Review of the Available Evidence on oral Sumatriptan in Adults and Children for the Treatment of Acute Migraine Attacks and Proposal for Inclusion

FOR THE WHO MODEL LIST OF ESSENTIAL MEDICINES (EML)

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WHO Model List Application, December, 2018

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ADDITIONAL MATERIAL: GRADE Evidence Profiles of included studies
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General Items

1. Summary statement of the proposal

In 2005 the WHO Expert Committee on the Selection and Use of Essential Medicines recommended that a full application for inclusion of a 5HT1 agonist (triptan) for migraine be submitted.

Based on currently available evidence it is suggested to consider a potential role for:

- oral sumatriptan 50mg in the WHO Model List of Essential Medicines (EML) Section 7 (Antimigraine medicines), subsection 7.1 (For treatment of acute attack), as a treatment in adult patients with acute migraine.

Inclusion of oral sumatriptan in the EMLc is not advised because:

- oral sumatriptan is not licensed in children and has not been studied in randomized controlled trials
- oral sumatriptan has been studied in adolescents 12 to 17 years of age with episodic migraine showing no superiority vs placebo in reaching pain freedom at 2 hours.
- Intranasal sumatriptan has been studied in adolescents 12 to 17 years of age showing to be more effective than placebo and is licensed in such patients by some regulatory agencies in western high-income countries. However, since the intranasal inhalation of the drug needs patient training, the effectiveness of this preparation observed in clinical trials may not be directly applicable in settings where training is impractical or not possible. Moreover, the cost-effectiveness of intranasal sumatriptan is substantially lower than the oral route.

There is a substantial body of evidence on the efficacy and safety of triptans in adults with episodic migraine.

Sumatriptan has been the most extensively studied triptan in terms of efficacy and safety, since it has been evaluated in several randomized controlled trials (RCTs) and systematic reviews (SRs), consistently showing a favorable benefit-risk profile for oral sumatriptan up to a dose of 100 mg in adults with acute migraine attack, with or without aura.

Evidence-based guidelines recommend its use in adults with migraine as first-line drug together with common analgesics such as paracetamol or acetylsalicylic acid (ASA).

Oral sumatriptan is available as 50 mg and 100 mg tablets, and the former is commonly considered as the standard dose in clinical practice: as effective as the 100mg dose and associated with less treatment-related adverse events.

Oral sumatriptan 50 mg is significantly more effective than placebo on clinically relevant outcomes: two hours after administration about half of the patients with acute migraine experience a relief of their headache, and about one third are pain-free. One third of patients taking sumatriptan have to take rescue medications during their migraine attacks, vs over 50% with placebo.

Sumatriptan 50mg is more effective than placebo also on symptoms associated with migraine, such as nausea, photophobia and functional disability.

When compared with other oral triptans, sumatriptan showed better efficacy on most clinically relevant outcomes than almotriptan, frovatriptan, naratriptan, and zolmitriptan. Rizatriptan 10 mg showed better efficacy on headache at 2 hours. Eletriptan 40 mg and 80 mg showed higher efficacy than sumatriptan 50 mg on all the clinically meaningful outcomes. However, comparative cost-effectiveness showed a clear superiority of sumatriptan over both rizatriptan and eletriptan, due to its lower average cost.

When compared with the anti-migraine drugs already included in the EML, oral sumatriptan 50 mg shows a similar risk/benefit balance. Overall, efficacy and frequency of adverse events (AEs) are comparable. When administered at a higher dose of 100 mg, sumatriptan shows a higher frequency of
adverse events than ASA 900 mg and paracetamol 1000 mg (both in combination with metoclopramide 10 mg). However, AEs associated with oral sumatriptan are usually mild, and serious adverse events, as well as withdrawals due to adverse events, are uncommon.

In terms of safety, oral sumatriptan may be particularly advantageous when considering women in child-bearing age, representing a substantial proportion of the persons affected by migraine.

Sumatriptan has shown no association with major congenital malformations or prematurity. The only anti-migraine drug currently included in the EML that can be safely administered during pregnancy is paracetamol. In pregnant women with worsening of migraine, where pharmacological treatment of acute attacks is indicated, paracetamol is the drug of choice, but sumatriptan could be a useful therapeutic option in order to avoid unnecessary suffering. Although there is no conclusive evidence of safety, available evidence is reassuring.

Sumatriptan has shown no association with major congenital malformations or prematurity. The only anti-migraine drug currently included in the EML that can be safely administered during pregnancy is paracetamol. In pregnant women with worsening of migraine, where pharmacological treatment of acute attacks is indicated, paracetamol is the drug of choice, but sumatriptan could be a useful therapeutic option in order to avoid unnecessary suffering. Although there is no conclusive evidence of safety, available evidence is reassuring.

Sumatriptan is indicated in adults for the treatment of acute migraine attacks by the main drug agencies. It is available as oral tablets, subcutaneous injection and intranasal spray. The latter is not available as a generic drug, unlike the subcutaneous and oral preparations.

Although the cost of sumatriptan oral preparations has lowered since it first was marketed, and they are currently available as unbranded generic drugs, their cost-effectiveness is lower than that of ASA. Low acquisition cost and a high coverage worldwide make ASA the most efficient intervention in managing migraine and one of the most efficient interventions to improve population health.

However, a recent cost-effectiveness analysis shows that using sumatriptan in combination with ASA in non-responders to simple analgesics within a stepped-care management could be a cost-effective strategy with a substantial population-level health gain, particularly if associated with consumer education and provider training. Currently the cost of sumatriptan is highly variable among countries. Including sumatriptan in the EML may facilitate the reduction of its average price, and economic modeling shows that reducing the applicable price of sumatriptan in each country would have a substantial impact on its cost-effectiveness profile.

Available evidence suggests that sumatriptan could be an effective, safe and cost-effective treatment option offered to most persons with migraine, in addition or as an alternative to the antimigraine medications already listed in the EML.
3. Name of the organization consulted and/or supporting the application
Medicines and Medical Devices Area | Health Care and Welfare Directorate, Community Care Service Emilia-Romagna Region; IRCCS Institute of Neurological Sciences of Bologna, – Bologna, Italy

4. International Nonproprietary Name (INN, generic name) and Anatomical Therapeutic Chemical (ATC) code of the medicine
The International Nonproprietary Name (INN) of the medicine is: sumatriptan.
The anatomical Therapeutic Chemical (ATC) code of the medicine is: N02CC01

5. Dose, formulation(s) and strength(s) proposed for inclusion

| Sumatriptan | 50 mg Tablets (oral route) |

Current market availability
A list of manufacturers that have active status in the Drug Master File of the Food and Drug Administration (FDA) is available in Annex 4. Sumatriptan is registered in high-income and many medium-low income countries. The choice of the manufacturer for sumatriptan will depend on the price and availability at the local or national level.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class
Listing is requested on the Model List of Essential Medicines as individual medicine, to be included in the Section 7 (Antimigraine medicines), subsection 7.1 (For treatment of acute attack) of the WHO EML.
7 - Treatment details, public health relevance and evidence appraisal and synthesis

7.1 Treatment details (requirements for diagnosis, treatment and monitoring)

The WHO EML and EMLc currently list three medicines for the treatment of acute attacks of migraine: acetylsalicylic acid (ASA) (tablet, 300mg to 500mg), ibuprofen (tablet, 200mg and 400mg), paracetamol (oral liquid 120mg/5mL, 125mg/5mL, tablet 300 mg to 500mg). The use of ibuprofen and of the oral liquid preparation of paracetamol is restricted to children. These drugs are intended to treat acute attacks of migraine as first-line therapies.

During its meeting in 2005, the WHO Expert Committee on the Selection and Use of Essential Medicines recommended that ergotamine be deleted from the Model List because of lack of evidence of efficacy. In 2007 the Committee recommended that the availability of effective and safe alternatives and that a full application for inclusion of a 5HT1 agonist (triptan) for migraine be submitted. In 2007 and in 2009, the Expert Committee rejected applications for the inclusion of sumatriptan on the Model List on the basis that the evidence provided did not demonstrate the superior comparative effectiveness, safety and cost-effectiveness of sumatriptan as compared to the currently available medicines for the treatment of acute migraine on the Model List. Sumatriptan for migraine has been recently mentioned among neurologic medicines that should be included in the EML. The inclusion in the EML and EMLc of sustainable treatments that may be added as first-line treatments of acute migraine attacks, and also used as alternative options if treatments now included in the EML-EMLc are not available or not tolerated, is warranted.

Sumatriptan was the first triptan introduced in 1992 as subcutaneous injection, and represented a significant advance in the management of migraine. Since that time, six more triptans have become available: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan. Although triptans are generally considered to be the most effective of the acute migraine medications overall, studies in Western Countries showed that among people with migraine who could benefit from triptans, only a relatively small percentage (3.4% to 24.5% in an European survey) actually take it. Underutilization of effective acute therapies has the potential to negatively impact quality of life for migraine sufferers.

Therefore, the availability of a triptan showing to be effective in controlling pain and associated symptoms during acute migraine attacks on pediatric as well as adult patients would be a useful treatment option in clinical practice, since it could be offered to the majority of persons with migraine.

Treatment details for sumatriptan

Sumatriptan is 1-[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-N-methylmethanesulfonamide (IUPAC name) and belongs to the class of triptans. Sumatriptan is indicated for acute relief of migraine attacks, with or without aura for the oral and nasal route of administration, while is indicated for the acute relief of migraine attacks, with or without aura, and for the acute treatment of cluster headache for subcutaneous injection (see also table 16).

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Among other seven drugs of the class of triptans (all available in oral dosage forms), only sumatriptan and zolmitriptan are used with the intranasal route and only sumatriptan is available as parenteral route. The route of administration of a triptan can affect its efficacy, tolerability and speed of onset: even if the oral route can be preferred by patients it may not be feasible in certain condition, such as significant nausea, so it may be useful to have different route of administration for the same drug.

**Pharmacodynamics**

Sumatriptan is a selective agonist that acts at 5-HT1 receptors (particularly the 5-HT1D and 5-HT1B subtypes located on trigeminal sensory neurons innervating dural blood vessels) and produces vasoconstriction of cranial arteries. So binding to these 5-HT1 receptor subtypes, sumatriptan inhibits adenylate cyclase activity via regulatory G proteins, increases intracellular calcium, and affects other intracellular events that lead to vasoconstriction and inhibition of sensory nociceptive (trigeminal) nerve firing and vasoactive neuropeptide release. Both these actions (cranial vasoconstriction and inhibition of trigeminal nerve activity) may contribute to the anti-migraine action of sumatriptan in humans. Radioligand studies have demonstrated that sumatriptan has a high degree of selectivity for 5-HT1D binding sites in brain tissue, but has virtually no affinity for 5HT1C, 5HT2, 5HT3, adrenergic, dopaminergic, muscarinic, or benzodiazepines binding sites. Antinociceptive studies in animals indicate that sumatriptan has no analgesic activity per se and, unless the permeability of the blood brain barrier is altered during migraine, sumatriptan is unlikely to be acting centrally since it only poorly penetrates the blood brain barrier. [3]

Human studies have established increases in the blood flow velocity of internal carotid and middle cerebral arteries after sumatriptan, while flow velocity in common and external carotid arteries remains unchanged. It acts entirely within the carotid circulation, and has no effect on cerebral blood flow or on perfusion of peripheral organs [4] [5]

**Pharmacokinetics**

Sumatriptan is rapidly absorbed but mean absolute oral bioavailability is 14% partly due to pre-systemic metabolism and partly due to incomplete absorption. After oral doses, peak plasma concentrations are achieved in about 2 hours. The bioavailability after intranasal doses is similar to the bioavailability after oral administration, belongs from 14-17%, with peak concentrations occurring in about 1,5 hours. After subcutaneous doses, instead, the bioavailability is much higher (96%) and also absorption is rapid with peak concentration reached in approximately 10 minutes. The onset of action (and consequently the relief of headache pain) begins within 30 minutes of oral administration, while for subcutaneous injection is less than 10 minutes. The mean maximum concentration following oral dosing with 25 mg is 18 ng/mL and 51 ng/mL following oral dosing with 100 mg of sumatriptan. This compares with a C max of 5 and 16 ng/mL following dosing with a 5 and 20 mg intranasal dose, respectively. The mean C max following a 6 mg subcutaneous injection is 71 ng/mL. The serum concentration range considered to be therapeutic is 18 to 60 nanograms/mL. The plasma proteins’ binding is low (14 – 21%) and has a mean apparent volume of distribution of 170 L. Sumatriptan is extensively metabolised in the liver predominantly by monoamine oxidase type A and is excreted mainly in the urine as the inactive indole acetic acid derivative and its glucuronide; small amounts of sumatriptan and its metabolites are released in the faeces and into breast milk. The elimination half-life is around 2 hours. [5,6, 7, 8, 9, 10]

**Drug Interactions – Enzyme induction**

Potential drug-drug interactions occurring with triptans are most commonly seen in drugs that also interact with monoamine oxidase A (MAO-A), CYP50 enzymes, and serotonin receptors. Each triptan is metabolized in the liver, but differs in the extent of metabolism via MAO-A and CYP enzymes. Sumatriptan and rizatriptan are metabolized only by MAO-A, whereas eletriptan, naratriptan and frovatriptan are metabolized only by CYP enzymes. Zolmitriptan is metabolized by both MAO-A and
CYP enzymes, similar to almotriptan. Therefore, it is useful to know also potential drug-drug interaction for deciding the best treatment option for the patient. [11]. Sumatriptan should not be given with ergotamine or related compounds (including methysergide) since there is an increased risk of vasospastic reactions. Licensed product information for sumatriptan contra-indicates its use with ergotamine or other related compounds or any other 5-hydroxytryptamine1 (5-HT1) receptor agonist. Even if the period of time of elapsing between treatment is not known and it also could depend on the size of doses and types of product used, it is advised to wait at least 24 hours following the use of ergotamine-containing preparations or another triptan/5-HT1 receptor agonist before administering sumatriptan. Conversely, it is advised to wait at least 6 hours following use of sumatriptan before administering an ergotamine product and at least 24 hours before administering another triptan/5-HT1 receptor agonist. Licensed product information for sumatriptan contra-indicates also concurrent administration of reversible (e.g. moclobemide) or irreversible (e.g. selegiline) monoamine oxidase inhibitors (MAOIs). The effect of the interaction is potential increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes), so sumatriptan should not be used with, and also for 2 weeks after stopping, an MAOI. However, a review of the use of sumatriptan with MAOIs, SSRIs, or lithium found little evidence of an increased risk of serotonin syndrome. It was concluded that most patients tolerate the combination of sumatriptan and an SSRI or lithium without incident. However, it was suggested that the use of sumatriptan with an MAOI should continue to be avoided until further data supporting safety becomes available. As there have since been rare reports of serotonin syndrome associated with the use of triptans with SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs), licensed product information for the triptans states that when such use is clinically warranted, appropriate observation of the patient is advised, particularly when starting treatment, with dose increases, or with addition of another serotonergic drug.

Patients with hypersensitivity to sulphonamides may have a similar reaction to sumatriptan: evidence of cross sensitivity is limited, but caution should be use when before treating these patients. Increased incidence of adverse effects, caused by increased serotonergic effects, have been reported following the use of St John's wort with triptans. Patients should be advised to stop taking St John's wort if treatment with a serotonin (5-HT1) agonist is necessary. Oral sumatriptan appeared to delay gastric emptying [12] and might affect the absorption of other drugs, as judged by its delaying effect on paracetamol absorption in migraine patients. [4, 6]

**Special patient populations**

*Pregnancy and breast feeding*

Sumatriptan crosses the placenta; however, only a very small quantity reaches the foetus. Post marketing data on the use of sumatriptan during the first trimester of pregnancy in over 1,000 women are available, experience with the use of sumatriptan in the second and third trimester is limited. A literature review concluded that exposure to sumatriptan in pregnancy posed no additional risk of birth defects compared with that in the general population [13], but as for other drugs, sumatriptan should only be used in pregnancy when the benefit justifies the potential risk to the foetus. No adverse effects have been seen in breast-fed infants of mothers given sumatriptan, and the last available guidance from the American Academy of Paediatrics considered that it is therefore usually compatible with breast feeding [14]. However, licensed product information suggests that infant exposure can be minimised by avoiding breast feeding for 12 hours after treatment. Product information for other triptans suggests avoiding breast feeding for 24 hours. The distribution of sumatriptan into breast milk after a 6-mg subcutaneous dose has been studied in 5 mothers [15]. The mean total recovery of sumatriptan in breast milk was estimated to be 14.4 micrograms or 0.24% of the dose. It was calculated that on a weight-adjusted basis an infant could receive a maximum of 3.5% of the maternal dose. [4, 6]
Proposed therapeutic dosage regimen

The dosage recommendations for migraine are the following (from Martindale: The Complete Drug Reference, database on the internet): [6]

Sumatriptan is used for the acute treatment of migraine attacks and of cluster headache. It should not be used for prophylaxis. It may be given orally, intranasally, subcutaneously, or transdermally as the succinate; it may also be given intranasally as the base. Doses are expressed in terms of the base; sumatriptan succinate 70 mg is equivalent to about 50 mg of sumatriptan.

