I.4 Carbamazepine – EML

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): TN is a neuropathic pain disorder characterized by recurrent, paroxysmal episodes of electric shock-like pain along the sensory distribution of the trigeminal nerve. TN involves hyperexcitable neuronal states and central sensitization, often due to demyelination or compression of the trigeminal nerve. The pain is brief (lasting from a few seconds to two minutes), unilateral and can be triggered by stimuli such as brushing teeth, chewing or speaking. TN affects essential daily activities, leading to a reduction in quality of life. Natural history varies but typically follows a chronic, episodic course of complete remission (weeks, months, or even years) between painful episodes. Over time, remissions often shorten, and untreated TN can progress to persistent pain or more complex, refractory syndromes. TN has been linked to a higher prevalence of anxiety, depression and suicide. It is rare in individuals under 30 years of age, but prevalence increases with age, especially over 60, and rates can reach 20 per 100,000, which still makes it a rare or very rare occurrence according to several definitions[1]. Onset can occur anywhere from 24 to over 90 years. The estimated lifetime prevalence of TN ranges from 0.16% to 0.3%, with an annual incidence of 4 to 29 cases per 100,000 person-years. TN is more commonly observed in women than men, with a female-to-male ratio of 1.5:1; evidence suggests similar clinical features and prevalence patterns across different groups. CBZ is used as the first-line treatment choice for TN with NNT of 1.7 -1.8. Clinical practice may support use of CBZ in TN, but this is empirical; no evidence from trials, from SR or overviews of reviews was found. Guidelines, issued from 2008 to 2020, are based on studies from the 1960s but are the best source of recommendations of use. The application is submitted by WHO Brain Health Unit, Department of Mental Health, Brain Health and Substance Use for a new indication of carbamazepine, as a treatment for trigeminal neuralgia (TN). No supporting letters were listed in the application. The proposal is being made due to the reported absence of any treatment options for TN in the current EML. The application states it means to apply for section 5 of the EML, which does not deal with pain in general, rather with Diseases of the Nervous System. There are only three subsections in section 5: 5.1 Antiseizure medicines; 5.2 Medicines for multiple sclerosis; and 5.3 Medicines for parkinsonism. Including carbamazepine in section 5 for a new indication would signify adding another subsection. However, adding it to '2.3 Medicines for other common symptoms in palliative care' would be more appropriate, in accordance with the rarity of TN as a condition, the palliative nature of the treatment and the lack of available quality evidence – apart from guidelines based on older studies – to support clinical care. I thus recommend inclusion of CBZ as a listing in subsection 2.3 of the EML - but not in Section 5 – making it available for the treatment of TN and other off-label conditions, since evidence for use in NT is empirical and derived from clinical practice.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? The proposed medicine exists as an anticonvulsant in Section 5. However, this is a case in which the indication proper is not listed in the EML. A separate subsection for listing in Sectio 5 would have to be included. The ATC code of carbamazepine is N03AF01. Dosage forms already included in the EML are Tablet (chewable, IR) 100mg, 200mg; Tablet (scored, IR) 100mg, 200mg, 400mg; Capsule (ER) 100mg, 200mg, 300mg; Oral suspension 100mg/5mL. In TN Initial dosage of 200 – 400mg/day is recommended and can be tapered until freedom from pain is achieved, up to a maximum dosage of 1200mg/day. In elderly patients, a lower start dosage of 100mg twice a day is recommended. (**https://list.essentialmeds.org/**)	☐ Yes ☐ No ☒ Not applicable

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? Six studies were reviewed: Rana et al. (2023), Naderi et al. (2024), Yang F. et al. (2018), Guo M. et al. (2024), Peterson-Houle G.M. et al. (2021), and Zhao X. et al. (2023). However, even if CBZ is proposed due to its efficacy in treating TN, none of the studies included in the systematic reviews provided strong evidence (high-tier randomized controlled trials – RCTs- with rigorous design and sufficient sample sizes), to firmly establish the efficacy of CBZ for TN. A Cochrane SR from 2017 studied oxcarbazepine (not CBZ), an anticonvulsant structurally related to CBZ (N03AF02), reportedly better tolerated than carbamazepine, for neuropathic pain. The review found little evidence to support the effectiveness of this derivative in any neuropathic pain. Additionally, the types of neuropathic pain that were studied in the five retrieved trials did not include TN[2]. Another Cochrane SR from 2014 is cited in the application (ref 18). However, the doi leads to a Cochrane review that does not involve carbamazepine, but gabapentin. It showed very limited evidence for effectiveness in neuropathic pain (not TN)[3]. One Cochrane overview from 2013, on anticonvulsants in neuropathic pain and fibromyalgia, found no evidence, insufficient evidence, or evidence of a lack of effect for CBZ in these conditions (not TN)[4]. In 2017, separate reviews were published both focusing on gabapentin, one for neuropathic pain (limited evidence, some pain relief and not TN)[5], and one for fibromyalgia (no evidence of effectiveness, not TN)[6]. No 2024 Cochrane review update (as the application states) could be retrieved. CBZ is used as the first-line treatment choice for TN with NNT of 1.7 -1.8. Clinical practice may support use of CBZ in TN, but this is empirical; no evidence from trials, from SR or overviews of reviews was found. Guidelines (NICE, American Academy of Neurology, STG South Africa, French Headache Society & French Neurosurgical Society, European Academy of Neurology), from 2008 to 2020, are based on studies from the 1960s but are the best source of recommendations of use.	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? AE of CBZ are well known. Common reported side effects include dizziness, drowsiness, nausea, ataxia and vomiting, usually dose-dependent and most people are able to tolerate them. From TN trials, particular side effects (CNS effects occurring together, hyponatraemia, leukopaenia, skin rash) have been reported that eventually cause treatment interruption. In the elderly, mild anticholinergic effects of CBZ may cause delirium, urinary retention and constipation. CBZ is teratogenic (category D drug) and should not be given in pregnancy and avoided in lactation. CBZ is a potent inducer of the cytochrome P450 (CYP450) enzyme system, leading to significant drug-drug interaction reducing effect of several drugs (lamotrigine, phenytoin, and valproate, warfarin and novel oral anticoagulants, primidone, oral contraceptives, statins, and certain antiretroviral agents).	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? According to the application, given the absence of alternative drugs with strong evidence for treatment of TN, CBZ remains the recommended choice, with overall benefits of using CBZ outweighing the risks. However, there is no evidence other than empirical use in clinical practice to substantiate this statement.	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? Diagnosis of TN requires careful clinical evaluation and may involve magnetic resonance imaging (MRI) to identify neurovascular compression or exclude secondary causes. Routine therapeutic monitoring of serum CBZ levels is not recommended (CBZ tests not included in WHO Essential Diagnostics List (EDL). However, elderly patients may require periodic testing to adjust dosage or discontinue treatment. Full blood count (to monitor for bone marrow suppression), liver function tests (to monitor hepatotoxicity and elevated liver enzymes), and kidney function tests (to monitor hyponatremia). Screening for serious interactions is needed, and dose adjustment of concomitant drugs may also be called for.	☒ Yes ☐ No ☐ Not applicable

Are there any issues regarding price, cost-effectiveness and budget implications in different settings? No data on the cost-effectiveness of CBZ in the treatment of TN is available.	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? CBZ can be found as a generic drug, is relatively affordable and widely available. CBZ is listed on the national EML of more than 134 countries worldwide.	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval? CBZ is generally registered across the world, including in LMICs. It is listed in several pharmacopeias. Market approval is mainly as anticonvulsant. Approval for other indications would normally require clinical trials with robust results.	☐ 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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