Sumatriptan

Essential medicine status

Section: 5. Medicines for neurological disorders > 5.1. Medicines for central nervous system disorders > 5.1.5. Medicines for headache disorders > 5.1.5.1. Medicines for acute migraine attacks

ATC codes: N02CC01

Indication	Migraine ICD11 code: 8A80.Z
INN	Sumatriptan
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid > tablet: 50 mg
EML status history	Application rejected in 2019 (TRS 1021) Added in 2021 (TRS 1035) Changed in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	eletriptan (ATC codes: N02CC06) Oral > Solid > tablet: 40 mg
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Sumatriptan
DrugBank	Sumatriptan

Expert Committee recommendation

The Expert Committee noted that migraine is a common disabling primary headache disorder characterized by recurrent moderate to severe pain. It is a cause of disability and results in a substantial socioeconomic burden, which is greater for women than for men. The Committee noted the very-low-quality evidence available on the efficacy of naproxen compared with placebo in terms of pain freedom and pain relief at 2 hours and the lack of head-to-head trials assessing the efficacy of naproxen versus aspirin or paracetamol (the currently available alternatives on the EML for this condition), or other non-steroidal anti-inflammatory drugs. However, indirect evidence reported similar rates of pain freedom at 2 hours. The Committee also noted that two randomized controlled trials showed no difference between naproxen and sumatriptan for the outcome of pain freedom at 2 hours (low and very low quality of evidence), while one showed that the 85 mg dose of oral sumatriptan was superior to oral naproxen 500 mg. The Committee noted that a recent network meta-analysis reported the combination of oral sumatriptan and naproxen had the greatest net benefit compared with monotherapy with a triptan (moderate-certainty evidence), a non-steroidal anti-inflammatory drug (high-certainty evidence), paracetamol (low-certainty evidence) or newer, more costly therapeutic classes, such as a calcitonin gene-related peptide antagonists (gepant, low-certainty evidence). Naproxen is generally well tolerated, with adverse effects rarely leading to discontinuation of treatment, and it is available in most countries at a reasonable price. The Committee noted that naproxen has a different pharmacokinetic profile compared with other non-steroidal anti-inflammatory drugs (e.g. aspirin, ibuprofen), with a longer half life and duration of action, which may be preferable for some patients. Based on these considerations, and in recognition of the importance for people with migraine to have a range of treatment options available to them, the Expert Committee recommended the addition of naproxen to the core list of the EML for adults with acute migraine as a therapeutic alternative under a square box listing for ibuprofen. The Committee recalled the 2021 decision to recommend the addition of sumatriptan to the core list of the EML for the treatment of adult patients with acute migraine and the consideration that there were likely to be benefits across the pharmacological class, but few data were available on efficacy, safety, price and

availability of other triptans. The Committee noted that eletriptan 40 mg and 80 mg showed significantly better efficacy than sumatriptan 50 mg and 100 mg for the outcome of pain freedom at 2 hours. Eletriptan was also superior to sumatriptan for outcomes of headache relief at 2 and 24 hours and relief of migraine-associated symptoms and required less use of rescue medications. The Committee noted that eletriptan is more costly than sumatriptan which is available as generics in several countries, and that at its current price, eletriptan is not cost-effective by most thresholds when used as a first-line triptan. Therefore, the Committee noted therapies with triptans should start with the one that has the lowest acquisition cost and more costly options can be used in cases of treatment failure or severe side-effects. In line with previous consideration of the Committee that it is important for people with migraine to have a range of treatment options available to them, particularly for those with suboptimal responses or who are at risk of specific adverse events from currently listed analgesics, the Expert Committee recommended the addition of eletriptan to the core list of the EML as an alternative treatment option to sumatriptan in adults with acute migraine.

