A.4 Baclofen – EML and EMLc

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): The application is submitted for addition of baclofen as an individual or square box listing to the EML and EMLc, under section 5, for the treatment of spasticity in children and adults with cerebral palsy, by the International Cerebral Palsy Society, Bath, United Kingdom, with collaboration from 26 associations and experts in 21 countries (Australia, Argentina, Brazil, France, Ghana, Greece, Italy, Ireland, Jordan, Kenya, Lebanon, Mauritius, Nigeria, Pakistan, People's Republic of China, Portugal, Spain, Switzerland, UK, USA, Yemen). Fifteen support letters representing some of these associations were annexed. This application focuses primarily on cerebral palsy (CP) and suggests baclofen as first line pharmacological treatment for spasticity, in the following dosage forms: Tablet 10mg, Liquid 10mg/5mL and Intrathecal pump 500 mcg/mL. Treating spasticity is urgent to reduce contractures, deformities and pain; and to improve posture, mobility and overall physical function. The are no alternatives to treat spasticity in either list. Specific surgery may not be safe or effective and other drugs, such as diazepam, which improves spasticity by potentiating the effects of gamma-aminobutyric acid (GABA) in the central nervous system, may be overly sedating, cause impaired memory/cognition and respiratory depression with higher doses. Paradoxical reactions to diazepam and acute withdrawal can be severe. It is estimated that 50 million people around the world have CP. Individuals with CP may have varying degrees of neurologic impairments such as weakness, sensory deficits, cognitive impairments, loss of selective motor control, incoordination and hypertonia including spasticity, dystonia and choreoathetosis. Even if no cure is available, early diagnosis and treatment can have a meaningful impact on an individual's overall function and quality of life. Early management of spasticity can help achieve improvement of function; prevention of contractures; help with care, comfort, and positioning; improve weight gain. Interventions include motion exercises, casting and bracing, rehabilitation therapies, neurolytic blocks, neurotoxin injections, rhizotomies and orthopedic surgeries, oral medications and intrathecal baclofen pump. However, quality of evidence supporting intrathecal baclofen is low and for oral baclofen evidence is mostly lacking. Most existing evidence is for children. Oral baclofen would provide a safe and inexpensive alternative for this population, since the requirement for intrathecal administration is a surgical intervention to place a subcutaneous device as well as maintenance and eventual replacement of this device, which is mostly unavailable or hard to come by in LMIC. Baclofen is a generic drug, with regulatory approval in several countries and availability. Cost of oral baclofen is acceptable for health systems in general, but ITB is very expensive. Placement under section 5 would involve a new subsection. Considering that some evidence exists but manly for ITB in children, even if this intervention is costly and requires adequate health services for implementation, and that oral baclofen might be a safe alternative in LMIC, even if use is not completely supported by evidence, but mainly based on use, I recommend, inclusion of intrathecal baclofen and oral baclofen in the EMLc, but not in the EML.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? Diazepam, but not listed for cerebral palsy specifically. (https://list.essentialmeds.org/)	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? Baclofen acts at the spinal cord level to neuro-inhibit the monosynaptic reflex arc and is commonly used to treat spasticity in children. Baclofen is reported to be a well-established medication that is listed as a first-line treatment for spasticity in multiple clinical guidelines, including in Brazil, France, Italy, UK and USA. Most evidence is based on the outcomes of studies in children, but with low quality of evidence, and more trials are needed to assess its efficacy in adults.	☒ Yes ☒ No ☐ Not applicable

