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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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.

In 2019 an application for the inclusion of sumatriptan in the core list of the EML for the treatment of acute migraine in adults was submitted by our Collaborative Center. The WHO Expert Committee on the Selection and Use of Essential Medicines did not recommend the addition of sumatriptan to the list. However, the Committee expressed the need for a future review with additional data on sumatriptan in the context of other migraine therapies to be considered.

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 has not been studied in randomized controlled trials and is not licensed in children younger than 12 years of age
- although sumatriptan, regardless of the formulation, showed a superiority vs. placebo in adolescents 12 to 17 years of age with episodic migraine, the oral formulation showed no significant superiority vs placebo in reaching pain freedom at 2 hours.

Sumatriptan is available as oral tablets, subcutaneous injection and intranasal spray. Since intranasal inhalation and subcutaneous injection need 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 of intranasal sumatriptan is substantially higher than the oral route. Therefore, this application is focused on oral sumatriptan.

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.

Sumatriptan is registered for the acute treatment of migraine with or without aura.

Evidence-based guidelines, issued by the main international scientific societies and agencies, consistently recommend sumatriptan or other triptans as first-line drug in adults with acute migraine.

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

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

Oral sumatriptan 50 mg is significantly more effective than placebo on most clinically meaningful outcomes (pain relief after two hours, reduction of rescue medications and reduction of symptoms associated with migraine, such as nausea, photophobia and functional disability).

Trials directly comparing sumatriptan with full analgesic doses of acetylsalicylic acid (ASA) and paracetamol show inconsistent results. In one trial sumatriptan showed higher efficacy when directly compared with ASA 900mg plus metoclopramide 10mg, while in one other trial no statistically significant differences vs ASA 1,000mg were observed, as well as in two trials comparing sumatriptan with paracetamol 1,000mg + metoclopramide 10mg.

It has to be noted, though that the efficacy and safety outcomes of such trials were observed over a short period of time (one to three consecutive migraine attacks), therefore their transferability in clinical practice (particularly among patients with high-frequency episodic migraine) is limited.

When compared with other oral triptans, sumatriptan showed overall better efficacy on most clinically relevant outcomes.

Sumatriptan has shown no association with major congenital malformations or prematurity, therefore it may be a particularly advantageous therapeutic option in pregnant women when most common analgesics are contraindicated or not effective. Sumatriptan can be safely administered to breastfeeding women.

Paracetamol and ASA are the only two analgesics currently included in the model list that can be routinely used in the symptomatic treatment of migraine.

They represent a limited therapeutic choice considering that:

- About half of the patients with medication overuse headache (MOH), a common, disabling and hard to manage sequel of migraine headache, develop it while taking NSAIDs, such as ASA
- Due to safety reasons, ASA not recommended during pregnancy and paracetamol is the only analgesic drug currently included in the EML that can be safely administered in pregnant women. About three quarters of migraine patients are women and, since the prevalence of migraine is the highest during a woman's reproductive age, they represent a substantial target population.
- The use of ASA and paracetamol at analgesic dosage by migraine patients is frequently chronic and in the long-term poses the risk of several potentially life-threatening adverse events, such as gastric damage, bleeding, blood pressure increase and renal insufficiency.

Adverse events associated with oral sumatriptan are usually mild. Serious adverse events, as well as withdrawals due to adverse events, are uncommon.

All triptans are currently available as unbranded generic drugs, and the cost of sumatriptan oral preparations is considerably lower than when it first was marketed, although its price is highly variable among different countries.

Available data on comparative cost-effectiveness are limited due to methodological issues of health economic analyses on migraine and to their poor transferability to low- and middle-income countries. A reduction of the price of sumatriptan may have a considerable impact on its cost-effectiveness, which in the available economic modeling studies appears to be highly cost-dependent.

When comparing the cost-effectiveness of sumatriptan vs. less expensive alternatives, such as ASA and paracetamol, long-term safety should be taken into account, other than the difference in direct cost.

Sumatriptan could be a useful, potentially cost-effective therapeutic option, easily self-administered without requiring special skills or monitoring, whenever analgesic medications already listed in the EML are contraindicated, not tolerated or ineffective.

In order to avoid unnecessary suffering, sumatriptan, recommended as first-line drug by evidence-based clinical practice guidelines, could be offered to most persons with migraine, including pregnant and breastfeeding women, for whom therapeutic options are limited.

3. Name of the organization consulted and/or supporting the application

Area Farmaci e Dispositivi Medici | Direzione Generale Cura della Persona Salute e Welfare, Regione Emilia-Romagna.
WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development in Reproductive Health.
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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 middle- and 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 21st WHO EML[1] and the 7th EMLc[2] 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). These drugs are intended to treat acute attacks of migraine as first-line therapies.
During its 2005 meeting 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 mentioned among neurologic medicines that should be included in the EML (Rimmer 2017).

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 (Katsarava 2018). Underutilization of effective acute therapies has the potential to negatively impact quality of life for migraine sufferers.

Therefore, the availability of a triptan, effective in controlling pain and associated symptoms during acute migraine attacks, that could be offered to most persons with migraine would be a useful treatment option in clinical practice.

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).
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.

[1] https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06

[2] https://www.who.int/publications/i/item/WHOMVPEMPIAU201907

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 (Kerry 1992).
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 (eMC; Martindale).

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 (Martindale; Scott 1994; Lacey 1995; Fuseau 2002; Moen 2006).

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 (US PHARM 2017).
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 (Rani 1006) and might affect the absorption of other drugs, as judged by its delaying effect on paracetamol absorption in migraine patients (eMC

; Martindale).

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, although 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 (Hilaire 2004), but as for other drugs, sumatriptan should only be used in pregnancy when the benefit justifies the potential risk to the foetus.

Data from humans about the presence of sumatriptan in breast milk and about the oral absorption by infants are limited.
The distribution of sumatriptan into breast milk after a 6-mg subcutaneous dose has been studied in 5 mothers (Wojnar-Horton 1996). 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 (eMC; Martindale).

Administration is probably compatible with breast feeding, since the amount of drug reaching the systemic circulation of a breastfeeding infant is likely negligible (Briggs 2015; AAP 2001).

Safety data and advice about sumatriptan use during pregnancy and breast feeding are provided in Chapter 10.5

Proposed therapeutic dosage regimen

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

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 [3]

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.

A tablet supplying a dose of85 mg of sumatriptan, as a fixed-dose combination with 500 mg of naproxen sodium (is also available in the USA; a single dose may be taken, repeated once within 24 hours if necessary, with a minimum interval of 2 hours.

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

[3] 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

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.

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.

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.

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 with specifically licensed drugs 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 medication overuse headache (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 is administered in as-needed fashion, in fixed dose and does not require special diagnostic or treatment facilities, monitoring or supervision by skilled health care providers.
Being an oral formulation, it is easily stored and self-administered.

Sumatriptan is indicated for the symptomatic treatment of episodic migraine and its diagnosis, based on specific criteria (IHS 2018) is clinical and based on history and medical examination.

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 (GBD 2019).
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) (IHS 2018).

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 (HS 2018). About 2.5-3% of patients with migraine develop chronic migraine within one year (Bigal 2008; Lipton 2015).
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.

In 2018 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 (IHS 2018). (**Annex 1)**

Complications of migraine

Rarely, a migraine attack may last for more than 72 hours, therefore being severely disabling; according to the IHS classification this condition is considered as a complication of migraine called “status migrainosus”, occasionally caused by anti-migraine medication overuse (IHS 2018).

Several data from observational studies indicate that migraine, especially migraine with aura, is associated with an increased risk of ischemic stroke, and cardiovascular events (Schűrks 2009; Sacco 2015), 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 (Dodick 2018). The existence of a genetic component in migraine, showed by population-based family and twin studies (Russell 1995; Stewart 1997; Mulder 2003), is further supported by Genome-Wide Association 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 (Gormley 2016).
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 (WHO Aids 2007).
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(Blau 1990; Giffin 2003; Dalkara 2013). Stress and negative emotions, and some odors are also listed as triggers by people with migraine (Giffin 2003; Andress-Rothrock 2010). 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 (Todd 2018).

Most women with migraine (up to over 80%) show a reduction in frequency and intensity of attacks during pregnancy (Mattsson 2003; Sances 2003; Melhado 2005), or even remission, mostly during the second and third trimesters (Aegidius 2009; Kvisvik 2011). However, in about 8% of cases, during pregnancy women experience a worsening of migraine attacks, in frequency and pain intensity (Maggioni 1997; Aube 1999).

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 2019 (GBD vizhub) estimates, including only studies where migraine was diagnosed according to ICHD-IIIβ, migraine is the sixth most prevalent out of 328

diseases and injuries, and its global age-standardized prevalence is 14.1% (12.3–16.2) overall; 17.9% (15.6–20.5) for women, and 10.3% (8.9–12.0) for men. (GBD vizhub).