Background

Eletriptan and naproxen have not previously been considered by the Expert Committee for inclusion on the EML for the acute treatment of migraine. In 2021, following consideration of an application for the inclusion of sumatriptan on the EML for acute treatment of migraine, the Expert Committee recommended its addition to the core list of the EML. The Committee noted that in comparison with other triptans, for the outcome of pain freedom at 2 hours, the efficacy of sumatriptan was comparable to other triptans, with the exception of eletriptan 40 mg and 80 mg, which showed significantly better efficacy than sumatriptan 50 mg and 100 mg. Eletriptan was also superior to sumatriptan for outcomes of headache relief at 2 and 24 hours, less use of rescue medications and relief of migraine-associated symptoms. Although the Committee thought benefits were likely across the pharmacological class, few data were available on the efficacy, safety, price and availability of other triptans. The Committee therefore did not recommend the addition of alternative triptans at the time but indicated that it would consider requests for listing in future (1).

Public health relevance

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, photophobia/phonophobia and sensitivity to external stimuli (light, noise and odours). Symptoms are disabling and affect participation in life activities, quality of life and productivity (2). In about 25% of people affected, episodes may be preceded by transient focal neurological symptoms – most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits. The global prevalence of migraine is estimated at 14–15% (more than 1 billion people worldwide) and it is 2–3 times higher in women than men (3). According to the Global Burden of Disease study 2021, migraine was the fourth highest cause of years lived with disability at level 4 (4). In an analysis of the Global Burden of Disease study 2016, migraine accounted for 45.1 million disability-adjusted life years (5). About 2–3% of people with episodic migraine (headache on fewer than 15 days/month) transition to more disabling chronic migraine (headache on ≥ 15 days/month most of which have symptoms of migraine) (6). One of the main risk factors for the transition to chronic migraine is poorly managed acute treatment and the overuse of acute medications (7).

Benefits

The application presented the results of a systematic literature review and meta-analysis conducted by the applicants for the purpose of the application. For the analysis of efficacy, the outcome measures were pain freedom at 2 hours from intake of medication and pain relief at 2 hours from intake. Eletriptan versus placebo Based on a meta-analysis by the applicants of 119 randomized controlled trials of the efficacy of triptans in the treatment of acute migraine, high-quality evidence was found to exist to recommend the use of eletriptan 20 mg and 40 mg for the acute treatment of migraine attacks. Evidence also supported the use oral almotriptan 12.5 mg, frovatriptan 2.5 mg, naratriptan 2.5 mg, rizatriptan 5 mg and 10 mg, sumatriptan 50 mg and 100 mg and zolmitriptan 2.5 mg, and subcutaneous sumatriptan 6 mg. Additionally, moderate quality evidence existed to recommend oral naratriptan 1 mg and sumatriptan nasal spray 10 mg and 20 mg. The results of this meta-analysis were not included in the application. Eletriptan versus other triptans In comparative randomized controlled trials, for the outcome of pain freedom at 2 hours, eletriptan 40 mg was significantly more effective than sumatriptan 100 mg (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.20 to 2.40; three randomized controlled trials, 2257 participants (8–10)), and naratriptan 2.5 mg (RR 1.93, 95% CI 1.36 to

