Verapamil

Essential medicine status

ATC codes: C08DA01

Indication	Trigeminal autonomic cephalalgias ICD11 code: 8A82
INN	Verapamil
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > tablet:** 120 mg (hydrochloride) (immediate-release) ; 40 mg (hydrochloride) (immediate-release) ; 80 mg (hydrochloride) (immediate-release) ; 120 mg (hydrochloride) (extended-release) ; 180 mg (hydrochloride) (extended-release) ; 240 mg (hydrochloride) (extended-release)
EML status history	First added 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	Verapamil
DrugBank	Verapamil

Expert Committee recommendation

The Expert Committee noted that cluster headaches are a severe and debilitating type of headache, for which the need for prompt treatment of acute attacks and prophylaxis is important to reduce the effect of the condition on sufferers. The Committee also noted that there are currently no treatments for cluster headache on the EML and that the medicines currently listed for acute treatment and prophylaxis of migraine are ineffective for cluster headache. The Committee noted that high-flow oxygen treatment and triptans are the recommended treatment for acute attacks, while verapamil is the most widely prescribed medication for prophylaxis. Glucocorticoids are also recommended as preventive therapy for people with episodic cluster headaches and infrequent active cluster periods but are primarily used as bridging therapy to prophylactic treatment. The Committee considered that the evidence presented in the application supported the efficacy and safety of subcutaneous sumatriptan for the acute management of cluster headache attacks, offering rapid symptom relief. However, the Committee also noted the role of inhaled oxygen in this setting, which may be associated with higher efficacy than subcutaneous sumatriptan. The Committee noted that the evidence supporting the use of verapamil as a first-line preventive treatment of cluster headache was limited. However, pooled estimates indicated that most people treated achieved either a complete response or a more than 50% reduction in attack frequency compared with placebo. With regard to safety, the Committee noted the need for dose titration when starting or stopping verapamil and that regular electrocardiographs are recommended to monitor cardiac function. Overall, the Committee considered that verapamil had a favourable balance of benefits and harms in this condition. In consideration of prednisolone, the Expert Committee noted that corticosteroids may be used for short-term bridging therapy during the start or adjustment of prophylactic treatments. The evidence reported in the application was for prednisone, an inactive prodrug that is metabolized to prednisolone in the liver. Prednisone and prednisolone are used to treat similar conditions and are generally considered equally effective and safe. In people with reduced hepatic function, prednisolone is usually preferred. The Committee considered that the available evidence supported the efficacy of prednisone (and by inference, prednisolone) as a rapid-acting, short-term preventive treatment for episodic cluster headache that can be used to attenuate the early cluster episode until long-term prevention has reached its full efficacy. With regard to safety, the

Committee recalled the well known adverse effect profile of prednisone/prednisolone and recognized that short term-use was associated with a better safety profile than longer-term use. Overall, the Committee considered that prednisone/prednisolone also had a favourable balance of benefits and harms in this condition. The Committee noted the cost–effectiveness assessments of the three medicines performed by the applicants but was unable to confidently judge the true cost–effectiveness due to substantial uncertainty in the inputs. However, the Committee considered that the medicines were generally low cost and affordable, with availability of generics. Based on these considerations, the Expert Committee recommended the inclusion on the core list of the EML of: i. subcutaneous sumatriptan for the acute treatment of cluster headache attacks; ii. prednisolone, as the representative medicine with prednisone as a therapeutic alternative, as bridging therapy for prophylactic treatment of cluster headache; and iii. verapamil for prophylactic treatment of cluster headache.

Background

Medicines for the treatment and prevention of cluster headache have not previously been evaluated for inclusion on the EML. Sumatriptan, prednisolone and verapamil are all already included on the EML for other indications. Currently listed medicines for the treatment and prophylaxis of migraine are not effective in the management of cluster headache.

Public health relevance

Cluster headache is a severe, debilitating primary headache disorder affecting about 1 in 1000 people globally, with a higher prevalence in men than in women (1). It is characterized by periods, lasting weeks or months, of frequently recurring short attacks of excruciating unilateral pain, typically around the eye or temple, usually accompanied by extreme agitation and autonomic symptoms such as tearing, nasal congestion and ptosis (2). Attacks may recur several times a day and substantially affect the productivity and quality of life of those affected both during attacks and throughout the cluster period. Cluster headache is associated with substantial health and economic burdens, with high health-care costs (3).

