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A.4 Baclofen

MSF strongly supports the inclusion of baclofen in the Core List of both the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc), for treatment of spasticity in adults and children with cerebral palsy.
The proposed formulations to be included are tablet 10 mg, liquid 10 mg/5 ml and intrathecal pump 500 mcg/ml.

Currently there are no medicines listed in the EML and EMLc with the indication to treat spasticity in adults and children with cerebral palsy. Diazepam is the only alternative medicine present on the EML and EMLc that has been used for spasticity, but it is not listed for this specific indication and presents several (and some serious) adverse effects including confusion, sedation, memory impairment, respiratory depression, paradoxical reactions, hypotension, and risk of overdose.

Baclofen acts on $GABA_B$ receptors on both pre- and post-synaptic neurons in the central and peripheral nervous systems. It inhibits reflex transmission at the level of the spinal cord. When baclofen binds to $GABA_B$ receptors, it causes hyperpolarization of neuronal membranes, reduces calcium influx into presynaptic nerve endings and stimulates inhibitory neuronal signaling in postsynaptic neurons. As a result, the episode of spasticity is relieved. In addition, it may act by decreasing the action potential of postsynaptic motor neurons, which in turn inhibits neuronal signaling. The clinical effect of baclofen as an analgesic agent is partially explained by its central action, which affects the release of excitatory neurotransmitters, among which is substance P. Substance P is considered a neuromodulator of the pain response in the central nervous system and appears to be a critical player in neuronal sensitization to pain, as well as implicated in cortical processing of the pain response in the brain, notably the emotional aspects of pain.

Baclofen oral and intrathecal is recommended in the 2023 WHO guidelines “Package of interventions for rehabilitation. Module 3. Neurological conditions”. Baclofen is recommended in several clinical guidelines issued by the Brazilian Medical Association, French Agency for Health Product Safety, Italian Society of Physical and Rehabilitative Medicine & Italian Society of Neuropsychiatry of Childhood and Adolescence, NICE (UK), American Academy for Cerebral Palsy and Developmental Medicine and American Academy of Physical Medicine and Rehabilitation.

Originally designed to treat epilepsy, baclofen has become the most commonly prescribed medicine to treat muscle spasticity. Muscle spasticity is defined as a disordered sensory-motor control caused by an upper motor neuron lesion that manifests as intermittent or prolonged involuntary muscle contractions. Spasticity presents in a variety of neurological conditions - including cerebral palsy, multiple sclerosis, spinal cord injuries and brain injuries - and can be associated with pain, sleep disturbances and motor impairment, which may have a substantial impact on the patient’s and caregiver’s quality of life and place a significant burden on the healthcare system. Many characteristics of pain caused by spasticity and its pain-related physical, psychological, and behavioral symptoms can present with neuropathic pain, and baclofen is used as an adjuvant analgesic for its management.

Baclofen is FDA-approved for managing episodes of reversible spasticity. It is effective in managing muscle spasticity by relieving flexor spasms and clonus, and the associated pain generated.

Intrathecal use of baclofen is also approved by the FDA to treat spasticity caused by a cerebral pathology, such as a traumatic brain injury, or severe spasticity from a spinal cord lesion, when these central etiologies are refractory to maximum dosing with oral baclofen or other approved antispasmodic agents. Off-label use of baclofen has also been shown effective for conditions such as intractable hiccups, nocturnal leg cramps from lumbar spinal stenosis, phantom limb pain, and for short-term treatment of spasticity from cerebral palsy in children. It is commonly used as an adjuvant analgesic for some forms of neuropathic pain, such as trigeminal neuralgia, and can be effective in the management of complex regional pain syndrome.

Since 2014, MSF has been using oral baclofen in the Reconstructive Surgery Project in Amman, Jordan, for management of painful spasticity associated with rehabilitative physiotherapy and as an adjuvant for treatment of perioperative neuropathic pain. In current local practice, treatment begins at 5 mg per os and is incrementally increased every 3 days after evaluation of possible side effects until an optimal response is achieved. The target dose is up to 20 mg three times a day. Patients are monitored for possible adverse effects of treatment, including transient sedation, confusion, muscle weakness, vertigo and nausea. Caution is noted for patients with renal or hepatic impairment and the elderly, and treatment avoided in pregnant women (pregnancy category C drug). Breast-feeding is not a contraindication due to the low drug level in breast milk, but newborns should be monitored for signs of sedation. Of note, abrupt cessation after more than 2 months of therapy can cause seizures and hallucinations.

Baclofen has a low potential for addiction but can lead to physical dependency in long-term or high-dose use. When discontinuing treatment, gradual dose reduction under medical supervision is recommended to prevent withdrawal symptoms, which may include anxiety, tremors or seizures. Other forms of dependency and cravings may develop, notably when it is used improperly or at very high doses. As a central nervous system depressant, baclofen toxicity produces clinical signs of sedation, depressed level of consciousness and respiratory depression, and can be fatal. Baclofen-related mortality is rare with most deaths caused by intentional toxicity and more often than not in patients with a history of mental health issues and substance abuse problems.

Baclofen has been approved in Europe since early 1970's (1974 in France), FDA-approved since 1977, and is already available as a generic. Its inclusion in the EML and EMLc will serve as a basis for National Essential Medicines lists and therefore should attract additional manufacturers, facilitate importations, alert manufacturers about the need for local registrations, allow for better competition between manufacturers in order to improve accessibility, particularly in low- and middle-income countries, and give a strong signal to manufacturers, generic producers, country programs and regulatory authorities.

Considering all these elements, MSF urges the 25th Expert Committee on the Selection and Use of Essential Medicines to include baclofen in the Core List of both the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children, for treatment of spasticity in adults and children with cerebral palsy.

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