2.75; one randomized controlled trial, 391 participants (11)). While estimates of effect favoured eletriptan 40 mg, there were no significant differences with rizatriptan 10 mg, (RR 1.30, 95% CI 0.89 to 1.89; one randomized controlled trial, 53 participants (12)), or zolmitriptan 2.5 mg (RR 1.22, 95% CI 0.97 to 1.53, one randomized controlled trial, 735 participants (13)). Similarly, for the outcome of pain relief at 2 hours, eletriptan was more effective than sumatriptan 100 mg (RR 1.16, 95% CI 1.08 to 1.23), naratriptan 2.5 mg (RR 1.33, 95% CI 1.09 to 1.64) and rizatriptan (RR 1.40, 95% CI 1.02 to 1.94). No significant difference was found between eletriptan 40 mg and zolmitriptan 2.5 mg (RR 1.07, 95% CI 0.96 to 1.20; one randomized controlled trial). A 2024 systematic review and network meta-analysis of 137 randomized controlled trials (89 445 participants) evaluated the comparative effects of 17 pharmacological interventions for treatment of acute migraine (14). In head-to-head comparisons, for pain freedom at 2 hours, there was very-low-certainty evidence that eletriptan was associated with significant benefit compared with naratriptan (odds ratio (OR) 3.01, 95% CI 2.13 to 4.25), sumatriptan (OR 1.46, 95% CI 1.18 to 1.81), and zolmitriptan (OR 1.52, 95% CI 1.17 to 1.97). For sustained pain freedom from 2 to 24 hours, eletriptan was also significantly more effective than naratriptan (OR 2.73, 95% CI 1.35 to 5.52), sumatriptan (OR 1.41, 95% CI 1.02 to 1.93) and zolmitriptan (OR 1.47, 95% CI 1.03 to 2.11) (low- or very-low-certainty evidence). Naproxen versus placebo Three randomized controlled trials (2179 participants) compared oral naproxen versus placebo for the treatment of acute migraine (15–17). For pain freedom at 2 hours, the pooled analysis showed benefits of naproxen 500 mg (RR 1.92, 95% CI 1.32 to 2.77) and 825 mg (RR 3.72, 95% CI 1.78 to 7.75) over placebo. For pain relief at 2 hours, both strengths of naproxen were associated with benefit compared with placebo (500 mg: RR 1.58, 95% CI 1.40 to 1.78; 825 mg: RR 1.61, 95% CI 1.16 to 2.22). The overall risk of bias was unclear and the quality of evidence very low. Naproxen versus sumatriptan One randomized controlled trial (88 participants) compared oral naproxen 500 mg versus oral sumatriptan 100 mg (18). No significant difference was found between treatments for pain freedom at 2 hours (RR 1.20, 95% CI 0.61 to 2.37). The risk of bias was unclear and the quality of evidence low. Two randomized controlled trials (1917 participants) compared oral naproxen 500 mg with oral sumatriptan 50 mg or 85 mg (15, 16). Overall, the quality of evidence was low that 85 mg sumatriptan was superior to naproxen 500 mg for pain freedom at 2 hours (RR 1.51, 95% CI 1.22 to 1.88) and pain relief at 2 hours (RR 1.21, 95% CI 1.08 to 1.35). No significant difference was seen between naproxen 500 mg and sumatriptan 50 mg for either outcome measure. The risk of bias was unclear and the quality of evidence very low. Naproxen versus other non-steroidal anti-inflammatory drugs No head-to-head randomized controlled trials were identified that assessed the efficacy of naproxen versus aspirin, paracetamol, ibuprofen or other non-steroidal anti-inflammatory drugs. Indirect evidence was derived by the applicants from a recent systematic review and meta-analysis, which reported a pain-free rate at 2 hours of 22% for naproxen, 23% for acetyl salicylic acid, 20% for ibuprofen and 19% for paracetamol. Pain response at 2 hours was achieved in 44% of participants with naproxen, 42% with acetyl salicylic acid, 43% with ibuprofen and 46% with paracetamol (14). Naproxen in combination with sumatriptan Seven randomized controlled trials evaluated combination treatment with naproxen 500 mg and sumatriptan 50 mg or 85 mg versus placebo (15, 16, 19–23). Meta-analysis of four randomized controlled trials (2728 participants) showed benefit associated with combination treatment with naproxen and sumatriptan 85 mg for pain freedom at 2 hours (RR 2.97, 95% CI 2.55 to 3.46) (19–22). More limited evidence from two randomized controlled trials (1811 participants) showed no significant difference between treatments for pain response at 2 hours (RR 1.54, 95% CI 0.78 to 3.03) (15, 22). In each analysis, the quality of evidence was low. One randomized controlled trial (491 participants) showed benefit associated with combination treatment with naproxen and sumatriptan 50 mg over placebo for pain freedom at 2 hours (RR 5.85, 95% CI 3.42 to 10.01) and pain relief at 2 hours (RR 2.42, 95% CI 1.93 to 3.03) (16). Meta-analysis of the remaining two randomized controlled trials showed benefits of combination treatment with naproxen and sumatriptan 85 mg for pain freedom at 2 hours (RR 2.73, 95% CI 1.85 to 4.04 and pain relief at 2 hours (RR 2.16, 95% CI 1.90 to 2.46) (15, 23). The overall risk of bias of these trials was unclear and the quality of evidence was very low.

