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: 50 mg
EML status history	Application rejected in 2019 (TRS 1021) Added in 2021 (TRS 1035)
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	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 that the available evidence supported the superior efficacy of sumatriptan compared with placebo. Evidence comparing sumatriptan with currently listed analgesics (acetylsalicylic acid, paracetamol and ibuprofen) showed mixed results, which might correlate to little or no difference between currently listed analgesics and sumatriptan. The Committee also considered that the clinical use of sumatriptan is well established and it is recommended as a first-line therapy for migraine in some national and international guidelines. The Committee considered that it was important for people with migraine to have a range of treatment options available to them, particularly for those who are at risk of specific adverse events from currently listed analgesics, those at risk of addiction and those who have little or no response to analgesics. The Committee noted that long-term use of acetylsalicylic acid, ibuprofen and paracetamol at analgesic or higher doses in patients with frequent migraine attacks poses a risk of severe adverse events (e.g. bleeding, hepatic impairment and medication-overuse headache). Sumatriptan appears to provide clinically relevant headache relief with few risks. Evidence of the safety of sumatriptan in pregnant women is still limited but, so far, accumulated data have not signalled that sumatriptan poses additional risks of birth defects compared with that in the general population. Based on a positive benefit-to-risk profile, the Committee recommended the addition of sumatriptan to the core list of the EML for the treatment of adult patients with acute migraine. Inclusion of other triptans were not part of the application. Although the Committee thought there were likely to be benefits across the pharmacological class, few data were available on efficacy, safety, price and availability of other triptans. Therefore, the Committee did not list alternative triptans at this time, but would consider requests for listing in future.

Background

Applications for the inclusion of sumatriptan on the EML have been considered by the Expert Committee on two previous occasions. Most recently in 2019, the Expert Committee noted that the available evidence supported the effectiveness of sumatriptan compared to placebo, but that evidence comparing sumatriptan with currently listed analgesics for migraine (acetylsalicylic acid (aspirin) and paracetamol)) showed varying results, including no difference in effect. The Committee therefore did not recommend the addition of sumatriptan to the list. However, they noted that sumatriptan is recommended as a first-line therapy for migraine in many international guidelines and requested a future review with additional data on sumatriptan in the context of other migraine therapies (1).

Public health relevance

According to the 2019 Global Burden of Disease estimates, migraine has a global age-standardized prevalence of 14.1% (95% uncertainty interval (UI) 12.3 to 16.2) overall; 17.9% (95% UI 15.6 to 20.5) for women and 10.3% (95% UI 8.9 to 12.0) for men. About 1.13 billion (95% UI 0.98 to 1.30) people were estimated to have experienced a migraine, causing 42.1 million (95% UI 6.42 to 95.6) years of life lived with disability, corresponding to 4·8% (95% UI 0·8 to 10·1) of the total years of life lived with disability in 2019 (2). Migraine has psychological, social and economic repercussions and can be associated with considerable morbidity as a result of the disability caused by frequent attacks and their treatment. Headache disorders are a public health concern given the associated disability and financial costs to society. For example, in the United Kingdom, 25 million working- or school-days are lost every year because of migraine alone (3), and it is estimated that more than 100 000 people are absent from work or school as a result of migraine every working day (4).

