

I.2 Amitriptyline – EML

Reviewer summary	<input type="checkbox"/> Supportive of the proposal <input checked="" type="checkbox"/> Not supportive of the proposal <p>Justification (based on considerations of the dimensions described below):</p> <p>This Application refers to the inclusion of amitriptyline tablet 25 mg for migraine prophylaxis in adults on the Model List of Essential Medicines List (EML). Propranolol is already included for this indication and an application requesting the inclusion of bisoprolol is under review (see I3). Amitriptyline is already listed as antidepressant and for other common symptoms in palliative care.</p> <p>Migraine is a common disabling primary headache disorder characterized by recurrent moderate to severe pain. It is a cause of disability and results in a substantial socioeconomic burden, which is greater for women than for men. Recurrent migraines can be functionally disabling and can impair quality of life, therefore people with episodic migraines would benefit from prophylactic treatment. Migraine prophylaxis is generally recommended in the presence of at least 4 migraine days per month and/or when migraine substantially impacts quality of life.</p> <p>The evidence suggests amitriptyline increases the proportion of patients who experience a 50% or more reduction in monthly migraine days, compared to placebo but also the proportion of patients who discontinue due to adverse events compared to placebo. The certainty of evidence was rated as moderate, downgraded only due to risk of bias although also the precision of the estimate may be considered suboptimal (Ref: https://doi.org/10.1186/s10194-023-01573-6). Very few data exist on amitriptyline efficacy compared to beta-blockers.</p> <p>Safety profile of amitriptyline is well-known for its use as antidepressant and may impair treatment compliance.</p> <p>Overall, amitriptyline does not appear to have a favourable and meaningful balance of benefits to harm migraine prophylaxis. Given also the availability of alternative treatments, this Reviewer does not support the inclusion of amitriptyline for migraine prophylaxis.</p>
<p>Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives?</p> <p>Antimigraine medicines > For prophylaxis Propranolol Oral > Solid: 40 mg tablet (hydrochloride); 20 mg tablet (hydrochloride) (https://list.essentialmeds.org/)</p> <p><i>To be noted: Application I.3 refers to the inclusion of bisoprolol – as alternative to Propranolol for migraine prophylaxis.</i></p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable
<p>Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?</p> <p>A systematic review showed that amitriptyline increases the proportion of patients who experience a 50% or more reduction in monthly migraine days, compared to placebo with an absolute risk difference: 165 more per 1,000 (95% CI 47 more to 327 more) [moderate certainty evidence, according to the authors]. However, these results, derived from three RCTs, are far from robust, especially because substantial drop out, randomisation issues and suspect of selective reporting of outcomes.</p> <p>Ref https://doi.org/10.1186/s10194-023-01573-6</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable
<p>Does adequate evidence exist for the safety/harms associated with the proposed medicine?</p> <p>Trials found moderate certainty evidence that amitriptyline increases the proportion of patients who discontinue due to adverse events compared to placebo (absolute risk difference: 50 more per 1,000 (95% CI 10 more to 100 more)).</p> <p>The most important adverse effects of amitriptyline are drowsiness and anticholinergic symptoms such as dry mouth, constipation, and tachycardia. Weight gain occurs in</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable

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

many patients together with elevated levels of leptin, insulin, and C peptide, and can be a limiting factor leading to impaired compliance and discontinuation. Occasionally, amitriptyline may provoke glaucoma, PQ and QT interval prolongation on electrocardiogram (ECG), as well as benign prostate hypertrophy. Amitriptyline is metabolized by cytochrome P450 (CYP) isoenzymes, particularly CYP2D6, which is responsible for multiple interactions	
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? Migraine prophylaxis with amitriptyline is typically long-term. Starting doses are usually low, with weekly increments of 10-25 mg as tolerated. People treated with amitriptyline should be reassessed periodically (e.g., every 3 to 6 months) to evaluate the effectiveness of the therapy and determine whether to continue, adjust, or discontinue treatment.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable
Is the medicine available and accessible across countries?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable
Does the medicine have wide regulatory approval?	<input checked="" type="checkbox"/> Yes, for the proposed indication <input type="checkbox"/> Yes, but only for other indications (off-label for proposed indication) <input type="checkbox"/> No <input type="checkbox"/> Not applicable