Carbamazepine
The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.
Rejected
Section:
5. Medicines for neurological disorders
ATC codes: N03AF01
Indication
Trigeminal neuralgia ICD11 code: 8B82.0
INN
Carbamazepine
Medicine type
Chemical agent
List type
Core
Formulations
Oral > Liquid: 100 mg per 5 mL
Oral > Solid > tablet: 100 mg (scored) ; 200 mg (scored) ; 100 mg (chewable) ; 200 mg (chewable) ; 400 mg (scored)
Oral > Solid > capsule: 100 mg (extended-release) ; 200 mg (extended-release) ; 300 mg (extended-release)
EML status history
Application rejected in 2025 (TRS 1064)
Sex
All
Age
Adolescents and adults
Therapeutic alternatives
The recommendation is for this specific medicine
Patent information
Patents have expired in most jurisdictions
Read more about patents.
Wikipedia
Carbamazepine
DrugBank
Carbamazepine
Expert Committee recommendation
☐
The Expert Committee noted that no medicines are currently included on the Model Lists for the treatment of trigeminal neuralgia and acknowledged the substantial impact of the condition on affected individuals. The Committee noted that carbamazepine has been routinely used in the treatment of trigeminal neuralgia for decades and is considered the standard of care in clinical practice. The Committee reviewed the evidence presented in the application and noted that while carbamazepine is widely used in clinical practice and recommended in several national and international guidelines as a first-line treatment for trigeminal neuralgia, high-quality clinical evidence for its use is lacking. The available data are largely derived from small, older trials, and recent systematic reviews have not identified high-quality randomized controlled trials to substantiate its efficacy. The Committee therefore considered that the quality of the available evidence was inadequate and therefore confidence in the reported benefits and harms was limited. Therefore, the Expert Committee did not recommend the inclusion of carbamazepine on the EML for the new indication of trigeminal neuralgia as the quality of the evidence did not meet the standard required for EML decision-making.
Background
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Carbamazepine has not previously been evaluated for inclusion on the EML for the treatment of trigeminal neuralgia. It is currently listed for use in the treatment of epilepsy and bipolar disorder. No alternative treatments for trigeminal neuralgia are currently included on the EML.
Public health relevance
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Trigeminal neuralgia is a neuropathic pain disorder characterized by paroxysmal and recurrent episodes of severe, electric shock-like pain along the sensory distribution of the trigeminal nerve. The pain is brief (lasting from a few seconds to 2 minutes), typically unilateral and can be triggered by innocuous stimuli such as brushing teeth, chewing or speaking (1, 2). The pathophysiology involves hyperexcitable neuronal states and central sensitization, often due to demyelination or compression of the trigeminal nerve. Diagnosis requires careful clinical evaluation and may involve magnetic resonance imaging to identify neurovascular compression or exclude secondary causes (3). Trigeminal neuralgia can be classified based on etiology into three types: classical (associated with neurovascular compression of the trigeminal nerve root); secondary (resulting from an underlying neurological condition such as multiple sclerosis or space-occupying lesions); and idiopathic (where no cause is found). Epidemiological data on the global burden of trigeminal neuralgia are limited. Available evidence estimates a lifetime prevalence of between 0.16% and 0.30%, with an annual incidence between four and 29 cases per 100 000 person-years (4, 5). Trigeminal neuralgia is more commonly seen in women than in men, with a female-to-male ratio of 1.5:1. Incidence increases with age, commonly presenting between ages 53 and 57 years and peaking after age 60 years, where rates reach up to 20 cases per 100 000 person-years. Although relatively uncommon in individuals younger than 30 years, onset can occur anywhere from 24 to > 90 years (2, 4, 5). Trigeminal neuralgia is a debilitating condition that significantly affects essential daily activities, including speaking, eating, drinking, and facial contact, leading to a marked reduction in quality of life. Its natural history varies significantly between individuals but the condition typically follows a chronic, episodic course characterized by periods of complete remission lasting weeks, months or even years between episodes. Over time, remissions often shorten and untreated trigeminal neuralgia can progress to persistent pain or more complex,

refractory syndromes (2, 4). Epidemiological studies have demonstrated a higher prevalence of anxiety and depression in affected individuals, along with an increased risk of suicide (6).

Benefits

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The applicants did a literature search of PubMed and the Cochrane Library to identify recent systematic reviews and meta-analyses on the treatment of trigeminal neuralgia. The search was limited to systematic reviews and meta-analyses published in the past 10 years, with full text, and in English. The search yielded six systematic reviews and meta-analyses (7–12). Quantitative meta-analysis was not feasible due to significant heterogeneity in the medicines investigated, study methods and the outcome measures assessed. Qualitative analysis of these studies noted a lack of robust, high-quality data on the efficacy of treatments for trigeminal neuralgia, including carbamazepine. No studies included in the systematic reviews provided strong evidence, such as high-tier randomized controlled trials with rigorous design and sufficient sample sizes, to firmly establish the efficacy of carbamazepine for trigeminal neuralgia. Thus, the findings of the systematic reviews were not elaborated on in the application. The application stated that the absence of comprehensive, high-quality evidence highlights the need for further well-designed studies to strengthen the foundation for evidence-based treatment guidelines. Since the recently published reviews provided low-quality evidence, existing guidelines on trigeminal neuralgia treatment were reviewed. Among these, the United Kingdom National Institute for Health and Care Excellence (NICE) guidelines were examined in detail (13). These guidelines found no robust studies that met the inclusion criteria to inform recommendations. Nonetheless, the NICE guideline development group acknowledged the debilitating nature of trigeminal neuralgia, underscoring the need for treatment, and noted that most patients in the United Kingdom with trigeminal neuralgia were already using carbamazepine, which suggests that the medicine has some efficacy over no treatment. Despite the paucity of robust evidence, the guideline development group made a strong recommendation to offer carbamazepine as initial treatment for trigeminal neuralgia. The NICE guideline and other guideline recommendations are based mainly on evidence from three randomized controlled trials from the 1960s (14–16). These trials compared carbamazepine to placebo in patients with trigeminal neuralgia and reported on its effectiveness in reducing the frequency and severity of pain. The first study was a randomized crossover study comparing carbamazepine and placebo in 70 adult participants with trigeminal neuralgia (14). Participants received carbamazepine and placebo alternately for 2 weeks at a time for a total of 8 weeks, beginning with either carbamazepine or placebo. The outcomes assessed were pain severity, number of paroxysms daily and effect on triggering mechanisms. Carbamazepine was associated with a significant improvement in severity of pain, number of paroxysms, disappearance of some triggers (eating and contact) and number of triggers becoming inactive. In the second study, 24 participants were randomized to receive carbamazepine or placebo for 3 months (15). All carbamazepine-treated patients experienced significant pain relief, with minimal or no response observed in the placebo group (definitive numbers were not provided). In the third study, 44 participants with trigeminal neuralgia were randomized to receive carbamazepine or placebo (16). After 4 years, 73% of carbamazepine-treated patients achieved a good or excellent clinical response, compared with 25% in the placebo group, with a number-needed-to-treat of 2.1. A 2024 Cochrane systematic review of 10 randomized controlled trials (480 participants) evaluated the efficacy and adverse effects of carbamazepine in the treatment of chronic neuropathic pain (including trigeminal neuralgia) and fibromyalgia in adults (17). Overall, no study provided first- or second-tier evidence for efficacy outcomes, with all falling under third-tier due to poorly defined outcomes, incomplete reporting and small sample sizes. In a subgroup analysis of studies of trigeminal neuralgia, the risk ratio (RR) for the outcome of any pain improvement was 6.02 (95% confidence interval (CI) 2.82 to 12.85), favouring carbamazepine (two studies, 98 participants). The review concluded that carbamazepine was likely effective for neuropathic pain, albeit with limitations due to the low quality of evidence, highlighting that none of the trials included was longer than 4 weeks duration, had good reporting quality or investigated outcomes equivalent to substantial clinical benefit. Given the severity of trigeminal neuralgia and the widespread recommendation for carbamazepine, it is unlikely (and arguably unethical) to conduct placebo-controlled studies for trigeminal neuralgia, suggesting high-quality placebo-controlled randomized controlled trials will remain scarce. Current research is now focused on finding alternative agents with comparable or superior efficacy to carbamazepine, although none has proven superior to date. Thus, despite limited evidence and reported side-effects, carbamazepine remains the recommended first-line treatment for trigeminal neuralgia, as adopted by other guidelines. A 2001 randomized controlled trial compared carbamazepine and oxcarbazepine in 48 patients with trigeminal neuralgia (18). All patients receiving oxcarbazepine and 19 (95%) receiving carbamazepine obtained a greater than 50% reduction in the number of pain attacks. However, the duration of follow-up, sample size calculation, assessment of outcome and allocation procedure were unclear from the study. A 2021 retrospective, real-world study of 354 patients with trigeminal neuralgia found similar efficacy between oxcarbazepine and carbamazepine for the proportion of patients achieving at least 30% reduction in pain (19). The proportions of respondents among patients treated with oxcarbazepine and carbamazepine were 90.9% (median dose 900 mg) and 88.3% (median dose 800 mg). A 2016 meta-analysis of 16 randomized controlled trials (1330 participants) evaluated the efficacy and safety of gabapentin compared with carbamazepine in the treatment of trigeminal neuralgia (20). All included trials were from China. After 4–10 weeks follow-up, response to treatment was similar between treatment groups as measured by the total effective rate (odds ratio (OR) 1.6, 95% CI 1.2 to 2·2; 14 studies, 1156 participants; low-quality evidence). This meta-analysis had multiple weaknesses, including different study designs, unclear sample size and allocation procedures, and absence of original studies in English. Other pharmacological agents that have been compared to carbamazepine and found to be of similar or inferior efficacy include botulinum toxin A, eslicarbazepine, lamotrigine, pimozide, tizanidine and topiramate (7). Studies on combination therapies have shown desirable effects, although no proper randomized trials are available. Notably, almost all combinations therapies involve carbamazepine (21–23). The evidence for these combination therapies is low. However, the reports of carbamazepine being included in almost all these reported combinations further supports the need to have carbamazepine as the first-line choice of treatment.

Harms

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Carbamazepine is frequently known to cause undesirable effects, limiting its optimal usage. Commonly reported side-effects include dizziness, drowsiness, nausea, ataxia and vomiting. These side-effects are usually dose-dependent and most people are able to tolerate them (24). Side-effects are more common in older people, necessitating careful monitoring and dose adjustments. From trigeminal neuralgia trials, side-effects reported that led to treatment interruption include central nervous system effects, hyponatraemia (19) and skin rash (14). In the 2024 Cochrane

systematic review, adverse events were common with carbamazepine, affecting 65% of carbamazepine users versus 27% with placebo. Adverse events reported in > 10% of patients receiving carbamazepine included dizziness, giddiness, somnolence and unsteadiness. Furthermore, 3% of carbamazepine users withdrew due to adverse effects, compared with no placebo-treated patients (17). From the retrospective, real-world study comparing carbamazepine and oxcarbazepine in patients with trigeminal neuralgia, the rate of side-effects was higher with carbamazepine than with oxcarbazepine (43.6% versus 30.3%; $P < 0.0001$) (19). Carbamazepine has mild anticholinergic effects and elderly patients may be at increased risk of delirium, urinary retention and constipation (24, 25). A 2015 review evaluated the safety of pharmaceutical treatments for trigeminal neuralgia in elderly people (26). However, no specific trials conducted for the elderly population are available. The reported trials usually excluded people with comorbid illnesses or on other medications, thus excluding most elderly people. If side-effects of carbamazepine are unacceptable in an elderly patient, consideration could be given to using oxcarbazepine instead (27, 28). Carbamazepine is a known teratogen and should only be used during pregnancy when the benefits outweigh the risk of congenital malformations (24). Carbamazepine is a potent inducer of the cytochrome P450 (CYP450) enzyme system, leading to significant drug–drug interactions. This enzyme induction accelerates the metabolism of many medications, reducing their efficacy. Common interactions occur with other antiseizure medications, such as lamotrigine, phenytoin and valproate, often necessitating dosage adjustments to maintain therapeutic levels. Anticoagulants such as warfarin and direct oral anticoagulants are also affected, increasing the risk of clot formation. Similarly, primidone, oral contraceptives, statins and certain antiretroviral agents may be strongly inhibited and become less effective (29).

Cost / cost effectiveness

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The application stated that no data existed on the cost–effectiveness of carbamazepine in the treatment of trigeminal neuralgia. The cost of treating trigeminal neuralgia with carbamazepine varies by region and health-care system, but as a generic medicine, carbamazepine is relatively affordable and widely available, even in low- and middle-income countries, where its long-standing use in epilepsy helps ensure continued access. A summary of carbamazepine prices in selected low- and middle-income countries was presented in the application. Prices per 200 mg tablet ranged from 0.01 United States dollars (US$) in India to US$ 0.34 in South Africa.

WHO guidelines

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WHO guidelines for trigeminal neuralgia are not currently available. Carbamazepine is recommended by the WHO Mental Health Gap Action Programme (mhGAP) guidelines for treatment of epilepsy and bipolar disorder (30). The use of carbamazepine is recommended as a first-line treatment for trigeminal neuralgia by various clinical guidelines, including NICE (13), the European Academy of Neurology (31), South African Standard Treatment Guidelines (32), French Headache Society and French Neurosurgical Society (33), and the American Academy of Neurology–European Federation of Neurological Societies (27).

Availability

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Carbamazepine has wide regulatory approval and availability globally. It is currently included on the national EML of 134 countries worldwide.

Other considerations

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Routine therapeutic monitoring of serum carbamazepine levels is not recommended and in vitro diagnostic testing for therapeutic drug monitoring of carbamazepine is not included in the WHO Essential Diagnostics List. However, certain individuals, particularly elderly patients, may require periodic testing, including a full blood count (to monitor bone marrow suppression), liver function tests (due to carbamazepine’s potential for hepatotoxicity and elevated liver enzymes), and kidney function tests (due to risk of hyponatraemia). In these cases, monitoring serum levels can be useful to help adjust dosages or discontinue treatment if the risk of toxicity is high.

☐ Show references Hide references

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