveness

The SANAD-II trial provided an economic evaluation alongside a randomized trial including 990 people comparing antiseizure medicines for people with newly diagnosed focal epilepsy in the United Kingdom (8). The study reported quality-adjusted life years (QALYs) calculated from participant-completed EuroQol-5 Dimension (EQ-5D) questionnaires scored using the United Kingdom tariff. The study took a National Health Services payer perspective and a personal social services perspective, which includes services provided by local communities. Lamotrigine was shown to be cost-saving and health-improving in the base case, dominating the other options. At a £20 000 per QALY threshold, lamotrigine had a greater than 99.9% probability of being the preferred option. This was the case in the adult subgroup analysis but not for people younger than 16 years, where levetiracetam was 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). The application presented a summary comparison of costs in the fully government-funded National Health Service in the United Kingdom of starting doses of levetiracetam and other EML-listed antiseizure medicines (Table 7, refer TRS 1049).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders (10) includes the following recommendations. • Monotherapy with lamotrigine or levetiracetam, or valproic acid (sodium valproate), should be offered as first-line treatment for generalized-onset seizures in men/boys and women/girls who are not of childbearing potential (strong recommendation, high certainty of evidence). • In women and girls of childbearing potential with generalized-onset seizures, lamotrigine or levetiracetam should be offered as first-line monotherapy (strong recommendation, high certainty of evidence). • Monotherapy with lamotrigine or levetiracetam should be offered as first-line treatment for focal onset seizures in children and adults with epilepsy. If neither lamotrigine nor levetiracetam are available, then carbamazepine should be used as an alternate first-line treatment for focal onset seizures in children and adults with epilepsy (strong recommendation, high certainty of evidence). • In adults with established status epilepticus (i.e. seizures persisting after two doses of benzodiazepines), either intravenous postherniation, intravenous phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproic acid (sodium valproate) should be considered with appropriate monitoring (conditional recommendation, low certainty of evidence). • In children with established status epilepticus (i.e. seizures persisting after two doses of benzodiazepines), intravenous fosphenytoin, intravenous phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproic acid (sodium valproate), should be considered with appropriate monitoring (conditional recommendation, moderate certainty of evidence).

Availability

Levetiracetam is available globally in originator and generic brands. Levetiracetam is already listed on the country-specific EMLs in Albania, Algeria, Bahrain, Bhutan, Bulgaria, Czechia, Estonia, Iran (Islamic Republic of), Iraq, Jordan, Latvia, Lithuania, Maldives, Mexico, Montenegro, North Macedonia, Oman, Poland, Portugal, Romania, Russian Federation, Rwanda, Serbia, Seychelles, Slovakia, Sweden, Syrian Arab Republic, Thailand, Timor Leste and Viet Nam (11).