For the acute treatment of migraine sumatriptan should be used as soon as possible after the onset of the headache phase, but efficacy is independent of the duration of the attack before starting treatment. If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

Administration in adults

It is given orally to adults aged 18 years and over; the recommended dose in the UK is 50 mg, although some patients may require 100 mg. A clinical response can be expected after about 30 minutes. If symptoms recur after an initial response, further doses may be given provided that there is a minimum interval of 2 hours between doses and that not more than 300 mg is taken in any 24-hour period. US licensed product information recommends that a lower dose of 25 mg may be used, although some patients require 50 or 100 mg. This may be followed by a second dose of up to 100 mg if the headache returns or the patient has a partial response provided that the total daily dose does not exceed the recommended maximum of 200 mg. A minimum interval of 2 hours is recommended between doses.

When used intranasally a clinical response can be expected in 15 minutes. Patients aged 18 years and over may be given a dose of 5, 10, or 20 mg; administration depends on the product being used. If symptoms recur, a second dose may be given at least 2 hours after the first dose. Not more than 40 mg should be used in a 24-hour period.

In patients aged 18 years and over, sumatriptan may be self-administered by subcutaneous injection in single doses of 3 mg, 4 mg, or 6 mg; a clinical response may be expected after 10 to 15 minutes. If symptoms recur, further doses may be injected at least one hour after the previous dose but not more than a total of 12 mg should be given in a 24-hour period. US licensed product information recommends using single doses of 1 to 5 mg if adverse effects are dose-limiting. A needle-free subcutaneous delivery system is also available for the delivery of 6-mg doses.

For the acute treatment of cluster headache, sumatriptan succinate is given by subcutaneous injection in similar doses to those used for migraine.

Administration in children

Sumatriptan may be given for the treatment of acute migraine in children and adolescents. Although not licensed for oral paediatric use in the UK, the BNFC (British National Formulary for Children) suggests that a single oral dose of 25 mg may be given to children aged 6 to 9 years, 50 mg to those aged 10 to 11 years, and 50 to 100 mg to those aged 12 to 17 years. The dose may be repeated once after at least 2 hours if symptoms recur after an initial response. Children aged 10 to 17 years may also be given the usual adult subcutaneous dose.

2 Information about an iontophoretic transdermal delivery system, supplying 6.5 mg of sumatriptan over 4 hours, has been omitted. Since 2016 manufacturer has discontinued the product and is no longer available
In the UK, intranasal sumatriptan is licensed for use in adolescents aged 12 to 17 years in a dose of 10 mg into one nostril; the dose may be repeated after at least 2 hours if symptoms recur within 24 hours although not more than 20 mg should be used within a 24-hour period. Alternatively, the BNFC suggests that the usual adult dose of 10 to 20 mg may be used in those aged 12 years and over. Alternatively, the higher-strength tablet used in adults may be used if required. The dose should not be repeated within a 24-hour period.

If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

Sumatriptan has also been tried in the treatment of acute cluster headache. The BNFC suggests that children aged 10 to 17 years may be given subcutaneous doses similar to those suggested in adults; alternatively, sumatriptan may be given intranasally to children aged 12 to 17 years in doses similar to those suggested for use in adolescents with migraine. [6]

Administration in hepatic impairment

Sumatriptan should be used with caution in patients with hepatic impairment. An oral dose of up to 50 mg is considered suitable. It should not be given to patients with severe impairment. [6]

Duration of treatment.

Sumatriptan is licensed for the symptomatic treatment of acute attacks of episodic migraine with or without aura. After the initial dose is ineffective, a second dose may be taken, at least 2 hours after the first one. If attacks become frequent, symptomatic treatments are not recommended, and prophylactic treatment should be considered. There is no specific threshold to define a high frequency of attacks, but in clinical practice this is generally considered as at least once per week or on 4 or more days per month. Frequent administration of triptans, as well as of other analgesics, poses the risk of MOH. Triptans should not be used as a prophylactic treatment of migraine.

Additional requirements associated with treatment with the medicine (diagnostic tests, specialized treatment facilities, administration requirements, monitoring requirements and skill levels of health care providers)

Oral sumatriptan administration does not require special diagnostic facilities, specific treatment facilities, monitoring or supervision by skilled health care providers. Being an oral formulation it is easily self-administered.

Sumatriptan is specifically indicated for the treatment of episodic migraine, and its diagnosis, being entirely clinical, requires evaluation by a clinician with expertise in headaches.

The listing for oral sumatriptan is being sought in the core list of the EML.
8. Information supporting the public health relevance

Definition of Migraine

Migraine is a common disabling primary headache disorder characterized by recurrent moderate to severe pain generally occurring on one side of the head. Migraine is a cause of pain and disability and has a substantial societal burden. Many epidemiological studies have documented its high prevalence and socio-economic and personal impact. [16] Migraine is classified into two major types: **migraine without aura** (a clinical syndrome characterized by headache with specific features and associated symptoms), and **migraine with aura** (primarily characterized by transient focal neurological symptoms that usually precede or sometimes are associated with the headache). [17]

Most patients with migraine experience a variety of prodromal symptoms that may occur hours or days before the headache begins and postdromal symptoms that may last several hours after the end of the headache. Prodromal and postdromal symptoms may include hyperactivity or hypoactivity, mood changes, cravings for specific types of food, recurrent yawning, fatigue, light sensitivity and neck stiffness and/or pain neck pain.

In migraine with aura headache is preceded by sensory disturbances, that most commonly are visual (such as zig-zag shaped or wavy lines, sickle- or C-shaped objects, bright or dark spots), but may also be sensory (such as numbness or tingling). Language dysfunction and vertigo are frequently reported during the aura, that commonly lasts from 5 to 60 minutes (in case of multiple symptoms occurring in succession, aura may last longer than an hour). If untreated, or unsuccessfully treated, headache may last from 4 to 72 hours and is typically (but not always) throbbing, moderate to severe, and unilateral. Although symptoms of migraine are diverse and highly variable, hypersensitivity to light and sound, cutaneous allodynia (the experience of normal touch as uncomfortable), worsening of pain during physical activity and nausea are also commonly reported during the migraine attack.

In childhood, migraine attacks tend to be of shorter duration and mostly associated with abdominal symptoms.

Based on the frequency of the attacks, migraine is defined as episodic or chronic. **Episodic migraine** occurs on less than 15 days per month and can be further divided into low frequency (1–9 days per month) and high frequency (10–14 days per month). **Chronic migraine** is defined by headache (with features of migraine headache on at least eight days per month) occurring on 15 or more days per month for more than three months. [17] About 2.5-3% of patients with migraine develop chronic migraine within one year. [18, 19]

Evaluation by a clinician with expertise in headache disorders is important, since diagnosis of migraine is clinical, based on the patient’s history and on the frequency, duration and features of the attack. In order to accurately collect such information, the patient is usually given a diary of headache and provided with instructions on how to keep it. Evaluation of the diary in time allows a correct diagnosis and an appropriate treatment, as well as monitoring the patient’s response to the prescribed drugs. Although some symptoms of migraine often lead to brain and cervical spine scans, neuroimaging is generally unnecessary, particularly if symptoms are transient and with a gradual onset.

Recently, the Headache Classification Committee of the International Headache Society (IHS) published the 3rd edition of The International Classification of Headache Disorders (ICHD-3), listing the diagnostic criteria for migraine and other types of headache. [17] (Annex 1)
Complications of migraine

Rarely, a migraine attack may last for more than 72 hours, therefore being severely disabling; according to the HIS classification this condition is considered as a complication of migraine called “status migrainosus”, occasionally caused by anti-migraine medication overuse.

Several data from observational studies indicate that migraine, especially migraine with aura, is associated with an increased risk of ischemic stroke, and cardiovascular events [20, 21], although the mechanisms underlying this association remain uncertain.

Etiology

Once considered as primarily a vascular disorder, in which headache is related to variations in brain and meningeal blood vessels, migraine now is regarded as a result of complex alterations of several structures of the central nervous system.

Neuroimaging studies performed during migraine attacks showed activation of several structures of the central nervous system (hypothalamus, thalamus, brain stem, and cortex) corresponding with various symptoms of a migraine attack, including those occurring in the prodromal and postdromal stages.

Migraine is a complex neurovascular disease, with a genetic component. [22] The existence of a genetic component in migraine, showed by population-based family and twin studies [23, 24, 25], is further supported by Genome-Wide Association (GWA) studies. A recent meta-analysis indeed identified 44 single-nucleotide polymorphisms, mapped to 38 susceptibility genes, significantly associated with migraine risk, thus suspected to contribute to the pathophysiology of migraine. [26]

Although no specific causes determining migraine have been identified yet, there is evidence that some triggers may facilitate the development of the attacks. When they are relevant to individual patients, they are usually self-evident and no specific diagnostic workup is needed to identify triggers. [27]

It is generally accepted that metabolic disturbances contribute to migraine in some patients, such as fluctuations in water balance, food intake (food deprivation and/or fasting), sleep deprivation or consistent interrupted or reduced sleep. [28, 29, 30] Stress and negative emotions, and some odors are also listed as triggers by people with migraine. [29, 31] Food, light, sound, and odor triggers that are reported by patients may in some cases be early symptoms of gastrointestinal and sensory sensitivity that are part of the attack.

A relationship between estrogen and migraine is recognized and fluctuations of estrogen levels during different phases of a woman life (e.g. puberty, menstruation, pregnancy) affect characteristics and frequency of migraine. [32]

Most women with migraine (up to more than 80%) show a reduction in frequency and intensity of attacks during pregnancy [33, 34, 35], or even remission, mostly during the second and third trimesters. [36, 37] However, in about 8% of cases, during pregnancy women experience a worsening of migraine attacks, in frequency and pain intensity. [38, 39]

8.1 Epidemiology of migraine

Prevalence

Migraine may begin in childhood, and its prevalence starts increasing at 10 to 14 years of age and until 35 to 39 years of age, after which it gradually decreases, particularly among women after menopause. According to the Global Burden of Disease 2016 [40] estimates, including only studies where migraine was diagnosed according to ICHD-3, migraine is the sixth most prevalent out of 328 diseases and injuries, and its global age-standardized prevalence is 14.4% (13.8–15.0) overall; 18.9% (18.1–19.7) for women, and 9.8% (9.4–10.2) for men. [16]

However, prevalence estimates according to the most recent updates of GBD 2017 [40] are not homogeneous, even within single economic regions.
In fact the prevalence varies with a similar wide range, among high income countries from 12.7% in Argentina to 27.6% in Italy while among low income countries it ranges from 7.3% in Tanzania to 24.5% in Nepal. In lower middle income countries the estimates show values from 10.8 % in Kenya to 23.1% in Tunisia and among upper middle income countries from 10.7% of China to 25.2% in Brazil. [40]

One of the reasons for these discrepancies could be an underdiagnosis and misdiagnosis of migraine, as reported in a population-based nationwide survey in China [41], due to family and community stigma. [42]

Low socioeconomic status seems to be associated to higher headache prevalence, regardless of country income [2, 43, 44, 45, 46, 47] and a higher prevalence of migraine seems also to be more common among those living in urban areas. [48]

**Sex differences**

The frequency of migraine attacks and the severity of pain show marked gender differences. The prevalence of migraine peaks between 30-39 years of age and in women it is 2 to 3 times higher than in men [49], although this ratio is not consistent across all age ranges, showing an increase, especially in women, after puberty [50, 51, 52] with the largest difference during reproductive years. [52]

Research observations show that women have more frequent, longer lasting and more severe attacks than men. [49, 53, 54]

In population based studies 20%-60% of women with migraine report association with menstruation, that seems to be a significant risk factor for migraine without aura. [55]

**Children**

The overall mean prevalence of migraine in children and adolescents was estimated 9.1% (95% CI 7.1-11.1), higher in girls 10.5% (95% CI 7.7-13.3) than in boys 7.6% (95% CI 6.3-9.0). [56]

**Incidence**

Few longitudinal studies have assessed migraine incidence in western countries.

A longitudinal study in Denmark found annual incidence of migraine of 8.1 per 1,000 (95% CI 5.7-10.5) with 6 times higher values for women compared to men, and decreasing with age (from 13.8/1000 in the age range 25-34 years to 2.6 between 55 and 64 years of age). [57]

Data from a primary care observational study show an overall incidence of 3.7 per 1,000 person-year, about 2.5 times higher in women than in men. [58]

Incidence estimates reported by GBD in 2017 showed a wide range of incidence in all ages from 7.5 new cases of migraine per 1,000 in Tanzania to 23.5 per 1,000 in Iran.

In interpreting these figures it has to be noted that most of the available data on migraine incidence are estimated through modeling from prevalence data.

**Morbidity**

Migraine has relevant psychological, social, and economic repercussions and can be associated with significant morbidity due to the disability caused by frequent attacks and/or to their treatment. Moreover, about a quarter of patients also present interictal symptoms (e.g. anxiety, avoidance of activities) with additional disability and impact on their lifestyle. [59]

The frequent use of analgesic drugs may lead to medication overuse headache (MOH), a disabling chronic headache often consequent to migraine or tension-type headache. [60, 17]

A cross-sectional, observational study on 669 patients with MOH in Europe (Germany, Denmark, Italy, Spain) and Latin America (Argentina and Chile) showed a marked variability in the headache-related healthcare utilization and in the type of overused drugs. While common analgesic were generally overused in about 47% of patients of the whole sample, ergotamine derivatives were overused mainly
among patients from Latin America (72.2 %), and only by 3.7 % of the European patients. In contrast, triptans were overused by 30.8 % of European patients with MOH and only by 5.6 % of Latin America patients. [61]

Medication overuse headache can be considered as derived from a preexisting migraine. Differently from GBD 2013 and 2015, in the most recent GBD report [16], medication overuse headaches is defined as a sequel of either migraine or tension-type headache. [17, 60]

Several observational studies and metaanalysis [62, 63, 21] showed an association of migraine (particularly migraine with aura) with ischemic heart disease, vascular events and stroke, although a causal relationship of migraine with these conditions is still unclear and the occurrence of a cerebrovascular event during a migraine attack is extremely rare.

An increased risk of ischemic stroke among women taking hormonal contraceptives has been suggested by a metaanalysis [64], although several studies and a technical report by WHO found no association between steroid hormone contraceptive use and cardiovascular events among women without specific risk factors such as smoking, hypertension, or diabetes.[65] As migraine prevalence is high in women of reproductive age, it is of concern whether the risk of ischemic stroke in women with migraine is increased by the use of hormonal contraceptives.