Benefits

The application presented evidence on the efficacy and safety of sumatriptan for treatment of acute migraine attacks in adults from two systematic reviews (5,6). Pooled data from 18 studies showed that oral sumatriptan 50 mg was more effective than placebo for the outcome of pain freedom at 2 hours for any pain-intensity at baseline. Slightly higher estimates were observed in pooled data from 21 studies of oral sumatriptan 100 mg. The number needed to treat was considered clinically meaningful for both sumatriptan 50 mg and 100 mg for this outcome and ranged from 3 to 7. For the outcomes of headache relief at 2 hours, sustained pain freedom at 24 hours and use of rescue medication, pooled analysis also showed clinically meaningful differences and numbers needed to treat favouring sumatriptan. The certainty in the estimates was rated high, according to the GRADE framework (5). Pooled data from four studies comparing sumatriptan 50 mg or 100 mg with acetylsalicylic acid 1000 mg and acetylsalicylic acid 900 mg + metoclopramide 10 mg showed a statistically significant difference in favour of sumatriptan 100 mg compared with acetylsalicylic acid 900 mg + metoclopramide 10 mg for the outcome of pain freedom at 2 hours ((odds ratio (OR) 1.62, 95% confidence interval (CI) 1.17 to 2.25). In absolute terms, 26% of patients treated with sumatriptan 100 mg and 16% of those treated with acetylsalicylic acid 900 mg + metoclopramide 10 mg were pain-free at 2 hours. The absolute risk difference was 10% in favour of sumatriptan. The difference between sumatriptan 50 mg and acetylsalicylic acid 1000 mg for pain freedom at 2 hours was not statistically significant; however the point estimate favoured sumatriptan (OR 1.22, 95% CI 0.97 to 1.53). In absolute terms, 32.2% of patients treated with sumatriptan 50 mg and 26.4% of patients treated with acetylsalicylic acid 1000 mg were pain-free at 2 hours. The absolute risk difference was 15% in favour of sumatriptan (5). For the outcome of headache relief at 2 hours, sumatriptan was more effective than both acetylsalicylic acid 1000 mg, and acetylsalicylic acid 900 mg + metoclopramide 10 mg (OR 1.27, 95% CI 1.09 to 1.47). Sumatriptan 100 mg did not show a statistically significant difference compared with paracetamol 1000 mg + metoclopramide 10 mg; however, the point estimate favoured sumatriptan with an absolute risk difference of 2% in its favour. For the outcome of reduction of rescue medication use, sumatriptan was more effective than paracetamol 1000 mg + metoclopramide 10 mg (OR 0.86, 95% CI 0.74 to 0.99). For the outcome of headache relief at 1 hour, acetylsalicylic acid 1000 mg was more effective than sumatriptan 50 mg (OR 0.78, 95% CI 0.61 to 0.98) (5). 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. The certainty in the estimates was rated as high, according to the GRADE framework (5). A network meta-analysis compared the relative efficacy, effectiveness and safety of triptans (alone or in combination with other drugs and for all administration routes and any dose) for treatment of acute migraine attacks in adults (> 18 years of age) compared with other triptans, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, paracetamol, ergots and opioids (6). To account for

modification of the effect related to dosage, sumatriptan doses were categorized as low (25 mg, four randomized trials including 850 patients), standard (50 mg, 23 randomized trials including 5870 patients) and high (100 mg, 23 randomized trials including 5210 patients). Efficacy was assessed for each dosage. The systematic review provided comparative effectiveness data both from direct and indirect comparisons through a network meta-analysis. Overall, considering all administration routes, freedom from pain at 2 hours was achieved in 18% to 50% of patients with acute migraine taking standard-dose triptans. Sumatriptan provided pain freedom at 2 hours in 27.7% (95% credible interval (CrI) 24.6% to 31.0%) of patients compared with 10.6% (95% CrI 10.0% to 11.3%) of patients taking the placebo. Triptans were effective in the largest proportion of patients on the outcome headache relief at 2 hours: 41.8% (95% CrI 32.6% to 51.5%)–75.7% (95% CrI 67.6% to 82.5%) of patients compared with 26.7% (95% CrI 25.7% to 27.7%) of patients taking the placebo. About half the patients taking sumatriptan 50 mg (49.7%, 95% CrI 46.3% to 53.1%) had headache relief at 2 hours compared with 26.7% (95% CrI 25.7% to 27.7%) of patients taking placebo. Estimates from pairwise comparisons of sumatriptan 50 mg versus placebo showed that sumatriptan was superior to placebo for pain freedom at 2 hours and other outcomes (headache relief at 2 and at 24 hours, sustained freedom from pain at 24 hours and reduced use of rescue medication). Estimates from pairwise comparisons of sumatriptan 50 mg versus other triptans showed eletriptan 40 mg to be superior for the outcome pain freedom at 2 hours (OR 0.59, 95% CI 0.45 to 0.78) and for all the other outcomes mentioned above. These results were consistent with those observed on direct comparisons in systematic review discussed earlier (5). The efficacy outcomes reported in these two systematic reviews are those recommended in the guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults (7). An additional randomized controlled trial was identified that compared intranasal sumatriptan and oral sumatriptan in adults with migraine (8). The primary outcome was the sum of pain intensity differences 30 minutes after administration, which is not a recommended outcome measure in the guidelines of the International Headache Society. Pain freedom at 2 hours was a secondary outcome, but no statistically significant difference was found between treatment groups. The application also presented evidence from one systematic review on the efficacy and safety of pharmacological interventions (not limited to triptans) by any route of administration for treatment of acute migraine attacks in children and adolescents (9). However, listing for sumatriptan was not proposed for children and adolescents because oral sumatriptan had not been studied in this population.

