| A.24 | Levetiracetam – epilepsy – EML and EMLc |
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| **Draft recommendation** | ☒ Recommended<br>☐ Not recommended<br>Justification:<br>Levetiracetam is a widely used antiepileptic medication that offers a range of benefits for the management of epilepsy. Its inclusion in the EML would be highly beneficial given its proven effectiveness, tolerability, and safety profile.<br><br>One key advantage of levetiracetam is its efficacy in treating both focal onset and generalized onset epilepsies, making it a valuable medication to have on the EML. For status epilepticus, MSF uses levetiracetam as a second-and third-line agent after benzodiazepines for both adults and children. Moreover, levetiracetam is well tolerated and has no negative effects on cognition and is free of long-term side effects. It has fewer side effects overall. Due to its safety profile, it is possible to increase the dose and reach adequate levels faster and without significant adverse effects compared to a medicine like lamotrigine. Similarly, due to having a wide therapeutic range with a low side effect rate, serum levetiracetam level monitoring is not required to assess for toxicity or subtherapeutic levels unlike older ASDs such as valproic acid for example. Levetiracetam has minimal interactions with other antiepileptic drugs, which makes it an option for patients who require polytherapy for seizure control and it does not interact with contraception or hormone replacement therapy. This is particularly relevant for individuals with epilepsy who require additional medications for comorbid conditions. Additionally, levetiracetam is safe for pregnant women with epilepsy, with no increased risk of teratogenicity.<br><br>Levetiracetam is also effective across all ages, including in the emergency treatment of status epilepticus without monitoring. Both oral and parenteral preparations in different strengths are available. |
| Does the proposed medicine address a relevant public health need? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br><br>Epilepsy is a neurological disorder that affects individuals of all ages, races, and ethnicities worldwide. Epilepsy affects approximately 50 million people globally, making it one of the most common neurological disorders worldwide. Epilepsy has a considerable impact on the quality of life of individuals who have the disorder and their families. It is a chronic condition characterized by recurrent seizures that can cause physical injury, emotional distress, and social stigmatization. Additionally, epilepsy imposes a significant economic burden on society through direct and indirect healthcare costs, lost productivity, and diminished quality of life. It is estimated that up to 75% of people with epilepsy in low- and middle-income countries do not receive appropriate treatment due to a lack of resources, infrastructure, and trained healthcare personnel. This highlights the need for improved access to diagnosis and treatment, to reduce the economic and social burden on individuals and society.<br><br>Levetiracetam is used as a first line drug in many types of seizures. |

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| Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?<br><br>(this may be evidence included in the application, and/or additional evidence identified during the review process) | ☒ Yes<br><br>☐ No<br><br>☐ Not applicable<br><br>Comments:<br><br>There is strong evidence supporting the efficacy and effectiveness of levetiracetam in the management of partial-onset seizures, generalized tonic-clonic seizures, and myoclonic seizures associated with juvenile myoclonic epilepsy. It has also been shown to have a favorable safety profile, with minimal drug-drug interactions and few adverse effects on cognition.<br><br>Randomized controlled trials have demonstrated the effectiveness of levetiracetam as first line and adjunctive therapy in treating partial-onset seizures in adults. Studies have shown that levetiracetam is more effective than carbamazepine in treating newly diagnosed partial-onset seizures in adults.<br><br>Levetiracetam is a safe and effective option commonly used in children for the management of epilepsy. It is approved for use in children as young as one month old for the treatment of partial onset seizures with or without secondary generalization. It is also approved for use in children six years of age and older for the treatment of primary generalized tonic-clonic seizures. Levetiracetam is well-tolerated in children. The dosing of levetiracetam may need to be adjusted based on the child's weight and renal function. |
| Does adequate evidence exist for the safety/harms associated with the proposed medicine?<br><br>(this may be evidence included in the application, and/or additional evidence identified during the review process) | ☒ Yes<br><br>☐ No<br><br>☐ Not applicable<br><br>Comments:<br><br>Levetiracetam has been extensively studied in clinical trials and its safety has been evaluated in various patient populations, including children and older adults. Overall, the available evidence supports the safety profile of levetiracetam as a treatment for epilepsy, with few significant adverse effects reported. Common adverse effects include dizziness, headache, and somnolence, but these are generally mild and transient. Unlike some other antiepileptic medications, levetiracetam is not associated with significant behavior and cognitive impairment.<br><br>Studies have also found that levetiracetam has a low potential for drug interactions, with no known interactions with hormonal contraceptives or hormone replacement therapy. Additionally, it is well-tolerated in patients with comorbid conditions, such as liver or cardiac disease.<br><br>Regarding long-term safety, studies have shown that levetiracetam does not appear to have any significant adverse effects on organ function or lead to any significant cognitive decline. However, dosage adjustment is required for patients with renal impairment as it is primarily eliminated through the kidneys. |