However, prevalence estimates according to the most recent updates of GBD 2019 are not homogeneous, even within single economic regions (GBD vizhub).
In fact, the prevalence varies with a similar wide range, among high income countries from 11.8% in Argentina to 20.7% in Italy while among low income countries it ranges from 8.1% in Tanzania to 15.6% in Nepal. In lower-middle income countries the estimates show values from 8.9 % in Kenya to 16.3% in Tunisia and among upper middle income countries from 13.3% of China to 19.0% in Brazil (GBD vizhub).

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 (Liu 2013), due to family and community stigma (Winkler 2010).

Low socioeconomic status seems to be associated to higher headache prevalence, regardless of country income (Katsarava 2018; Hagen 2002; Lipton 2005; Queiroz 2009; Ayzenberg 2012; Gururaj 2014) and a higher prevalence of migraine seems also to be more common among those living in urban areas (Woldemanuel 2017).

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 (Vetvik 2017), although this ratio is not consistent across all age ranges, showing an increase, especially in women, after puberty (Wang 2005; Abu-Arafeh 2010; Victor 2010) with the largest difference during reproductive years (Victor 2010).
Research observations show that women have more frequent, longer lasting and more severe attacks than men (Vetvik 2017; Murtaza 200; Bolay 2015).
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 (MacGregor 2015).

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) (Wober-Bingol 2013).

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) (Lyngberg 2005).
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 (Becker 2008).
Global incidence estimates reported by GBD showed a wide range of incidence in all ages from 6.5 new cases of migraine per 1,000 in Japan, to 14.4 per 1,000 in Paraguay (GBD 2019), with 87.6 millions new cases overall in 2019 (95% uncertainty interval [UI] 76·6–98·7) (GBD vizhub).
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 (Saylor 2018).

The frequent use of analgesic drugs may lead to **medication overuse headache** (MOH), a disabling and hard-to-manage chronic headache, representing a common sequel of migraine headache or tension-type headache (IHS 2018; Diener 2016). About half of the patients with MOH develop overuse while on NSAIDs (Find 2015).
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 (Find 2015).
Medication overuse headache can be considered as derived from a preexisting migraine. Differently from GBD 2013 and 2015, in the 2016 GBD report (GBD 2018), medication overuse headaches was defined as a sequel of either migraine or tension-type headache (IHS 2018; Diener 2016).

Several observational studies and metanalysis (Spector 2010; Sacco 2013; Sacco 2015) 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 metanalysis (Gillum 2000), 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 (WHO 1998).
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 (Sacco 2017). 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 (Bousser 2000).
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 (WHO Aids 2007).

Mortality

Although GBD estimates indicate no deaths from migraine (GBD 2019), the increased risk of cardiovascular and cerebrovascular mortality, especially for migraine with aura, is still debatable (Schürks 2011).

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 (WHO Factsheets Headache).

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-Saharian Africa, are lacking.

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 (Steiner 2018).

According to the GBD study, in 2019 1.13 billion (95% uncertainty interval [UI] 0·98–1·30) people were estimated to have a migraine causing 42.1 million (95% UI 6.42-95.6) years of life lived with disability (YLDs), corresponding to the 4·8% (0·8–10·1) of total 2019 YLDs. Migraine headache makes up 88·2% (60·7–97·7) of the burden of headache disorders (IHME Healthdata).

Migraine is a relevant burden also among children and adolescents between 5 and 14 years of age (5.0 % YLDs, (95% CI 0.2-11.8), and among persons aged 50-69 years (3.4% YLDs, 95% CI 0.8-6.9) (GBD vizhub).
When considering the most productive years of one's life, eg. the age range from 15 to 49 years, the impact of disability caused by migraine is impressive: 7.3 % of overall YLDs (95% CI 1.1-15.1), higher for women (8.0%, 95% CI 1.2-16.7) than for men (6.3%, 95% CI 1.1-12.8). Among women in this age range migraine caused 18.3 million (95% UI 2.4–42.1) YLDs in 2019 (GBD vizhub).

Migraine is a relevant burden also among children and adolescents between 5 and 14 years of age (5.0 % YLDs, (95% CI 0.2-11.8), and among persons aged 50-69 years (3.4% YLDs, 95% CI 0.8-6.9) (GBD vizhub).

The burden of migraine can be investigated in terms of direct (medications and health interventions) as well as indirect cost (loss of productivity, quality of life impairment). Available data suggest that the lost productivity caused by migraine and the consequential financial costs are substantial.

The estimated total annual mean per-person cost of episodic migraine in Europe varies between €486.28 (France) and 1,092.48 (Spain) (Bloudek 2012). A 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 (Bloudek 2012; Berra 2015) [4].

Few studies focused on loss of productivity, showing that it affects both genders, particularly for chronic migraine. Lost paid workdays 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). (Steiner 2014; D'Amico 2017; Zebenigus 2017).

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 (NICE 2012).

[4] Such estimate does not consider the recently approved calcitonin gene-related peptide (CGRP) inhibitors class, indicated in the prophylaxis of chronic migraine.

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 (D'Amico 2017)[5]

In a recent study in Germany, the average yearly gross monetary loss was €3,714, and €2,779 for paid and unpaid works per person respectively. Two thirds (64.6%) of the estimated productivity losses were experienced by females, and among all hours lost, more than half (55.2%) were losses due to unpaid work activities. The majority of losses of unpaid work activities of the were experienced by females (75.1%) (Seddik 2020).

Such gender differences are comparable with those from US surveys (about $ 14,400 for men and $ 7,100 for women) (Serrano 2013). The fact that women show a higher paid workdays loss than men appears conflicting with a lower loss of income for women, who 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 workdays (Serrano 2013; Vetvik 2017).

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) (Saylor 2018).

A 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 (Singh 2017).

Treatment of Migraine

The optimal treatment of migraine includes accurate diagnosis according to internationally recognized clinical criteria (IHS 2018), 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. Triptans, in particular are more effective if taken early in the attack, when pain is still mild.
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 or intranasal 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, calcium antagonists and recently the new class of calcitonin gene-related peptide (CGRP) inhibitors.
Nutraceuticals and nonprescription therapies (coenzyme Q10, magnesium, melatonin, petasites and riboflavin) are widely used for the prevention of migraine (Charles 2017).

Evidence-based guidelines (WHO Aids 2017; Worthington 2013; NICE 2012; SIGN 2018) 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 (MTC) 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 (SIGN 2018; Simpson 2016).

Monoclonal antibodies acting on the calcitonin gene-related peptide (Anti-CGRP Ab) (e.g. galcanezumab and fremanezumab) or on its receptor (erenumab) are new drugs recently approved for the prophylaxis of migraine in adults (FDA US approval) who have at least 4 migraine days per month (EMA, EU approval). They have shown effective when used as prophylactic treatment in increasing headache free days and determined a higher percentage of $\geq$50% responders compared with placebo both in high frequency episodic migraine and in chronic migraine, when other treatments have failed or are not tolerated. Anti-CGRP Ab can be self-administered by appropriately trained patients and are available in subcutaneous formulation.

Emerging drug treatments

Migraine is associated with the release of numerous neurotransmitters and neuromodulators, including the pituitary adenylate cyclase-activating peptide (PACAP) that is being studied in animal models and in a phase I trial (Moldovan Loomis 2019; ALD1910).

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 (Saylor 2018).

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 (WHO Factsheets Headache).

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) (Katsarava 2018).

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 (Katsarava 2018).
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) (Linde 2015).

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 (WHO Atlas 2011).
Inadequate acute treatment efficacy is associated with increased risk of transformation from episodic migraine to chronic (Lipton 2015), 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 (Lu 2006).

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 (Katsarava 2018).

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. (Diener 2019).

8.2 Assessment of current use

According to the data of the 2011 World Atlas of Headache Disorders and Resources (WHO Atlas 2011) 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% (Victor 2010).

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. About 75% of people suffering from migraine are women, and its prevalence is the highest for ages 20 to 50 years, during a woman's reproductive age (Silberstein 2004).
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 (NICE 2012; SIGN 2018).
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 (Ephross 2014; Marchenko 2015; Spielmann 2018).

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 a European survey, triptans are underused among people with migraine that could potentially benefit from them (3.4%-24.5%) (Katsarava, 2018).

Sumatriptan may have a favorable impact on migraine not only because of its effectiveness and safety, but also being an alternative option to the medicines currently listed in the EML for routine control of pain, including episodic migraine attacks: ASA and acetaminophen.

A wider availability of an effective, safe and easily administered treatment for acute migraine would not only allow avoiding unnecessary suffering, but also contribute preventing potentially dangerous overuse or abuse of other treatments and the consequent risk of drug-related adverse events.

Although effective in controlling pain and with a favorable benefit/risk profile, ASA and paracetamol pose several potential risks, especially when used often by patients with high-frequency episodic migraine at analgesic dosage (500mg to 900mg for ASA and 500 to 1,000mg for paracetamol).
ASA is the first ranking drug among hospital admissions for drug-related adverse drug reactions (Pirmohamed 2004).