Harms

Among 20 049 patients treated with oral sumatriptan, only two treatment-related serious adverse events were reported: heart palpitations after treatment with sumatriptan 85 mg, and chest tightness/pressure after treatment with sumatriptan 300 mg. Withdrawals due to adverse events were uncommon: in placebo-controlled studies, excluding those using high doses of sumatriptan (> 100 mg), the proportion of patients withdrawing due to adverse events among patients treated with sumatriptan was equivalent to that of placebo (0.71% (45/6349) and 0.65% (19/2926), respectively) (5). Pooled estimates of comparisons of sumatriptan versus other triptans did not show significant differences in adverse events. Acetylsalicylic acid 900 mg + metoclopramide 10 mg and paracetamol 1000 mg + metoclopramide 10 mg showed a significantly lower of adverse events than sumatriptan 100 mg (5). Although in migraine trials acetylsalicylic acid and paracetamol showed a lower frequency of adverse events than sumatriptan in the short term, the application noted that their long-term use at analgesic doses in patients with frequent migraine attacks posed a risk of severe and potentially life-threatening adverse events. An industry-funded systematic review and network meta-analysis assessed the tolerability of orally administered treatments in adults with acute migraine (10). The review included 141 randomized controlled trials evaluating triptans, non-steroidal anti-inflammatory drugs or barbiturates in any combination, without any other limitation on sample size or treatment concealing. The quality of the included studies was not formally assessed, and the results should be interpreted with caution. Data from direct comparisons were available for sumatriptan versus placebo from 39 studies. Compared to placebo, sumatriptan was associated with a significantly higher incidence of any adverse events (OR 1.80, 95% CI 1.57 to 2.05), and treatment-related adverse events (OR 2.23, 95% CI 1.86 to 2.70). Serious adverse events were uncommon resulting in estimates with wide confidence intervals. Data from observational studies indicate that migraine, especially migraine with aura, shows an association with ischaemic heart disease, vascular events and stroke. However, a causal relationship with migraine is unclear and the occurrence of a cerebrovascular event during a migraine attack is very rare (11–13). There was initial concern about the potential adverse events of sumatriptan on the cardiovascular system, especially when different centres for monitoring adverse reactions started receiving reports of chest and angina pain soon after the marketing of sumatriptan in 1992 (14,15), and postmarketing surveys of Dutch general practitioners (16,17). A meta-analysis of four observational studies assessed the risk of severe cardiovascular events associated with either recent use of or intensity of exposure to triptans or ergotamine in people with migraine (18). Pooled analysis showed no significant differences in the overall risk of cardiovascular events of patients