Benefits

Sumatriptan A 2013 Cochrane systematic review and meta-analysis of six randomized controlled trials evaluated the efficacy and tolerability of triptans compared to placebo and other active interventions for acute treatment of cluster headache in adults (4). The review found low-quality evidence that subcutaneous sumatriptan 6 mg was significantly superior to placebo for the primary outcomes of pain-free at 15 minutes (risk ratio (RR 2.72, 95% confidence interval (CI) 1.82 to 4.21; two randomized controlled trials, 258 participants, number needed to treat (NNT) = 4) and headache relief at 15 minutes (RR 2.31, 95% CI 1.77 to 3.03; two randomized controlled trials, 258 participants, NNT = 3). The proportions of attacks that were pain-free at 15 minutes were 48% and 15% for sumatriptan and placebo, respectively. The proportions of attacks with headache relief at 15 minutes were 78% and 32% for sumatriptan and placebo, respectively. A 2022 network meta-analysis of 13 randomized controlled trials evaluated the relative effectiveness and harms of acute treatment options for cluster headache (5). Interventions included high- and low-flow oxygen, subcutaneous sumatriptan, nasal zolmitriptan, octreotide, and non-invasive vagal nerve stimulation. For the outcome of headache response at 15 and 30 minutes compared to placebo, high-flow oxygen was the most effective (odds ratio (OR) 9.0, 95% credible interval (CrI) 5.3 to 15.9), followed by subcutaneous sumatriptan (OR 6.4, 95% CrI 3.8 to 11.1). Subcutaneous sumatriptan was more effective than all other interventions studied, with the exception of oxygen. Prednisone/prednisolone Note: The study described below investigates prednisone, the prodrug of prednisolone. They are generally considered to be equally effective and safe. A 2021 randomized, multicentre, double-blind, placebo-controlled trial in Germany evaluated the efficacy and safety of prednisone in the short-term prevention of episodic cluster headache (6). Participants were randomized 1:1 to receive 100 mg prednisone for 5 days followed by a tapering of 20 mg every 3 days, or matching placebo while being titrated up to prophylactic verapamil 120 mg three times daily. Study duration was 28 days and the primary endpoint was the mean number of attacks within the first week of treatment. Results showed that participants in the prednisone group had a significantly lower mean number of attacks within the first week compared with those in the placebo group (7.1 standard deviation (SD) 6.5 versus 9.5 SD 6.0), a difference of −2.4 attacks (95% CI −4.8 to −0.03). Prednisone or prednisolone are primarily used in the short term as bridging treatment to other prophylactic treatments for cluster headache. Verapamil The applicants identified and described 10 heterogeneous studies (including two randomized controlled trials) that evaluated the effectiveness of verapamil as prophylactic treatment for cluster headache (7–16). The studies differed in design, interventions and outcome measures, but all reported benefit for verapamil. Pooled analysis of four non-comparative observational studies that reported outcomes of complete response or ≥ 50% reduction in attack frequency showed that 73% of patients who received verapamil reached either a complete response or ≥ 50% reduction in the attack frequency. Of the two randomized controlled trials, one was a small (n = 30) double-blind crossover trial comparing verapamil 360 mg daily versus lithium 900 mg daily in patients with chronic cluster headache. Both medicines were associated with significant improvements in headache index (improvement after the first 7 days of treatment) and analgesic consumption

(11).The other was a small (n = 30) placebo-controlled trial in patients with episodic cluster headache that showed that verapamil 360 mg decreased daily attack frequency (mean 0.66, SD 0.88 versus. 1.65, SD 1.01) and daily analgesic use (mean 0.5, SD 0.87 versus. 1.2, SD 1.03) (12).

Harms

The safety profiles of sumatriptan, prednisolone and verapamil are well known from their use in other indications. Sumatriptan is associated with a potential risk of cardiovascular events and is contraindicated in people with a history of ischemic heart disease, uncontrolled hypertension or cerebrovascular disease. Subcutaneous administration of sumatriptan is associated with mild, transient injection site reactions, tingling and pressure sensations (17). Short-term use of prednisolone is generally considered safe. Commonly reported adverse events include increased appetite, mood swings and insomnia. Long-term use is associated with greater risks, including adrenal suppression, osteoporosis and increased susceptibility to infection (3). Common adverse events associated with verapamil include constipation, dizziness, fatigue and oedema, which are usually mild and manageable with dose adjustment (18). Verapamil can lead to heart block, therefore baseline and periodic electrocardiograph monitoring to detect potential cardiac issues is recommended.

Cost / cost effectiveness

The application stated that economic studies of the proposed medicines for the treatment or prevention of cluster headache are not available. De novo modelled cost–effectiveness assessments were presented instead. For acute treatment with sumatriptan, costs per healthy life year gained were calculated to be 120 623 United States dollars (US$) and US$ 47 892, depending on the price input. For prophylactic treatment with prednisolone and verapamil, cost per healthy live year gained was calculated as US$ 37 875. When a stopping rule was applied whereby repeated use in subsequent cluster periods was limited to only individuals with a good response in the first cluster period, the cost per healthy life year gained was US$ 1544.The analyses for prophylactic treatment did not account for interictal lost health, which is expected to be averted by the reduction in duration of cluster periods.

WHO guidelines

WHO guidelines for the management of cluster headache are not currently available. The application provided a brief summary of recommendations on subcutaneous sumatriptan, prednisone/prednisolone and verapamil as key treatments for cluster headache from various current national and international clinical guidelines.