Eight systematic reviews and meta-analyses are cited as evidence of baclofen for cerebral palsy. Seven studies found that ITB had from any to significant impact[1] on the reduction of spasticity, and an effective option for managing severe spasticity. However, evidence was of low or very low quality. For oral baclofen, research on efficacy is limited. One review cites that data is insufficient to support or refute use in children and adolescents. One SR recommends oral baclofen may be considered for adults with cerebral palsy, and oral or intrathecal baclofen for children with cerebral palsy[2]. NICE (2019)[3] guidance on cerebral palsy in adults suggests that some limited evidence for effectiveness in children and young people could be extrapolated to the adult population, despite no evidence of oral baclofen for treating spasticity in adults with cerebral palsy. All six studies included in a Cochrane review suggest intrathecal baclofen is effective for reducing spasticity in children with cerebral palsy. The outcomes include a) significant differences ($p<0.05$) in tone in the lower extremities between the placebo values and each of the baclofen dose values; The review highlights that these findings are limited by small sample sizes and methodological issues, including high or unclear risk of bias, in the studies in this review[4].	
Does adequate evidence exist for the safety/harms associated with the proposed medicine? There is less reported evidence for safety, if compared to effectiveness. Sedation may happen but sedating effects generally improve over several days to weeks. Baclofen therapy is associated with potential complications, including life-threatening toxicity and withdrawal syndrome. These disorders require prompt recognition and a high index of suspicion. While these complications can develop following administration of either oral or intrathecal baclofen, the risk is greater with the intrathecal route[5]. In 501 ITB implantations, 203 medical complications were reported, including six new-onset seizures (2.96% of medical complications), seven increased seizure frequency (3.45%), 33 infections (16.26%), eight meningitis (3.94%), and 16 cerebrospinal fluid leaks (7.88%). Delivery system complications, including 75 catheter and pump complications, were also reported[1].	☐ Yes ☒ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? I was not able to reach a conclusion as to a favourable and meaningful balance of benefits to harms, because existing evidence for effectiveness is low-quality and safety evidence is less reported. This is case of experience of use, and of studies trying to support practice, but with feeble results. Recommendations for this drug are not made in light of hard evidence.	☐ Yes ☒ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? Oral baclofen does not cross the blood brain barrier easily; therefore, relatively higher doses are needed for ensuring effectiveness. Oral baclofen dosing is roughly based on body weight. Starting dose is at 2.5–5 mg/day, titrated up every few days to a maximum of 20-60 mg/ day. Intrathecal infusion effectively reduces spasticity more than oral baclofen and the intrathecal dose to reduce hypertonia is often only 1/1,000 of the oral dose. The United States Food and Drug Administration (FDA) approved ITB pumps for spasticity of cerebral origin in 1996. The pump can infuse baclofen in different modes from a simple continuous constant dose to variable intermittent doses. The total daily doses can vary between 50 and 1,500 mcg/day depending on hypertonia severity, treatment efficacy, and baclofen tolerance. A child weighing 15kg is big enough to accommodate a pump, implanted through an invasive procedure into the intrathecal space between the lower thoracic and upper cervical levels. The drug reservoir is accommodated subcutaneously, usually in the right lower quadrant of the abdomen and must be replaced. The pump needs to be refilled every few months, refills are done by inserting a needle through the skin into the pump reservoir. The pump's battery life lasts typically 5 to 8 years, and the entire pump is exchanged when the battery is depleted. A common initial infusion program is a total daily dose of 50-100 mcg at a simple continuous rate with baclofen concentration of 500 mcg/ml. The ITB dose and infusion mode are periodically adjusted as clinically appropriate. Cervically administered intrathecal baclofen seems to improve upper extremity spasticity and function, without causing more complications than thoracolumbar intrathecal baclofen. However, complications have not been thoroughly investigated and the available literature is of poor methodological quality. Further research is needed to confirm the efficacy and safety of one procedure over the other[6].	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☒ Yes ☐ No ☐ Not

Despite being the preferred clinical intervention for spasticity, access to intrathecal baclofen is limited, given the costs associated with placement and maintenance of a baclofen pump. Current economic literature supports the use of ITB therapy at least in the short-term. On average, intrathecal baclofen therapy increased the 5-year cost of treatment by $49 000 relative to alternative treatment, accompanied by an average gain of 1.2 quality-adjusted life-years. The net result was an ICER of $42 000 per quality-adjusted life-year. However, the additional cost and the need for surgical expertise mean that intrathecal baclofen is not available in many LMIC countries. Oral baclofen is available in HIC and in LMIC, and reasonably affordable by health systems. A comparative overview of its cost shows that average price for monthly treatment varies form 36 USD (US) to 4.50 USD (Bangladesh). There are no recent studies on its cost-effectiveness compared to other treatments.	applicable
Is the medicine available and accessible across countries? Baclofen, ATC code M03BX01, was first synthesized in 1962, It is a generic medication and additionally, is produced under different brand names, including Beklo, Baclodol, Flexibac, Gablofen, Kemstro, Liofen, Lioresal, Lyflex, Clofen, Muslofen, Bacloren, Baklofen, Sclerofen, Pacifen, Ozobax, Fleqsuvy and Lyvispah. Baclofen is currently included in the national EML of at least 46 countries.	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval? Baclofen was approved in Europe and the US (FDA) in the following decade. The intrathecal formulation was subsequently approved in 1984. Baclofen is also approved by other regulatory agencies including the European Medicines Agency (EMA), Swissmedic, and Japanese Health Authority PMDA, Spanish Agency of Medicines and Medical Devices (AEMPS), by several RA in South America, such as Anvisa (Brazil). It is listed in several pharmacopeias, including US, European and BP.	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable

Additional references

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3. NICE. Cerebral palsy in adults. NICE guideline Published: 15 January 2019. Available at: www.nice.org.uk/guidance/ng119

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5. Romito JW, Turner ER, Rosener JA, Coldiron L, Udipi A, Nohrn L, Tausiani J, Romito BT. Baclofen therapeutics, toxicity, and withdrawal: A narrative review. SAGE Open Med. 2021 Jun 3;9:20503121211022197. doi: 10.1177/20503121211022197.

6. Jacobs NW, Maas EM, Brusse-Keizer M, Rietman HJS. Effectiveness and safety of cervical catheter tip placement in intrathecal baclofen treatment of spasticity: A systematic review. J Rehabil Med. 2021 Jul 9;53(7):jrm00215. doi: 10.2340/16501977-2857.