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| Are there any adverse effects of concern, or that may require special monitoring? | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments:<br>Levetiracetam is generally considered to be a safe medication with few significant adverse effects reported. The most reported adverse effects of levetiracetam include dizziness, headache, and somnolence. These effects are generally mild and transient and tend to occur most frequently during the first few weeks of treatment.<br><br>In rare cases, levetiracetam may cause more serious sleep disturbance, behavioral or psychiatric disturbances, including suicidal thoughts or behaviors especially in children and adolescents. Therefore, these patients need to be monitored closely for any changes in mood or behavior while taking levetiracetam. Also, rarely it may also cause hypersensitivity reactions. While levetiracetam has a low potential for drug interactions, it may interact with valproate and phenytoin which may require drug level monitoring in case of adverse effects. |
| Are there any special requirements for the safe, effective and appropriate use of the medicines?<br><br>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) | ☐ Yes<br>☐ No<br>☐ Not applicable<br><br>Comments:<br>Levetiracetam has a wide therapeutic index, and there is no established correlation between levetiracetam levels and clinical efficacy or toxicity. Therefore, routine laboratory monitoring of levetiracetam levels is generally not necessary. However, drug level monitoring is helpful in case of breakthrough seizures despite being on a stable dose of levetiracetam. Dosage adjustment is required for patients with renal impairment as it is primarily eliminated through the kidneys. While levetiracetam is generally well-tolerated, some patients may experience mood changes or behavioral effects, such as irritability, aggression, and depression. Patients and caregivers should be advised to report any changes in mood or behavior to their healthcare provider. Abrupt discontinuation of levetiracetam can increase the risk of seizures. |
| Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: The value of Levetiracetam inclusion for treatment of the epilepsies is important especially in LMICs that experience suboptimal diagnoses, inadequate access to treatment, poor health education, and many other barriers that are specific to these environments. The inclusion of this generic molecule into the WHO EML and potentially into national EMLs will result in an opportunity to widen the treatment options for patients to receive for management of seizure disorder. Also, generic formulation of Levetiracetam, would be a relatively cheaper anti-seizure medication compared to lamotrigine which is already on the WHO EML>. |

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| Are there any issues regarding the registration of the medicine by national regulatory authorities?<br><br>(e.g. accelerated approval, lack of regulatory approval, off-label indication) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments:<br><br>Levetiracetam had already received regulatory approval from various regulatory agencies around the world as an adjunctive therapy and monotherapy in the treatment of partial-onset seizures with or without secondary generalization in adults. In the US FDA has approved levetiracetam for use in children aged 4 years and older with partial-onset seizures as adjunctive therapy, and for the treatment of myoclonic seizures in children aged 12 years and older with juvenile myoclonic epilepsy. In the European Union, levetiracetam has been approved for use in children from 1 month of age with epilepsy for the treatment of partial-onset seizures with or without secondary generalization. Levetiracetam has also been approved for use in children in many other countries including Canada, Australia, and Japan. |
| Is the proposed medicine recommended for use in a current WHO guideline?<br><br>(refer to: https://www.who.int/publications/who-guidelines) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: It is recommended as first-line treatment in many guidelines (e.g. American Epilepsy Society, NICE guidelines, German Neurological Society).<br><br>WHO Mental Health Gap Action Programme (mhGAP) Guideline, the Guidelines Development Group recommendations include:<br>• 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.<br>• In women and girls of childbearing potential with generalized onset seizures, lamotrigine or levetiracetam should be offered as first line monotherapy.<br>• 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.<br>• 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 |