with migraine treated with triptans compared with controls in relation to intensity of treatment (OR 0.86, 95% CI 0.52to 1.43). Because of the heterogeneity of the results of the included studies, pooled analysis of the risk of cardiovascular events and stroke in relation to recent use was not done. A meta-analysis of six controlled, observational studies assessed the risk of adverse pregnancy outcomes (major congenital malformations, prematurity and spontaneous abortion) of women with migraine exposed to triptans during pregnancy compared with women with migraine not exposed to triptans and healthy women (19). Pooled analysis showed that the risk of major congenital malformations and prematurity was not increased in women with migraine taking triptans during pregnancy compared with women with migraine not taking triptans. Women exposed to triptans during pregnancy had a higher rate of spontaneous abortion compared with healthy controls, although this difference was observed in only a relatively small sample of women exposed to triptans (n = 178). Women with migraine not taking triptans had a higher risk of major congenital malformations compared with healthy controls. A systematic review by the United Kingdom's National Clinical Guideline Centre found conflicting evidence (very low quality) for adverse pregnancy outcomes from a pooled analysis of three observational studies comparing women with migraine exposed and not exposed to triptans during pregnancy (4). The guideline panel concluded that the evidence reviewed, although inconclusive, did not indicate an increased risk of adverse pregnancy outcomes from the use of triptans during pregnancy. No safety data are available on the use of oral sumatriptan in children. The overall frequency of any adverse event in adolescents taking triptans is higher than placebo, although most adverse events were mild (9).

Cost / cost effectiveness

All triptans are currently available as unbranded generic drugs, and the cost of oral sumatriptan varies in different countries. Of all available triptans, sumatriptan is consistently the cheapest, including in low- and middle-income countries, but it is more expensive than paracetamol and acetylsalicylic acid. The cost–effectiveness of sumatriptan in acute migraine is largely dependent on the cost of the medicine. Achieving a reduction of its average price could have a considerable impact on its cost–effectiveness when compared with less expensive alternatives, such as acetylsalicylic acid and paracetamol. If comparative cost–effectiveness modelling takes into account long-term safety, sumatriptan may become an attractive option even at its current price in situations of low willingness-to-pay by decision-makers.

WHO guidelines

In 2007, WHO, in collaboration with Lifting the Burden and the European Headache Federation, published guidance on the management of common headache disorders in primary care, with a multilanguage information leaflet for patients (20). The guidance was based on a review of all published treatment guidelines in use in Europe and selection of the main recommendations. The guidance recommended a two-step management of acute migraine attacks, treating three attacks at each step before proceeding to the next, starting with common analgesics (such as acetylsalicylic acid, ibuprofen, diclofenac, ketoprofen, naproxen or, where these are contraindicated, paracetamol) followed, if needed, by antiemetics (such as domperidone or metoclopramide). Triptans are recommended as a second step, among specific antimigraine drugs, to be offered to all patients in whom treatment has failed in step one. The recommended starting formulation was oral; sumatriptan by subcutaneous injection was suggested when all other triptans were ineffective. Analgesics only were recommended for children. The application identified three clinical practice guidelines that include recommendations on use of triptans for the treatment of acute migraine in adults. Sumatriptan (50 mg or 100 mg) is recommended as the first-line monotherapy treatment in adults by the Scottish Intercollegiate Guidelines Network (SIGN), with the suggestion of trying alternative triptans in case of failure (21). The National Institute for Health and Care Excellence (NICE) guideline recommends an oral triptan alone or combined with a non-steroidal anti-inflammatory drug or paracetamol in adults and children. In young people (12–17 years), nasal triptan is preferred (4). The Canadian Headache Society guideline recommends sumatriptan, or another triptan, for moderate to severe migraine attacks in adults. If triptan alone is insufficient, its use in combination with naproxen sodium 500 mg is recommended (22). In summary, there is overall consensus among the retrieved guidelines in recommending triptans (specifically, sumatriptan) as first-line treatment, or as an alternative to other analgesics in treating acute migraine attacks. According to the SIGN and NICE guidelines, triptans can be used for treatment of acute migraine during pregnancy and in women in child-bearing age (4,21). The NICE guideline recommends balancing the potential side-effects of non-steroidal drugs, especially gastric ulceration and bleeding and cardiovascular risks, against the more rapid and prolonged benefit when used in combination with a triptan for treating an acute migraine episode (4).

Availability

Sumatriptan is available globally in branded and generic forms.

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