Data linking stroke and oral contraceptive use in patients with migraine is limited and conflicting, in part because the absolute risk is very low, and partly because other confounders may influence risk differences (such as dose of combined estrogens and other specific risk factors for vascular events). Consequently, guidance on the use on oral contraceptives by women with migraine is inconsistent. A consensus document by the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC) recommends against the use of hormonal contraceptive in women with migraine with aura.3 Conversely, the IHS guidelines warn of a potential increased risk of stroke in patients who have migraine with aura, but there are no specific recommendations to not use OCPs in these patients.[66]

Guidance by WHO recommends against combined hormonal contraceptives in women with migraine with aura, while progestogen-only contraception is acceptable. Hormone replacement therapy is not contraindicated in migraine. [27]

Mortality

Although GBD estimates indicate no deaths from migraine [16], the increased risk of cardiovascular and cerebrovascular mortality, especially for migraine with aura, is still debatable. [67]

The global burden of migraine

Headache disorders are a public-health concern given the associated disability and financial costs to society. As headache disorders are most troublesome in the productive years (late teens to 50s), estimates of their financial cost to society – mainly from lost working hours and reduced productivity – are massive. In the United Kingdom, for example, some 25 million working- or school-days are lost every year because of migraine alone. [68]

The main source of data about the burden of migraine worldwide is the GBD study, although its estimates refer mainly to a selected population of high income countries, while data from important and populous low- and middle income countries, such Indonesia, Vietnam, Bangladesh, Egypt, South Africa, Democratic Republic of Congo and several countries in sub-Saharan Africa, are lacking. According to the GBD study, 1.04 billion (95% uncertainty interval [UI] 1·00–1·09) people were estimated to have a migraine in 2016. [16]

Migraine has a profound effect on wellbeing and general functioning, not only during the acute attack, but also in terms of work performance, family and social relationships, and school achievement. Migraine carries a substantial individual, societal and economic burden, ranking as the second cause of disability. [69]

According to the GBD study, in 2016 migraine was estimated to have caused 45.1 million (95% UI 29.0-62.8) years of life lived with disability (YLDs), and in 2017 overall 5.54% (95% CI 3.91-7.5) of total YLDs were attributed to migraine. [40]

When considering the most productive years of one’s life, e.g. the age range from 15 to 49 years, the impact of disability caused by migraine is impressive: 8.2% of overall YLDs (95% CI 5.77-11.0), ranking number one for women (9.5%, 95% CI 6.8-12.7) and 6.6% (95% CI 4.6-9.1) for men [40]. Among women in this age range migraine caused 20.3 million (95% UI 12.9–28.5) YLDs in 2016. [16]

Migraine is a relevant burden also among children and adolescents less than 15 years old (4.3% YLDs, 95% CI 2.8-6.2), and among persons 50-69 years old (4.2% YLDs, 95% CI 2.9-5.5). [70]

A review of population-based studies on personal and societal burdens of headache showed that lost productive time from paid work due to migraine ranges from 2% of total available time (India) to 6% in Zambia and for household work from 2% (India) to 5% (Ethiopia, Zambia and Lithuania). [59]

A recent pan-India cross-sectional study on 705 patients with migraine showed that 73% of patients (46%) had a moderate to severe disability assessed with the Migraine Disability Assessment Score (MIDAS), leading to an impaired quality of life (Migraine Specific Quality of Life score of 3), interfering with their social life, leisure time activities, daily activities and work. [71]

The lost-productivity and consequential financial costs are substantial. A recent survey by the Italian Ministry of Health showed that that the average yearly direct cost for the management of a patient with chronic migraine is € 2,250 to € 2,648 [72, 73]. Few studies focused on loss of productivity, showing that it affects both genders, particularly for chronic migraine. Lost paid work days are higher for men than women (2.9-9.4 days vs. 1.9-6.8 days, respectively) while the lost household work is more prevalent for women than men (4.5-6.1 days vs. 2.2-4.2 days, respectively). [74, 75, 76]

In the UK it is estimated that migraine occurs in 15% of the UK adult population, and more than 100,000 people are absent from work or school as a result of migraine every working day. [77]

The annual per-person cost of migraine in Europe was estimated as €1,222 (95% CI 1,055-1,389). In Italy the indirect cost of migraine due to loss of productivity is higher for men than women, estimated for each patient with chronic migraine as about € 12,500 for men and about € 5,200 for women. [75]

Such figures are comparable with those from US surveys (about $ 14,400 for men and $ 7,100 for women). [78] The fact that women show a lower loss of income for women, which have higher migraine-related disability and therefore a higher lost productive time and cost would be expected. However, the median income is on average higher for men than women. Moreover, women spend more hours working at home, that are not accounted for as paid work days. [78, 49]

**Treatment of Migraine**

The treatment of migraine requires accurate diagnosis by trained health professionals, appropriate pharmacological management with cost-effective drugs, lifestyle modifications and patient education. Specific classes of drugs are used for acute pain during migraine attacks, for relieving headache-associated symptoms and for preventing migraine attacks within prophylactic strategies in persons affected by episodic migraine with frequent attacks (generally considered as at least once per week or on 4 or more days per month) or by chronic migraine.

Acute treatment should be taken as early as possible in the headache phase with the aim of aborting an attack. Symptom-relieving therapies commonly aim at eliminating head pain and reducing the symptoms associated with migraine, including nausea, phonophobia, and photophobia.
Patients with nausea associated with headache may find it difficult to take oral preparations, therefore several classes of drugs, among which triptans, are available as non-oral administration route (subcutaneous, intranasal and rectal preparations). Subcutaneous preparations of triptans have been developed also to achieve a faster effect on pain. Several classes of drugs are used as prophylactic treatment to reduce the frequency and severity of migraine attacks, such as tricyclic antidepressants, beta-blockers, anticonvulsants and calcium antagonists. Nutraceuticals and nonprescription therapies (coenzyme Q10, magnesium, melatonin, petasites and riboflavin) are widely used for the prevention of migraine. [79] Evidence-based guidelines [27, 70, 77, 80] recommend the following treatments for the acute migraine attack: Acetylsalicylic acid 900 mg, paracetamol 1,000 mg and ibuprofen (400 mg, and if ineffective, up to 600 mg) are recommended as first-line treatments for acute treatment of episodic migraine. Triptans (in particular sumatriptan 50 mg to100 mg) are included among recommended first line treatments, as an alternative monotherapy to other analgesics or in combination with them. Ergots or opioids are not recommended for the treatment of acute migraine.

**Antiemetics**

Metoclopramide 10 mg is recommended as a symptomatic treatment of nausea and can be useful to allow oral treatments with this specific symptom.

**Preventive treatment**

Propranolol (80–160 mg daily) and topiramate (50–100 mg daily) are considered as first-line prophylactic treatment for patients with episodic or chronic migraine. Amitriptyline (25–150 mg at night) and flunarizine (10 mg daily) should be considered as options for preventive treatment. Candesartan (16 mg daily) and sodium valproate (400–1,500 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine.

In patients with chronic migraine prophylactic treatment with onabotulinumtoxin A showed to be effective in increasing headache-free days and is probably effective in improving health-related quality of life. It is recommended for the of patients with chronic migraine where medication overuse has been addressed and when other prophylactic migraine treatments have failed. Onabotulinum toxin A is required to be administered by appropriately trained personnel in hospital specialist centers, which may have implications for service delivery. [80, 81]

**Emerging drug treatments**

Migraine is associated with the release of numerous neurotransmitters and neuromodulators, including the calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating peptide (PACAP), that have recently considered as having an important role in the pathogenesis of migraine. Monoclonal antibodies acting as antagonists of the CGRP receptor have recently been studied in clinical trials as prophylactic treatment of chronic migraine, when other treatments have failed or are not tolerated, and are currently available in the US and in some EU countries. [82]

**Unmet needs**

Even though the burden of migraine worldwide is considerable, accurate diagnosis, quality of care and rates of drug utilization are still insufficient across countries and settings. Worldwide, only 40% of people with migraine are professionally diagnosed. [59]

Since it is not a life-threatening condition, it is mostly episodic, and it is not contagion, headache is often not considered as a relevant health care issue. Therefore, national health care systems often do not
consider that direct costs of migraine treatments are small in comparison with the huge indirect-cost savings that could be achieved by reducing the productivity loss in terms of working days, if health care resources were allocated to treat headache disorders appropriately. [68]

Indeed, evidence indicates that people with headache are underdiagnosed and undertreated, even in high-income regions of Europe and North America. Eurolight - an initiative supported by the European Commission Executive Agency for Health and Consumers (EHAC), and an activity within the Global Campaign against Headache conducted by Lifting The Burden (LTB), a UK-registered non-governmental organization in official relations with the World Health Organization, performed a cross-sectional survey in 10 countries, representing > 60% of the adult population (18–65 years) of the European Union (EU). [2]

Drug coverage, intended as the proportion of persons needing a treatment who actually receive it, is also an issue, particularly in middle- and low-income countries. Considering migraine-specific medications, a great variability in their utilization had been reported between countries. Specifically, the use of triptans in population-based samples was between 3.4 and 22.4% and it was associated with the consultation with a specialist. The use of preventive treatment was even lower: 1.6-13.7% of those eligible. For subjects with migraine the best care was achieved when consulting a specialist, while those self-medicating were inadequately treated. [2]

Cost-effectiveness analyses based on sales data in middle-income BRIC countries (Russia, India and China) and in low-income countries (Zambia) show low estimates of coverage for treatments of acute migraine drugs (0% to 2% for triptans and 50% to 80% for ASA). [83]

Moreover, according to previous data, the use of ergotamine was still relevant globally. It was however recognized the need to improve the availability of triptans, given the inferior efficacy of ergotamine, and the concerns on toxicity, accumulation and overuse potential.[84] Inadequate acute treatment efficacy is associated with increased risk of transformation from episodic migraine to chronic, [19] with associated higher economic and social burden. In a survey on the pattern of migraine management among neurologist in Taiwan, sumatriptan was underutilized (67.5 % of responders had ever prescribed it for migraine), and the main reason was the high cost of this drug. [85]

Poor availability and inconsistent use of anti-migraine drugs may in part explain the apparent inefficacy of current treatments. Although prophylactic treatments are indicated in many persons suffering from migraine and frequent attacks or from chronic migraine, there are underused. Moreover, treatments currently used in the prevention of migraine have a limited efficacy and are poorly tolerated in the long term. [2]

Treatment outcomes in migraine

In clinical trials investigating drugs for acute migraine attacks, treatment response can be measured by means of different outcomes. The choice of a clinically meaningful, reproducible and reliable outcome in migraine, and in general in all headache disorders, is very important and challenging at the same time, since the severity of migraine cannot be measured but with self-evaluation by the patient. An accurate evaluation by an experienced clinician is crucial not only for a correct diagnosis, but also for reliably assessing the patient’s response to treatment. The IHS issued guidance for researchers in the choice of outcomes when planning headache trials.

Freedom from pain at two hours before any rescue medication is the efficacy outcome recommended by the IHS as primary outcome in clinical trials, since it is simple, clinically relevant, reflecting patients’ expectations and independent of the potential effect of other interfering treatments. Other outcome commonly used in clinical trials and systematic reviews, combining scientific rigor and patient preferences, are: sustained pain freedom at 24 hours, relief of headache at two hours, sustained headache relief at 24 hours, relapse of headache from 2 to 48 hours after study drug administration, and rescue medication use.
Other outcomes (usually considered as secondary efficacy measures) are related to headache-associated symptoms in migraine, such as nausea, phonophobia, photophobia. [86]

8.2 Assessment of current use

According to the data of the 2011 World Atlas of Headache Disorders and Resources [84] globally, preferred drugs for acute treatment of episodic migraine are NSAIDs (86% of countries among responders), followed by paracetamol (69%) and aspirin (52%), that were the preferred single drugs overall and were already included in the EML. Among specific anti-migraine drugs ergotamine (34% of countries among responders) and sumatriptan (33%) were used with similar frequency. However, sumatriptan was preferred in Europe and West Pacific, while ergotamine in the rest of the world. Moreover, while these specific anti-migraine medications are prescription-only in most countries, ergotamine was available as over-the-counter in 23%. [52]

More recent data show that in India the most widely used drugs were paracetamol (47%), naproxene (12.9%) and sumatriptan (12.2 %). [87]

8.3 Target populations

Oral sumatriptan is indicated in adults for the treatment of acute migraine attacks, both as monotherapy and in combination with other analgesics, such as NSAIDs.

*Women with migraine in child-bearing age and in pregnancy*

Women in child-bearing age represent a substantial proportion of persons affected by episodic migraine. Treatment of migraine during pregnancy is challenging due to the potential teratogenesis of the drugs commonly prescribed to treat migraine in the acute phase and as prophylactic treatments. If drug treatment is recommended in the acute attack, acetaminophen is the drug of choice. [77, 80]

Available evidence from observational studies, mostly including women treated with sumatriptan during pregnancy, does not suggest an increased risk for major congenital malformations, even among women taking sumatriptan during the first trimester. [88, 89]

8.4 Likely impact of treatment on disease

Despite its relevant social and economic impact, migraine is globally undertreated, in terms of both acute and prophylactic treatment.

According to an European survey, [2] triptans are underused among people with migraine that could potentially benefit from them (3.4%-24.5%).

The availability of oral sumatriptan, an easily self-administered drug not requiring special skills or monitoring, in the EML could increase the proportion of persons with migraine using an effective and specific treatment for acute attacks recommended as first-line treatment by evidence-based clinical practice guidelines. When compared to available analgesics, the benefits of sumatriptan are not impressive, but even a small benefit in the treatment of migraine would have a huge impact on a population scale, considering the prevalence of migraine and its social and economic burden. Moreover, a wider availability of one more effective treatment for acute migraine attacks would contribute preventing the overuse of other less effective treatments and the consequent risk of adverse events and of complications of episodic migraine, such as MOH, often associated with NSAIDs.[60]

9.1 - Identification of clinical evidence

The identification of clinical evidence on efficacy and safety of oral sumatriptan in adults and children with acute migraine attack was searched through the following publication types: systematic reviews (SR), randomized controlled trials (RCT), guidelines (GL). Ongoing studies were also searched. The intervention considered was oral sumatriptan at any dosage, compared with placebo or other drugs licensed for the treatment of migraine. Studies on substance-induced headache (for example cilostazol-induced migraine) were not considered. Similarly, studies on triptans not providing data on oral sumatriptan as intervention or control, and studies reporting only data on sumatriptan compared with drugs excluded from EML (eg. ergotamine) because of lack of evidence of efficacy and the availability of effective and safe alternatives were not considered.

The main efficacy outcome considered was “pain free at 2 hours” (recommended as primary outcome by IHS). [86]

Study quality was determined on this outcome, when available, according to the GRADE methodology, distinguishing four levels of certainty in the estimate: “High” (further research is very unlikely to change our confidence in the estimate of effect), “Moderate” (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), “Low” (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) and “Very Low” (any estimate of effect is very uncertain). [90-94]

The following efficacy outcomes were also considered:
- relief of headache at 2 hours
- sustained freedom from pain (24 hours),
- sustained relief of headache (24 hours)
- rescue medication use

Safety was assessed by considering any adverse event (AE) reported in the studies, serious adverse events (SAEs), treatment-related adverse events (TRAEs) and withdrawals due to adverse events.

To find additional sources of published data, the bibliographies of the retrieved articles were examined.

Systematic Reviews

To be included, Systematic Reviews (SRs) had to comply with the PRISMA 2009 criteria, [95] or at least:
- clearly state its objectives with pre-defined eligibility criteria for studies;
- describe an explicit, reproducible methodology,
- describe the sources (electronic databases or other sources) where the eligible studies have been systematically searched, including the date last searched
- assess the validity of the findings of the included studies (risk of bias assessment)
- present a synthesis of the characteristics and findings of the included studies.
- Present qualitative or quantitative synthesis of the results

In assessing comparative effectiveness of sumatriptan vs. placebo or other active treatments, we first looked at the availability of direct, head-to-head comparisons.
If direct evidence was lacking we looked for evidence from indirect comparisons.

Systematic reviews were searched by consulting the following databases from 2013 to October 2018:

Databases of SRs and technology assessments:

- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Library: Technology Assessments database
- Database of Abstracts of Reviews of Effects (DARE)
- BMJ Clinical Evidence
- HTA.UK - www.hta.ac.uk
- AHRQ - www.ahrq.gov/
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- National Institute for Health and Clinical Excellence (NICE)
- Haute Autorité de Santé - http://www.has-sante.fr/portail/index.jsp

The strategy adopted was specific to each source. In synthesis, if a “search” function was available the database was checked with the term “sumatriptan”; if a “search” engine was not available the documents were searched through the “browse” function.

Databases of primary publications

- National Library of Medicine’s MEDLINE database;
- EMBASE

RCTs

Randomised controlled studies were searched from 2013 to October 2018 and appraised if they had not been included in the selected SRs.

To be included, RCTs had to be randomized, double-blind, controlled with placebo or with an active control (licensed drug), using oral sumatriptan to treat an attack of migraine with or without aura, and present results for at least one of the outcomes listed above.

We consulted the following sources:

- Database of RCTs
  - Cochrane Central Register of Controlled Trials (CENTRAL)
- Databases of primary publications
  - National Library of Medicine’s MEDLINE database;
  - EMBASE

Guidelines

To be included, guidelines had to present a series of recommendations produced through a systematic search of the biomedical literature by a multidisciplinary panel and adopting a grading system of the recommendations.

Guidelines containing recommendations on the use of sumatriptan in the treatment of acute migraine attacks were also searched by consulting the following sources (October 2018):

- World Health organization (WHO)
- National Institute for Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- American Academy of Neurology (AAN)
- International Headache Society (IHS)
- TRIP Database

Guidelines were selected if they were produced or updated in the last 10 years.

The strategy adopted was specific to each source. In synthesis, if a “search” function was available the database was checked with the term “migraine”; if a “search” engine was not available the documents were searched through the “browse” function. Only guidelines
originally developed by the authors were considered; guidelines adapted from other existing guidelines were not included in this document.

**Ongoing studies**

We searched the following sources (October 2018):

- MetaRegister of Controlled Trials (mRCT): [http://www.isrctn.com/](http://www.isrctn.com/)
- EU Clinical Trials Register: [https://www.clinicaltrialsregister.eu/](https://www.clinicaltrialsregister.eu/)
- Clinicaltrials.gov [https://www.clinicaltrials.gov/](https://www.clinicaltrials.gov/)

The specific search strategies and the results of the search are summarized in **Annex 3**.
9.2 - Summary of available data (appraisal of quality, outcome measures, summary of results)

The statements reported below are based on data from available systematic reviews and clinical trials enrolling patients affected by migraine with or without aura.

Available data come mainly from RCTs conducted in high income countries.