Among chronic users of NSAIDs, potential abuse, accidental overdosage and drug-specific adverse events (such as gastrointestinal bleeding, hypertension, myocardial infarction and stroke, particularly in people with cardiovascular diseases) may be severe and life-threatening (Davis 2016; FDA NSAIDs). Impaired renal function may be worsened by chronic use of NSAIDs, with an increased risk of renal failure, particularly - although not only - among elderly people (Nelson 2019).

In Europe and the UK, paracetamol is the most commonly reported drug among hospital presentations and admissions for drug overdose. Paracetamol poisoning can occur as an intentional overdose with self-harm purposes or accidentally after overuse of over-the-counter (OTC) preparations labeled with different brand names. The resulting acute liver failure, although rare, can be life-threatening if not followed promptly by liver transplant (FDA paracetamol; Daly 2008).

9. Review of benefits: summary of evidence of comparative effectiveness.

9.1 - Identification of clinical evidence

Clinical evidence on efficacy and safety of oral sumatriptan in adults and children with acute migraine attack was searched through the following publication types: clinical practice guidelines (CPGs), systematic reviews (SR) and randomized controlled trials (RCT).
Published as well as ongoing studies were 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) and safety studies on healthy subjects 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) (Diener 2019).

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.

The following types of publications were considered:

Systematic Reviews

To be included, SRs had to comply with the PRISMA 2009 reporting criteria (Moher 2009), or at least:

- clearly state background and objectives
- Provide pre-defined eligibility criteria for studies, including a reference to study design, and study characteristics: participants, interventions, comparisons and outcomes (PICO);
- Provide a protocol describing an explicit and 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 (meta-analysis) synthesis of the results
- Report funding sources and potential sources of conflict of interest by the authors

Systematic reviews not complying with all the criteria mentioned above were considered if deemed relevant and quality issues were discussed.
In assessing comparative effectiveness of sumatriptan vs. placebo or other active treatments, we first looked at the availability of direct, head-to-head comparisons.

Systematic reviews on safety including non-randomised trials were also considered. If direct evidence was lacking, we looked for evidence from indirect comparisons.

Systematic reviews were searched by consulting the following databases on October 28, 2020:

- 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 and EMBASE were searched on October 2018 starting from the search date (October 2013) of the first high-quality SR retrieved in the databases mentioned above (Cameron 2015). The search was updated on October 28, 2020.

Randomised-controlled trials

We included prospective, randomized, double-blind trials, comparing oral sumatriptan with placebo or an active control (licensed drug), to treat an attack of migraine with or without aura, presenting results as number of patients reaching at least one of the outcomes listed above. Uncontrolled, before-after, concurrent cohort comparisons, non-experimental and quasi-randomised trials were not considered for efficacy assessment, as well as studies expressing results by means of continuous outcomes. We did not contact the authors in case of missing data.

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

Quality assessment

Study quality of the RCTs was assessed for each outcome, when available, according to the Grading of Recommendations, Assessment, Development and Evaluation (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) (Guyatt 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d).

Guidelines

To be included, CPGs 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 12 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 CPGs originally developed by the authors were considered; CPGs adapted from other existing guidelines were not included in this document.

Ongoing studies

We searched the following sources (October 22, 2020):

- International Clinical trials Registry Platform (WHO)http://www.who.int/ictrp/en/
- MetaRegister of Controlled Trials (mRCT): http://www.isrctn.com/
- EU Clinical Trials Register: https://www.clinicaltrialsregister.eu/
- 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.

Our search retrieved 5 SRs (1 SR of RCTs on children/ adolescents (Richer 2016), 2 SRs of RCTs in adults (Derry 2012, Cameron 2015), 2SRs of observational studies on safety of triptans (Roberto 2014, Marchenko 2015), one RCT (Tepper 2015) (Table 5).
We considered recommendations on triptans from 4 CPGs (Worthington 2013; NICE 2012; SIGN 2018; AAN-AHS 2019).
We also considered one registry to assess the safety of triptans (Ephross 2014).
A list of the excluded studies with the reason for exclusion in provided in Annex 6.

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

Oral sumatriptan for acute migraine attacks in <u>children and adolescents</u>

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 (Richer 2016; Patniyot 2016).

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. (Patniyot 2016).

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 (Richer 2016).

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 sumatritptan 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.

<u>Oral sumatriptan vs placebo</u>

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”.

<u>Sumatriptan (any administration route) vs placebo</u>

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 in children and adolescents *(statistically significant differences in bold)* (Richer 2016).

	Children			Adolescents		
Triptan	**N studies**	**N of participants**	**RR (95%CI)**	**N studies**	**N of participants**	**RR (95%CI)**
Sumatriptan	2	145	2.29 (1.00-5.23)	10	**2415**	**1.27 (1.10-1.48)**
Oral sumatriptan	-			6	925	1.03 (0.75-1.43)
Zolmitriptan (2 studies oral; 2 non-oral)	-			4	1532	**1.66 (1.16-2.38)**
Rizatriptan (oral)	1	200	**1.31(0.89-1.92)**	4	1526	**1.34 (1.13-1.60)**
Almotriptan (oral)	-			1	714	1.10 (0.88-1.39
Eletriptan (oral)	-			1	274	1.46 (0.88-2.43)
Naratriptan (oral)	-			1	300	1.06 (0.65-1.75
Total	**3**	**345**	**1.67 (1.06-2.62)**	**21**	**6761**	**1.32 (1.19-1.47)**

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 <u>adults</u>

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 (Derry 2012) [5] and a second one on the efficacy and tolerability of triptans (Cameron 2015).

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 metanalysis (NMA) by the Canadian Agency for Drugs and Technologies in Health (CADTH) focused on triptans (Cameron 2015).

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 in adults)

	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Zolmitriptan	ASA	Paracetamol 1000 mg + MTC 10mg
Sumatriptan 25mg					● (Derry 2012)	● (Derry 2012 **; Cameron 2015)		
Sumatriptan 50mg	● (Derry 2012 **; Cameron 2015)	● (Derry 2012; Cameron 2015)	■ (Cameron 2015)	■ (Cameron 2015)	● (Derry 2012; Cameron 2015)	● (Derry 2012; Cameron 2015)	● (Derry 2012; Cameron 2015)	■ (Cameron 2015)
Sumatriptan 100mg	● (Derry 2012; Cameron 2015)	● (Derry 2012; Cameron 2015)		● (Derry 2012) **; Cameron 2015)	● (Derry 2012; Cameron 2015)	● (Derry 2012) **; Cameron 2015)	●* (Derry 2012; Cameron 2015)	● (Derry 2012)

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

<u>Oral sumatriptan vs placebo</u>

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".

[5] 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) (Derry 2012). 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)* (Derry 2012)

Sumatriptan	N studies	N of participants	RR (95%CI)	RD	NNT	GRADE Certainty
50 mg	7*	1514*	**2.0 (1.7, 2.4) ***	**23%**	**4.4**	⊕⊕⊕⊕ High
	13**	6447 **	**2.7 (2.4, 3.1) ****	**19%**	**6.1**	⊕⊕⊕⊕ High
100 mg	5 *	1240 *	**2.41 (2.06, 2.81) ***	**34%**	**3.0**	⊕⊕⊕⊕ High
	16 **	6571 **	**3.2 (2.8, 3.6) ****	**21%**	**4.7**	⊕⊕⊕⊕ High

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

Oral sumatriptan vs active comparators

ASA and paracetamol

- Outcome **"pain freedom at 2 hours"** (recommended by the IHS as primary outcome in headache trials).The results of pooled analyses comparing sumatriptan vs. active comparators relative to are summarised in Table 4 (all results from Derry 2012).

  Four studies compared sumatriptan 50 mg and 100 mg with effervescent **ASA 1,000 mg** (2 studies, 726 participants) and **ASA 900 mg + MTC 10 mg** (2 studies, 575 participants), respectively.

  Sumatriptan 100mg was significantly more effective than **ASA 900mg + MTC 10mg** (OR 1.62; 95%CI 1.17, 2.25). In absolute terms, 26% of patients treated with sumatriptan 100 mg and 16% of those on ASA 900mg + MTC 10 mg were pain-free at 2 hours (Absolute Risk Difference (ARD): 10% in favor of sumatriptan). These data suggest that up to 84% of patients exposed to ASA + MTC may not be pain free at 2 hours, and therefore they could be potential candidates to sumatriptan. Patients not responding to ASA+MTC could favor the net benefit observed with oral sumatriptan vs ASA.

  The difference between effervescent **ASA 1,000mg** and sumatriptan 50mg was not statistically significant, although the point estimate favors sumatriptan. 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 (ARD: 15% in favor of sumatriptan).

- Outcome "**headache relief at 2 hours"** (recommended outcome by the IHS in headache trials): sumatriptan was more effective than effervescent **ASA 1000mg** and than **ASA 900mg + MTC 10mg** (OR 1.27; 95%CI 1.09, 1.47).

  When compared to **paracetamol 1000 mg + MTC 10 mg** sumatriptan 100 mg showed no statistically significant difference (2 studies, 1035 participants), although the point estimate was in favor of sumatriptan (ARD: 2%).

