

Proposal for the addition of levetiracetam to the Model Lists of Essential Medicines and Essential Medicines for Children for the treatment of focal onset and generalized onset epilepsy

Comments from the Department of Mental Health and Substance Use

The application provides evidence of the effectiveness and safety of levetiracetam for the treatment of generalized-onset seizures and focal-onset seizures in adults and children based on a recent Cochrane review: 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.

Levetiracetam is an anti-seizure medication that is listed as a mainstay treatment for epilepsy in a number of guidelines including the 2022 National Institute of Health and Care Excellence guideline on epilepsies in children, young people and adults.

WHO's mhGAP guideline for mental, neurological, and substance use (MNS) disorders includes recommendations for the management of epilepsy. This guideline is currently being updated and will be published later this year. The Guideline Development Group has reviewed the evidence for the use of levetiracetam and will be including it in the epilepsy treatment recommendations. A point to be noted is that levetiracetam is included as additional medication to the currently recommended medications. The full set of recommendations is the following:

Monotherapy with any of the standard antiseizure medications (carbamazepine, phenobarbital, phenytoin, and valproic acid) should be offered to children and adults with convulsive epilepsy. Given the acquisition costs, phenobarbital should be offered as a first option if availability can be assured. If available, carbamazepine should be offered to children and adults with focal onset seizures.(mhGAP guideline 2015 update).

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

The advantages of levetiracetam over other antiseizure medicines are in terms of its side effect profile. Especially of note is its safety in women and girls of child bearing potential. Given the risks associated with sodium valproate if prescribed to women and girls who are able to have children, levetiracetam should be used as first-line treatment in this population.

Most of the evidence described in the application is from high income settings though many issues especially safety in women and girls of child bearing potential are equally relevant to all.

In the evidence that is provided in the application, the network metaanalyses allowed comparison of levetiracetam with carbamazepine and lamotrigine, the antiseizure medication considered as first choice in focal epilepsy.

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

Comparisons of levetiracetam with other antiseizure medicines could not be performed.

The application also notes that though it is quite difficult to obtain accurate costings for levetiracetam in many settings, based on the available data, levetiracetam may be a cost-effective option especially in generic formulation.

The evidence profile does not provide data specifically for children or adults. However, age range for the network metaanalysis was 1-95 years old and sensitivity analysis results adjusted for age returned estimates similar to those displayed in main results.

The application proposes 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.

The evidence provided in the application supports this proposal and we are in agreement with this. Additional of levetiracetam to WHO's model essential medicines list for the treatment of epilepsy will address issues around availability, affordability and feasibility especially in low- and middle-income countries.

The application also provides the evidence on the efficacy of levetiracetam for status epilepticus in adults and children that does not respond to benzodiazepines and it proposes that levetiracetam is added to the current medications listed for treating benzodiazepine-refractory status epilepticus (phenobarbital, valproic acid/sodium valproate). We would suggest that this is considered in the complementary list considering the need for specialist monitoring in cases of benzodiazepine-refractory status epilepticus.