**Oral sumatriptan for acute migraine attacks in children and adolescents**

Our search for the evidence on the efficacy and safety of sumatriptan in the treatment of acute migraine attacks in children and adolescents retrieved two SRs. [96, 97]

One qualitative SR on treatments for acute migraine on patients aged <18 years was not considered because it included 7 studies on sumatriptan, 3 of which were open label, and the remaining 4 were included in the SR by Richer et al. [97]

The Cochrane SR by Richer et al. compared any pharmacological intervention by any route of administration for symptomatic acute treatment of a migraine attack in children (under 12 years of age) and adolescents (12 to 17 years of age). Acceptable comparators included placebo or other active drug treatments. The primary outcome was the percentage of pain-free participants at two hours. [96]

Most data on triptans in children and adolescents come from treatment with sumatriptan. The only oral triptan studied in children is rizatriptan (one placebo-controlled RCT).

Both in children and adolescents, evidence from direct comparisons between sumatriptan vs other triptans or vs other analgesics (such as ASA or paracetamol) and between different triptans is lacking.

Only intranasal sumatriptan has been studied in clinical trials in children.

**Oral sumatriptan vs placebo**

A pooled estimate of six studies oral sumatriptan in adolescents with acute migraine showed no difference between oral sumatriptan and placebo in reaching pain freedom at 2 hours. In absolute terms, the proportion of patients pain-free at 2 hours with sumatriptan was 21.7% vs 20% with placebo (RD: 1.7%, 95%CI: -4.3, 7.1). (Table 1)

Triptans as a class showed higher efficacy on the outcome “pain freedom at 2 hours”, and also on “headache relief at 2 hours” and “use of rescue medication”.

According to GRADE, the certainty in the estimates is “Moderate”.

**Sumatriptan (any administration route) vs placebo**

Relative to the outcome “pain-free at 2 hours”, clinical trials in adolescents show superiority of sumatriptan vs placebo, while in children the estimate does not reach statistical significance. (Table 1) Absolute estimates show that 49.3% of children vs and 23.6% with placebo are pain-free at two hours (RD 25.7%, 95%CI 10.0, 39.6), while 34.8% of adolescents on sumatriptan vs 25.1% on placebo (RD 9.7% (95%CI: 4.8; 14.4)).

Triptans considered as a class (regardless of the formulation) showed superiority vs placebo in reaching the outcome “pain freedom at 2 hours”, both among children (RD:16.3 (95%CI: 6.2-25.9)) and adolescents (RD 7.6% (95%CI:5.4;9.7)). (Table 1)
Table 1 - Efficacy of triptans (all routes of administration) vs placebo in reaching pain freedom at 2 hours among children and adolescents (*statistically significant differences in bold*) [97]

<table>
<thead>
<tr>
<th>Triptan</th>
<th>Children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N studies</td>
<td>N of participants</td>
</tr>
<tr>
<td>Sumatriptan</td>
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<td>145</td>
</tr>
<tr>
<td>Oral sumatriptan</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan (2 studies oral; 2 non-oral)</td>
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<td></td>
</tr>
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<td>Rizatriptan (oral)</td>
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</tr>
<tr>
<td>Almotriptan (oral)</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>345</td>
</tr>
</tbody>
</table>

Oral sumatriptan in combination with other drugs

One study compared a fixed association of sumatriptan and naproxen at different doses (10 mg+60mg, 30 mg+180mg, 85mg+ 500mg) with placebo involving 490 adolescents. The study showed for the “pain-free at 2 hours” outcome a RR 2.66 (95% CI 1.57 to 4.51).

No RCTs on children and adolescents published after the search date of the SR by Richer et al were retrieved.
Oral sumatriptan for acute migraine attacks in adults

The evidence on the efficacy and safety of sumatriptan in the treatment of acute migraine attacks in adults comes from two SRs, one focused on the efficacy and safety of oral sumatriptan [98] and a second one on the efficacy and tolerability of triptans. [99]

Table 2 shows the availability of direct (black dots) and indirect evidence (white dots) on the efficacy of sumatriptan from the two SRs we considered.

As previously mentioned in section 9.1, we looked for direct evidence from head-to-head comparisons whenever available. If estimates from direct comparisons were not available, we looked for indirect comparisons in the SR and network metaanalysis (NMA) by the Canadian Agency for Drugs and Technologies in Health (CADTH) focused on triptans. [99]

Table 2 - Available pooled estimates from direct (head-to-head) and indirect comparisons on outcome “pain freedom at 2 hours” (sumatriptan vs other triptans or vs other treatments for migraine)

<table>
<thead>
<tr>
<th>Sumatriptan</th>
<th>Almotriptan</th>
<th>Eletriptan</th>
<th>Frovatriptan</th>
<th>Naratriptan</th>
<th>Rizatriptan</th>
<th>Zolmitriptan</th>
<th>ASA</th>
<th>Paracetamol 1000 mg + metoclopramide 10mg</th>
</tr>
</thead>
</table>

• = Direct comparison; ○ = Indirect comparison; * ASA 900 mg + metoclopramide 10mg; ** 1 study included in SR but no pooled estimates provided;

Oral sumatriptan vs placebo

Pooled data from 18 studies, showed higher efficacy than placebo on the outcome “pain freedom at 2 hours” among patients with migraine taking oral sumatriptan 50 mg, for any intensity of pain at baseline. Slightly higher estimates were observed when considering 21 studies on oral sumatriptan 100 mg. In absolute terms, both sumatriptan 50 mg and 100 mg compared with placebo gave clinically meaningful NNTs (Table 3).

Similarly, relative to the outcomes headache relief at 2 h, sustained pain freedom at 24 hours and use of rescue medication, pooled analysis showed clinically meaningful differences and NNTs in favor of sumatriptan 50 mg and 100 mg.

Efficacy in sustained pain freedom at 24 hours was lower among patients with moderate-severe pain at baseline (NNT 9.5).

Pooled estimates showed a higher efficacy for the higher dose (100 mg) than lower dose (50 mg) of sumatriptan.

Removing studies with a lower methodological quality did not change the results of pooled analyses.

The overall certainty in the estimates of this SR, according to GRADE is “High”.

---

4 The Cochrane SR and metanalysis by Derry C et al on oral sumatriptan was one of the included references despite it was published in 2012 (outside the time range of our search strategy) because the authors updated it in May 2015, and the review was declared as stable (Issue 5, 2015 of the Cochrane Library). [98] It compared the efficacy and tolerability of oral sumatriptan (25, 50, 100, 200 and 300 mg) to placebo and to other active interventions in the treatment of acute migraine attacks in adults.
Table 3 - Efficacy of sumatriptan 50 mg and 100 mg vs placebo in reaching the outcome “pain freedom at 2 hours” in adults (statistically significant differences in bold) [98]

<table>
<thead>
<tr>
<th>Sumatriptan</th>
<th>N studies</th>
<th>N of participants</th>
<th>RR (95%CI)</th>
<th>RD</th>
<th>NNT</th>
<th>GRADE certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>7*</td>
<td>1514*</td>
<td>2.0 (1.7, 2.4) *</td>
<td>23%</td>
<td>4.4</td>
<td>☒☒☒☒ High</td>
</tr>
<tr>
<td></td>
<td>13**</td>
<td>6447 **</td>
<td>2.7 (2.4, 3.1) **</td>
<td>19%</td>
<td>6.1</td>
<td>☒☒☒☒ High</td>
</tr>
<tr>
<td>100 mg</td>
<td>5 *</td>
<td>1240 *</td>
<td>2.41 (2.06, 2.81) *</td>
<td>34%</td>
<td>3.0</td>
<td>☒☒☒☒ High</td>
</tr>
<tr>
<td></td>
<td>16 **</td>
<td>6571 **</td>
<td>3.2 (2.8, 3.6) **</td>
<td>21%</td>
<td>4.7</td>
<td>☒☒☒☒ High</td>
</tr>
</tbody>
</table>

* mild baseline intensity; ** moderate/severe baseline intensity

Oral sumatriptan vs active comparators

The efficacy of sumatriptan on pain freedom at 2 hours was comparable to that of the other triptans, except for eletriptan 40 and 80 mg, that showed significantly better efficacy vs sumatriptan 50 mg and 100 mg. (Table 4)

Eletriptan was superior to sumatriptan also in providing headache relief at 2 and 24 hours, less use of rescue medications, and relief of migraine-associated symptoms.

Rizatriptan 10 mg showed better efficacy than sumatriptan 100 mg on pain freedom at 2 hours and headache relief at 1 hour. In interpreting these results it has to be noted that rizatriptan 5 mg and 10 mg offered no significant advantage over sumatriptan 50 mg. (Table 4)

For zolmitriptan 2.5 mg and 5 mg, pooled estimates were calculated only for headache relief at 1 and 2 hours, and the differences vs sumatriptan 50 mg were not statistically significant.

Four studies compared sumatriptan 50 mg and 100 mg with effervescent ASA 1000 mg (2 studies, 726 participants) and ASA 900 mg + metoclopramide 10 mg (2 studies, 575 participants), respectively. The pooled analysis of the former comparison showed no statistically significant differences relative to the outcome “pain freedom at 2 hours”, while in the latter a significant difference in favor of sumatriptan 100 mg was observed. In absolute terms, 32.3% of patients treated with sumatriptan 50 mg and 26.4% of those on ASA 1000 mg were pain-free at 2 hours (RD 15% in favor of sumatriptan). (Table 4)

Considering other outcomes, effervescent ASA 1000 mg was more effective than sumatriptan 50 mg on headache relief at 1 hour (OR 0.78; 95%CI 0.61, 0.98), while sumatriptan was better on headache relief at 2 hours (OR 1.27; 95%CI 1.09, 1.47).

Sumatriptan 100 mg was more effective than paracetamol 1000 mg + metoclopramide 10 mg in reducing rescue medication use (OR 0.86; 95%CI 0.74, 0.99).

Sumatriptan 100 mg was also more effective than ASA 900 mg in providing pain freedom at 2 hours (OR 1.62; 95%CI 1.17, 2.25).

Sumatriptan 100 mg was compared to paracetamol 1000 mg + metoclopramide 10 mg relative to the outcome headache relief at 2 hours (2 studies, 1035 participants), showing no difference. [98]

Table 4 - Efficacy of oral sumatriptan vs active comparators in reaching pain freedom at 2 hours in adults (statistically significant differences in bold; differences not in favor of sumatriptan in italic) [98]

<table>
<thead>
<tr>
<th>Active comparator</th>
<th>Sumatriptan (dose)</th>
<th>N studies</th>
<th>N of participants</th>
<th>RR (95%CI)</th>
<th>NNT</th>
<th>GRADE certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan 12.5mg</td>
<td>100 mg</td>
<td>2</td>
<td>754</td>
<td>1.20 (0.97, 1.49)</td>
<td>NS</td>
<td>☒☒☒☒ High</td>
</tr>
<tr>
<td>Eletriptan 40 mg</td>
<td>50 mg</td>
<td>2</td>
<td>721</td>
<td>0.74 (0.55, 0.98)</td>
<td>17.8</td>
<td>☒☒☒☒ High</td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>3</td>
<td>2263</td>
<td>0.74 (0.65, 0.85)</td>
<td>12.5</td>
<td>☒☒☒☒ High</td>
</tr>
<tr>
<td>Eletriptan 80 mg</td>
<td>50 mg</td>
<td>2</td>
<td>706</td>
<td>0.58 (0.44, 0.76)</td>
<td>8.3</td>
<td>☒☒☒☒ High</td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>2</td>
<td>604</td>
<td>0.54 (0.41, 0.72)</td>
<td>6.2</td>
<td>☒☒☒☒ High</td>
</tr>
</tbody>
</table>
A network metaanalysis (NMA) by the Canadian Agency for Drugs and Technologies in Health (CADTH) compared the relative efficacy, effectiveness and safety of triptans alone or in combination with other drugs, all administration routes, any dose, compared with other triptans, NSAIDs, acetylsalicylic acid, paracetamol, ergots, opioids in the treatment of acute migraine attacks in adults (> 18 years of age).

In order to account for modification of the effect related to dosage, sumatriptan doses were categorized as “low” (25mg, studied in 4 RCTs including 850 patients), “standard” (50mg studied in 23 RCTs including 5870 patients), and “high” (100mg, studied in 23 RCTs including 5210 patients). Efficacy was assessed for each dosage.

The SR by the CADTH provided comparative effectiveness data both from direct and indirect comparisons through a NMA. [99]

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%CI 24.6, 31%) of patients, compared with 10.60% (95%CI 10.0, 11.3%) for placebo.

Triptans showed to be effective in the largest proportion of patients on the outcome “headache relief at 2 hours”: 42% to 76% of patients, compared to 26.70 (95%CI 25.7, 27.7) for placebo.

Fifty percent of patients taking sumatriptan 50 mg (95%CI 46.3, 53.1) vs 27% (95%CI 25.7, 27.7) with placebo had a headache relief at 2 hours

Estimates from pairwise comparisons of sumatriptan 50 mg vs placebo were substantially consistent with those from the metaanalysis by Derry et al. in that sumatriptan was superior to placebo on the outcome “pain freedom at 2 hours” (RR 2.38, 95%CI 1.99, 2.84; OR 3.12 95%CI 2.54, 3.82) and other outcomes (headache relief at 2 and at 24 hours, sustained freedom from pain at 24 hours and reduced use of rescue medication). [98, 99]

Similarly, estimates from pairwise comparisons of sumatriptan 50 mg vs other triptans showed a superiority of eletriptan 40 mg on the outcome “pain freedom at 2 hours” (OR 0.59; 95%CI 0.45, 0.78) and all the other outcomes mentioned above. These results were consistent with those observed on direct comparisons in the SR by Derry et al. [98, 99]

In the NMA estimates, rizatriptan showed a better efficacy than sumatriptan on the outcomes “pain freedom” and “pain relief at 2 hours”. [99]

The SR and NMA by Cameron et al provided estimates from indirect comparisons between sumatriptan vs. frovatriptan and sumatriptan vs naratriptan, where estimates from direct comparisons were not available. [99]

Oral frovatriptan (1 mg, 2.5 mg, 5 mg) was compared to placebo in five RCTs included in the NMA, one of which compared dosages up to 40 mg with placebo.

Direct evidence vs placebo (pairwise metaanalysis) showed that frovatriptan was more effective than placebo in reaching pain freedom at 2 hours (OR 4.31, 95%CI 2.94, 6.34).

The estimate of the NMA pooling indirect evidence vs sumatriptan 50 mg showed no significant difference in reaching the outcome “pain freedom at 2 hours” (OR 1.39, 95% CI 0.85, 2.32).

Oral naratriptan (1 mg and 2.5 mg) was compared to placebo in four RCTs and to rizatriptan 10 mg in one RCT included in the NMA. One RCT compared naratriptan with sumatriptan, but outcomes at 2 hours were not reported.
Direct evidence vs placebo (pairwise metaanalysis) showed that naratriptan was more effective than placebo in reaching pain freedom at 2 hours (OR 1.68, 95% CI 0.74, 3.84). The estimate of NMA pooling indirect evidence vs sumatriptan 50 mg showed that naratriptan was significantly less effective than sumatriptan (OR 0.55, 95% CI 0.34, 0.90). [99]

**Sumatriptan in fixed combination with naproxen**

A SR by Law et al.[100] on sumatriptan 85 mg in fixed combination with naproxen 500 mg was retrieved but not included in the evidence base of this application. Since naproxen is not currently available among the drugs in the EML, only studies comparing the sumatriptan plus naproxen combination with sumatriptan were considered, relatively to the sumatriptan only treatment arm. All studies included in the SR by Law et al were vs placebo, or included in the SR by Derry 2012. One study included in the SR compared a fixed combination of sumatriptan 85mg plus naproxen 500mg with a fixed combination of acetaminophen 325 mg + caffeine 40 mg + butalbital 50 mg. [100]

**Studies on efficacy not included in the systematic reviews**

We retrieved two randomized, double-blind, double-dummy crossover studies, not included in the SRs, comparing oral sumatriptan with an active treatment in acute migraine attacks. [101, 102] (Table 5)

The first RCT (COMPASS) compared AVP-825, a breath-powered intranasal delivery system of sumatriptan, with sumatriptan oral tablets 100 mg in adult patients with migraine. The primary outcome of the study was the Sum of Pain Intensity Differences 30 minutes after administration (SPID-30). Pain intensity is measured with a numerical 4-point scale (from 0= no headache to 3=severe headache). The SPID-30 SPID is not recommended as a primary outcome by the HIS guidelines on controlled trials of drugs in migraine [86] Moreover, the outcome SPID-30 was formally presented as the primary outcome after patients’ enrolment was completed. The outcome pain freedom at 2 hours was among the secondary outcomes, with data reported in full. The study showed a superiority of the intranasal preparation of sumatriptan vs oral sumatriptan 100mg at 30 minutes post-dose (least squares mean SPID-30 = 10.80 vs 7.41, adjusted mean difference 3.39 [95% confidence interval 1.76, 5.01]; P < .001). The percentage of attacks with pain relief and pain freedom were statistically higher among patients treated with the intranasal preparation at 15 to 90 minutes post-dose, while at 2 hours there was no statistically significant difference. [102]

The certainty of the estimate, according to GRADE, was “Very Low”.