Other considerations

Women and girls of childbearing potential Very specific risks arise in females with epilepsy that need to be considered across the lifespan (12). It is important that antiseizure medicines have limited interactions with contraception or hormone replacement therapy and that medications with limited teratogenic risk are available (9). Enzyme-inducing medications such as carbamazepine, phenytoin and 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 contraceptives thereby making it preferred for women taking these products. Levetiracetam is also the antiseizure medicine with the best overall safety in pregnancy (12, 13). Levetiracetam is not thought to substantially increase teratogenic risk above that seen in the general population. By contrast, valproic acid increases the risk of structural anomalies (e.g. spina bifida, cleft lip, cleft palate, cardiac anomalies) up to around 10% and women taking valproic acid through pregnancy have a 30–40% risk that their offspring will have neurodevelopmental anomalies (autism, learning disabilities) (13). Older people Levetiracetam has previously been reported as effective in reducing seizure frequency in older adults aged > 65 years (14). In that study, 76.9% of patients had at least a 50% reduction in seizure frequency, with only 19.2% experiencing an adverse event leading to discontinuation. Levetiracetam is not an enzyme-inducing antiseizure medicine. The reduced drug–drug interactions are particularly important in older people who may be on polytherapy. Levetiracetam also does not have an adverse effect on bone health, giving it additional advantages over carbamazepine, phenytoin, phenobarbital and valproic acid. Specific ethnic populations Many antiseizure medicines can cause skin rashes, including carbamazepine, lamotrigine and phenytoin. However, the HLA-B*1502 allele, which is more common in people of Han Chinese origin, is associated with a marked increase in the risk of severe skin rashes with carbamazepine and phenytoin (15). Levetiracetam is substantially less likely to be associated with rash, even in people who have experienced dermatological reactions with one of the other antiseizure medicines. Status epilepticus Status epilepticus is defined as a convulsive seizure lasting more than 5 minutes. It is associated with a significant risk of morbidity and mortality and expedient management is essential. Benzodiazepines (diazepam, lorazepam) are established as first-line treatment, but the choice of second-line treatment if benzodiazepines are ineffective is uncertain. Two recent studies have evaluated different antiseizure medicines for use in status epilepticus. The Established Status Epilepticus Treatment Trial (ESETT) randomized 384 adult participants to receive levetiracetam, fosphenytoin or valproic acid. Efficacy and incidence of adverse events were similar for all agents (16). The EcLiPSE trial randomly assigned 1432 children aged 6 months to 18 years to receive phenytoin or levetiracetam for benzodiazepine-refractory status epilepticus (17). Levetiracetam was not significantly superior to phenytoin for status epilepticus, which concurs with another study (ConSEPT) (18). However, the EcLiPSE study investigators concluded that the ease of administration of levetiracetam meant that it could be an appropriate

treatment for benzodiazepine-refractory status epilepticus. Although levetiracetam is not necessarily more effective than either phenytoin or valproic acid in treating established status epilepticus, there may be some specific advantages in resource-constrained settings of having levetiracetam available to treat status epilepticus.

1. Epilepsy – fact sheet [internet]. Geneva: World Health Organization; 2023 (https://www.who.int/news-room/fact-sheets/detail/epilepsy, accessed 6 October 2023).
2. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet. 2019;393(10172):689–701.
3. Kwan P, Brodie MJ. Clinical trials of antiepileptic medications in newly diagnosed patients with epilepsy. Neurology. 2003;60(11 Suppl 4):S2–12.
4. Nevitt SJ, Sudell M, Cividini S, Marson AG, Tudur Smith C. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev. 2022;4(4):CD011412.
5. Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018;91(2):74–81.
6. Leone MA, Giussani G, Nevitt SJ, Marson AG, Beghi E. Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure. Cochrane Database Syst Rev. 2021;5(5):CD007144.
7. Kanner AM, Bicchi MM. Antiseizure medications for adults with epilepsy: a review. JAMA. 2022;327(13):1269–81.
8. Marson A, Burnside G, Appleton R, Smith D, Leach JP, Sills G, et al. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet. 2021;397(10282):1375–86.
9. Veroniki AA, Cogo E, Rios P, Straus SE, Finkelstein Y, Kealey R, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med. 2017;15(1):95.
10. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders, third edition. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/374250, accessed 21 November 2023).
11. Global essential medicines [internet]. Geneva: World Health Organization; 2019 (https://global.essentialmeds.org/dashboard/countries, accessed 6 October 2023).
12. Stephen LJ, Harden C, Tomson T, Brodie MJ. Management of epilepsy in women. Lancet Neurol. 2019;18(5):481–91.
13. Antiepileptic drugs in pregnancy: updated advice following comprehensive safety review [internet]. London: Medicines and Healthcare Products Regulatory Agency; 2021 (https://www.gov.uk/drug-safety-update/antiepileptic-drugs-in-pregnancy-updated-advice-following-comprehensive-safety-review, accessed 6 October 2023).
14. Ferrendelli JA, French J, Leppik I, Morrell MJ, Herbeuval A, Han J, et al. Use of levetiracetam in a population of patients aged 65 years and older: a subset analysis of the KEEPER trial. Epilepsy Behav. 2003;4(6):702–9.
15. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med. 2011;364(12):1126–33.
16. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med. 2019;381(22):2103–13.
17. Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet. 2019;393(10186):2125–34.
18. Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. Lancet. 2019;393(10186):2135–45.