- Outcome **"reduction of rescue medication use"** (recommended outcome by the IHS in headache trials): sumatriptan was more effective than **paracetamol 1000mg + MTC 10mg** (OR 0.86; 95%CI 0.74, 0.99).
- Outcome **"headache relief at 1 hour": effervescent ASA 1000 mg** was more effective than sumatriptan 50 mg (OR 0.78; 95%CI 0.61, 0.98).

Other triptans

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. 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.

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.

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)* (Derry 2012)

Active comparator	Sumatriptan (dose)	N studies	N of participants	RR (95%CI)	NNT	GRADE certainty
Almotriptan 12.5mg	100mg	2	754	1.20 (0.97, 1.49)	NS	⊕⊕⊕⊕ High
Eletriptan 40 mg	50 mg	2	721	***0.74 (0.55, 0.98)***	***17.8***	⊕⊕⊕⊕ High
	100 mg	3	2263	***0.74 (0.65, 0.85)***	***12.5***	⊕⊕⊕⊕ High
Eletriptan 80 mg	50 mg	2	706	***0.58 (0.44, 0.76)***	***8.3***	⊕⊕⊕⊕ High
	100 mg	2	604	***0.54 (0.41, 0.72)***	***6.2***	⊕⊕⊕⊕ High
Rizatriptan 5 mg	50 mg	2	2209	1.06 (0.95, 1.19)	NS	⊕⊕⊕⊕ High
Rizatriptan 10mg	50mg	2	2230	*0.89 (0.80, 1.00)*	*NS*	⊕⊕⊕⊕ High
	100 mg	2	936	***0.82 (0.69, 0.98)***	***16.7***	⊕⊕⊕⊕ High
ASA 1000 mg	50 mg	2	726	1.22 (0.97, 1.53)	NS	⊕⊕⊕⊕ High
ASA 900 mg + MTC 10 mg	100 mg	2	575	**1.62 (1.17, 2.25)**	**6.2**	⊕⊕⊕⊕ High

A network metanalysis (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 (Cameron 2015).

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 metanalysis 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) (Derry 2012; Cameron 2015).
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. (Derry 2012; Cameron 2015).
In the NMA estimates, **rizatriptan** showed a better efficacy than sumatriptan on the outcomes "pain freedom" and "pain relief at 2 hours" (Cameron 2015).

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 (Cameron 2015).

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 metanalysis) 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 metanalysis) 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) (Cameron 2015).

Sumatriptan in fixed combination with naproxen

A SR by Law et al. (Law 2016) on a licensed preparation of sumatriptan 85 mg in fixed combination with naproxen 500 mg was retrieved but not included in the evidence base of this application. Naproxen is not currently available among the drugs in the EML, therefore we considered only studies comparing the sumatriptan plus naproxen combination with oral sumatriptan and we retrieved data relative 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 (Law 2016).

Studies on efficacy not included in the systematic reviews

We retrieved one randomized, double-blind, double-dummy crossover study, not included in the SRs, comparing oral sumatriptan with an active treatment in acute migraine attacks (Tepper 2015) (Table 5). A list of the excluded studies with the reason for exclusion in provided in Annex 6.

The **COMPASS** RCT 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 IHS guidelines on controlled trials of drugs in migraine (Diener 2019). 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 (Tepper 2015).

The certainty of the estimate, according to GRADE, was “Very 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 pooled 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) and recommended by the International Headache Society in clinical trials on migraine.
- Pooled estimates of high quality direct comparisons showed a statistically significant difference in favour of sumatriptan compared to ASA 900 mg + MTC 10 mg on our primary outcome (pain freedom at 2 hours).
- Pooled estimates of high quality direct comparisons shows no statistically significant differences between sumatriptan 50 and 100 mg and ASA 1,000mg and paracetamol 100mg + MTC 10mg, on our primary outcome, although point estimates of risk ratios and absolute risk differences are in favour of sumatriptan
- Pooled estimates of high quality direct comparisons between sumatriptan and other triptans for our primary outcome are available for almotriptan, eletriptan and rizatriptan. Evidence from indirect comparisons shows no efficacy difference between sumatriptan and naratriptan or frovatriptan.
- Pooled estimates of high quality direct comparisons 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 considered.
- Pooled estimates of high quality direct comparisons showed a significant difference in favour of rizatriptan 10 mg vs sumatriptan 100 mg on our primary outcome but this result has to be interpreted with caution, since no differences were observed vs lower doses of sumatriptan.

Ongoing studies

The search for ongoing studies on sumatriptan in the treatment of acute migraine retrieved two RCTs.

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.No results have been published yet (https://clinicaltrials.gov/ct2/show/NCT03185143 accessed December 9, 2020).

The second retrieved study is a phase 3, double blind RCT, aimed at evaluating the efficacy and safety of sumatriptan nasal powder (ONZETRA® Xsail®) compared to placebo in the treatment of migraine episodes with or without aura in adolescents (12 through 17 years of age). The study was started in 2017 and is still active, although not recruiting (https://clinicaltrials.gov/ct2/show/NCT03338920- accessed 30 October 2020).

Table 5 – Evidence on triptans for acute migraine considered in the present application.

Author (year)	Study design	N of studies (Type) N of participants (Type)	Intervention	Control	Outcomes	Notes
Richer 2016	SR	**27*** **(RCT on** antimigraine drugs**)** N= 7630 (children and adolescents) 24 RCT on triptans 4 RCT on other treatments for migraine (+/- triptans). --- **Studies on triptans:** Children (<12 years) 3 RCT Adolescents (12-17) years 17 RCT Mixed population (children and adolescents) 6 RCT diagnosis of migraine with or without aura, according to International Classification of Headache Disorders, (ICHD-3 beta) and HIS 1988	**Intranasal sumatriptan** (2 RCTs children) **Oral and intranasal sumatriptan** 10 RCT in adolescents 25 mg, 50 mg, 100 mg Paediatrics dosages calculated by Body Surface Area or body weight **---** **Other triptans**: Riztriptan (4 RCT), Almotriptan (1 RCT), Eletriptan (1RCT), Naratriptan (1) Zolmitriptan (4 RCT), Sumatriptan+naproxen (1 RCT) **Other medications:** Paracetamol (1 RCT) Ibuprofen (3 RCT) Dihydroergotamine (1 RCT)	**Placebo**	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	Search date: February 2016 Comparisons vs placebo only, no head-to-head studies. Pairwise metanalysis.
Derry 2012	SR	61 (RCT) N=37,250 adults (>18 years)	**Oral sumatriptan** 25mg, 50mg, 100mg, 200mg, 300mg	Placebo Other active interventions (ASA, almotriptan, eletriptan, ibuprofen, paracetamol, rizatriptan, zolmitriptan)	Efficacy: - pain-free at 1 h & 2 h (no rescue medication) - headache relief at 1 h & 2 h - sustained pain-free during 24 h post-dose (pain-free at 2 h & 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	Search date October 2011, update May 2015 Pairwise metanalysis.

Cameron 2015	SR	133 (RCT) ¶ 50,929 #	**Triptans** (Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) (all administration routes, all doses)	NSAIDs, acetylsalicylic acid (ASA), acetaminophen, ergots, opioids, or anti-emetics	Efficacy: - headache relief at 2 hours* - freedom from pain at 2 hours - sustained headache response at 24 hours* - sustained freedom from pain at 24 hours - use of rescue medication * headache relief defined as a reduction in headache intensity from moderate or severe to mild or none at 2 or 24 hours	Search date October 2013 Network metanalysis (direct and indirect comparisons among triptans, and between triptans and other drugs)
Marchenko 2015	SR	6 (observational: 5 cohort, 1 case-control) N=4,208 (Infants of women using triptans)	Women with migraine using triptans	- Healthy women - Women with migraine not using triptans	Safety: - Major congenital malformations - Prematurity - spontaneous abortions	Search date December 2013
Roberto 2014	SR	4 (observational: 1 retrospective cohort, 3 nested case-control) ** N=50,868* Persons with migraine using triptans	Persons exposed to triptans	Persons unexposed to triptans	Safety: - Cardiovascular events - stroke	
Tepper 2015	RCT Double blind, double-dummy, cross-over	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)	breath-powered intranasal delivery system of sumatriptan 22 mg	sumatriptan oral tablets 100 mg	Primary outcome: SPID-30 (sum of pain intensity differences from baseline through 30 minutes post-dose) Secondary, exploratory outcomes (at 10, 15, 30, 45, 60, 90, and 120 min. post-dose): - pain relief and pain freedom - sustained pain relief (at 120 minutes followed by no worsening of pain or second dose of study medication or rescue medication - through 24 and 48 hours after initial dose), - sustained pain freedom (no pain at 120 minutes with no recurrence of headache, use of a second dose of study medication or rescue medication taken through 24 and 48 hours after initial dose), - pain freedom for headaches treated when the baseline intensity was - mild vs moderate/severe - migraine- associated symptoms (nausea, photophobia, phonophobia, or vomiting) - subject self-assessment of meaningful pain relief, pain reduction, clinical disability	

					- consistency of pain relief across multiple migraines (for the first two, ≥two of the first three, or three of the first three migraines in each period). Safety: - treatment-emergent adverse events (at 120 minutes post-dose), serious adverse events, withdrawals for adverse events	

* 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 four CPGs featuring recommendations on triptans in the acute treatment of episodic migraine.
Three CPGs (Worthington 2013; SIGN 2018; Oskoui 2019) are focused on migraine, while the fourth one is on headaches, including migraine (NICE 2012).
Recommendations on treatment with triptans (monotherapy or combination therapy) in adults and children above 12 years of age are included in one guideline (NICE 2012); one guideline addressed specifically acute treatment of migraine in children and adolescents (Oskoui 2019).
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 alternative triptans in case of failure (SIGN 2018).
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 (NICE 2012).
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 (Worthington 2013).