The second study, by Pini et al., was a double blind, double-dummy, cross over, non-inferiority RCT that compared paracetamol 1000mg + caffeine 130mg (PCF) with oral sumatriptan 50 mg, in adult patients with migraine attacks according to International Classification of Headache Disorders, (ICHD-II). Patients were allocated to assume either one dose of PCF and two sumatriptan, or two PCF and one sumatriptan in a randomized sequence treatment, to treat 3 consecutive migraine attacks. The primary outcome was the sum of pain intensity differences (SPID), from baseline through post-dose assessment, evaluated during the 4 h post-dose period. Pain intensity was measured with a numerical 4-point scale (0= no headache to 3=severe headache) and pain relief using a 5-point scale (0 = no relief to 4=complete relief). The outcome “pain freedom at 2 hours” was not reported (although it was mentioned in the abstract as one of the assessed efficacy outcomes).

The ITT analysis included 92 patients who took at least one of the treatments; globally 264 migraine attacks were evaluated. The study showed a non-inferiority of the combination PCF versus sumatriptan as for SPID in the 4-h observation period (SPID mean value in PCF and sumatriptan groups was 3.2 (± 3.8) and 3.2 (± 3.7), respectively, P=0.88). Similarly, no difference was observed comparing the two treatments (mean value 7.0 (± 3.6) vs 7.4 (± 3.6), P=0.48 in PCF and sumatriptan groups, respectively). [101]
The certainty of the estimate, according to GRADE, was “Low”.

9.3 - Summary of available estimates of comparative effectiveness

Children and adolescents

- Most data on triptans come from treatment with sumatriptan.
- No clinical trials in children are available on the efficacy of oral sumatriptan.
- Evidence from direct comparisons between sumatriptan vs other triptans or vs other analgesics (such as ASA or paracetamol) and between different triptans is lacking
- Sumatriptan in both intranasal and oral formulation have been studied in adolescents.
- Available data do not allow conclusions relative to the efficacy (outcome “pain freedom at 2 hours”) of oral sumatriptan, since pooled estimates show no difference in adolescents between oral sumatriptan and placebo
- Indirect evidence (from comparing risk differences between active treatment arms and placebo arms) suggests that in both children and adolescents the efficacy of ibuprofen is higher than sumatriptan.

Adults

- High quality evidence showed that sumatriptan is more effective than placebo on all the outcomes considered in two SRs (pain freedom and headache relief at 2 hours and 24 hours, use of rescue medications, relief of headache-associated symptoms of migraine).
- Pooled estimates of high quality direct comparisons between sumatriptan and other triptans for the outcome “pain freedom at 2 hours” are available for almotriptan, eletriptan and rizatriptan, showing no significant difference. Evidence from indirect comparisons shows no efficacy difference between sumatriptan and naratriptan or frovatriptan.
- High quality, direct evidence showed a statistically significant difference in favour of eletriptan 40 mg and 80 mg compared to sumatriptan 50 and 100 mg. Superiority of eletriptan vs sumatriptan was observed in relation to all the efficacy outcomes mentioned above, and was clinically meaningful for the 80 mg dose.
- Direct evidence showed a significant difference in favour of rizatriptan 10 mg vs sumatriptan 100 mg, but this result has to be interpreted with caution, since no differences were observed vs lower doses of sumatriptan.
- Direct evidence shows no substantial differences on any outcome between sumatriptan 50 and 100 mg and standard doses of ASA and paracetamol. High quality direct evidence showed a statistically and clinically meaningful difference in favour of sumatriptan compared to ASA 900 mg + metoclopramide 10 mg.
- Two RCTs not included in the aforementioned SRs provided data that do not change the conclusions of the SRs.
**Ongoing studies**


The study (ANODYNE 2) is a single site, phase 2B, double-blind RCT aimed at assessing the efficacy and safety of “ALLOD-2” (combination of two marketed drugs) vs sumatriptan and placebo in the acute treatment of migraine with associated nausea in adults. The follow up is up to 9 weeks. The primary outcomes are freedom from pain at 2 hours and the proportion of patients with nausea-free at 2 hours. Recruitment is completed and the final data collection date for primary outcome measure was May 7, 2018.

Other studies were retrieved comparing non-oral formulations of sumatriptan with oral formulations or placebo, in adult and paediatric populations or on healthy subjects with migraine or with pharmacologically induced migraine.
Table 5 – Evidence on triptans for acute migraine considered in the present application.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>N of studies (Type)</th>
<th>N of participants (Type)</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richer (2016) [96]</td>
<td>SR</td>
<td>27* (RCT on antimigraine drugs)</td>
<td>N= 7630 (children and adolescents)</td>
<td>Intranasal sumatriptan (2 RCTs children)</td>
<td>Placebo</td>
<td>Efficacy: - Pain-free participants at 2 hours (no rescue medication) - Headache relief at two hours (prior to use of rescue medication) - Rescue medication (at 2 h or earlier to a maximum of 6 h after the test drug) - Headache recurrence (recurrence of any headache from 2 to 48 h). - Presence of nausea (at 2 h) - Presence of vomiting (within 2 h) Safety: Any adverse events (as any unwanted effect that occurred during treatment)</td>
<td>Search date: February 2016 Comparisons vs placebo only, no head-to-head studies. Pairwise metaanalysis.</td>
</tr>
<tr>
<td>Derry (2012) [98]</td>
<td>SR</td>
<td>61 (RCT)</td>
<td>N=37,250 adults (&gt;18 years)</td>
<td>Oral sumatriptan 25mg, 50mg, 100mg, 200mg, 300mg</td>
<td>Placebo</td>
<td>Efficacy: - pain-free at 1 h &amp; 2 h (no rescue medication) - headache relief at 1 h &amp; 2 h - sustained pain-free during 24 h post-dose (pain-free at 2 h &amp; no use of rescue medication or recurrence of moderate to severe pain within 24 h); - sustained headache relief during 24 h post-dose (headache relief at 2 h, sustained for 24 h, with no use of rescue medication or second dose of study medication) Tolerability: - any adverse event withdrawal</td>
<td>Search date October 2011, update May 2015 Pairwise metaanalysis.</td>
</tr>
<tr>
<td>Author</td>
<td>Study Type</td>
<td>Cohort Details</td>
<td>N</td>
<td>Study Details</td>
<td>Efficacy:</td>
<td>Safety:</td>
<td>Search Date</td>
</tr>
<tr>
<td>-------------------</td>
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<td>---------------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>Cameron (2015)</td>
<td>SR</td>
<td>133 (RCT) ¶</td>
<td>50,929 #</td>
<td>Triptans (Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) (all administration routes, all doses)</td>
<td>NSAIDs, acetylsalicylic acid (ASA), acetaminophen, ergots, opioids, or anti-emetics</td>
<td>* headache relief defined as a reduction in headache intensity from moderate or severe to mild or none at 2 or 24 hours</td>
<td>October 2013</td>
</tr>
<tr>
<td>Roberto (2014)</td>
<td>SR</td>
<td>4 (observational: 1 retrospective cohort, 3 nested case-control) N=50,868*</td>
<td></td>
<td>Persons exposed to triptans</td>
<td>Persons unexposed to triptans</td>
<td>Cardiovascular events - Stroke</td>
<td></td>
</tr>
<tr>
<td>Tepper (2015)</td>
<td>RCT</td>
<td>Double blind, double-dummy, cross-over</td>
<td>N studies = 1 N participants = 275 (Adults 18-65 years with diagnosis of migraine with or without aura, according to the International Classification of Headache Disorders (2nd edition, 1st revision, 2005))</td>
<td>breath-powered intranasal delivery system of sumatriptan 22 mg</td>
<td>sumatriptan oral tablets 100 mg</td>
<td>Primary outcome: SPID-30 (sum of pain intensity differences from baseline through 30 minutes post-dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary, exploratory outcomes (at 10, 15, 30, 45, 60, 90, and 120 min, post-dose):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pini (2012) [101]</td>
<td>RCT Double blind, double-dummy, cross-over, non inferiority trial</td>
<td>92 participants (≥18 years) with diagnosis of migraine with or without aura, according to International Classification of Headache Disorders, (ICHD-II)</td>
<td>Paracetamol 1000 mg + caffeine 130 mg</td>
<td>Oral sumatriptan 50 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Primary outcome: value of the SPID (sum of pain intensity differences from baseline through post-dose assessment) evaluated hourly during the 4 h post-dose period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total pain relief (TOTPAR), calculated as the sum of every post-dose assessment.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety:</strong> Any adverse events (recorded by the investigator or by the patient in a symptom check-list, hourly for 4 h post assumption).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* the total number of studies is greater than 27 as some studies compared multiple medications
** In one observational study included in the SR the number of patients exposed to triptans was not specified
¶ 88 of which with available data relative to the outcome “Pain freedom at 2 hours”
# With data relative to the outcome “Pain freedom at 2 hours”
Recommendations by clinical practice guidelines

Our search retrieved three guidelines featuring recommendations on triptans in the acute treatment of episodic migraine. Two guidelines [70, 80] are focused on migraine, while the third one is on headaches, including migraine. [37]

Recommendations on treatment with triptans (monotherapy or combination therapy) in adults and children above 12 years of age are included in one guideline. [77]

A comparative synopsis of the recommendations provided by the guidelines that we identified is provided in Annex 2.

Sumatriptan (50mg or 100 mg) is recommended as the first line monotherapy treatment in adults by the SIGN guideline, with the suggestion of trying other triptans in case of failure. [80]

The NICE guideline recommends an oral triptan in monotherapy or combined with NSAID or paracetamol in adults and children. In young subjects (12-17 years of age) nasal triptan is preferred. [77]

The Canadian Headache Society guideline recommends sumatriptan, or another triptan, for moderate-severe migraine attacks in adults. If the triptan in monotherapy is insufficient, it is recommended the association with naproxen sodium 500 mg. [70]

According to SIGN and NICE guidelines triptans can be used for treatment of acute migraine during pregnancy and in women in child bearing age.

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.

In 2007 the WHO in collaboration with Lifting the Burden and with the European Headache Federation published guidance on the management of common headache disorders in primary care, with multi-language information leaflet for patients. [27] The guidance was a review of all published treatment guidelines in use in Europe harmonized through selection of the main recommendations. It recommended a stepped management of acute migraine attacks, treating three attacks at each step before proceeding to the next, starting from 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 were recommended at the second step, among specific drugs, to be offered to all patients failing step one. The starting recommended formulation was oral, and sumatriptan by subcutaneous injection was suggested when all other triptans are ineffective. Analgesics only were recommended for children.

In summary, there is overall consensus among the retrieved guidelines in recommending triptans (specifically, sumatriptan) as the first line treatment, or as one of the possibly effective treatments in treating acute attack of episodic migraine.
10. Review of harms and toxicity: summary of evidence on safety

10.1 Estimate of total patient exposure to date

Sumatriptan has been marketed since 1992, therefore estimating how many patients with migraine have been exposed to the drug is difficult. Data from post-marketing surveillance indicate that in the first 6 years after approval, through December 1998, sumatriptan (any administration route) had been used by more than 9 million patients to treat more than 236 million migraine attacks worldwide. [103]

One SR focused on oral sumatriptan reports that 37,250 participants have been included in RCTs alone (retrieved and selected with rigorous methodological criteria) through October 2011. [98]

Over 4000 infants of women exposed to sumatriptan during pregnancy have been included in observational studies alone. [89]

Overall, it is reasonable to estimate that several million patients with migraine have been exposed to oral sumatriptan to date.

10.2 Description of adverse effects/reactions and estimates of their frequency

Adverse effects of sumatriptan: data from Martindale 5

The most commonly reported adverse effects of serotonin (5-HT1) agonists such as sumatriptan include dizziness, flushing, weakness, drowsiness, and fatigue. Nausea and vomiting may occur. Dyspnoea and sensory disturbance including paraesthesia and hypoaesthesia have been reported. Pain or sensations of heaviness, heat or cold, pressure, or tightness have also been commonly reported, can affect any part of the body including the throat and chest, and may be intense. These symptoms may be due to vasospasm, which on rare occasions has resulted in severe cardiovascular events including cardiac arrhythmias, myocardial ischaemia, or myocardial infarction. There have been isolated reports of associated cerebrovascular events in patients receiving sumatriptan. Transient increases in blood pressure may occur soon after treatment. Rarely, significant increases in blood pressure, including hypertensive crisis with acute impairment of organ systems, have occurred even in patients without a history of hypertension. Hypotension, bradycardia or tachycardia, palpitations, peripheral vascular disorders such as Raynaud’s syndrome, and ischaemic colitis have been reported. Visual disturbances have also occurred. Medication-overuse headache has been reported with sumatriptan and may necessitate withdrawal of the drug. Sumatriptan has occasionally been associated with minor disturbances in hepatic function. There have also been rare reports of seizures with sumatriptan. Hypersensitivity reactions ranging from rashes to, more rarely, anaphylaxis have occurred. Transient pain at the injection site is common after subcutaneous sumatriptan injections; stinging, burning, erythema, bruising, and bleeding have also been reported. Irritation of the nasal mucosa and throat and epistaxis have been reported after intranasal use. Application site reactions such as pain, paraesthesia, pruritus, warmth, and discomfort have been commonly reported after use of the iontophoretic transdermal delivery preparation.

Incidence of adverse effects

5 Information about an iontophoretic transdermal delivery system, supplying 6.5 mg of sumatriptan over 4 hours, has been omitted. Since 2016 manufacturer has discontinued the product and is no longer available.
In a Dutch postmarketing survey [104] completed by 1187 patients the most common adverse reactions attributed to sumatriptan were paraesthesia (reported by 11.7% of patients), dizziness (8.1%), feeling of heaviness (8.0%), chest pain (7.9%), nausea and/or vomiting (7.3%), drowsiness/sedation (7.0%), flushing (5.1%), fatigue (4.6%), pressure in throat (3.3%), headache (3.1%), injection site reaction (3.0%), palpitations (2.8%), abdominal pain (2.6%), muscle pain (2.4%), and dyspnoea (2.2%). The safety and tolerability of the triptans have been reviewed. [105, 106]

Effects on the cardiovascular system.

About 10 months after sumatriptan injection had been made available commercially, the UK CSM noted that it had received 34 reports of pain or tightness in the chest and 2 reports of myocardial ischemia. [107] The Netherlands Centre for Monitoring of Adverse Reactions to Drugs declared about the same time that it had received 12 reports of chest or anginal pain mostly associated with oral sumatriptan. [108]. A later postmarketing survey based on data from Dutch general practitioners identified chest pain in 1.3% of 1727 patients [109], a figure considered to be lower than that seen in earlier studies, but in a subsequent questionnaire completed by 1187 of these patients 7.9% reported chest pain [104]. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) [110] stated in December 1994 that it had received 114 reports of chest pain since sumatriptan had been marketed in mid 1992. Most patients had recovered quickly but 2 had died. The first developed a fatal myocardial infarction after coronary artery dissection but the causal relation with sumatriptan was unclear. The second patient, who had hypertrophic obstructive cardiomyopathy, developed ventricular fibrillation a few hours after the onset of chest pain and this led to fatal cardiac arrest.

One group of workers [111] who studied the effect of sumatriptan 16 mg given subcutaneously suggested that the symptoms of chest pain might be due to an effect of sumatriptan on oesophageal function, but others have argued against this suggestion. [112] ADRAC [110] considered that the reaction in the 28 reports of throat tightness they had received by December 1994 was a different reaction to that of chest pain, and probably resulted from changes in oesophageal motility.

Several reports have provided details of individual cases of the adverse cardiovascular effects of sumatriptan including arrhythmias (ventricular tachycardia [113], ventricular fibrillation, [114], [114] or atrial fibrillation [115, 116]), acute myocardial infarction, [117, 118, 119, 120, 121, 122, 123,124]; and unstable angina, [125] Most of these reports concerned subcutaneous sumatriptan, but myocardial infarction [119, 122, 123, 124] and cardiac arrhythmias [114, 116] (sometimes fatal) may occur after oral use.

These adverse effects have also been reported in patients with no predisposing factors. [109, 114, 122, 123, 124] A review [126] of published reports on chest pain as well as relevant data held by the UK manufacturer considered that the risk of myocardial ischaemia after vasoconstriction induced by sumatriptan was small. However, the contra-indications and cautions given under Precautions, Sumatriptan Succinate, should be observed. A study [127] published in 2004 of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of cardiovascular death in those patients treated with serotonin agonists.

Effects on the cerebrovascular system

Adverse cerebrovascular effects have been reported after the use of subcutaneous sumatriptan including hemiparesis [128], stroke [129, 130], and intracerebral haemorrhage [131]. Cerebral vasospasm has also been reported [132] with the use of oral sumatriptan. However, a study [127] of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of stroke in those patients treated with serotonin agonists.

Effects on the gastrointestinal tract
Ischaemic colitis and mesenteric ischaemia have been reported in a few patients receiving sumatriptan, [133, 134, 135] including repeated episodes in 2 patients [134], each within hours of a dose; some of these episodes were associated with doses above the recommended daily maximum. [134] Oesophageal constriction or throat tightness has been reported in some patients using sumatriptan and may be due to a direct effect on the oesophagus.

