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The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards
(HPS) 20 Avenue Appia
CH-1211 Geneva 27

March 27th, 2023

Subject: Statement of support for the addition of Levetiracetam to the WHO Model List of Essential Medicines

Reference: "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", submitted by Arjune Sen (arjune.sen@ndcn.ox.ac.uk) and Helen Cross (h.cross@ucl.ac.uk): *Click here to the original application by Arjune Sen and Helen Cross*

Dear Expert Committee Members,

UCB, as the innovator of Levetiracetam, is providing this letter in support of the application for Levetiracetam to be added to the WHO Model List of Essential Medicines (WHO EML).

At UCB, we believe everyone deserves to live the best life that they can – as free as possible from the challenges of disease. We develop solutions across neurology, immunology, and other areas where our expertise, innovation, and ambition align with the needs of those who live with severe diseases. UCB has a rich heritage in epilepsy, with over 30 years of experience in the research and development of antiseizure medications drugs. As a company with a long-term commitment to epilepsy research, we want to contribute to solutions that address unmet medical needs for all patients living with epilepsy.

Epilepsy is a brain disease characterized by abnormal brain activity causing seizures. It carries neurological, cognitive, psychological, and social consequences through stigma and discrimination and accounts for a significant proportion of the world's burden of disease[1], affecting around 50 million people worldwide. The number of people with epilepsy is expected to increase further due to rising life expectancy worldwide and an increasing proportion of

people surviving insults which often lead to epilepsy. This is why, in 2019, WHO presented a first global report describing epilepsy a public health imperative to achieve the health-related Sustainable Development Goals (SDGs).[2]

Patients with epilepsy in low- and middle-income countries (LMICs) experience multiple deficiencies that result in health consequences. The recurrence of seizures and their physical and psychological consequences make epilepsy a burdensome neurological disorder. However, medical treatment of epilepsy with first line antiseizure medications can render up to 70% of patient's seizure free and often must be continued for life.[3]

Nearly 80% of people with epilepsy live in low- and middle-income countries (LMIC)[4], where treatment gaps exceed 75% in most low-income countries and 50% in most middle-income countries despite the effectiveness of available antiseizure medicines[5].

Access to essential medications for neurological disorders is low in primary care settings across WHO regions, particularly in the African and South-East Asia regions. If epileptic seizures are recognized and properly diagnosed in most countries, often only older generation anticonvulsants (such as carbamazepine, phenobarbital, phenytoin, or valproic acid) are available in the primary care setting[5]. Compounds like carbamazepine, phenytoin, and phenobarbital as hepatic enzyme inducers carry significant metabolic disadvantages by reducing the duration and action of other comedications like anticoagulants, cytotoxics, analgesics, antiretrovirals, glucocorticoids, statins, antihypertensives, oral contraceptives, psychoactive drugs, immunosuppressants and increase the risk for comorbidities, including osteoporosis, sexual dysfunction, and vascular disease.[6] In addition, valproate is not recommended for women of childbearing age for the risk of congenital malformations and cognitive deficits and neurodevelopmental disorders in children[7] (FDA safety Announcement[8], MHRA advice[9]).

Hence availability of modern anticonvulsants is a problem that must be given high priority and should be part of global goals and targets. We therefore support the actions and goals of the intersectoral action plan on epilepsy and other neurological disorders 2022 – 2031 and here specifically to goals to make anti-seizure medicines more widely available and to provide affordable access in low- and middle-income countries through appropriate policy, funding and partnerships between the research community, health professionals, policymakers and the private sector.

Levetiracetam therapeutic efficacy in patients with epilepsy has been assessed in a large number of clinical trials and it has been approved for the use in focal and generalized epilepsy in more than 90 countries (for focal epilepsies by EMA (adjunctive therapy) and FDA (monotherapy) from $\geq$ 1 month of age) and is recommended as first-line treatment in many guidelines (e.g. American Epilepsy Society[10], NICE[11], German Neurological Society[12]). Levetiracetam has a wide safety margin and provides potent, broad-spectrum seizure protection.

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It does not modulate any of the three main mechanisms accounting for the anticonvulsive action of classical antiseizure medications but is binding to the synaptic vesicle protein 2A (SV2A), thought to be involved in the regulation of vesicle exocytosis. It has a linear PK, low extent of metabolism, does not induce hepatic enzymes, is not significantly protein-bound (< 10%), is unlikely to interact with the pharmacokinetic (PK) of other drugs, and is available as tablets, oral solution, and for intravenous use. Prolonged use of Levetiracetam in pregnant women has not-identified a drug-associated risk of major birth defects or miscarriage based on data and experience from over two decades and risk of neurodevelopmental disorders seems low[13].

The value of Levetiracetam inclusion for treatment of the epilepsies should be recognised, 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 mostly 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 – as scientific evidence shows - a safe and efficacious medicine. This in combination with the local anchoring of epilepsy into the continuum of care at the primary health care level bears a promise " ... to address the health needs of people with epilepsy through a person-centred approach."[14]

Adding Levetiracetam to the WHO EML is an important step in supporting the global community in moving from evidence to action.

DocuSigned by:
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