

I.10 Prednisolone, sumatriptan and verapamil – EML

Reviewer summary	<input checked="" type="checkbox"/> Supportive of the proposal <input type="checkbox"/> Not supportive of the proposal Justification (based on considerations of the dimensions described below): <p>The evidence supporting these interventions is limited. Based on it, the benefits of using subcutaneous sumatriptan, verapamil, and prednisolone for cluster headache outweigh the risks, provided that standard monitoring and short-term use practices are followed. Their addition to the WHO Essential Medicines List is justified based on their efficacy, safety, and critical public health impact</p>
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (https://list.essentialmeds.org/)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (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;) Sumatriptan: <ul style="list-style-type: none"> SR of 2 RCT showed that 6 mg subcutaneous sumatriptan provides rapid relief within 15 minutes in about 48% of patients versus 17% with placebo. This was consistent with results from observational studies It consistently outperformed other triptans and acute treatments like oxygen in network meta-analyses. Verapamil: <ul style="list-style-type: none"> SR, including 5 studies (including 2 RCTs) showed that 73% of patients achieve either a complete response or a ≥50% reduction in attack frequency. Prednisolone: <ul style="list-style-type: none"> A RCT showed that prednisolone significantly reduced the number of attacks (mean of 7.1 attacks vs. 9.5 attacks with placebo in the first week). This was supported by observational study Its use is short-term due to the risk of long-term side effects, but in this context, it's considered effective. 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (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;) Subcutaneous Sumatriptan <ul style="list-style-type: none"> Safety profile is well characterized. Main side effects are mild such as: Local injection site reactions (mild, transient), Tingling, tightness or pressure sensations (mild and short-lived). Nausea occasionally reported. Potential for serious adverse events (Mainly due to vasoconstriction- Coronary artery spasm, myocardial infarction, stroke are described. This allows to screening and monitoring for patients that require it. Additionally, contraindications are defined (History of ischemic heart disease, uncontrolled hypertension, history of cerebrovascular disease) Verapamil	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable

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<ul style="list-style-type: none"> • Safety profile is well characterized. • Main side effects are mild such as: Constipation, fatigue, dizziness, hypotension • Serious adverse effects are well recognized, and appropriate monitoring can be implemented and is required. These include bradycardia and AV block (need regular EKGs), hypotension (BP monitoring). • It is worse highlighting that an alternative preventive treatment is lithium which has higher systemic toxicity, like renal and thyroid dysfunction). <p>Prednisolone</p> <ul style="list-style-type: none"> • Safety profile is well characterized. • This medication is intended to be used for short-term as bridging therapy, making it unlikely to lead to severe adverse events (Adrenal suppression, osteoporosis, immunosuppression). 	
<p>Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?</p> <p>The proposed medicines have a favorable and meaningful balance of benefits to harms for the treatment and prevention of cluster headache, according to limited evidence.</p> <ul style="list-style-type: none"> • Subcutaneous sumatriptan offers the fastest relief among acute treatments • Verapamil is effective, widely used, and relatively safe with monitoring — there's no better preventive option available. • Prednisolone fills an important bridging role to prevent suffering while verapamil becomes effective, with risks minimized by limiting therapy duration. 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable
<p>Are there any special requirements for the safe, effective and appropriate use of the medicines?</p> <p>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p> <p>Sumatriptan:</p> <ul style="list-style-type: none"> • Pre-treatment cardiovascular risk assessment (history of ischemic heart disease, stroke, hypertension). • Patient education for self-injection technique. <p>Verapamil:</p> <ul style="list-style-type: none"> • Baseline and regular ECG monitoring (especially when doses ≥ 240 mg/day). • Monitoring for bradycardia, AV block and hypotension <p>Prednisolone:</p> <ul style="list-style-type: none"> • Use only short-term (2–3 weeks maximum). Gradual tapering of the dose to prevent adrenal suppression. • Monitor for corticosteroid side effects (hyperglycemia, hypertension, mood changes, etc.) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable
<p>Are there any issues regarding price, cost-effectiveness and budget implications in different settings?</p> <p>The document reports several important issues regarding price, cost-effectiveness, and budget implications, especially when comparing high-income and low-/middle-income countries (LMICs)</p> <p>Subcutaneous Sumatriptan</p> <ul style="list-style-type: none"> • Price varies significantly: but it can be expensive, mainly in LMICs. • Cost-Effectiveness Analysis: • At UK prices, cost per healthy life year (HLY) gained = US\$120,623, NOT cost-effective. • At Brazilian price (~US\$12.63), cost per HLY gained drops to US\$47,892 — still 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable

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<p>high, but better.</p> <ul style="list-style-type: none"> Currently not highly cost-effective based on strict thresholds. If broader benefits (e.g., prevention of disability, improved productivity) are considered, its value improves. <p>Verapamil</p> <ul style="list-style-type: none"> Price is very low. Cost-Effectiveness Analysis: Highly cost-effective by global standards. Special Consideration: Needs ECG monitoring. <p>Prednisolone (Short-term bridging)</p> <ul style="list-style-type: none"> Price is very low — median price ~US\$0.053 per 5 mg tablet. Cost-Effectiveness Analysis: Initial analysis: Cost per HLY gained = US\$37,875 (not very cost-effective). Cost-effective if used in rapid responders only 	
<p>Is the medicine available and accessible across countries?</p> <p>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p> <p>Verapamil and Prednisolone are widely available.</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p>
<p>Does the medicine have wide regulatory approval?</p> <p>Subcutaneous sumatriptan is officially approved for cluster headache treatment. Verapamil and prednisolone are off label for cluster headache but are widely approved and accessible for other indications.</p>	<p><input type="checkbox"/> Yes, for the proposed indication.</p> <p><input checked="" type="checkbox"/> Yes, but only for other indications (off-label for proposed indication)</p> <p><input type="checkbox"/> No <input type="checkbox"/> Not applicable</p>