**Hypersensitivity**

Reactions to sumatriptan such as rashes and, more rarely, anaphylaxis have been noted by the manufacturer. Published reports include angioedema occurring in a patient 5 minutes after subcutaneous sumatriptan [136], and urticaria occurring 20 to 24 hours after oral or subcutaneous sumatriptan in another patient. [137]

**Medication-overuse headache**

Sumatriptan and other triptans may have a similar risk of misuse to that associated with analgesics and ergotamine compounds in patients with medication-overuse headache (Antimigraine Drugs). There have been reports [138,139, 140] of patients using one or more daily doses of sumatriptan to control migraine. Many of the patients had a history of abuse of other antimigraine drugs and were using sumatriptan to prevent recurrence of headache. Whether misuse of sumatriptan was due to addiction or rebound headache, as seen with ergotamine, is unknown. A postmarketing study in 952 patients receiving sumatriptan found that 36 of the patients (4%) used sumatriptan daily or more than 10 times each week. This overuse was related to poor efficacy and not to rebound headache [117]. One study [141] and an anecdotal report [142] suggest that, rather than producing euphoria or other effects associated with drugs of abuse such as morphine, sumatriptan is more likely to be associated with dysphoria and apathetic sedation.

The development of medication-overuse headache has also been reported with other serotonin (5-HT1) agonists including naratriptan and zolmitriptan [143]. Indeed, US licensed product information for the triptans states that the safety of treating an average of more than 3 or 4 migraine attacks in a 30-day period has not been established.

**Precautions**

Sumatriptan and other serotonin (5-HT1) agonists should only be used where there is a clear diagnosis of migraine or cluster headache and care should be taken to exclude other potentially serious neurological conditions. They should not be used for prophylaxis and should not be given to patients with basilar, hemiplegic, or ophthalmoplegic migraine.

Serotonin (5-HT1) agonists are contra-indicated in patients with uncontrolled hypertension, ischaemic heart disease (coronary artery disease), a history of myocardial infarction, coronary vasospasm (Prinzmetal’s angina), peripheral vascular disease, or a previous cerebrovascular accident or transient ischaemic attack. Unrecognised cardiovascular disease should be excluded before the use of serotonin (5-HT1) agonists in postmenopausal women, men over 40 years of age, and those with risk factors for ischaemic heart disease. If chest pain and tightness occur during use, appropriate investigations should be performed. Sumatriptan should not be used intravenously because of the increased risk of producing coronary vasospasm.

Drowsiness may occur after treatment with serotonin (5-HT1) agonists and patients thus affected should not drive or operate machinery.

Sumatriptan should be used with caution in patients with hepatic or renal impairment, and should generally be avoided if hepatic impairment is severe.

There have been rare reports of seizures after use of sumatriptan and it should therefore be used with caution in patients with a history of epilepsy or other conditions predisposing to seizures. Patients with hypersensitivity to sulfonamides may have a similar reaction to sumatriptan.
Asthma

The manufacturers reviewed data from more than 75 clinical studies of sumatriptan involving 12,701 patients and reported [144] that the incidence of adverse events related to asthma did not differ between patients with or without the condition. Earlier there had been concern over the safety of sumatriptan in patients with asthma after 2 reports of bronchospasm and a report of a patient with asthma who died during a study of sumatriptan although the patient had not received sumatriptan in the month before her death.

Cerebrovascular disorders

A patient with a superior sagittal sinus thrombosis who presented with headache and was misdiagnosed as having migraine variant developed a cortical stroke within minutes of a second 6-mg subcutaneous injection of sumatriptan [129]. The importance of establishing a diagnosis of typical migraine or cluster headache before using sumatriptan was emphasised and caution given against its use in any patient who may have unstable cerebrovascular disease or raised intracranial pressure. Additionally, there was no clinical evidence that a second injection would relieve a headache when the initial injection had been ineffective.

Porphyria

The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sumatriptan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. [145]

10.3 - Summary of available data (appraisal of quality, summary of results)

Data on safety of oral sumatriptan were retrieved from the SR by Derry et al. [98] and from the two clinical trials not included in the SR. [101, 102] Moreover, three SRs [89, 146, 147] and one observational study not included in the SRs, [88] focused on the safety of triptans were also considered.

Children and adolescents

No safety data are available on oral sumatriptan in children. Overall, triptans in children did not show a higher frequency of AEs vs placebo. Considering intranasal sumatriptan, the RD is statistically higher than placebo. The overall frequency of any AE in adolescents taking triptans is higher than placebo (Table 6) although most AEs were mild.
Table 6 - Any AEs (children and adolescents) triptans (any administration route) vs placebo. *statistically significant differences in bold* [96]

<table>
<thead>
<tr>
<th>Triptan</th>
<th>N of studies</th>
<th>N of participants</th>
<th>Any adverse events RD (95%CI)</th>
<th>N of studies</th>
<th>N of participants</th>
<th>Any adverse events RD (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>10</td>
<td>2969</td>
<td>0.18 (0.09, 0.27)</td>
<td>2</td>
<td>145</td>
<td>0.13 (0.01, 0.26)</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>1</td>
<td>720</td>
<td>0.05 (0.00, 0.09)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>1</td>
<td>242</td>
<td>0.14 (0.02, 0.26)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>1</td>
<td>300</td>
<td>0.16 (0.05, 0.27)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>4</td>
<td>1706</td>
<td>0.04 (-0.02, 0.10)</td>
<td>1</td>
<td>275</td>
<td>0.0 (-0.09,0.09)</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>4</td>
<td>1939</td>
<td>0.14 (0.07, 0.20)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>7876</td>
<td>0.13 (0.08-0.18)</td>
<td>3</td>
<td>420</td>
<td>0.06 (-0.04, 0.17)</td>
</tr>
</tbody>
</table>

Adults

Adverse events are more common among patients treated with sumatriptan than placebo.

**Serious treatment-related adverse events** (SAEs) were rare. In the Cochrane SR by Derry et al, among 20,049 patients treated with oral sumatriptan (25 mg to 300 mg), only two treatment-related serious adverse events were reported: one after treating with sumatriptan 85 mg (heart palpitations), one after treating with sumatriptan 300 mg (chest tightness and pressure). [98]

Among 212 patients treated with ibuprofen 400 mg, one SAE was reported (perforation of duodenal ulcer), while no SAEs were reported among 689 patients treated with ASA (900 mg to 1,000 mg). **Withdrawals due to AEs** were uncommon; in placebo-controlled studies, excluding those using high doses of sumatriptan (>100mg), the rate of adverse event withdrawal among patients treated with sumatriptan was equivalent to that of placebo (0.71% (45/6349) and 0.65% (19/2926), respectively). [98]

One industry-funded **SR and NMA** assessed the tolerability of treatments administered by oral route in adults (> 18 years of age) with acute migraine. The SR included 141 RCTs evaluating triptans, non-steroidal anti-inflammatory drug (NSAIDs) or barbiturates in any combination, without any other limitation regarding sample size or treatment concealing. The quality of the included studies was not formally assessed. [147]

In order to account for modification of the effect related to dosage, doses were categorized as “Common” (50mg), “Low” (25mg) and “High” (100mg), and the “common” dose was used as the reference dose.

Primary outcomes were **any adverse events** (AEs), **treatment-related AEs** and **serious AEs**. Secondary outcomes were several specific AEs (fatigue, dizziness, chest discomfort, somnolence, nausea and vomiting). Heterogeneity was high among the latter, since the reporting was highly inconsistent across trials and on average each of the secondary outcomes was reported in about half of the included studies.

Data from direct comparisons were available for sumatriptan vs. placebo (39 studies), naproxen (6 studies), naproxen + sumatriptan (4 studies), selective cox-inhibitors (1 study), ergotamine (1 study), paracetamol (1 study), eletriptan (3 studies), rizatriptan (8 studies), naratriptan (2 studies), zolmitriptan (4 studies) and almotriptan (2 studies).
Sumatriptan showed a significantly higher incidence of any AEs than placebo (OR 1.80, 95%CI 1.57, 2.05), as well as sumatriptan + naproxen, zolmitriptan and rizatriptan. Among the non-triptan treatments, ergot derivatives was the only one showing a higher frequency of AEs vs placebo (OR 1.61, 95%CI 1.1, 2.28).

Sumatriptan, sumatriptan + naproxen zolmitriptan, rizatriptan, eletriptan and paracetamol showed a higher frequency of treatment-related AEs vs placebo (sumatriptan OR 2.23, 95%CI 1.86, 2.70). Serious adverse events show estimates with wide CIs (SAEs are uncommon, many trials reported zero events in at least one arm, and the definition of SAE varied among trials).

Secondary outcomes associated with triptans showed a higher frequency with a dose-effect vs placebo, but since they were reported inconsistently across studies (half of the trials included in the SR) heterogeneity was not assessed.

Due to the limitations of the evidence provided by this SR, these results need to be cautiously interpreted (GRADE quality of certainty was not assessed).

Overall, AEs within 24 hours from administration were more common among patients treated with sumatriptan (particularly at the 100 mg dose) than placebo. (Table 7)

Table 7 - Adverse events of sumatriptan vs placebo (any adverse event in adults) (statistically significant differences in bold) [98]

<table>
<thead>
<tr>
<th>Sumatriptan</th>
<th>N of studies</th>
<th>N of participants</th>
<th>RR (95%CI)</th>
<th>NNH (95%CI)</th>
<th>GRADE certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>5</td>
<td>1242</td>
<td>2.26 (1.62, 3.16) *</td>
<td>11 (8.0, 18)*</td>
<td>☀️☀️☀️ High</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3728</td>
<td>1.30 (1.17, 1.44)**</td>
<td>13 (9.7, 22)**</td>
<td>☀️☀️☀️ High</td>
</tr>
<tr>
<td>100 mg</td>
<td>4</td>
<td>941</td>
<td>2.75 (1.87, 4.05)*</td>
<td>8.3 (6.1, 13)*</td>
<td>☀️☀️☀️ High</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>3257</td>
<td>1.69 (1.50, 1.91)**</td>
<td>5.2 (4.4, 6.2)**</td>
<td>☀️☀️☀️ High</td>
</tr>
</tbody>
</table>

* mild baseline intensity; ** moderate/severe baseline intensity

Pooled estimates of comparisons of sumatriptan vs other triptans did not show significant differences. Acetylsalicylic acid 900 mg and paracetamol in combination with metoclopramide 10 mg showed a significantly lower frequency of AEs compared to sumatriptan 100 mg. (Table 8)

Table 8 - Adverse events of sumatriptan vs active comparators (any adverse event in adults) (statistically significant differences in bold, difference not in favor of sumatriptan in italic) [98]

<table>
<thead>
<tr>
<th>Active comparator</th>
<th>Sumatriptan (dose)</th>
<th>N studies</th>
<th>N of participants</th>
<th>RR (95%CI)</th>
<th>NNH</th>
<th>GRADE certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan 12.5mg</td>
<td>100 mg</td>
<td>2</td>
<td>754</td>
<td>n.s.</td>
<td>n.s.</td>
<td>☀️☀️☀️ High</td>
</tr>
<tr>
<td>Eletriptan 40 mg</td>
<td>50 mg</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>☀️☀️☀️ High</td>
</tr>
<tr>
<td>Eletriptan 40 mg</td>
<td>100 mg</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>☀️☀️☀️ High</td>
</tr>
<tr>
<td>Eletriptan 80 mg</td>
<td>50 mg</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>☀️☀️☀️ High</td>
</tr>
<tr>
<td>Eletriptan 80 mg</td>
<td>100 mg</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>☀️☀️☀️ High</td>
</tr>
<tr>
<td>Rizatriptan 5 mg</td>
<td>50 mg</td>
<td>2</td>
<td>1160</td>
<td>1.2 (1.0, 1.3) n.s.</td>
<td>☀️☀️☀️ High</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan 10 mg</td>
<td>50 mg</td>
<td>2</td>
<td>1177</td>
<td>1.2 (1.0, 1.3) n.s.</td>
<td>☀️☀️☀️ High</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan 10 mg</td>
<td>100 mg</td>
<td>2</td>
<td>856</td>
<td>n.s.</td>
<td>☀️☀️☀️ High</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan 2.5 mg</td>
<td>50 mg</td>
<td>2</td>
<td>1771</td>
<td>1.0 (0.88, 1.2) n.s.</td>
<td>☀️☀️☀️ High</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan 2.5 mg</td>
<td>100 mg</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>☀️☀️☀️ High</td>
</tr>
<tr>
<td>Zolmitriptan 5 mg</td>
<td>50 mg</td>
<td>2</td>
<td>1790</td>
<td>0.91 (0.80, 1.0) n.s.</td>
<td>☀️☀️☀️ High</td>
<td></td>
</tr>
<tr>
<td>ASA 1000 mg</td>
<td>50 mg</td>
<td>2</td>
<td>730</td>
<td>1.2 (0.85-1.6) n.s.</td>
<td>☀️☀️☀️ High</td>
<td></td>
</tr>
<tr>
<td>ASA 900 mg + metoclopramide 10 mg</td>
<td>100 mg</td>
<td>2</td>
<td>575</td>
<td>1.53 (1.20, 1.94) 7.7 (4.9, 17)</td>
<td>☀️☀️☀️ High</td>
<td></td>
</tr>
<tr>
<td>Paracetamol 1000 mg + metoclopramide 10 mg</td>
<td>100 mg</td>
<td>2</td>
<td>1328</td>
<td>1.64 (1.42, 1.89) 5.5 **</td>
<td>☀️☀️☀️ High</td>
<td></td>
</tr>
</tbody>
</table>

* pooled estimates not available; ** calculated
Pregnancy

Sumatriptan was the first approved triptan and has been the most studied triptan in pregnant women. Studies investigating its teratogenic potential [148, 149] gave conflicting results. The Food and Drug Administration (FDA) issued a labelling of Pregnancy Category C (animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Current section 8.1 of the FDA Summary of Product Characteristics States that sumatriptan “Based on animal data, may cause fetal harm.” [https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020132s029lbl.pdf]

Table 9 – Pregnancy outcomes among women with migraine exposed to triptans compared to those not exposed to triptans and to healthy controls from observational studies *(statistically significant differences in favor of healthy controls are in bold,)* [89]

<table>
<thead>
<tr>
<th></th>
<th>Migraine</th>
<th></th>
<th>Healthy controls</th>
<th>Migraine</th>
<th></th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No triptan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCM = 0.84 (0.61, 1.16)</td>
<td>(Exposed=4069; unexposed=1732)</td>
<td>PRE = 0.90 (0.35, 2.30)</td>
<td>(Exposed=1581; unexposed=1231)</td>
<td>SA = 1.27 (0.58, 2.79)</td>
<td>(Exposed=172; unexposed=188)</td>
</tr>
<tr>
<td>Healthy controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCM = 1.18 (0.97, 1.44)</td>
<td>(Exposed=4208; unexposed=1,465,082)</td>
<td>PRE = 1.16 (0.67, 1.99)</td>
<td>(Exposed=1720; unexposed=251,085)</td>
<td>SA = 3.54 (2.24, 5.59)</td>
<td>(Exposed=178; unexposed=50,865)</td>
</tr>
<tr>
<td></td>
<td>MCM = 1.41 (1.11, 1.80)</td>
<td>(Exposed=1735; unexposed=1,408,557)</td>
<td>PRE = 1.44 (0.66, 3.16)</td>
<td>(Exposed=1274; unexposed=194,560)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MCM= major congenital malformations, PRE=prematurity, SA= spontaneous abortion

A metanalysis of 6 observational studies assessed the risk of pregnancy outcomes (major congenital malformations (MCM), prematurity and spontaneous abortion) of women with migraine prenatally exposed to triptans, comparing them with those of women with migraine not taking triptans and with healthy women.

Overall, 4,208 infants of women who used triptans and 1,466,994 children of women who did not use triptans during pregnancy were included. Sumatriptan was included among the exposure medications in all of them.

Pooled analysis showed that the rate of MCM and prematurity is not increased among women with migraine taking triptans during pregnancy when compared with women with migraine not taking triptans. Women exposed to triptans during pregnancy showed a higher rate of spontaneous abortion, and women with migraine not taking triptans compared to healthy controls showed a higher risk of MCM. (Table 9) It has to be noted that this latter difference has been observed on a relatively small sample (178 triptan-exposed women). [89]

These estimates should be interpreted with caution, considering that they were not adjusted for potential confounders, such as length and dose of triptan and associated comorbidities (such as depression) often present in patients with migraine that may prompt the use of co-treatments potentially associated with a higher risk of preterm birth and/or malformations. This is particularly true when comparing women with migraine (especially women with migraine not using triptans) with healthy controls.

The overall certainty in the estimates of this SR, according to GRADE is “Very low”.