The **American Academy of Neurology / American Headache Society** Guideline recommends ibuprofen oral solution (OS) (10 mg/kg) as an initial treatment option to reduce pain in children and adolescents with migraine. For adolescents with migraine, sumatriptan/naproxen oral tablet (10/60, 30/180, 85/500 mg), zolmitriptan nasal spray (5 mg), sumatriptan nasal spray (20 mg), rizatriptan oral dispersible tablet (5 or 10 mg), or almotriptan oral tablet (6.25 or 12.5 mg) are recommended to reduce headache pain.

The CPG recommends that an alternate triptan is offered if one triptan fails to provide pain relief, to find the most effective agent to reduce migraine symptoms; it is also recommended that in adolescents whose migraine is incompletely responsive to a triptan, NSAIDs (ibuprofen or naproxen) are offered in addition to a triptan to improve migraine relief.
All of the recommendations are graded Level B and take into account the availability of registered products in the US [6] (Oskoui 2019).

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 (NICE 2012).

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 (WHO Aids 2007). The guidance was a review of

[6] only almotriptan (for patients aged 12 years and older), rizatriptan (for patients aged 6–17 years), sumatriptan/naproxen (for patients aged 12 years and older), and zolmitriptan NS (for patients aged 12 years and older) are approved by the Food and Drug Administration (FDA) for use in children.

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 MTC).
Triptans were recommended as a 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 CPGs in recommending triptans (specifically, sumatriptan) as the first line treatment, or as one of the possibly effective treatments alternative to other analgesic drugs in treating acute migraine attacks.

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 world-wide (Welch 2000).
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 201 (Derry 2012).
Over 4000 infants of women exposed to sumatriptan during pregnancy have been included in observational studies alone (Marchenko 2015).
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 [7]

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

[7] 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 (Ottervanger 1994) 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 (Nappi 2003; Tfelt-Hansen 2011).

<u>Effects on the cardiovascular system.</u>

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. (CSM 1992) 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. (Stricker 1992). A later postmarketing survey based on data from Dutch general practitioners identified chest pain in 1.3% of 1727 patients (Ottervanger 1993) , 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 (Ottervanger 1994). The Australian Adverse Drug Reactions Advisory Committee (ADRAC) (Boyd 1994) 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 (Houghton 1994) 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 (Hood 1994).
ADRAC (Boyd 1994) 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 (Curtin 1992), ventricular fibrillation, (Curtin 1992; Laine 1999) or atrial fibrillation (Morgan 2000; Devadathan 2006)), acute myocardial infarction, (Ottervanger 1996, Kelly 1995; O'Connor 1995; Mueller 1996; Main 1998; Hack 2004; Anghileri 2006; Weir 2007); and unstable angina (Walton-Shirley 1995). Most of these reports concerned subcutaneous sumatriptan, but myocardial infarction (Kelly 1995; Hack 2004; Anghileri 2006; Weir 2007) and cardiac arrhythmias (Laine 1999; Devedathan 2006) (sometimes fatal) may occur after oral use.
These adverse effects have also been reported in patients with no predisposing factors. (Ottervanger 1993; Laine 1999; Hack 2004; Anghileri 2006; Weir 2007).
A review (Hillis 1993) 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 (Hall 2004) 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.

<u>Effects on the cerebrovascular system</u>

Adverse cerebrovascular effects have been reported after the use of subcutaneous sumatriptan including hemiparesis (Luman 1993), stroke (Cavazos 1994, Meschia 1998), and intracerebral haemorrhage (Edwards 1995). Cerebral vasospasm has also been reported (Dash 2004) with the use of oral sumatriptan. However, a study Hall 2004) 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, (Knoudsen 1998; Liu 2000; Naik 2002) including repeated episodes in 2 patients (Liu 2000), each within hours of a dose; some of these episodes were associated with doses above the recommended daily maximum (Liu 2000).
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 (Dachs 1995), and urticaria occurring 20 to 24 hours after oral or subcutaneous sumatriptan in another patient (Pradalier 1996).

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 (Osborne 1994; Kaube 1994; Gaist 1994) 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 (Ottervanger 1996). One study (Sullivan 1992) and an anecdotal report (Bakshi 1996) 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 (Limmroth 1999). 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 (Lloyd 1993) 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 (Meschia 1998). 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 (Db Porphyria)

10.3 - Summary of Available Data on Safety (appraisal of quality, summary of results)

Data on safety of oral sumatriptan were retrieved from the SR by Derry et al. (Derry 2012) and from the RCT not included in the SR (Tepper 2015).
Moreover, three SRs (Marchenko 2015; Roberto 2015; Thorlund 2017) and one observational study not included in the SRs, (Ephross 2014) focused on the safety of triptans were also considered.

Safety in 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)* (Richer 2016).

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

Safety in 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) (Derry 2012).
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). (Derry 2012).

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 (Thorlund 2017).
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 were the only ones 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.

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)* (Derry 2012).

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

* 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 MTC 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)* (Derry 2012).

Active comparator	Sumatriptan (dose)	N studies	N of participants	RR (95%CI)	NNH	GRADE certainty
Almotriptan 12.5mg	100mg	2	754	n.s.	n.s.	⊕⊕⊕⊕ High
Eletriptan 40 mg	50 mg	*	*	*	*	
	100 mg	*	*	*	*	
Eletriptan 80 mg	50 mg	*	*	*	*	
	100 mg	*	*	*	*	
Rizatriptan 5 mg	50 mg	2	1160	1.2 (1.0, 1.3)	n.s.	⊕⊕⊕⊕ High
Rizatriptan 10mg	50mg	2	1177	1.2 (1.0, 1.3)	n.s.	⊕⊕⊕⊕ High
	100 mg	2	856	n.s.	n.s.	⊕⊕⊕⊕ High
Zolmitriptan 2.5 mg	50mg	2	1771	1.0 (0.88, 1.2)	n.s.	⊕⊕⊕⊕ High
	100 mg	*	*	*	*	
Zolmitriptan 5 mg	50 mg	2	1790	0.91 (0.80, 1.0)	n.s.	⊕⊕⊕⊕ High
	100 mg	*	*	*	*	
ASA 1000 mg	50 mg	2	730	1.2 (0.85-1.6)	n.s.	⊕⊕⊕⊕ High
ASA 900 mg + MTC 10 mg	100 mg	2	575	***1.53 (1,.20, 1.94)***	***7.7 (4.9, 17)***	⊕⊕⊕⊕ High
Paracetamol 1000 mg + MTC 10 mg	100 mg	2	1328	***1.64 (1.42, 1.89)***	***5.5 *****	⊕⊕⊕⊕ High

* pooled estimates not available; ** calculated, MTC=metoclopramide

Cardiovascular events and stroke

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

A **metanalysis of 4 observational studies** assessed 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 (Roberto 2015).

10.4 - Summary of comparative safety against comparators

- Safety data on triptans come mainly from exposure to sumatriptan, the most widely used triptan in clinical practice; since its first authorization in 1992, millions of patients have been exposed to it.
- Compared to placebo, the frequency of adverse events is higher among patients taking sumatriptan (particularly the 100 mg dose).
- Most adverse events associated with the use of sumatriptan are mild. Serious adverse events are uncommon. No death has been reported associated with the use of triptans
- The available evidence does not suggest substantial differences across different triptans in terms of safety.
- Although in migraine trials ASA and paracetamol showed a lower frequency of adverse events than sumatriptan in the short term, their long-term use at analgesic doses in patients with frequent migraine attacks poses a risk of severe and potentially life-threatening adverse events
- Pooled data from observational studies do not show an increased risk of severe cardiovascular events associated with sumatriptan use. Available data on a possible stroke risk associated with the use of sumatriptan do not allow pooled analyses.
- One RCT not included in the aforementioned SRs provided data that do not change the conclusions of the SRs.

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

Safety of sumatriptan during pregnancy and breastfeeding

Although up to 80% of women show a reduction in frequency and intensity of attacks during pregnancy (Mattsson 2003; Sances 2003; Melhado 2005), 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 (Maggioni 1997; Aube 1999).