Harms

A 2017 systematic review and network meta-analysis of 141 randomized controlled trials evaluated the comparative tolerability of 15 oral treatments for acute migraine (24). Among the triptan class, eletriptan, rizatriptan, sumatriptan, sumatriptan in combination with naproxen, and zolmitriptan were associated with significantly increased odds of any adverse event or treatment-related adverse events compared with placebo. With the exception of naratriptan, there was no significant increase in the odds of serious adverse events. No significant differences were reported between naproxen and placebo for any, treatment-related or serious adverse events. Results of selected comparisons are shown in Table 6 (refer to TRS 1064). A 2016 systematic review and network meta-analysis of 88 randomized controlled trials compared the relative efficacy and tolerability of non-steroidal anti-inflammatory drugs and triptans for the treatment of migraine (25). The results suggested that eletriptan offered the best efficacy

and acceptable tolerability among the 10 medicines evaluated. Triptans The presence of 5HT1B receptors in the coronary arteries has given rise to concerns about the risk of triptan-induced coronary arterial narrowing, further supported by individual cases of acute myocardial infarction in close temporal relationship with triptan intake. However, the incidence of triptan-induced serious cardiovascular adverse events in both clinical trials and clinical practice appears to be extremely low and limited to migraine patients with significant cardiovascular risks or with overt cardiovascular diseases. In line with these observations, analyses of reports of the United States Food and Drug Administration, observational studies and general practice research databases failed to reveal an increased risk of cardiovascular or cerebrovascular incidents in triptan users in the absence of vascular risk factors (26). Triptans are associated with a statistically significant increase in odds of any adverse events or treatment-related adverse events compared with placebo, although they are usually mild to moderate in intensity, transient and resolve spontaneously. The most frequent adverse events include flushing, nausea, paresthesia and tingling. Chest-related adverse events, characterized by chest pressure, chest pain, shortness of breath, palpitations and anxiety are not related to myocardial ischaemia according to aggregated data from trials, real-world experiences and pharmacodynamic instrumental assessments by electrocardiogram, myocardial scintigraphy and angiography. Therefore, these should be considered non-serious adverse events. Although rare, central nervous system adverse events (e.g. abnormal dreams, abnormal thinking, agitation, aphasia, asthenia, ataxia, confusion, dizziness, headache, somnolence, speech disorder, tremor, vertigo and other focal neurological symptoms) may occur. The rates of incidence largely overlap among triptans with higher values for eletriptan 80 mg and lower values for almotriptan 12.5 mg. The vasoconstrictive potential of triptans has led to the exclusion of patients older than 65 years with vascular diseases from phase III studies and thus they are not recommended for use in these patients. Nevertheless, several studies reported the use of triptans as safe in patients with stable vascular diseases, including people older than 65 years. Triptans are contraindicated in patients with coronary artery disease or coronary artery vasospasm, history of stroke, transient ischaemic attack, hemiplegic or basilar migraine, intracerebral or subarachnoid haemorrhage, hypertensive crisis, Wolff–Parkinson–White syndrome or other cardiac accessory conduction pathway disorders or arrhythmias, peripheral vascular disease, ischaemic bowel disease and severe hepatic impairment. Naproxen The application stated that no differences were detected in the trials assessed in this review between 500 mg naproxen and placebo (24). No difference was detected when comparing the combination naproxen and sumatriptan versus sumatriptan alone. The occurrence of adverse effects was lower in participants treated with naproxen alone compared with participants treated with a combination of naproxen and sumatriptan. No serious adverse events were reported in the available randomized controlled trials.