A SR by the UK National Clinical Guideline Centre (NCGC), [77] commissioned by the NICE to inform an NHS guideline on headache found conflicting evidence of very low quality regarding the
pregnancy outcomes from a pooled analysis of three observational studies published between 1998 and 2010, one of which was included in the SR by Marchenko. [89] The population compared in this SR were women with migraine who took triptans during pregnancy and women with migraine who did not; unlike the SR by Marchenko, healthy controls were not considered in the comparisons. Regarding major malformations and spontaneous abortion, the estimates of the SR by the NCGC are consistent with the SR by Marchenko. [89]

Prematurity (gestational age <37 weeks) seemed to be significantly more common in a small sample of 34 women with migraine exposed to triptans during pregnancy. The guideline panel agreed that the evidence reviewed, although inconclusive, did not indicate an increased risk of the use of triptans during pregnancy.

Since high doses of aspirin recommended for migraine are potentially harmful in pregnancy, the guideline panel recommended paracetamol as a first choice, and to consider a triptan or an NSAID. [77]

The Sumatriptan, Naratriptan and Treximet® Pregnancy Registry is a prospective, observational, uncontrolled, international study sponsored by GlaxoSmithKline. [88] The registry collected pregnancy data of women exposed at any time during their pregnancy to sumatriptan, naratriptan or the association of sumatriptan and naproxen sodium (Treximet®) from health care providers enrolled on a voluntary basis in 18 countries. Data were gathered during 16 years of observation, including a total of 904 exposed pregnant women, with 689 pregnancy outcomes. Six-hundred-and-ten women (67%) with 626 pregnancy outcomes (91%) had been exposed to sumatriptan. The frequency of major birth defects following any trimester of exposure to sumatriptan was 4.2% (24/576; 95%CI 2.7, 6.2). The same frequency was observed considering 528 pregnancy outcomes after exposure during the first trimester (4.2% 95%CI 2.6%, 6.5%). The authors compared these data with those from other observational studies, showing birth defect frequencies of 4-5% among migraineurs, concluding that there is no signal of teratogenicity associated with major birth defects for sumatriptan.

However, data from this registry should be interpreted with caution, due to its limitations (25% loss to follow up, absence of a control group, indirect comparisons with other observational studies adopting different definitions of birth defects and low recruitment in some of the participating countries, that could be due to lack of use of sumatriptan during pregnancy or to lack of reporting by health care providers). [88]

The certainty in the estimates of this case series, according to GRADE is “Very low”.

**Cardiovascular events and stroke**

Cardiovascular safety is an important concern when using triptans in clinical practice since, through heterogeneous mechanisms, they can induce vasoconstriction that may potentially increase the risk of cardiovascular events.

A metaanalysis of 4 observational studies assessing the risk of severe cardiovascular events among persons with migraine taking triptans or ergotamine. The authors distinguished the risk of cardiovascular events and stroke associated with the intensity (number of prescribed/dispensed doses) and with the recency of migraine-specific use.

Pooled analysis showed no significant differences in the overall risk of cardiovascular events of patients with migraine treated with triptans (intensity of treatment) as compared with controls (OR 0.86; 95% CI 0.52, 1.43, I squared 24.5%).

Due to the high heterogeneity of results of the included studies, pooled analysis of the risk of CV events and stroke in relation to recency was not performed. [146]

The level of certainty in the estimates of this SR, according to GRADE is “low”.

42
10.4 - Summary of comparative safety against comparators

- Most safety data on triptans come from exposure to sumatriptan, the most widely used triptan in clinical practice; since its first authorization in 1992 many millions of patients have been exposed to it.
- Overall, the frequency of adverse events is higher among patients taking sumatriptan (particularly the 100 mg dose) compared to placebo.
- Most adverse events associated with the use of sumatriptan are mild, and serious adverse events are uncommon.
- There is no substantial difference across different triptans in terms of safety.
- Acetylsalicylic acid and paracetamol showed a lower frequency of adverse events than sumatriptan.
- Safety of sumatriptan among pregnant women with migraine and cardiovascular safety are the main concerns in clinical practice.
- Evidence on the pregnancy safety of sumatriptan is limited and of scarce quality, due to residual confounding and other limitations of the available observational studies.
- No clear signal of risk for major birth defects or prematurity has appeared among women with migraine taking sumatriptan during pregnancy. The possible association between use of triptans during pregnancy and spontaneous abortion comes from a limited sample and needs confirmation.
- As per cardiovascular safety of sumatriptan, pooled data from observational studies do not show an increased risk of severe cardiovascular events. Available data on a possible stroke risk associated with the use of sumatriptan do not allow pooled analyses.

10.5 Identification of variation in safety due to health systems and patient factors

Sumatriptan during pregnancy and breast feeding

Although up to 80% of women show a reduction in frequency and intensity of attacks during pregnancy [33, 34, 35], or even remission, about 8% of pregnant women with migraine experience a worsening of frequency and pain intensity, possibly associated with the hormonal alterations of pregnancy. [38, 39]

Sumatriptan received an FDA warning in pregnancy (“Based on animal data, may cause fetal harm”, see section 10.4).

Sumatriptan is compatible with breast feeding, [14] although it is recommended to minimise infant exposure by avoiding breast feeding for 12 hours.

The risk of congenital malformations and other pregnancy outcomes is discussed in section 10.4.

Currently, conclusive evidence of safety during pregnancy is lacking but available evidence (observational studies including women mostly treated with sumatriptan, among available triptans) does not indicate a higher risk associated with the use of sumatriptan. [77, 89]

The risk of developing major congenital malformations, prematurity and spontaneous abortion was assessed in a meta-analysis of observational studies including 4,208 infants of women who were exposed to sumatriptan or other triptan medications during pregnancy. [89]

Sumatriptan in patients with cardiovascular disease

Triptans can induce vasoconstriction that may potentially increase the risk of cardiovascular events (see section 10.2 and 10.4).

Sumatriptan is not indicated in patients with history of cardiovascular- or cerebrovascular disease.
Current evidence does not indicate a higher risk of severe cardiovascular events among patients with episodic migraine treated with sumatriptan.

**Sumatriptan in elderly patients**

Available evidence on sumatriptan comes from studies that recruited mainly women in an age range between 34 and 41 years. Evidence on patients older than 65 is limited, therefore it is not possible to determine whether they respond differently to sumatriptan from younger patients. Moreover, cardiovascular conditions (the main contraindication of sumatriptan) are frequent in this population. According to regulatory agencies such as FDA, Health Canada and the Australian Department of Health sumatriptan is not indicated in patients older than 65. (Table 16)
11. Summary of available data on comparative costs and cost-effectiveness

We used the *International Drug Price Indicator Guide* to summarize the comparative cost effectiveness, taking acetylsalicylic acid and paracetamol (anti-migraine medicines for the treatment of acute attack which are already include in the EML) as a reference.

**Table 10 - International Drug Price Indicator Guide: price of analgesics for acute treatment of migraine included in the EML**

<table>
<thead>
<tr>
<th>Drug</th>
<th>DDD</th>
<th>High/Low Ratio</th>
<th>Price (US $)</th>
<th>Price DDD (US $)</th>
<th>WHO EML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic Acid 500 mg TAB-CAP (PO)</td>
<td>3g</td>
<td>2.13</td>
<td>0.0047/TAB-CAP (median)</td>
<td>0.0282</td>
<td>E</td>
</tr>
<tr>
<td>Supplier Number of Prices=8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buyer Number of Prices=2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracetamol 500 mg TAB-CAP (PO)</td>
<td>3 g</td>
<td>26.19</td>
<td>0.0490/TAB-CAP (median)</td>
<td>0.0391</td>
<td>E</td>
</tr>
<tr>
<td>Supplier Number of Prices=13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buyer Number of Prices=5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In high-income countries the price of triptans varies considerably. Branded drugs are generally more expensive, but currently all oral route triptans are generic.

**Range of costs of the proposed medicine**

The price of sumatriptan available from on-line databases vary: some databases (such as the Italian Farmadati and the US Center for Medicare and Medicaid Services, CMS) the retail price and some others (such as the UK Prescription Services) the reimbursement price. The Common European Drugs Database, CEDD) is not currently active. In Europe sumatriptan had been authorized through national instead of centralized procedure.

This makes it difficult to make cost comparisons of sumatriptan in different countries. When available we reported the retail price, since the wholesale price and reimbursement price may be influenced by local agreements, rules and negotiations. When available we reported the retail price, since the wholesale price and reimbursement price may be influenced by local agreements, rules and negotiations.

In the tables that follow, prices - for branded and non-proprietary products (NPP), when available - are expressed in US $, EUR and GBP, with a currency exchange rate as of December 7, 2018 (http://www.xe.com/it/currencyconverter/).
**Table 11** - UK reimbursement price for triptans, paracetamol and aspirin
(http://www.ppa.org.uk/ppa/edt_intro.htm [accessed on December 03, 2018])

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity</th>
<th>Basic Price per unit (pence)</th>
<th>Unit Price (£)</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan 12.5mg tablets</td>
<td>6</td>
<td>1635</td>
<td>27.25</td>
<td></td>
</tr>
<tr>
<td>Eletriptan 20mg tablets</td>
<td>6</td>
<td>2250</td>
<td>37.50</td>
<td>X</td>
</tr>
<tr>
<td>Eletriptan 40mg tablets</td>
<td>6</td>
<td>2250</td>
<td>37.50</td>
<td>X</td>
</tr>
<tr>
<td>Frovatriptan 2.5mg tablets</td>
<td>6</td>
<td>539</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan 10mg tablets</td>
<td>3</td>
<td>595</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan 5mg tablets</td>
<td>6</td>
<td>2674</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan 5mg tablets</td>
<td>6</td>
<td>360</td>
<td>6</td>
<td>X</td>
</tr>
<tr>
<td>Zolmitriptan 2.5mg odispersible tablets sugar free</td>
<td>6</td>
<td>992</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td><strong>Sumatriptan 100mg tablets</strong></td>
<td>6</td>
<td>410</td>
<td>6.83</td>
<td></td>
</tr>
<tr>
<td><strong>Sumatriptan 50mg tablets</strong></td>
<td>6</td>
<td>405</td>
<td>6.75</td>
<td></td>
</tr>
<tr>
<td>Paracetamol 500mg tablets</td>
<td>32</td>
<td>49</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Aspirin 300mg tablets</td>
<td>32</td>
<td>342</td>
<td>1.07</td>
<td></td>
</tr>
</tbody>
</table>

**Table 12** - CMS US - Weekly NADAC Reference File (as of 12/03/2018). Retail community pharmacy price for generic cheapest almotriptan, frovatriptan eletriptan, rizatriptan, zolmitriptan and sumatriptan

[https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html](https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html) [accessed on December 03, 2018]

<table>
<thead>
<tr>
<th>NDC Description</th>
<th>NADAC * Per Unit (US $)</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALMOTRIPTAN MALATE 12.5 MG TAB</td>
<td>20.09659</td>
<td>11/21/2018</td>
</tr>
<tr>
<td>FROVATRIPTAN SUCC 2.5 MG TAB</td>
<td>20.18911</td>
<td>11/21/2018</td>
</tr>
<tr>
<td>ELETRIPTAN HBR 20 MG TABLET</td>
<td>7.79009</td>
<td>11/21/2018</td>
</tr>
<tr>
<td>ELETRIPTAN HBR 40 MG TABLET</td>
<td>6.54604</td>
<td>11/21/2018</td>
</tr>
<tr>
<td>RIZATRIPTAN 10 MG TABLET</td>
<td>0.78291</td>
<td>11/21/2018</td>
</tr>
</tbody>
</table>
Table 13 - Italy pharmacy retail price of triptans, paracetamol and aspirin
http://www.farmadati.it/ (accessed on December 3, 2018).

<table>
<thead>
<tr>
<th>Drug</th>
<th>NPP Unit Price (€)</th>
<th>Brand Unit Price (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan 100mg tablets</td>
<td>3,25</td>
<td>3,75</td>
</tr>
<tr>
<td>Sumatriptan 50mg tablets</td>
<td>1,5</td>
<td>2</td>
</tr>
<tr>
<td>Eletriptan 20mg tablets</td>
<td>-</td>
<td>4,92</td>
</tr>
<tr>
<td>Eletriptan 40mg tablets</td>
<td>3,095</td>
<td>3,62</td>
</tr>
<tr>
<td>Almotriptan 12.5mg tablets</td>
<td>2,89</td>
<td>3,31</td>
</tr>
<tr>
<td>Paracetamol 500mg tablets</td>
<td>0,175- 0,3</td>
<td>0,245</td>
</tr>
<tr>
<td>Aspirin 500mg tablets</td>
<td>0,175</td>
<td>0,324</td>
</tr>
</tbody>
</table>

NPP=Non-Proprietary Name

Table 14 – European retail price of triptans, paracetamol and aspirin

<table>
<thead>
<tr>
<th>Drug</th>
<th>France^</th>
<th>Germany§</th>
<th>Norway°</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPP Unit Price range (€)</td>
<td>Brand Unit Price range (€)</td>
<td>NPP Unit Price (€)</td>
</tr>
<tr>
<td>Sumatriptan 100mg tablets</td>
<td>-</td>
<td>-</td>
<td>3,27</td>
</tr>
<tr>
<td>Sumatriptan 50mg tablets</td>
<td>1,49</td>
<td>1,96</td>
<td>3,37</td>
</tr>
<tr>
<td>Eletriptan 20mg tablets</td>
<td>1,64</td>
<td>2,84</td>
<td>5,36</td>
</tr>
<tr>
<td>Eletriptan 40mg tablets</td>
<td>1,64</td>
<td>2,84</td>
<td>5,70</td>
</tr>
<tr>
<td>Almotriptan 12.5mg tablets</td>
<td>1,40</td>
<td>1,40</td>
<td>7,32</td>
</tr>
<tr>
<td>Paracetamol 500mg tablets</td>
<td>1,49</td>
<td>1,96</td>
<td>0,067</td>
</tr>
<tr>
<td>Aspirin 500mg tablets</td>
<td>1,64</td>
<td>2,84</td>
<td>0,11</td>
</tr>
</tbody>
</table>

NPP=Non-Proprietary Name; ^ France http://base-donnees-publique.medicaments.gouv.fr/index.php#result (03.12.2018);
Comparative cost-effectiveness

A cost-effectiveness analysis of interventions for migraine in low- and middle-income countries, using the methods and tools developed by WHO-CHOICE showed that the annual cost of different therapeutic strategies may vary greatly, and that variation is mainly driven by the cost of drugs. Common analgesic drugs (specifically ASA) was the most cost-effective strategy of management of acute migraine attack, generating a whole year of healthy life for 24 to 73 US $. Adding to analgesics additional non-pharmacological strategies, such as training of primary care physicians and consumers’ education may increase cost-effectiveness in the modelling. In view of the high health care burden of migraine, the health gain in society would be considerable.

Sensitivity analysis showed that sumatriptan 50 mg was the most cost-sensitive drug, due to the great variability of its price across countries. (Table 14) Therefore, a hypothetical reduction of its average price in each country by 50% would have a considerable effect on the cost-effectiveness of sumatriptan, although simple analgesics would still be more cost-effective. [83]

Based on a cost-effectiveness analysis, the NICE guideline on headache disorders updated in 2012 [77] recommended a triptan in combination with NSAID as the most cost-effective treatment for the management of acute migraine.

Triptan in combination with paracetamol was the second most cost-effective intervention, although being more costly than other strategies.

Table 14 - Drug supplier prices used for generically produced drugs from the International Drug Price Indicator Guide (2015) and the IMS database (updated for India and South Africa at December 2018).
(Adapted from Linde et al. [83])

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Source</th>
<th>China</th>
<th>Russia</th>
<th>Zambia</th>
<th>India</th>
<th>South Africa **</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>500 mg</td>
<td>International Drug Price indicator guide</td>
<td>$ 0.004</td>
<td>$ 0.004</td>
<td>$ 0.004</td>
<td>$ 0.004</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>50 mg</td>
<td>IMS database</td>
<td>$ 0.81</td>
<td>$ 1.07</td>
<td>$ 0.66</td>
<td>$ 0.68 *</td>
<td>$ 3.35</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>12.5 mg</td>
<td></td>
<td>$ 5.19</td>
<td>$ 5.19</td>
<td>$ 5.19</td>
<td>$ 1.18 *</td>
<td></td>
</tr>
</tbody>
</table>


** South African Medicine Price Registry (Database of Medicine Price) [http://www.mpr.gov.za/PublishedDocuments.aspx?DocCatId=21](http://www.mpr.gov.za/PublishedDocuments.aspx?DocCatId=21) (accessed December 3, 2018) Sumatriptan 50 mg 46.04 ZAR/unit = US$ 3.35; Eletriptan 40 mg 71.17 ZAR/unit = US $ 5.18

In summary, cost-effectiveness modelling suggested that common analgesics (acetylsalicylic acid in particular) are the most cost-effective strategy for managing acute episodic migraine.

A triptan in combination with acetylsalicylic acid seems a cost-effective intervention, although with a higher absolute cost, that however would be largely offset by savings in terms of gained health.

All triptans are available as generic drugs, but sumatriptan has the lowest price in most countries, including low- and middle-income countries.

Oral eletriptan shows superiority to oral sumatriptan relative to all relevant outcomes. However, eletriptan is, on average, substantially more expensive than sumatriptan even considering the non-proprietary name preparations.
12. Summary of regulatory status of the medicine

Sumatriptan was approved by the Food and Drug Administration in the USA in 1992 for subcutaneous use as injectable formulation and after 1995 FDA approved the formulation in tablets for oral route and nasal spray. Oral sumatriptan is indicated for acute treatment of migraine attacks with or without aura (Table 16). In Australia branded injectable sumatriptan (Imigran™) is also indicated for the acute treatment of cluster headaches. [150]
In Europe sumatriptan was not approved following a centralized authorization, therefore a European Summary of Product Characteristics by the European Medicines Agency (EMA) is not available.

Sumatriptan tablets 50 mg is considered the standard dose for the oral route. The DDDs for the selective serotonin 5HT1 agonists are based on the recommended initial dose in acute attacks of migraine. [151]

In 2013 FDA approved an iontophoretic transdermal system for sumatriptan and in 2016 the Manufacturer voluntarily suspended sale, marketing, and distribution due to reported cases of serious application site reactions.

In 2016 FDA approved a new dosage for subcutaneous injection (3 mg/ml) and a new formulation for nasal route (11 mg powder) that are not available as generic products.

**Formulation(s) and strength(s) available** [152]

<table>
<thead>
<tr>
<th>Sumatriptan</th>
<th>25 mg, 50 mg, 100 mg Tablets (oral route)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mg/0.5 ml, 4 mg/0.5 ml, 6 mg/0.5 ml solution/injection (Subcutaneous route)</td>
</tr>
<tr>
<td></td>
<td>5 mg, 20 mg nasal spray (nasal route). 11 mg nasal powder</td>
</tr>
</tbody>
</table>
### Table 15 – ATC classification and DDDs, indications and generic drug availability of triptans

<table>
<thead>
<tr>
<th>ATC *</th>
<th>Name INN</th>
<th>DDD *</th>
<th>U *</th>
<th>Admin Route *</th>
<th>Recommended dose** (max.dose in 24 h)</th>
<th>Adults (age 18-65)</th>
<th>Adolescents (age 12-17)</th>
<th>Children (age &lt; 11)</th>
<th>Generic drug availability ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>N02CC01</td>
<td>sumatriptan</td>
<td>20 mg</td>
<td>N</td>
<td>nasal spray: 20 mg (40 mg)</td>
<td>yes</td>
<td>under specialist/physician consultation. Recommended dose: 10 mg (20 mg)</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg</td>
<td>O</td>
<td>50 mg (300 mg)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mg</td>
<td>P</td>
<td>6 mg (12 mg)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N02CC02</td>
<td>naratriptan²</td>
<td>2.5 mg</td>
<td>O</td>
<td>2.5 mg (5 mg)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>N02CC03</td>
<td>zolmitriptan</td>
<td>2.5 mg</td>
<td>O</td>
<td>2.5 mg (10 mg)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5 mg</td>
<td>N</td>
<td>5 mg (10 mg)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>N02CC04</td>
<td>rizatriptan²</td>
<td>10 mg</td>
<td>O</td>
<td>10 mg (20 mg)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>N02CC05</td>
<td>almotriptan</td>
<td>12.5 mg</td>
<td>O</td>
<td>12.5 mg (25 mg)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>N02CC06</td>
<td>eletriptan</td>
<td>40 mg</td>
<td>O</td>
<td>40 mg (80 mg)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>N02CC07</td>
<td>frovatriptan</td>
<td>2.5 mg</td>
<td>O</td>
<td>2.5 mg (5 mg)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>

N=nasal, O=oral, P=parenteral; INN=International Non-Proprietary Name


### Table 16 – Authorized indications of sumatriptan and use in specific populations

**Sumatriptan injection** is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache. Limitations of use: use only if a clear diagnosis of migraine or cluster headache has been established. If a patient has no response to the first migraine or cluster headache attack treated with sumatriptan injection, reconsider the diagnosis before sumatriptan injection is administered to treat any subsequent attacks. Sumatriptan injection is not indicated for the prevention of migraine or cluster headache attacks.

**Pediatric Use**
Safety and effectiveness in pediatric patients have not been established. Injection is not recommended for use in patients younger than 18 years of age.

**Geriatric Use**
Clinical trials of sumatriptan injection did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. A cardiovascular evaluation is recommended for geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving sumatriptan injection.

**Sumatriptan Nasal Spray** is indicated for the acute treatment of migraine attacks with or without aura in adults. Nasal Spray is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of Nasal Spray have not been established for cluster headache, which is present in an older, predominantly male population.
Pediatric Use: Safety and effectiveness of sumatriptan Nasal Spray in pediatric patients under 18 years of age have not been established; therefore, nasal Spray is not recommended for use in patients under 18 years of age.

Geriatric Use: The use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly.

Sumatriptan tablets are indicated for the acute treatment of migraine with or without aura in adults. Limitations of use: use only if a clear diagnosis of migraine headache has been established. If a patient has no response to the first migraine attack treated with sumatriptan, reconsider the diagnosis of migraine before sumatriptan is administered to treat any subsequent attacks.

Sumatriptan is not indicated for the prevention of migraine attacks. Safety and effectiveness of sumatriptan tablets have not been established for cluster headache.

Pediatric use
Safety and effectiveness in pediatric patients have not been established. Sumatriptan tablets are not recommended for use in patients younger than 18 years of age.

Geriatric use
Clinical trials did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

Contraindications
- History of coronary artery disease or coronary artery vasospasm
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine
- Peripheral vascular disease
- Ischemic bowel disease
- Uncontrolled hypertension
- Recent (within 24 hours) use of another 5-HT1 agonist (e.g., another triptan) or of an ergotamine-containing medication

Sumatriptan tablets, injection and nasal spray are indicated for the acute relief of migraine attacks with or without aura. Sumatriptan injection is also indicated for the acute treatment of cluster headaches.

Adolescents (12-17 years) and Children (under 12 years)
The efficacy of oral sumatriptan has not been established in placebo-controlled trials carried out in 794 adolescent migraineurs. High placebo responses were found in these studies and there was a lack of statistically significant difference between placebo and oral doses ranging from 25 to 100 mg. The safety profile of oral and intranasal sumatriptan is similar to that of adults. The safety and effectiveness of sumatriptan in children under the age of 12 years has not been established.

Adolescents (12-17 years): The recommended dose of sumatriptan nasal spray is 10 mg – 20 mg, with consideration given to the patient’s body weight and patient variability of migraine attacks. The dose of nasal spray should be administered into one nostril.

Patients Over 65 Years
Experience of the use of sumatriptan in patients aged over 65 is limited. However the pharmacokinetics do not differ significantly from a younger population. Until further clinical data are available, the use of sumatriptan in patients aged over 65 is not recommended.

Contraindications
- A history of myocardial infarction
- Peripheral vascular disease or symptoms or signs consistent with ischaemic heart disease.
- Prinzmetal's angina/coronary vasospasm.
- Uncontrolled hypertension.
- Cerebrovascular accident or transient ischaemic attack.
- Severe hepatic impairment.

Sumatriptan injection is indicated for the acute treatment of migraine attacks with or without aura. Is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population.

Pediatrics (<18 years of age):
The safety and efficacy of sumatriptan succinate in children has not been established and its use in this age group is not recommended.

Geriatrics (>65 years of age):
Experience of the use of sumatriptan succinate in patients aged over 65 years is limited. Therefore the use of sumatriptan injection in patients over 65 years is not recommended.

Sumatriptan Nasal Spray is indicated for the acute treatment of migraine attacks with or without aura. Is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population.

Pediatrics (<18 years of age)
The safety and efficacy of sumatriptan Nasal Spray in children has not been established and its use in this age group is not recommended.

**Geriatrics (> 65 years of age)**
Experience in the use of sumatriptan Nasal Spray in patients aged over 65 years is limited. Therefore the use of sumatriptan Nasal Spray in patients over 65 years is not recommended.

**Sumatriptan tablets** is indicated for the acute treatment of migraine attacks with or without aura. Sumatriptan is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population.

**Pediatrics (< 18 years of age)**
The safety and efficacy in children have not been established and its use in this age group is not recommended.

**Geriatrics (> 65 years of age)**
Experience of the use in patients aged over 65 years is limited. Therefore the use SDZ Sumatriptan in patients over 65 years is not recommended.

**Contraindications**
- History, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias).
- Other significant underlying cardiovascular diseases (e.g. atherosclerotic disease, congenital heart disease).
  - Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g. stable angina of effort and vasospastic forms of angina such as the Prinzmetal’s variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud’s syndrome.
  - Uncontrolled or severe hypertension.
  - Concurrent administration of MAO inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated.
  - The use of Sumatriptan succinate within 24 hours before or after treatment with other 5-HT1 receptor agonists, or ergotamine-containing drugs or their derivatives (e.g. dihydroergotamine, methysergide) is contraindicated.
  - Severe hepatic impairment.


### 13. Availability of pharmacopoeial standards

- British Pharmacopeia: yes (as sumatriptan)
- US Pharmacopeia (USP 31th revision): yes (as sumatriptan)
- European Pharmacopeia: yes (as sumatriptan)
14. Reference list


151. [WHO ATC-DDD] WHO Collaborating Centre for Drug Statistics Methodology https://www.whocc.no
Annex 1 - IHS diagnostic criteria of migraine [17]

Migraine without aura

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)\(^2,3\)
C. Headache has at least two of the following four characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Migraine with aura

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. visual
   2. sensory
   3. speech and/or language
   4. motor
   5. brainstem
   6. retinal
C. At least three of the following six characteristics:
   1. at least one aura symptom spreads gradually over \(\geq 5\) minutes
   2. two or more aura symptoms occur in succession
   3. each individual aura symptom lasts 5–60 minutes\(^2\)
   4. at least one aura symptom is unilateral\(^2\)
   5. at least one aura symptom is positive\(^1\)
   6. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis.

Chronic migraine

A. Headache (migraine-like or tension-type-like\(^1\)) on \(\geq 15\) days/month for >3 months, and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura
C. On \(\geq 8\) days/month for >3 months, fulfilling any of the following:\(^2\)
   1. criteria C and D for 1.1 Migraine without aura
   2. criteria B and C for 1.2 Migraine with aura
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.\(^3-5\)
Annex 2 - Synopsis of the recommendations from guidelines on treatment of the acute migraine attack

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults and adolescents</td>
<td>Adults and children &gt;12 years</td>
<td>Adults</td>
</tr>
<tr>
<td>Disorder</td>
<td>Migraine</td>
<td>Headache</td>
<td>Migraine</td>
</tr>
<tr>
<td>Acute treatment</td>
<td>Triptans recommended as first-line treatment. The first choice is sumatriptan (50–100 mg); other triptans may be used if sumatriptan fails. Paracetamol (1,000 mg) can be considered for treatment of patients with acute migraine who are unable to take other acute therapies. Combination therapy sumatriptan (50–85 mg) and naproxen (500 mg) should be considered.</td>
<td>Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol (<em>) For young people aged 12-17 years consider a nasal triptan in preference to an oral triptan. For people who prefer to take only one drug, consider monotherapy with an oral triptan, NSAID, aspirin (900 mg) or paracetamol (</em>) When prescribing a triptan, start with the one that has the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans. (*) taking into account the person's preference, comorbidities and risk of adverse events.</td>
<td>Triptans are recommended for migraine attacks that are likely to become moderate or severe. If migraine response to sumatriptan is inadequate, consider naproxen sodium 500 mg to be given simultaneously with the triptan. Patients with migraine attacks that are usually moderate or severe in intensity should be advised to take triptans early during their migraine attacks Strong recommendation, moderate quality evidence. If a patient does not respond well to one triptan or tolerates it poorly, other triptans should be tried over time in subsequent attacks. It is recommended that patients wait 24 hours before trying another triptan.</td>
</tr>
<tr>
<td>Episodic migraine</td>
<td></td>
<td>Strong recommendation, high quality evidence</td>
<td></td>
</tr>
<tr>
<td>Pregnancy-child bearing age</td>
<td>Triptans are recommended for the treatment of patients with acute migraine associated with menstruation. Sumatriptan can be considered for treatment of acute migraine in pregnant women in all stages of pregnancy. The risks associated with use should be discussed before commencing treatment. Paracetamol is first choice for the short-term relief of mild to moderate headache during any trimester of pregnancy.</td>
<td>Offer pregnant women paracetamol for the acute treatment of migraine. Consider the use of a triptan or an NSAID after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy.</td>
<td>Not considered</td>
</tr>
<tr>
<td>Children/Adolescents</td>
<td>Not considered</td>
<td>-For young people aged 12–17 years consider a nasal triptan in preference to an oral triptan.</td>
<td>Not considered</td>
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</tbody>
</table>
Annex 3 – Search strategies; results of the search strategy and process of inclusion

- Cochrane Library: (headach* OR migrain* OR cephalgi* OR cephalalgi*) AND (sumatriptan OR Imitrex OR Imigran)
- National Library of Medicine’s MEDLINE database; EMBASE database (from 2013 to October 2018): (((headach* OR migrain* OR cephalgi* OR cephalalgi*)) OR (Headache[mh] OR Headache Disorders[mh] OR Migraine Disorders[mh])) AND (sumatriptan OR Imitrex OR Imigran)

Clinical guidelines

| Potentially relevant citations identified and screened for retrieval | 8 |
| Documents excluded (not relevant or duplications) | 5 |
| Relevant clinical guidelines included in the present application | 3 |

SRs

| Potentially relevant citations identified and screened for retrieval (since 2013) | - PUBMED: 39 |
| - EMBASE: 62 |
| - Cochrane Library: 12 |
| Documents excluded (duplications): 38 |
| Potentially relevant documents retrieved for evaluation | 75 |
| Documents excluded (not relevant): 69 |
| Relevant SRs included in the present application | 6 |

RCTs

| Potentially relevant citations identified and screened for retrieval (since 2013) | - CENTRAL: 149 |
| - PUBMED: 43 |
| - EMBASE: 97 |
| Citations excluded: 103 (duplications) |
| Potentially relevant documents retrieved for evaluation | 186 |
| Documents excluded (not relevant): 184 |
| Relevant RCTs included in the present document | 2 |

Ongoing studies

| Potentially relevant citations identified and screened for retrieval (since 2013) | - International Clinical trials Registry Platform (WHO): 4 record |
| - metaRegister of Controlled Trials (mRCT): 0 |
| - EU Clinical Trials Register: 12 |
| - Clinicaltrials.gov: 14 |
| Excluded: 29 |
| Relevant ongoing studies included in the present application | 1 |
Annex 4 - List of manufacturers that have active status in the *Drug Master File* of the Food and Drug Administration (FDA)

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<td>SUMATRIPTAN</td>
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<td>20590</td>
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<td>21711</td>
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### Annex 5 - International availability and proprietary names of sumatriptan *

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<tr>
<th>Medicine</th>
<th>Country, trade name and pharmaceutical industry</th>
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<tbody>
<tr>
<td><strong>International availability and proprietary names of sumatriptan</strong></td>
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</tr>
<tr>
<td>AFRICA</td>
<td>SOUTH AFRICAN REPUBLIC: Imigen®</td>
</tr>
<tr>
<td>AMERICAS</td>
<td>ARGENTINA: Imigran®</td>
</tr>
<tr>
<td>ASIA</td>
<td>PHILIPPINES: Imigran®</td>
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<tr>
<td>EUROPE</td>
<td>AUSTRIA: Imigran®</td>
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<tr>
<td>OCEANIA</td>
<td>AUSTRALIA: Clustran®</td>
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</tbody>
</table>

* Codifa – L’Informatore farmaceutico. [https://www.codifa.it/](https://www.codifa.it/) (accessed December 3, 2018)
Annex 6 – List of studies evaluated in full text (reasons for exclusion)

<table>
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<tr>
<th>Study</th>
<th>Study type</th>
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<tbody>
<tr>
<td>Allais 2018</td>
<td>Review</td>
<td>Non systematic methodology</td>
</tr>
<tr>
<td>Asadollahi 2014</td>
<td>RCT</td>
<td>Control arm: promethazine</td>
</tr>
<tr>
<td>Friedman 2017</td>
<td>Review</td>
<td>Non systematic methodology</td>
</tr>
<tr>
<td>Law 2016</td>
<td>SR</td>
<td>Three studies with oral sumatriptan in the control arm, already included in Derry 2012</td>
</tr>
<tr>
<td>Maasumi 2017</td>
<td>Review</td>
<td>Non systematic methodology</td>
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<tr>
<td>Macone 2017</td>
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<tr>
<td>Menshawy 2018</td>
<td>SR</td>
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<td>Messali 2014</td>
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<td>Silberstein 2014</td>
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