A.24 Levetiracetam

- Tablets (250mg, 500mg, 750mg, 1g)
- Oral solution (100mg/mL)
- Injectable solution (5mg/mL, 10mg/mL, 15mg/mL, 100mg/mL)

MSF strongly supports the inclusion of levetiracetam for the treatment of adults and children with focal onset and/or generalized onset epilepsy and/or status epilepticus in Section 5 “Anticonvulsants/antiepileptics” of both the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc).

Epilepsy, a disorder that manifests as recurrent seizures, has significant neurobiological, cognitive, social, and economic consequences for individuals, communities, and countries. Around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally with nearly 80% of these living in low- and middle-income countries (LMICs). While seizures can be controlled with appropriate anti-seizure drugs (ASDs) resulting in up to 70% of people living with epilepsy achieving remission, the reality of a majority of LMICs, is that epilepsy remains a largely untreated condition with a treatment gap ranging from 70 to 94%.

Though access to appropriate diagnosis and treatment of epilepsy is low, MSF strives to provide appropriate management of epilepsy including ASDs. Indeed, MSF manages patients with seizures and epilepsy throughout its programs worldwide in multiple settings including: emergency departments where status epilepticus is a common presentation, in-hospital care, primary care and outpatient clinics.

MSF clinical guidelines and pharmacopoeia include phenytoin, phenobarbital, sodium valproate, carbamazepine, and benzodiazepines. Levetiracetam was introduced in MSF programs 5 years ago for managing epilepsy and status epilepticus due to its safety profile for both children and adults.

MSF would like to draw the attention of the expert Committee to the following facts:

1- Phenytoin, phenobarbital, sodium valproate and carbamazepine do not cover the needs of all patients living with epilepsy in our contexts:

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1 https://www.who.int/news-room/fact-sheets/detail/epilepsy
a. Women: Many ASDs are not indicated for women of childbearing age due to the potential teratogenic effect on the fetus, especially valproic acid which is absolutely contraindicated in women of childbearing age. Moreover, pharmacological interactions with certain types of contraceptive pills further limit the choice of ASDs in this population.

b. Elderly people: Current ASDs in the EML are not appropriate for elderly people due to their cognitive side effects.

c. Drug-drug interactions: All 4 ASDs have more major drug-drug interactions compared to levetiracetam. Sodium valproate has 21 major interactions, carbamazepine has 210 major interactions, phenytoin has 212 major interactions, and phenobarbital has 213 major interactions. The classes of medications that either preclude the use of ASDs or require very close monitoring include many commonly prescribed medications in these contexts. For example, the main antiretroviral regimens used in HIV/AIDS, benzodiazepines, multiple classes of antidepressants, estrogen containing products including contraceptives, anti-hypertensives like calcium channel blockers, and important classes of antibiotics like macrolides and carbapenems. Levetiracetam, by contrast, has 5 major interactions, and these are rarely prescribed medications in these contexts such as ketamine and specific opioid formulations.

2- The efficacy of levetiracetam is comparable to older ASDs and can be used in a broader range of clinical scenarios than any single older ASD:

a. It has a broader spectrum of use and includes both generalised and focal onset epilepsy with fewer side effects overall.

b. For status epilepticus, MSF uses levetiracetam as a second-and third-line agent after benzodiazepines for both adults and children. It is easier to dose without requiring the same cardiac monitoring of drugs like phenytoin.

c. 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.

d. Similarly, due to having a wide therapeutic range with a low side effect rate, it is not required to check serum levels of levetiracetam to assess for toxicity or subtherapeutic levels unlike older ASDs such as valproic acid for example.

e. Levetiracetam has few interactions with other antiepileptic drugs, which makes it an option for patients who require polytherapy for seizure control.

In most of the contexts in which MSF operates, having an ASD that is easier and safer to prescribe and also allows harmonisation of treatment across populations is the key to improving quality of life for people living with epilepsy. Simplifying the acute seizure management treatment algorithm for medical staff also opens the potential for task sharing, safer remote management, and increased access to care.

3- Some medications are subject to various levels of importation and prescribing restrictions as controlled substances (INCB List of Psychotropic Substances under International Control (Green List)) as phenobarbital, which can severely limit the access and availability to patients.
In recent years, global supply chain disruptions with respect to medications as well as their component parts, have been experienced further limited availability. The addition of a new drug is important to close an access gap in such increasingly common situations.

Challenges to providing optimal care go beyond the medicines used, and include the complications from underlying etiologies, the capacity to provide acute emergency care with monitoring, airway protection, and drugs, the time required to reach a therapeutic dose and clinical stabilization, and organization of long-term follow-up care which includes reliable access to services, trained care providers, and drugs. This is in addition to the stigma that is often associated with neurological conditions like epilepsy.

While these challenges remain unaddressed, the addition of a safer drug to the pharmacopeia of ASDs can certainly improve the acute management of status epilepticus as well as the long-term management of epilepsy in all ages, but particularly in women, elderly people, and people living with HIV/AIDS and other comorbidities who rely on other drugs that may limit the ASD options. MSF supports the introduction of levetiracetam in the EML and EMLc to address above-described challenges seen in MSF operational work and which may be minimised by levetiracetam inclusion.

In light of all these elements, MSF urges the 24th Expert Committee on the Selection and Use of Essential Medicines to include levetiracetam in Section 5 “Anticonvulsants/antiepileptics” of both the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc), for the treatment of adults and children with focal onset and/or generalized onset epilepsy and/or status epilepticus.

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