In the management of pain during pregnancy, acetaminophen should be considered and ASA, particularly of chronic or intermittent high doses (like is the case in women with episodic migraine), should be avoided since it may expose the mother and the newborn to potentially severe adverse events (higher haemorrhagic

risk, increased perinatal mortality, intrauterine growth restriction, and teratogenic effects). High doses of ASA may also be associated with premature closure of the ductus arteriosus, with possible pulmonary hypertension of the newborn (Briggs 2015; NICE 2012).
The American Academy of Pediatrics recommends cautious use of ASA by the mother during lactation because of potential adverse effects in the nursing infant (AAP 2001).

Sumatriptan was the first approved triptan and is the most studied triptan in pregnant women.
The available evidence from registries and observational studies including thousands of women exposed to sumatriptan during pregnancy, although with the limitations of estimates from non-randomised studies, suggest that sumatriptan can be reasonably considered as a safe therapeutic option for the treatment of migraine attacks in pregnant and breastfeeding women.

Pregnancy

Data from human and animal studies data suggest moderate teratogenic risk associated with sumatriptan use during pregnancy, due to the lack of consistent patterns among the reported birth defects.
Sumatriptan has caused toxicity and malformations in one animal species, but the drug does not appear to present a major teratogenic risk in humans (Briggs 2015).

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"). This drug should only be given during pregnancy when benefit outweighs risk.
Current section 8.1 of the FDA Summary of Product Characteristics states that sumatriptan "Based on animal data, may cause fetal harm." (FDA Label).

The **Australian Categorisation System for Prescribing Medicines in Pregnancy** labelled sumatriptan with Category B3 (Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans).

A number of **observational studies** on pregnant women taking sumatriptan during pregnancy is available.

A **metanalysis of 6 observational controlled 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) (Marchenko 2015).

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.

Table 9 – **Pregnancy outcomes among women with migraine exposed to triptans compared to those not exposed to triptans and to healthy controls from observational controlled studies** *(statistically significant differences in favor of healthy controls are in bold,)* (Marchenko 2015).

Migraine **No triptan**	MCM = 0.84 (0.61, 1.16) (Exposed=4069; unexposed=1732) PRE = 0.90 (0.35, 2.30) (Exposed=1581; unexposed=1231) SA = 1.27 (0,58, 2.79) (Exposed=172; unexposed=188)	
Healthy controls	MCM = 1.18 (0.97, 1.44) (Exposed=4208; unexposed=1,465,082) PRE = 1.16 (0.67, 1.99) (Exposed=1720; unexposed=251,085) **SA = 3.54 (2.24, 5.59)** (Exposed=178; unexposed=50,865)	**MCM = 1.41 (1.11, 1.80)** (Exposed=1735; unexposed=1,408,557) PRE = 1.44 (0.66, 3.16) (Exposed=1274; unexposed=194,560)
	Migraine **Triptan**	**Migraine** **No triptan**

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

A SR by the **UK National Clinical Guideline Centre (NCGC)**, commissioned by the NICE to inform an NHS guideline on headache (updated in 2015) 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 (Shuhaiber 1998) was included in the SR by Marchenko (Marchenko 2015).
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 (Marchenko 2015).
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 ASA for migraine are potentially harmful in pregnancy, the guideline panel issued guidance informed by this SR, recommending paracetamol as a first choice, and to consider a triptan or an NSAID as an alternative option after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy (NICE 2012).

The **Sumatriptan, Naratriptan and Treximet® Pregnancy Registry** was a prospective, observational, uncontrolled, international study sponsored by GlaxoSmithKline performed from January 1, 1996 to September 19, 2012 (Ephross 2014). 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. Observation included 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.
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) (Ephross 2014).

Breastfeeding

Sumatriptan is excreted in maternal milk (see chapter 7.1).
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 (AAP 2001).
However, licensed product information suggests that infant exposure can be minimised by avoiding breast feeding for 8 (Briggs 2015) or 12 hours (FDA Label) after taking sumatriptan.
Product information on the use of triptans other than sumatriptan during breastfeeding reports that available evidence is poor or suggests avoiding breast feeding for 24 hours.

Sumatriptan in patients with cardiovascular disease

Triptans can induce vasoconstriction that may potentially increase the risk of cardiovascular events (see section 10.2 and 10.3). Therefore, sumatriptan is not indicated in patients with history of cardiovascular- or cerebrovascular disease.
Current evidence does not suggest 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 17).

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

Drug	DDD	High/Low Ratio	Price (US $)	Price DDD (US $)	WHO EML
Acetylsalicylic Acid 500 mg TAB-CAP (PO)	3g				E
Supplier Number of Prices=8		2.13	0.0047/TAB-CAP (median)	0.0282	
Buyer Number of Prices=2		26.19	0.0490/TAB-CAP (median)	0.0391	
Paracetamol 500 mg TAB-CAP (PO)	3 g				E
Supplier Number of Prices=13		2.03	0.0044/TAB-CAP (median)	0.0264	
Buyer Number of Prices=5		1.94	0.0058/TAB-CAP (median)	0.0348	

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 varies: some databases (such as the Italian Farmadati and the US Center for Medicare and Medicaid Services, CMS) provide the retail price and some others (such as the UK Prescription Services) the reimbursement price.
The Common European Drugs Database (CEDD) is not currently updated.
In Europe sumatriptan has been authorized through national instead of centralized procedure, making it difficult to compare its cost across 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.

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 November 26,2020 (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 November 26, 2020))

Drug	Quantity	Basic Price pence	Unit Price £	Brand
Almotriptan 12.5mg tablets	6	1668	2,78	
Eletriptan 20mg tablets	6	2250	3,75	**X**
Eletriptan 40mg tablets	6	2250	3,75	**X**
Frovatriptan 2.5mg tablets	6	614	1,02	
Rizatriptan 10mg tablets	3	287	0,96	
Rizatriptan 5mg tablets	6	2673	4,46	
Zolmitriptan 5mg tablets	6	3600	6	**X**
Zolmitriptan 2.5mg odispersible tablets sugar free	6	992	1,65	
Sumatriptan 100mg tablets	**6**	**150**	**0,25**	
Sumatriptan 50mg tablets	**6**	**129**	**0,22**	
Paracetamol 500mg tablets	32	113	0,04	
Aspirin 300mg tablets	32	342	0,11	

Table 12 - CMS US - Weekly NADAC Reference File *(as of 25/11/2020)*. **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
(accessed November 26, 2020)

NDC Description	NADAC * Per Unit (US $)	Effective Date
ALMOTRIPTAN MALATE 12.5 MG TAB	19,03958	11/25/2020
FROVATRIPTAN SUCC 2.5 MG TAB	30,740370	11/25/2020
ELETRIPTAN HBR 20 MG TABLET	5,71553	11/25/2020
ELETRIPTAN HBR 40 MG TABLET	5,50641	11/25/2020
RIZATRIPTAN 10 MG TABLET	0,63988	11/18/2020
RIZATRIPTAN 5 MG TABLET	0,78431	11/18/2020
ZOLMITRIPTAN 2.5 MG TABLET	5,04306	11/18/2020
ZOLMITRIPTAN 5 MG ODT	4,78939	11/18/2020
SUMATRIPTAN SUCC 100 MG TABLET	0,56470	**11/18/2020**
SUMATRIPTAN SUCC 50 MG TABLET	0,55349	**11/18/2020**

* **NADAC Per Unit**: The National Average Drug Acquisition Cost per unit is the result of a survey of US retail prices produced by Myers & Stauffer, LC. NADAC files provide state Medicaid agencies covered outpatient drug information regarding retail prices for prescription drugs.

Table 13 - Italy pharmacy retail price of triptans, paracetamol and aspirin
http://www.farmadati.it/ (accessed November 26, 2020)

Italy Pharmacy retail price		
Drug	**NPP Unit Price (€)**	**Brand Unit Price (€)**
Sumatriptan 100mg tablets	3,25	3,75
Sumatriptan 50mg tablets	1,5	2
Eletriptan 20mg tablets	2,61-	3,94
Eletriptan 40mg tablets	3,5	4,83
Almotriptan 12.5mg tablets	2,89	3,31
Paracetamol 500mg tablets	0,14-0,25	0,18
Aspirin 500mg tablets	0,18	0,365

NPP=Non-Proprietary Name

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

	France^		**Germany§**		**Norway°**	
Drug	**NPP Unit Price range (€)**	**Brand Unit Price range (€)**	**NPP Unit Price (€)**	**Brand Unit Price (€)**	**NPP Unit Price (€)**	**Brand Unit Price (€)**
Sumatriptan 100mg tablets	-	-	3,2	8,57	3,9	3,9
Sumatriptan 50mg tablets	1,47	1,53	2,8	5,16	2,88	2,88
Eletriptan 20mg tablets	1,46	1,46	5,24	6,71	3,01	3,01
Eletriptan 40mg tablets	1,46	1,46	5,48	5,49	2,89	3,01
Almotriptan 12.5mg tablets	1,46	1,46	-	7,14	4,62	4,62
Paracetamol 500mg tablets	0,13	0,13	0,06	0,24	-	-
Aspirin 500mg tablets	0,13	-	0,19	0,33 0,35	-	-

NPP=Non-Proprietary Name; ^ *France http://base-donnees-publique.medicaments.gouv.fr/index.php#result (accessed 26.11.2020)*
§ Germany https://www.dimdi.de/dynamic/en/drugs/reference-pricing/ (accessed 26.11.2020)
° Norway https://legemiddelverket.no/english/price-and-reimbursement/maximum-price#determination-of-maximum-price (accessed 26.11.2020)

Comparative cost-effectiveness

Available evidence on cost-effectiveness of triptans in acute migraine has several limitations.