Additional evidence

A 2025 systematic review and network meta-analysis evaluating the benefits and harms of pharmacological treatments for acute episodic migraine attacks was identified during the review process (27). The review reported the combination a triptan and a non-steroidal anti-inflammatory drug had greater net benefit for outcomes of pain freedom at 2 hours and pain relief at 2 hours compared with triptan monotherapy (moderate-certainty evidence), a non-steroidal anti-inflammatory drug monotherapy (high-certainty evidence), paracetamol (low-certainty evidence) and newer, more costly therapeutic classes, such as a calcitonin gene-related peptide antagonists (low-certainty evidence).

Cost / cost effectiveness

Eletriptan The application noted that several studies have assessed the pharmacoeconomics of eletriptan, and were summarized in a manufacturer-funded review published in 2015 (28). This review reported “a consistent pattern [in which] eletriptan 40 mg, rizatriptan 10 mg and almotriptan 2.5 mg were shown to be more cost-effective than other triptans”. This conclusion was based on costs at the time of publication of each included study, when generics were less widely available and pricing was less competitive. The application described various cost analyses that were performed, the results of which are summarized in the following subsections. Cost per treatment success For the outcomes of pain freedom at 2 hours and headache relief, it was estimated that eletriptan 40 mg was, respectively, 13.2 times and 15.5 times more expensive than sumatriptan 100 mg. Cost per healthy life year gained For the outcomes of pain freedom at 2 hours and headache relief, the costs per healthy life year gained for eletriptan 40 mg were estimated at 10 971 United States dollars (US$) and US$ 5709, respectively. Incremental cost–effectiveness for eletriptan 40 mg versus sumatriptan 100 mg For the outcomes of pain freedom at 2 hours and headache relief, the costs per healthy life year gained for eletriptan 40 mg compared with sumatriptan 100 mg were estimated at US$ 37 993 and US$ 38 350, respectively. Naproxen No studies reporting the comparative cost or cost–effectiveness of naproxen in the treatment of acute migraine were identified in the application. Various cost analyses were performed as described in the application and the results are summarized

in the following subsections. Cost per treatment success For the outcome of pain freedom at 2 hours, it was estimated that naproxen 500 mg was 4.2 times more expensive than ibuprofen 400 mg, and sumatriptan 100 mg was 3 times more expensive than naproxen 500 mg. For the outcome of headache relief, naproxen 500 mg was estimated to be 3.2 times more expensive than ibuprofen 400 mg, and sumatriptan was 3.5 times more expensive than naproxen 500 mg. Cost per healthy life year gained For the outcome of pain freedom at 2 hours, the cost per healthy life year gained for naproxen 500 mg was US$ 387 or US$ 1001 (depending on the price input used). For the outcome of headache relief, the cost per healthy life year gained for naproxen 500 mg was US$ 146 or US$ 387 (depending on the price input used). Incremental cost–effectiveness for the combination of naproxen 500 mg and sumatriptan 50 mg versus sumatriptan 50 mg The incremental cost–effectiveness ratio for naproxen plus sumatriptan compared with sumatriptan was calculated to be US$ 1026 per healthy life year gained.

WHO guidelines

WHO guidelines for the treatment of acute migraine are not currently available. The application provided a brief summary of recommendations on the use of eletriptan and naproxen in acute migraine from various current national and international clinical guidelines.

Availability

A survey conducted among members of the International Headache Society reported naproxen was available in more than 70 countries globally, either as prescription or over-the-counter products. Multiple generic versions are available. A survey conducted among members of the International Headache Society reported naproxen was available in more than 50 countries globally, as a prescription only product. Generic versions are available in a small number of countries.

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