Availability

Subcutaneous sumatriptan has wide regulatory approval for use in the acute treatment of cluster headache. Availability of the subcutaneous formulation may be limited in some settings. Generics are available. The use of prednisolone and verapamil for prophylaxis of cluster headache is off-label. Both medicines are widely available in generic forms.

Other considerations

The Department of Mental Health, Brain Health and Substance Use provided comments on the application and supported the proposal. They also highlighted a need for a review of the evidence for oxygen therapy for cluster headache, which has been shown to be an effective first-line treatment for acute attacks.

1. Ribeiro RT, Gonçalves AL, Nobre ME, Carvalho D de S, MFP P. Cluster headache: review of current understandings. Headache Medicine. 2012;3(1):5–12 (https://doi.org/https://doi.org/10.48208/HeadacheMed.2012.2).
2. Wei DY, Khalil M, Goadsby PJ. Managing cluster headache. Pract Neurol. 2019;19(6):521–8 (https://doi.org/10.1136/practneurol-2018-002124).
3. May A, Evers S, Goadsby PJ, Leone M, Manzoni GC, Pascual J et al. European Academy of Neurology guidelines on the treatment of cluster headache. Eur J Neurol. 2023;30(10):2955–79 (https://doi.org/10.1111/ene.15956).
4. Law S, Derry S, Moore RA. Triptans for acute cluster headache. Cochrane Database Syst Rev. 2013;2013(7):CD008042 (https://doi.org/10.1002/14651858.CD008042.pub3).
5. Medrea I, Christie S, Tepper SJ, Thavorn K, Hutton B. Network meta-analysis of therapies for cluster headache: effects of acute therapies for episodic and chronic cluster. Headache. 2022;62(4):482–511 (https://doi.org/10.1111/head.14283).
6. Obermann M, Nägel S, Ose C, Sonuc N, Scherag A, Storch P et al. Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: a multicentre, double-blind, randomised controlled trial. Lancet Neurol. 2021;20(1):29–37 (https://doi.org/10.1016/s1474-4422(20)30363-x).
7. Meyer JS, Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. Headache. 1983;23(6):266–77 (https://doi.org/10.1111/j.1526-4610.1983.hed2306266.x).
8. Gabai IJ, Spierings EL. Prophylactic treatment of cluster headache with verapamil. Headache. 1989;29(3):167–8 (https://doi.org/10.1111/j.1526-4610.1989.hed2903167.x).
9. Pompilio G, Migliore A, Integlia D. Systematic literature review and Bayesian network meta-analysis of episodic cluster headache drugs. Eur Rev Med Pharmacol Sci. 2021;25(3):1631–40 (https://doi.org/10.26355/eurrev_202102_24874).

10. Blau JN, Engel HO. Individualizing treatment with verapamil for cluster headache patients. Headache. 2004;44(10):1013–8 (https://doi.org/10.1111/j.1526-4610.2004.04196.x).
11. Bussone G, Leone M, Peccarisi C, Micieli G, Granella F, Magri M et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. Headache. 1990;30(7):411–7 (https://doi.org/10.1111/j.1526-4610.1990.hed3007411.x).
12. Leone M, D''Amico D, Frediani F, Moschiano F, Grazzi L, Attanasio A et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. Neurology. 2000;54(6):1382–5 (https://doi.org/10.1212/wnl.54.6.1382).
13. Petersen AS, Lund N, Jensen RH, Barloese M. Real-life treatment of cluster headache in a tertiary headache center – results from the Danish Cluster Headache Survey. Cephalalgia. 2021;41(5):525–34 (https://doi.org/10.1177/0333102420970455).
14. Lee MJ, Park JW, Chu MK, Moon HS, Chung PW, Chung JM et al. Treatment pattern and response for cluster headache in Korea: a prospective multicenter observation study. Cephalalgia. 2023;43(4):3331024231159627 (https://doi.org/10.1177/03331024231159627).
15. Tuncer Issı Z, Akbulut N, Öztürk V. Cluster headache: a single tertiary center study. Neurol Res. 2022;44(4):342–52 (https://doi.org/10.1080/01616412.2021.1992101).
16. Cotton S, Andrews JS, Nichols RM, Jackson J, Tockhorn-Heidenreich A, Milligan G et al. Clinical characteristics and treatment patterns of patients with episodic cluster headache: results from the United States, United Kingdom and Germany. Curr Med Res Opin. 2023;39(12):1637–47 (https://doi.org/10.1080/03007995.2023.2237741).
17. Schindler EAD, Wright DA, Weil MJ, Gottschalk CH, Pittman BP, Sico JJ. Survey analysis of the use, effectiveness, and patient-reported tolerability of inhaled oxygen compared with injectable sumatriptan for the acute treatment of cluster headache. Headache. 2018;58(10):1568–78 (https://doi.org/10.1111/head.13405).
18. Lund NLT, Petersen AS, Fronczek R, Tfelt-Hansen J, Belin AC, Meisingset T et al. Current treatment options for cluster headache: limitations and the unmet need for better and specific treatments – a consensus article. J Headache Pain. 2023;24(1):121 (https://doi.org/10.1186/s10194-023-01660-8).