Firstly, when addressing comparative cost-effectiveness, one should consider that in migraine, unlike other conditions, **economic factors** linked to the cost of illness (including direct and indirect costs) and the potential savings that may be achieved by implementing specific management strategies have not been thoroughly assessed yet (Mennini 2008).
A recent overarching review found that the most recent economic modelling on triptans in episodic migraine was published in 2013 (Ruggeri 2020).
Moreover, most of the available literature on cost-effectiveness and cost-utility of migraine treatments provides inconsistent results, due to heterogeneous methodological approaches.

Secondly, published health economic evaluations are mainly performed in **high-income countries**, therefore their conclusions cannot be generalized, and only in part transferred, to low- and middle-income countries. Transferability of results is particularly poor for economic evaluations of symptomatic treatments for migraine, such as triptans (Ruggeri 2020).
For example, the NICE guideline on headache disorders issued by NICE in 2012 recommended a triptan in combination with NSAID as the most cost-effective treatment for the management of acute migraine. Such guidance was informed by a cost-effectiveness analysis suggesting that a triptan in combination with paracetamol was the second most cost-effective intervention, although being more costly than other strategies (NICE 2012). However, such estimates were modelled in a high-income country and may not be transferable to a low- or middle-income country.

Thirdly, when comparing triptans with NSAIDs, **long-term safety** is a crucial factor to be considered, in addition to the direct cost of the drug.
Using triptans for acute migraine implies incremental direct cost in comparison with ASA or other less expensive NSAIDs and paracetamol. However, if the comparative risk of medium- and long-term adverse events is considered, comparative cost-effectiveness and incremental cost-effectiveness ratio (iCER) may change considerably.
Head-to-head trials in migraine show for ASA and paracetamol a lower frequency of adverse events than sumatriptan (Derry 2012). However, in these trials efficacy and safety were measured over one to three consecutive attacks, without considering the long term-risk of adverse events associated with chronic use of NSAIDs, that should be included in the population perspective of a health economic evaluation.

A cost-effectiveness analysis of interventions for migraine in low- and middle-income countries was performed by means of the methods and tools developed by WHO-CHOICE, suggesting that the annual cost of different therapeutic strategies may vary greatly, and that variability is mainly driven by the cost of drugs.
ASA was the most cost-effective management strategy of acute migraine, 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 (Linde 2015).
Data on which this model was based allow better transferability to low- and middle-income countries. However, the main limitation of this study was that it did not take into account paracetamol among the treatment options, as well as the indirect cost of migraine (representing a substantial factor when evaluating cost-effectiveness) and the differential cost of adverse events associated with chronic use of NSAIDs vs. alternative treatments, such as triptans.

Given their good safety profile, incorporating a benefit-risk balance instead of just efficacy as the outcome may give results more favorable for triptans, even when compared with less expensive alternatives.

A network metanalysis compared all seven available triptans and their cost-effectiveness by means of a decision-tree model, assuming as the primary outcome the incremental cost per additional sustained pain-freedom with no adverse events. The results suggested that at willingness-to-pay thresholds by payers lower than US $ 44 per outcome, sumatriptan was the best treatment choice when considering cost-effectiveness (Asseburg 2012). In other words, on a population health perspective, the cost-effectiveness of reaching a favorable clinical outcome associated with no adverse events depends largely on the payer's willingness to pay for it, which in the case of triptans may be largely determined by the cost of the drug.

Due to the great variability of its price across countries (Table 15), sumatriptan is a highly cost-sensitive treatment. Achieving a reduction of its average price by 50% would have a considerable effect on its cost-effectiveness (Linde 2015).

Another factor that should be considered when addressing the cost-effectiveness of triptans is the timeliness of treatment, since triptans are most effective if used early in migraine attacks, when pain is still mild (Goadsby 2008). Basing on this assumption, in some countries (Germany, New Zealand, United Kingdom, Sweden) triptans have been re-classified as OTC drugs, valuing not only a timely access to medicines by patients, but also enhancement of self-management (Gauld 2014). However, risks include suboptimal therapy due to poor adherence and adverse effects. In fact, health authorities of some countries, like Australia, rejected re-classification, based on safety concerns.
However, a modeled economic evaluation combining efficacy and safety data from various sources suggested that, in the Australian health care system, reclassifying triptans as OTC drugs is likely to be considered cost-effective by decision-makers. In such model the adverse events associated with the use of triptans were balanced with gastro-toxicity and MOH as risks of treatment with NSAIDs (Parkinson 2019).

Lastly, when comparing cost of sumatriptan and ASA several factors need to be considered. A simple price comparison shows that sumatriptan is many times more expensive than ASA. However, unlike sumatriptan, indicated only as symptomatic treatment in migraine, ASA is mass-produced and available in many dosages with numerous indications in a number of conditions, both as preventive and as symptomatic treatment. Such aspects are important in determining a low production cost for ASA and therefore its low price. In facts, most essential medicines would compare negatively to ASA in terms of final price. The main question is whether the current price of triptans constitutes a major drain on resources that could be used for other purposes, or whether it can be considered a viable investment given the advantages associated with this class of medicines.

In summary, all triptans are available as generic drugs, but sumatriptan has the lowest price in most countries, including low- and middle-income ones.
Cost-effectiveness of sumatriptan in acute migraine is largely dependent on the cost of the drug. Achieving a reduction of its average price could have a remarkable impact on its cost-effectiveness when compared with less expensive alternatives, such as ASA and paracetamol.
If comparative cost-effectiveness modeling takes into account long-term safety, sumatriptan may become appealing even at its current price in situations of low willingness-to-pay by decision-makers.

Table 15 - 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 November 26, 2020) (Adapted from Linde 2015 and updated).

Drug	***Dose***	***Source***	***China***	***Russia***	***Zambia***	***India****	***South Africa *****
ASA	500 mg	International Drug Price indicator guide	$ 0.004	$ 0.004	$ 0.004	$ 0.004	
Sumatriptan	50 mg	IMS database	$ 0.81	$ 1.07	$ 0.66	$ 0.69 *	$ 2.23**
Almotriptan	12.5 mg		$ 5.19	$ 5.19	$ 5.19	$ 1,18	

* Government of India, National Pharmaceutical Pricing Authority. http://www.nppaindia.nic.in/index1.html (accessed December 3, 2018) List of Ceiling prices fixed for scheduled formulation under DPCO 2013 (NLEM 2015). Updated 25/03/2020. Sumatripan 50 mg= 51,38 Rs/unit = US$ 0,69

** South African Medicine Price Registry (Database of Medicine Price) https://medicineprices.org.za/#search:sumatrip (accessed November 26,2020 Sumatriptan 50 mg 34,17 ZAR/unit = US$ 2,23 ;

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 (TGA).
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 (WHO ATC-DDD)

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 formulation for subcutaneous injection (3 mg/ml) and a new dosage form for nasal route (11 mg powder) and in 2019 approved a new dosage form as nasal spray (10 mg), that are all not available as generic products.

Formulation(s) and strength(s) available (DrugBank).

Sumatriptan	25 mg, 50 mg, 100 mg Tablets (oral route)
	3 mg/0.5 ml, 4 mg/0.5 ml, 6 mg/0.5 ml solution/injection (Subcutaneous route)
	5 mg, 10 mg, 20 mg nasal spray (nasal route). 11 mg nasal powder

Table 16 – ATC classification and DDDs, indications and generic drug availability of triptans

ATC *	Name INN	DDD *	U *	Admin Route *	Recommended dose** (max.dose in 24 h)	Adults (age 18-65)[1] **	Adolescents (age 12-17) **	Children (age < 11) **	Generic drug availability ***
N02CC01	sumatriptan	20	mg	N	nasal spray:20 mg (40 mg) [3]	yes	under specialist/physician consultation. Reccomended dose: 10 mg (20 mg)	no	Yes[4]
		50	mg	O	50 mg (300 mg)	yes	no	no	
		6	mg	P	6 mg (12 mg)	yes	no	no	
N02CC02	naratriptan[2]	2.5	mg	O	2,5 mg (5 mg)	yes	no	no	yes
N02CC03	zolmitriptan	2.5	mg	O	2,5 mg (10 mg)	yes	no	no	yes
		2.5	mg	N	5 mg (10 mg)	yes	no	no	no
N02CC04	rizatriptan	10	mg	O	10 mg (20 mg)	yes	no	no	yes
N02CC05	almotriptan	12.5	mg	O	12,5 mg (25 mg)	yes	no	no	yes
N02CC06	eletriptan	40	mg	O	40 mg (80 mg)	yes	no	no	yes
N02CC07	frovatriptan	2.5	mg	O	2,5 mg (5 mg)	yes	no	no	yes

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

***** WHO Collaborating Centre for Drug Statistics Methodology (WHO ATC-DDD); ****** Electronic Medicines Compendium (eMC)

[1] All drugs are not recommended in patients older than 65 age. [2] not available in Italy [3] 10 mg (30 mg) for 10 mg nasal spray

******* Generic availability: UK (https://www.medicines.org.uk/emc/), Canada (https://www.drugbank.ca/), Italy:https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/home) US (https://www.drugs.com/sumatriptan.html).

