

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):

baclofen for the treatment of spasticity in adults and children with cerebral palsy

note: reducing muscle tone is a surrogate outcome for improving function

Medicine

Oral or intrathecal administration

Oral is less favored because of a large variability in oral absorption and elimination creating difficulties in determining the appropriate dosage in pediatric patients; poor blood–brain barrier penetration and a short half-life of 3-4 hours, necessitating repeated daily dosing

Oral is often used to assess response and tolerance and thus whether the patient may benefit from the intrathecal route.

baclofen can be titrated to individual patient needs

disadvantage of long-term maintenance requirements, particularly for Intrathecal baclofen

one alternative is selective dorsal rhizotomy but too invasive and not widely available

Efficacy:

Intrathecal baclofen versus placebo

2015 Cochrane SR (outdated)

2024 SR: intrathecal baclofen therapy delivered via spinal implant

- spasticity levels reduction; Ashworth Scale or Modified Ashworth Scale scores: SMD –1.70 (95% CI –2.15 to –1.25). SMD values suggests large effects; timeframe not reported by median follow up in included studies is around 12 months
- motor function; Gross Motor Function Measure (GMFM): GMFM scores: SMD 0.15 (95% CI 0.08 to 0.22). SMD values suggest trivial effect (reported in the SR as small) ; timeframe not reported by median follow up in included studies is around 12 months

While the authors did not assess certainty of evidence, there are concerns about heterogeneity, and risk of bias.

Oral baclofen versus placebo

2015 SR (outdated): “There is some limited short-term evidence that intrathecal baclofen is an effective therapy for reducing spasticity in children with cerebral palsy. The effect of intrathecal baclofen on long-term spasticity outcomes is less certain.”

Oral baclofen versus other therapies

Alternatives include diazepam and tizanidine. Apparently there no high enough certainty evidence to support reliable conclusions about the comparative efficacy and safety of these medicines.

Safety:

2024 SR: intrathecal baclofen therapy delivered via spinal implant; 501 participants:

- 75 catheter or pump complications, including: 16 reports of cerebrospinal fluid leaks; also dislocations, malfunctions, and disconnections
- 203 medical complications, including: 6 reports of new-onset seizures, 7 reports of increased seizure frequency; 33 reports of infections, including 8 reports of meningitis

	<p><u>oral baclofen</u> has moderate systemic side effects including somnolence, confusion, polyuria, headache, weakness, memory deficits, orthostatic hypotension; and severe neurological side effects including sudden withdrawal syndrome, baclofen overdose, and risk of seizures</p> <p>Specific groups:</p> <ul style="list-style-type: none"> • Individuals with history of stroke may have reduced tolerance for baclofen • Individuals with history of psychiatric conditions may experience a temporary increase in symptoms. • Individuals prone to autonomic dysreflexia, may experience an episode with specific stimuli or sudden withdrawal of baclofen • Individuals with epilepsy may experience variability in seizure control <p>baclofen may affect patients who rely on muscle spasticity to maintain posture or mobility</p> <p>Balance:</p> <p>Probably favorable for intrathecal but less clearly favorable for oral baclofen for the treatment of spasticity in adults and children with cerebral palsy.</p> <p>Special requirements for use:</p> <p>Given the potential for adverse reactions with sudden discontinuation of baclofen (hallucinations, seizures, increased muscle tone) dosage should be tapered gradually; similarly a gradual dose reduction before delivery can help prevent withdrawal symptoms in neonates of mothers taking baclofen</p> <p>Budget issues:</p> <p>Intrathecal baclofen is expensive (cost of the medicine, surgical procedure, regular interventions to refill and maintain the pump); might be cost effective in HIC</p> <p>Oral baclofen is more affordable, no recent studies on its cost-effectiveness</p> <p>Regulatory approval:</p> <p>Baclofen tablets are widely available globally.</p> <p>Baclofen oral liquid and intrathecal injection formulations are not widely available.</p>
<p>Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives?</p> <p>(https://list.essentialmeds.org/)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Diazepam may be used for the same indication</p>
<p>Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?</p> <p>(e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Probably yes for intrathecal</p> <p>Unclear for oral</p>
<p>Does adequate evidence exist for the safety/harms associated with the proposed medicine?</p> <p>(e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Both intrathecal and oral baclofen have significant adverse effects profiles</p>
<p>Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Probably favorable for intrathecal but not for oral baclofen for the treatment of spasticity in adults and children with cerebral palsy.</p>
<p>Are there any special requirements for the safe, effective and appropriate use of the medicines?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p>

25th WHO Expert Committee on Selection and Use of Essential Medicines
Expert review

(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	Caution re: side effects
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Yes for oral, less available for injectable
Does the medicine have wide regulatory approval?	<input type="checkbox"/> Yes, for the proposed indication <input type="checkbox"/> Yes, but only for other indications (off-label for proposed indication) <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable