I.2 Amitriptyline – EML

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Migraine is a debilitating disorder that significantly burdens affected individuals. The global migraine prevalence is 14–22%, with reliable estimates show that migraine accounts for 4.9% of global population. The disorder is ubiquitous, despite regional variations and affect 2-3 times higher in women than men. Migraine manifests with recurrent and unpredictable attacks of head pain, often severe, accompanied by other disabling symptoms such as nausea, vomiting, intolerance to sensory stimuli (photophobia and phonophobia), all of which impair function. Inadequately treated, it may increase in frequency and evolve into chronic migraine, with commensurate increases in ill-health and disability burdens, and in direct and indirect costs. Migraine often requires preventive treatment, especially in highly frequent episodic and chronic migraine. While there is a body of evidence that investigates the efficacy and safety of migraine preventive drugs, there is limited evidence on their comparative efficacy with each other. Several classes of medication are commonly used for migraine prophylaxis, including antidepressants, anticonvulsants, antihypertensives, gepants, and calcitonin gene-related peptide (receptor) monoclonal antibodies (CGRP(r)mAbs. Newer drugs (CGRP(r)mAbs and gepants), are available at a much higher cost restricting access to their use. Drugs for migraine prophylaxis reduce monthly migraine days by a percentage that varies from 30 to 75%. So far, it is not possible to predict which subject will respond to a drug, nor the extent of the response. The 23rd (2023) edition of the EML includes propranolol 20 mg and 40 mg tablets as the sole option for migraine prevention. Its efficacy, measured in randomized controlled trials (RCTs) as proportion of responders (those in whom attack frequency is reduced by at least half) is <50%. In addition, beta-blockers have certain adverse effects that may limit their use in the general population. These effects, typical of non-cardioselective beta-blockers such as propranolol, are mainly associated with antagonism of beta-2 receptors located in the smooth muscle cells of the lungs, pancreas, bladder, uterus, blood vessels and gastrointestinal tract. They affect the relaxation of these smooth muscles and modify certain metabolic processes such as glycogenolysis and insulin release by pancreatic beta cells. Caution is advised in patients with a history of asthma, due to the risk of reduced pulmonary function and induction of bronchospasm, and in patients with advanced peripheral arterial disease. Beta-blockers are therefore contraindicated in patients with decompensated asthma and congestive heart failure. Because of the risk of bradyarrhythmia, they should not be used in patients with recent myocardial infarction, coronary artery disease, congestive heart failure or cardiac dysrhythmias. Bradycardia and hypotension may limit their use. Gastrointestinal disturbances, including nausea, abdominal cramps and diarrhoea, weight gain, paresthesia. Also, beta-blockers can cause impaired glucose metabolism with new-onset diabetes. Propranolol is a lipophilic beta-blocker and can cross the blood–brain barrier, leading to neurologic symptoms like disorders of sleep, dizziness, vertigo, fatigue, and data from literature indicates that depression is commonly reported after the use of beta-blockers. Additional caution is required in subjects taking triptans, as beta-blockers increase plasma concentrations of triptans. **Other options are therefore needed.** Amitriptyline was discovered in the late 1950s, the beneficial use of amitriptyline in migraine was first reported in the late 1960s and was approved by the U.S. Food and Drug Administration in 1961 for depression. The exact mechanism of action of amitriptyline in migraine prophylaxis is unclear. The neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) is involved in migraine pathophysiology and the acute antimigraine medication class of triptans targets the 5-HT receptor subtypes 5-HT1B/1D/(1F). Tricyclic antidepressants inhibit the uptake of 5-HT in the synaptic cleft, so it is likely that the antimigraine effect of amitriptyline results from its effects on serotonergic transmission. The mode of

	action of amitriptyline in migraine prevention is assumed to be different from that of propranolol, so that failure of propranolol does not predict failure of amitriptyline. Therefore, amitriptyline represents a valid alternative for the subjects who did not benefit or did not tolerate propranolol. Amitriptyline has a similar profile of efficacy as propranolol. Studies of migraine preventive use in the USA show that tricyclic antidepressants are the second most prescribed medication for migraine prevention, after topiramate. It is recommended among the first- or second-line treatment options for migraine prevention in several guidelines. Amitriptyline is considered as a level B drug for migraine prophylaxis by the American Headache Society (AHS) and American Academy of Neurology (AAN), meaning it is regarded as "probably effective" even though it has not been approved by the FDA for the prophylactic use in migraine. In Europe, amitriptyline is considered as a 'drug of second choice'.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**) propranolol 20 mg and 40 mg tablets	☒ Yes ☐ No ☐ 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;)	☒ Yes ☐ No ☐ 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;) Amitriptyline can cause side effects in some people, but many people have no side effects or only minor ones. The more common reported side effects tend to be milder and go away within a few days. The most commonly encountered include weight gain and gastrointestinal symptoms like constipation, xerostomia, dizziness, headache, and somnolence but also : - due to alpha-adrenergic receptor blockade, can cause orthostatic hypotension, dizziness, and sedation - can also cause heart rate variability, slow intracardiac conduction, induce various arrhythmias, and cause QTc (corrected QT) prolongation. - due to anticholinergic side effects include blurred vision, dry mouth, urinary retention, tachycardia, acute angle glaucoma, confusion, and delirium. - due to antihistamine effects, we can have sedation, increased appetite, weight gain, confusion, and delirium. - asymptomatic, transient, and reverses abnormalities in liver function tests - caution in patients with angle-closure glaucoma, urinary retention, and seizures.	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) The following are significant contraindication considerations: - Hypersensitivity reactions - History of QTc prolongation, recent myocardial infarction, arrhythmias, or heart failure, The FDA has issued a black box warning regarding the use of amitriptyline in adolescents and young adults (ages less than 24 years). The drug can increase the risk of suicidal ideation and behavior.	☒ Yes ☒ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☐ Yes ☒ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval?	☐ Yes, for the proposed indication ☒ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable