PROPOSAL FOR THE ADDITION OF CARBAMAZEPINE TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF ADULTS WITH TRIGEMINAL NEURALGIA

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1.0 SUMMARY STATEMENT OF THE PROPOSAL

This submission supports the addition of carbamazepine (CBZ) to the Essential Medicines List (EML) for a new indication as a treatment for trigeminal neuralgia (TN), within section 5. The proposal is being made due to the absence of any treatment options for TN in the current EML. CBZ is proposed due to its efficacy in treating TN and its widespread availability across the world. Additionally, CBZ is already included in the EML for use in the treatment of epilepsy and bipolar disorder.

TN is a debilitating neuropathic pain disorder characterized by recurrent, paroxysmal episodes of severe, electric shock-like pain along the sensory distribution of the trigeminal nerve. 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. Evidence suggests similar clinical features and prevalence patterns across different groups. Its prevalence increases notably with age, especially in individuals over 60, where rates can reach 20 per 100,000. It is rare in individuals under 30 years of age. TN is more commonly observed in women than men, with a female-to-male ratio of 1.5:1.

The available evidence supports CBZ as an effective first-line treatment for TN, with a number-needed-to-treat (NNT) of 1.7 to 1.8. Including CBZ in the EML for the treatment of TN will significantly address the therapeutic needs of TN patients, raise awareness of the condition's burden, and improve access to treatment, ultimately enhancing the quality of life for those affected.

2.0 CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

Not applicable

3.0 OTHER ORGANIZATIONS(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

Not applicable

4.0 KEY INFORMATION SUMMARY TABLE FOR THE PROPOSED MEDICINE(S)

Table 1: Summary table for the proposed medicines

INN	Carbamazepine		
ATC code	N03AF01		
Indication	Trigeminal neuralgia		
ICD-11 code	8B82.0 Trigeminal neuralgia		
Dosage form	**Strength**	**EML**	**EMLc**
Tablet (chewable, IR)	100mg, 200mg	Yes	No
Tablet (scored, IR)	100mg, 200mg, 400mg	Yes	No
Capsule (ER)	100mg, 200mg, 300mg	Yes	No
Oral suspension	100mg/5mL	Yes	No

INN - International non-proprietary name; ATC – Anatomical therapeutic chemical; IR – immediate release; ER – extended release; EML – Essential Medicine List; EMLc – Essential Medicine List for children

5.0 LISTING AS AN INDIVIDUAL MEDICINE OR AS REPRESENTATIVE OF A PHARMACOLOGICAL CLASS OR THERAPEUTIC GROUP ('SQUARE BOX' LISTING)

This submission proposes the listing of CBZ for TN. This application is supported by its recommendation in multiple clinical guidelines (see Section 9), absence of other pharmacological agents whose efficacy is superior to CBZ and its global availability, as it is already included in the WHO EML for epilepsy and bipolar disorder.

6.0 INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

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 two 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 (MRI) to identify neurovascular compression or exclude secondary causes[3].

TN can be classified into three categories, based on aetiology;

1. Classical TN: Associated with neurovascular compression of the trigeminal nerve root;
2. Secondary TN: Results from an underlying neurological condition such as multiple sclerosis or space-occupying lesion;
3. Idiopathic: no cause is found.

Epidemiological data on the global burden of TN is limited. However, available evidence estimates a lifetime prevalence of TN between 0.16% to 0.3%, with an annual incidence between 4 and 29 cases per 100,000 person-years[4,5]. TN is more commonly observed in women than in men, with a female-to-male ratio of 1.5:1. The incidence of TN increases with age, commonly presenting between ages 53 and 57 and peaking after age 60, where rates reach up to 20 cases per 100,000 person-years in this age group. Although TN is relatively uncommon in individuals under 30, onset can occur anywhere from 24 to over 90 years.[2,4,5].

TN is a profoundly 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 among individuals, but the condition typically follows a chronic, episodic course characterized by periods of complete remission lasting 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[2,4]. Epidemiological studies have demonstrated a higher prevalence of anxiety and depression among affected individuals, along with an increased risk of suicide[6].

These findings underscore the critical need for timely diagnosis, appropriate investigations, and effective management of this condition.

The inclusion of CBZ as first-line treatment option for TN would address the therapeutic needs of people with TN, enhance awareness of the condition's impact, and improve its access and availability, ultimately leading to better quality of life for those affected.

7.0 TREATMENT DETAILS

7.1 Dosage and formulations

CBZ is available in tablet, capsule or liquid forms.

Dosage:

- Initial dosage of 200 – 400mg/day is recommended. The dosage can be increased slowly 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.

The administration of CBZ for TN is not different from that used for epilepsy. It can be prescribed in any hospital setting – from primary health care to tertiary facilities, once the clinical diagnosis is made.

7.2 Drug monitoring

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

8.0 REVIEW OF EVIDENCE FOR BENEFITS AND HARMS

8.1 Methodology

8.1.1 PICO question

The following PICO question was formulated to address the management of TN, as summarized below:

Table 2: PICO Research Question
Is CBZ better than (more effective than) placebo or alternative pharmacological interventions for adults suffering from TN?
Population (P): adults with TN
Intervention (I): CBZ
Comparator (C): placebo, alternative pharmacological interventions
Outcomes (O): Reduction in frequency of painful attacks/ reduction in severity of pain / pain freedom

8.1.2 Search strategy and assessment of quality of evidence

A focused literature search was conducted to identify recent systematic reviews and meta-analyses on the treatment of TN. The search involved querying key databases, including PubMed and the Cochrane Library, using the following search terms (for PubMed): *("Trigeminal Neuralgia"[MeSH Terms] OR trigeminal neuralgia[Title/Abstract] OR tic douloureux[Title/Abstract]) AND ("Drug Therapy"[MeSH Terms] OR "Pharmacological Treatment"[Title/Abstract] OR "Medication"[Title/Abstract] OR Therap*[Title/Abstract] OR "Anticonvulsants"[MeSH Terms] OR carbamazepine[Title/Abstract] OR oxcarbazepine[Title/Abstract] OR gabapentin[Title/Abstract] OR pregabalin[Title/Abstract] OR "Pain Management"[MeSH Terms])*.

The following filters were further added to streamline the results: publications in the last 10 years, full text, meta-analyses, systematic reviews and published in the English language.

The quality of evidence of the individual review was quoted as reported by the authors in the papers using a CiNeMA (Certainty in Network Meta-Analysis) approach in case of network meta-analysis.

8.1.3 Search results and implication on clinical recommendations

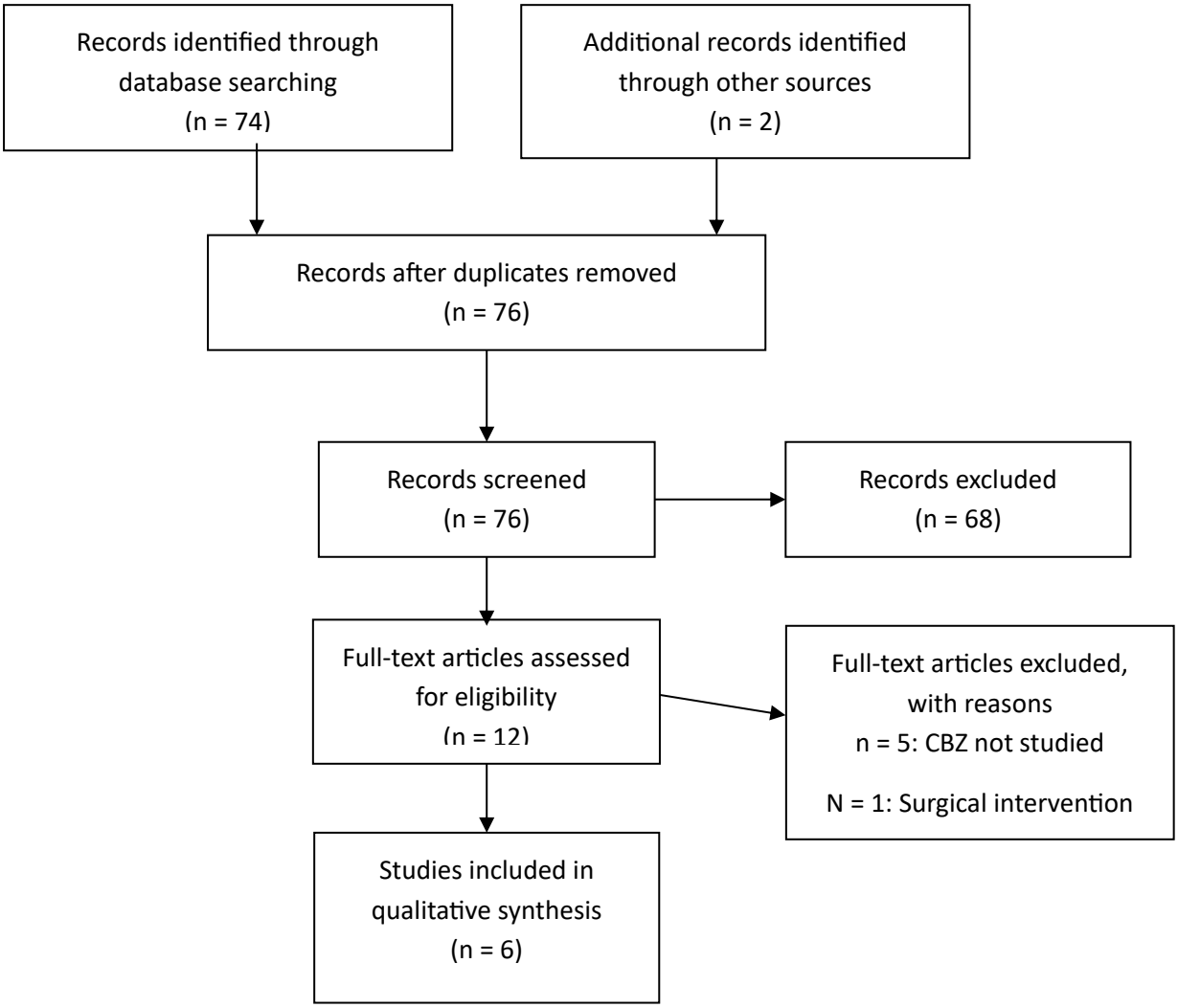
The search yielded six systematic reviews and meta-analysis papers that were qualitatively analysed. Quantitative meta-analysis was not feasible due to significant heterogeneity in the investigated drugs, study methodologies, and the outcomes assessed. The six studies reviewed include: Rana et al. (2023)[7], Naderi et al. (2024)[8], Yang F. et al. (2018)[9], Guo M. et al. (2024)[10], Peterson-Houle G.M. et al. (2021)[11], and Zhao X. et al. (2023)[12].

Across these systematic reviews and meta-analyses, there is a notable lack of robust, high-quality data on the efficacy of treatments for TN, including CBZ, which is widely recommended as a first-line therapy by many existing guidelines. None of the studies included in the systematic reviews provided strong evidence, such as high-tier randomized controlled trials (RCTs) with rigorous design and sufficient sample sizes, to firmly establish the efficacy of CBZ for TN.

This underscores a critical gap in the literature, where clinical recommendations continue to rely on limited and outdated data, often extrapolated from small, older CBZ-placebo RCTs. The absence of comprehensive, high-quality evidence highlights the need for further well-designed studies to strengthen the foundation for evidence-based treatment guidelines.

Below is a PRISMA flow chart of the included systematic reviews and meta-analyses.

Figure 1: PRISMA flow diagram for the systematic review of reviews and meta-analyses for the PubMed and Cochrane databases search.



8.2 Review of current guidelines for CBZ evidence

Since the recent published reviews are of low-quality evidence, the existing guidelines on TN treatment were reviewed. Among these, the NICE guidelines were examined in detail due to their rigorous evidence synthesis process and established recommendations on TN, first published in 2013 and updated in 2020[13]. The NICE guidelines didn't find any robust studies that met inclusion criteria to inform recommendations. Nonetheless, the NICE guideline development group acknowledged the debilitating nature of TN, underscoring the need for treatment, using the available evidence[13,14]. The NICE guidelines, therefore, strongly recommends CBZ as treatment of TN as indicated in their recommendation and justification below:

> *"The (GDG) agreed that part of the reason why it may be difficult to conduct research in this area is that most patients in the UK are already on CBZ and do not wish to risk not receiving the drug. The GDG also felt that, in the absence of robust evidence, this may show that there is at least some efficacy of this drug over no treatment for these patients. Consequently, despite the paucity of robust evidence and because treatment with carbamazepine is current practice, the GDG wanted to make a strong recommendation for carbamazepine. The GDG decided that there was insufficient evidence to make a recommendation to change current practice."*[10]

This recommendation of CBZ by NICE guidelines and other guidelines (see Table 3) primarily rests on three RCTs from the 1960s. Campbell et al. (1966)[15], Killian et al. (1968)[16], and Nicol et al. (1969)[17] compared CBZ to placebo in TN treatment, reporting effectiveness in reducing the frequency and severity of pain. In Killian et al., 24 patients were randomized to CBZ or placebo for three months, with all CBZ patients experiencing significant pain relief and minimal response in the placebo group (definitive numbers not provided). Nicol et al. enrolled 44 patients in a four-year follow-up, showing that 73% of CBZ patients responded well compared to 25% in the placebo group, with a number-needed-to-treat (NNT) of 2.1. Campbell et al. employed a crossover design in 70 patients, also showing significant improvements with CBZ, though outcome assessment details were unclear (See Table 3).

A Cochrane Database systematic review on CBZ for chronic neuropathic pain and fibromyalgia, first published in 2011 and updated in 2024, further supports CBZ's use in TN[18]. This review included RCTs on CBZ for chronic neuropathic pain (including TN) or fibromyalgia, with at least 10 participants per treatment group. They identified 10 studies, including the three CBZ-placebo RCTs described above. Overall, no study provided first- or second-tier evidence, with all falling under third-tier due to poorly defined outcomes, incomplete reporting, and small sample sizes. Among 480 participants, CBZ generally provided better pain relief than placebo, but adverse events were common, affecting 65% of CBZ users versus 27% with placebo, meaning two of every five treated experienced an adverse event unique to CBZ. Furthermore, 3% of CBZ users withdrew due to adverse effects, compared to none on placebo. In a subgroup analysis of TN, a risk ratio for the outcome of interest (pain freedom/reduced painful attacks) was 6.02 (95% CI 2.82 – 12.85), favouring CBZ over placebo. The review concluded that CBZ is likely effective for TN, albeit with limitations due to the low quality of evidence.

Given TN's severity and the widespread recommendation for CBZ, it is unlikely (and arguably unethical) to conduct placebo-controlled studies for TN, suggesting high-quality CBZ-placebo RCTs will remain scarce. Current research is now focused on finding alternative agents with comparable or superior efficacy to CBZ, though none have proven superior to date (see next section).

Thus, despite limited evidence and reported side effects, CBZ remains the recommended first-line treatment for TN, as adopted by other guidelines.

Table 3: Summary of RCT on CBZ versus placebo

Author & Year	Study design & Location	Number of participants	Follow-up duration	Quality of evidence (GRADE)	Outcomes /NNT	Side effects (S/E)
Campbell et al[15], 1966	RCT, double blind, multicenter, UK	70	8 weeks	Low	Severity of pain and number of pain paroxysms statistically improved in CBZ condition compared with placebo condition. NNT not reported	50% in the CBZ had S/E most commonly unsteadiness, dizziness, and drowsiness. 24% in the placebo group had S/E, the type of S/E not stated
Killian et al[16], 1968	RCT, double blind, single center, USA	24	3 months	Very low	Definite response (e.g., disappearance or decrease of pain) to CBZ in all patients, no or minimal response to placebo in all patients (exact numbers not stated). NNT ~1	13% in the CBZ group had S/E, most commonly skin rash, dizziness, abnormal liver enzymes, leukopenia. Side effects in placebo group not reported
Nicol et al[19], 1969	RCT, double blind, single center, USA	44	4 years	Low	27 (73%) patients had an excellent or good response to CBZ; 6 (25%) patients had an excellent or good response to placebo. NNT ~2.1	Number of participants with S/E not reported. Common S/E were – drowsiness (27%), staggering gait (14%), tremulousness (4%)

NNT: Number-needed-to-treat, RCT: Randomized control trial, GRADE: Grading of Recommendations Assessment, Development and Evaluation, CBZ: Carbamazepine

Table adapted from Bendtsen et al[1]

8.3 Comparison of CBZ with other agents

Due to the side effects of CBZ, there has been a search for alternative treatments for TN. Varying pharmacological interventions have been and continue to be investigated, but none so far provides superiority evidence to CBZ.

In 2001, Liebel et al conducted an RCT with 48 patients randomized to Oxcarbazepine (OXC) and CBZ. The study found that all patients receiving OXC and 19 (95%) on CBZ obtained more than a 50% reduction in the number of pain attacks. However, the duration of follow-up, sample size calculation, assessment of outcome and allocation procedure was unclear from the study. The findings of this RCT, though of low quality evidence, is similar to findings from a real-world data by Di Stefano et al (2021)[20]. This retrospective review of 354 patients found similar efficacy between OXC and CBZ. However, the rate of side effects was higher with CBZ than with OXC (43.6% vs 30.3%, $p < .0001$)[20]. Currently, there are no OXC RCTs demonstrating efficacy in treating TN and its availability is limited due to price and registration status (see table 4).

Another drug that has been investigated for treatment of TN is gabapentin. Yuan et al (2016)[21] performed a meta-analysis of 14 RCTs, including 1156 patients randomized to CBZ versus gabapentin. After four to ten weeks follow-up, response to gabapentin was similar to CBZ (odds ratio 1·6 [95% CI 1·2 to –2·2]). 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 CBZ and found to be of similar or inferior efficacy include lamotrigine, botulinum toxin A, topiramate, tizanidine, pimozide and eslicarbazepine[7].

8. 4 Combination therapies

Due to the challenges of managing TN and the side effect profiles of high dosages of CBZ, there is a clinical practice of combining different medications to improve pain control. Studies on combination therapies have shown desirable effects, although no proper randomized trials are available. It is worth noting that almost all combinations therapies have CBZ. Some of the reported combinations include; pregabalin and CBZ[22], lidocaine and CBZ[23] and baclofen and CBZ[24]

The evidence for these combination therapies is low. However, the reports of CBZ being included in almost all these reported combinations further supports the need of having CBZ as first line choice of treatment.

8.5 Safety/Tolerance

Despite being effective in treating TN, CBZ is frequently known to cause undesirable effects. Common 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[25]. From TN trials, particular side effects have been reported that eventually cause treatment interruption. These include:

- Multiple CNS effects occurring together (Di Stefano et al, 2021)[20]
- Hyponatraemia (Di Stefano et al, 2021)[20]
- Leukopaenia (ariyawardana et al., 2003)[26]
- Skin rash (Campbell et al., 1966)[27]

As can be noted from the three CBZ-placebo RCTs (Table 2), and reported in observational studies[4,20] and recent reviews[7], it is clear that side effects are common with CBZ. This frequency of side effects underscores the need for alternative therapeutic options to be available to ensure treatment continuity and avoid adverse reactions. Given the absence of such alternative drugs with strong evidence for treatment of TN, CBZ remains the recommended choice with overall benefits of using CBZ outweighing the risks.

8.6 Special groups

8.6.1 Older people

With some mild anticholinergic effects of CBZ, there are increased risks of delirium, urinary retention and constipation in the elderly population[25,28].

A review by Oomens et al[29] looked at the safety profile of TN medications in the elderly population. However, there are no specific trials conducted for the elderly population. The reported trials usually exclude people with comorbid illnesses or on other medications; and this eventually excludes the majority of elderly people. According to the current evidence, if the side effects are unacceptable (which tends to be a common thing in the elderly population), the patient should be switched to OXC[30,31].

8.6.2 Pregnant women

As an anti-convulsant, CBZ is known to be teratogenic and is classified as category D drug during pregnancy.

8.6.3 Patients on multiple drugs

CBZ 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[32]. Common interactions occur with other anti-seizure medications (such as lamotrigine, phenytoin, and valproate), often necessitating dosage adjustments to maintain therapeutic levels. Anticoagulants like warfarin and novel oral anticoagulants (NOACs) are also affected, as CBZ can reduce their

anticoagulant effects, increasing the risk of clot formation. Similarly, primidone, oral contraceptives, statins, and certain antiretroviral agents may be strongly inhibited and become less effective[32].

Given the broad range of interactions, it is advisable to cross-check medications when initiating CBZ therapy.

8.7 Summary of evidence

Currently, CBZ is used as the first-line treatment choice for TN with NNT of 1.7 -1.8 [19]. However, its optimal usage is limited by side effects, with a NNH of 3.4 for minor effects and 24 for major effects[33,34]. Some of the common reported side effects include dizziness, sleepiness, and gastrointestinal disturbances, and these can impact adherence. These side effects are more prominent in older people, necessitating careful monitoring and dose adjustments. The present limitations of side effects from usage of CBZ calls for continued research in finding safe and effective treatment for TN. Until such treatment options are available, CBZ remains the treatment of choice for TN.

9.0 SUMMARY OF RECOMMENDATIONS IN CURRENT CLINICAL GUIDELINES

9.1 Recommendations in existing WHO guidelines

Trigeminal Neuralgia is currently not covered in WHO guidelines. CBZ is recommended by the WHO Mental Health Gap Programme (mhGAP) Guidelines for treatment of epilepsy and bipolar disorder.

9.2 Recommendations in other current clinical guidelines

With the debilitating nature of TN, the use of CBZ is recommended as first-line treatment option for TN by various clinical guidelines, as listed in table 4.

Table 4: Examples of guidelines recommending the use of CBZ for TN

Guideline & Reference	Year of issue	Summary statement
NICE[14,35]	2020	Offer carbamazepine as initial treatment for trigeminal neuralgia. If initial treatment with carbamazepine is not effective, is not tolerated or is contraindicated, consider seeking expert advice from a specialist and consider early referral to a specialist pain service or a condition-specific service.
European Academy of Neurology[33]	2019	For long-term treatment, carbamazepine or oxcarbazepine are recommended as drugs of first choice. Lamotrigine, gabapentin, botulinum toxin type A, pregabalin, baclofen and phenytoin may be used either alone or as add-on therapy.
Standard Treatment Guidelines AND EML for South Africa[36]	2019	Carbamazepine, oral 100 mg 12 hourly, initial dose. Increase dose slowly. Doses of up to 1 200 mg daily may be required
French Headache Society & French Neurosurgical Society (FHS & FNS)[37]	2017	Carbamazepine is effective to treat trigeminal neuralgia and provides complete initial relief in at least 70% of treated patients. Carbamazepine has marketing approval in France for the treatment of CTN. In the absence of contraindications, it is the first-line pharmacological treatment
American Academy of Neurology – European Federation of Neurological Societies (AAN-EFNS)[30]	2008	Carbamazepine (stronger evidence) or oxcarbazepine (better tolerability) should be offered as first-line treatment for pain control.

10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS

The cost of treating TN with CBZ varies by region and healthcare system, but as a generic drug, CBZ is relatively affordable and widely available, even in LMICs, where its long-standing use in epilepsy can support ensuring continued access.

There is no data on the cost-effectiveness of CBZ in the treatment of TN.

Table 5, showing the pricing of CBZ in selected countries, further supports its affordability.

11. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPEIAL STANDARDS SECTION

This application is for addition of an indication for use of CBZ. The current EML has CBZ listed for the following indications.

- Antiseizure medication:
    - Oral liquid: 100 mg/5 mL
    - Tablet (chewable): 100mg; 200mg
    - Tablet (scored): 100mg; 200mg; 400mg
- Bipolar disorders: Table (scored) 100mg, 200mg, 400mg

Since CBZ has been in use as anti-seizure medication and treatment for bipolar disorders, backed by its presence in the WHO EML, it is generally registered and available at affordable price across the world, including in LMICs as seen in Table 5. Moreover, CBZ is listed on the national EML of more than 134 countries worldwide.

Table 5: Availability and pricing of CBZ (compared with OXC) from selected countries.

Country	Carbamazepine (200 mg)			
	Quantity	Price/Price per tablet (USD)	Listed on National EML	Registration Status
Malawi	30 tablets	3.4 / 0.11	Yes	Registered
Zambia	30 tablets	1.8 / 0.06	Yes	Registered
Zimbabwe	30 tablets	2.70 / 0.09	Yes	Registered
South Africa	30 tablets	10.2 / 0.34	Yes	Registered
Brazil	30 tablets	2.2 / 0.07	Yes	Registered
Tunisia	50 tablets	0.82 / 0.01	-	-
Ghana	50 tablets	9.5 / 0.19	Yes	Registered
India	30 tablets	0.5 / 0.01	Yes	Registered
Kenya	30 tablets	4.3 / 0.14	Yes	Registered
Philippines	Per tablet	0.06 / 0.06		

12. 0 PHARMACOPOEIAL STANDARDS

(a) United States Pharmacopoeia:

https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/carbamazepine-ert-pmp-20240126.pdf

https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/oxcarbazepine_oral_suspension.pdf

(b) European Pharmacopoeia:

https://sds.edqm.eu/pdf/SDS/EDQM_201600145_1.0_SDS_EN.pdf

https://sds.edqm.eu/pdf/SDS/EDQM_201600668_2.0_SDS_EN.pdf?ref=1717478357

(c)British Pharmacopoeia:

https://www.pharmacopoeia.com/shop/products/1000014932?journey-type=CRS

(d) Japanese Pharmacopoeia:

https://www.mhlw.go.jp/content/11120000/000912386.pdf

REFERENCES

1. Bendtsen L, Zakrzewska JM, Heinskou TB, et al. Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia. *Lancet Neurol*. 2020;19(9):784-796. doi:10.1016/S1474-4422(20)30233-7

2. Lambru G, Zakrzewska J, Matharu M. Trigeminal neuralgia: A practical guide. *Pract Neurol*. 2021;21(5):392-402. doi:10.1136/practneurol-2020-002782

3. Sait Ashina, Carrie E. Robertson, Anan Srikiatkhachorn, Giulia Di Stefano, Anne Donnet, Mojgan Hodaie, Mark Obermann, Marcela Romero-Reyes, Young Seok Park GC& LB. Trigeminal neuralgia. *Nat Rev*. Published online 2024. doi:10.1038/s41572-024-00523-z

4. Di Stefano G, La Cesa S, Truini A, Cruccu G. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain. *J Headache Pain*. 2014;15(1):1-5. doi:10.1186/1129-2377-15-34

5. Katusic S, Beard CM, Bergstralth E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. *Ann Neurol*. 1990;27(1):89-95. doi:10.1002/ana.410270114

6. Karayannis N V., Sturgeon JA, Chih-Kao M, Cooley C, Mackey SC. Pain interference and physical function demonstrate poor longitudinal association in people living with pain: A PROMIS investigation. *Pain*. 2017;158(6):1063-1068. doi:10.1097/j.pain.0000000000000881

7. Rana MH, Khan AAG, Khalid I, et al. Therapeutic Approach for Trigeminal Neuralgia: A Systematic Review. *Biomedicines*. 2023;11(10):1-18. doi:10.3390/biomedicines11102606

8. Naderi Y, Rad M, Sadatmoosavi A, et al. Compared to oxcarbazepine and carbamazepine, botulinum toxin type A is a useful therapeutic option for trigeminal neuralgia symptoms: A systematic review. *Clin Exp Dent Res*. 2024;10(2). doi:10.1002/cre2.882

9. Yang F, Lin Q, Dong L, Gao X, Zhang S. Efficacy of 8 different drug treatments for patients with trigeminal neuralgia: A network meta-analysis. *Clin J Pain*. 2018;34(7):685-690. doi:10.1097/AJP.0000000000000577

10. Guo M, Shen W, Zhou M, et al. Safety and efficacy of carbamazepine in the treatment of trigeminal neuralgia: A metanalysis in biomedicine. *Math Biosci Eng*. 2024;21(4):5335-5359. doi:10.3934/mbe.2024235

11. Peterson-Houle GM, AbdelFattah MR, Padilla M, Enciso R. Efficacy of medications in adult patients with trigeminal neuralgia compared to placebo intervention: a systematic review with meta-analyses. *J Dent Anesth Pain Med*. 2021;21(5):379. doi:10.17245/jdapm.2021.21.5.379

12. Zhao X, Ge S. The efficacy and safety of gabapentin vs. carbamazepine in patients with primary trigeminal neuralgia: A systematic review and meta-analysis. *Front Neurol*. 2023;14(5). doi:10.3389/fneur.2023.1045640

13. NICE. Neuropathic pain in adults : pharmacological management in non-specialist settings. *NICE Guidel*. 2013;updated 20(April 2018):1-36. www.nice.org.uk/guidance/cg173

14. Neuropathic pain-pharmacological management The pharmacological management of neuropathic pain in adults in non-specialist settings Update information. 2020;(September). http://guidance.nice.org.uk/CG173

15. F. G. CAMPBELL JGGA. Clinical trial of carbazepine (Tegretol) in trigeminal neuralgia. *J Neurol Neurosurg Psychiat*. 1966;29:265-267.

16. Killian JM, Fromm GH. Carbamazepine in the Treatment of Neuralgia: Use and Side Effects. *Arch Neurol*. 1968;19(2):129-136. doi:10.1001/archneur.1968.00480020015001

17. NICOL CF. A FOUR YEAR DOUBLE-BLIND STUDY OF TEGRETOLrIN FACIAL PAIN. *Headache J Head Face Pain*. 1969;9(1):54-57. doi:10.1111/j.1526-4610.1969.hed0901054.x

18. Moore RA, Wiffen PJ, Derry S, Rice ASC. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2014;2017(3). doi:10.1002/14651858.CD007938.pub3

19. Sindrup SH, Jensen TS. Pharmacotherapy of trigeminal neuralgia. *Clin J Pain*. 2002;18(1):22-27. doi:10.1097/00002508-200201000-00004

20. Di Stefano G, De Stefano G, Leone C, et al. Real-world effectiveness and tolerability of carbamazepine and oxcarbazepine in 354 patients with trigeminal neuralgia. *Eur J Pain (United Kingdom)*. 2021;25(5):1064-1071. doi:10.1002/ejp.1727

21. Yuan M, Zhou HY, Xiao ZL, et al. Efficacy and Safety of Gabapentin vs. Carbamazepine in the Treatment of Trigeminal Neuralgia: A Meta-Analysis. *Pain Pract*. 2016;16(8):1083-1091. doi:10.1111/papr.12406

22. Eide PK. Familial occurrence of classical and idiopathic trigeminal neuralgia. *J Neurol Sci*. 2022;434(December 2021):120101. doi:10.1016/j.jns.2021.120101

23. Zhang J, Yang M, Zhou M, He L, Chen N, Zakrzewska JM. Non-antiepileptic drugs for trigeminal neuralgia. *Cochrane Database Syst Rev*. 2013;2013(12). doi:10.1002/14651858.CD004029.pub4

24. Jawahar R, Oh U, Yang S, Lapane KL. A systematic review of pharmacological pain management in multiple sclerosis. *Drugs*. 2013;73(15):1711-1722. doi:10.1007/s40265-013-0125-0

25. Saadabadi. JSMT vi HDA. Carbamazepine - StatPearls - NCBI Bookshelf. *StatPearls Publ Treasure Isl*. Published online 2021:1-12. https://www.ncbi.nlm.nih.gov/books/NBK482455/#article-18838.r15

26. Ariyawardana A, Pallegama R, Sitheeque M, Ranasinghe A. Use of single- and multi-drug regimens in the management of classic (idiopathic) trigeminal neuralgia: an 11-year experience at a single Sri Lankan institution. *J Investig Clin*

Dent. 2012;3(2):98-102. doi:10.1111/j.2041-1626.2011.00109.x

27. Janaki S, Sehgal AD, Kothari HS. Trial of carbazepine (tegretol) in trigeminal neuralgia. *Neurol India*. 1968;16(1):17-19.

28. Hmouda H, Salem C Ben, Grira M, Slim R, Bouraoui K. Letter to the Editors: Carbamazepine-induced urinary retention. *Br J Clin Pharmacol*. 2007;64(6):833-834. doi:10.1111/j.1365-2125.2007.03002.x

29. Oomens MAEM, Forouzanfar T. Pharmaceutical Management of Trigeminal Neuralgia in the Elderly. *Drugs and Aging*. 2015;32(9):717-726. doi:10.1007/s40266-015-0293-6

30. Cruccu G, Gronseth G, Alksne J, et al. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol*. 2008;15(10):1013-1028. doi:10.1111/j.1468-1331.2008.02185.x

31. Gronseth G, Cruccu G, Alksne J, et al. Practice Parameter: The diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review). *Neurology*. 2008;71(15):1183-1190. doi:10.1212/01.wnl.0000326598.83183.04

32. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: Interactions between antiepileptic drugs and other drugs. *Lancet Neurol*. 2003;2(8):473-481. doi:10.1016/S1474-4422(03)00483-6

33. Bendtsen L, Zakrzewska JM, Abbott J, et al. European Academy of Neurology guideline on trigeminal neuralgia. *Eur J Neurol*. 2019;26(6):831-849. doi:10.1111/ene.13950

34. Brick N. Carbamazepine for acute and chronic pain in adults. *Clin J Oncol Nurs*. 2011;15(3):335-336. doi:10.1188/11.CJON.335-336

35. NICE. Appendix A : Summary of evidence from surveillance. *Natl Clin Guidel Cent*. 2017;35(2014):1-49. https://www.nice.org.uk/guidance/cg177/evidence/appendix-a-summary-of-new-evidence-from-surveillance-pdf-4550088782

36. National Department of Health. *Standard Treatment Guidelines And Essential Medicines List for South Africa: Hospital Level 2012 Edition*.; 2015.

37. Donnet A, Simon E, Cuny E, et al. French guidelines for diagnosis and treatment of classical trigeminal neuralgia (French Headache Society and French Neurosurgical Society). *Rev Neurol (Paris)*. 2017;173(3):131-151. doi:10.1016/j.neurol.2016.12.033