[4] New FDA approvals are not available as generic

Table 17 – Authorized indications of sumatriptan and use in specific populations

US Food and Drugs Administration (FDA)*	**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 dosing 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
Australian Government, Dept. of Health, Therapeutic Goods Administration**	**Sumatriptan tablets, injection and nasal spray** 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. There is no information available on the use of sumatriptan in the treatment of basilar or hemiplegic migraine. **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.
Health Canada #	**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.

*https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020080 (Accessed December 1, 2020)

** https://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg (Accessed December 1, 2020)

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index-eng.php (Accessed December 1, 2020)

13. Availability of pharmacopoeial standards

- British Pharmacopeia: yes (as sumatriptan)
- US Pharmacopeia (USP 31th revision): yes (as sumatriptan)
- European Pharmacopeia: yes (as sumatriptan)

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Annex 1 - IHS diagnostic criteria of migraine (IHS 2018)

Migraine without aura

A. At least five attacks[1] 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 ≥5 minutes
   2. two or more aura symptoms occur in succession
   3. each individual aura symptom lasts 5–60 minutes[1]
   4. at least one aura symptom is unilateral[2]
   5. at least one aura symptom is positive[3]
   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 ≥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 ≥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

Guideline Producer (year) ***Title***	**SIGN** **(2018)** (SIGN 2018) *Pharmacological Management of Migraine*	**Canadian Headache Society** **(2013)** (Worthington 2013) *Acute Drug Therapy for Migraine Headache*
Population	Adults and adolescents	Adults
Disorder	Migraine	Migraine
Acute treatment Episodic migraine	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.	*Strong recommendation, high quality evidence* 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.
Pregnancy-child-bearing age	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	Not considered
Children/ Adolescents	Not considered	Not considered

Annex 2 - Synopsis of the recommendations from clinical practice guidelines on treatment of the acute migraine attack (contd.)

Guideline Producer (year) Title	**American Academy of Neurology/American Headache Society (2019)** [Oskoui 2019] *Practice guideline update summary: Acute treatment of migraine in children and adolescents*	**NICE** (**2012**, updated **2015**) [77] *Diagnosis and Management of Headaches in Young People and Adults*
Population	Children and adolescents	Adults and children >12 years
Disorder	Migraine	Headache - Migraine
Acute treatment Episodic migraine	Clinicians should prescribe ibuprofen oral solution (OS) (10 mg/kg) as an initial treatment option to reduce pain in <u>children and adolescents</u> with migraine (Level B)* For <u>adolescents</u> with migraine, clinicians should prescribe sumatriptan/naproxen oral tablet (OT) (10/60, 30/180, 85/500 mg), zolmitriptan nasal spray (NS) (5 mg), sumatriptan NS (20 mg), rizatriptan oral dispersible tablet (ODT) (5 or 10 mg), or almotriptan OT (6.25 or 12.5 mg) to reduce headache pain (Level B).* Clinicians should offer an alternate triptan, if 1 triptan fails to provide pain relief, to find the most effective agent to reduce migraine symptoms (Level B). In adolescents whose migraine is incompletely responsive to a triptan, clinicians should offer ibuprofen or naproxen in addition to a triptan to improve migraine relief (Level B).	Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol (*) 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 (*) 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.
Children/ Adolescents	* only almotriptan (for patients aged 12 years and older), rizatriptan (for patients aged 6–17 years), sumatriptan/naproxen (for patients aged 12 years and older), and zolmitriptan NS (for patients aged 12 years and older) are approved by the Food and Drug Administration (FDA) for use in children.	For <u>young people aged 12–17 years</u> consider a nasal triptan in preference to an oral triptan.
Pregnancy-child-bearing age	*Not considered*	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

Annex 3 – Search strategies; results of the search strategy and process of inclusion

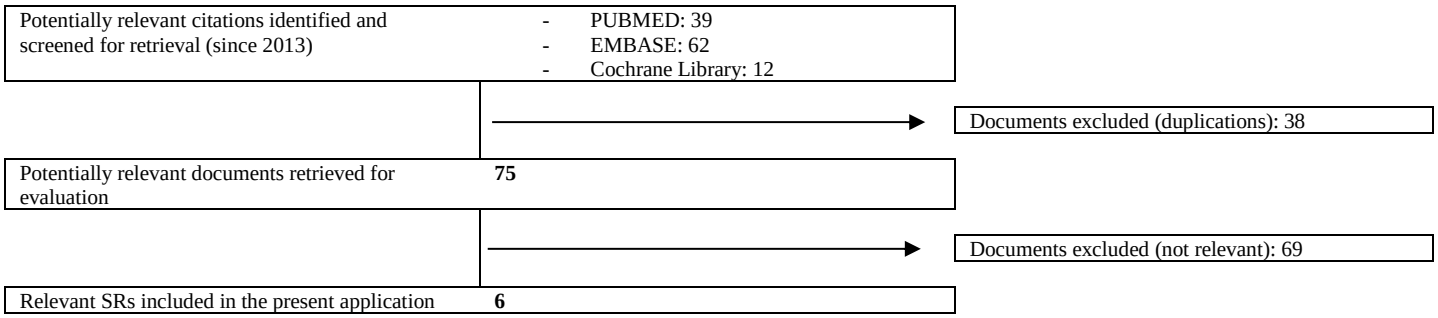
The following search strategy was performed in October 2018:

- **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)

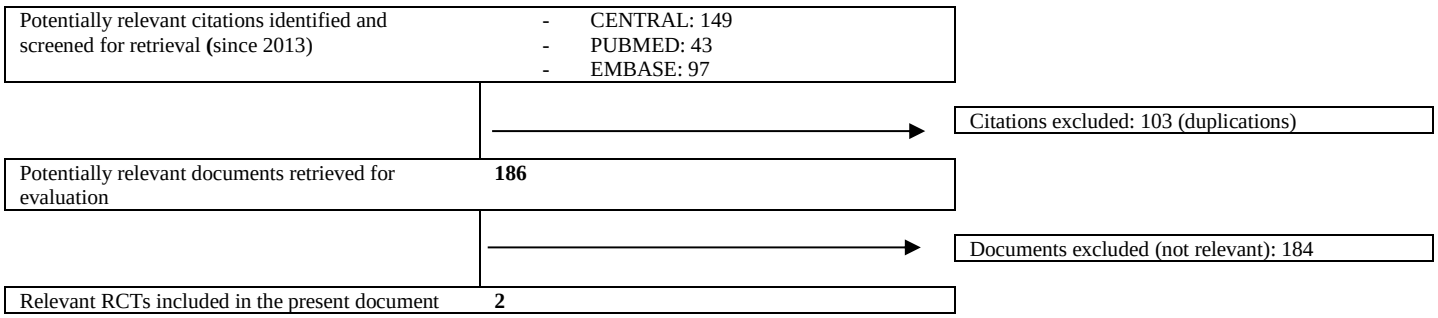
PRISMA Flow Diagram

Clinical guidelines

SRs



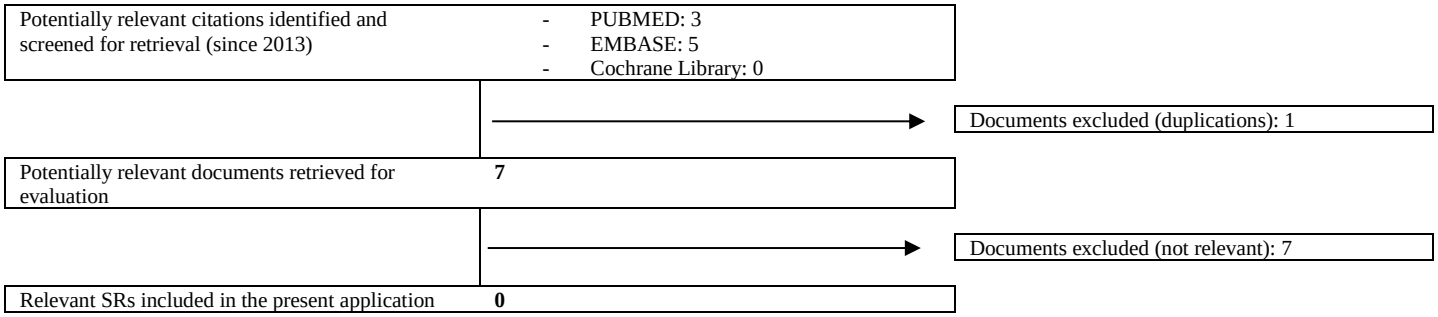
RCTs



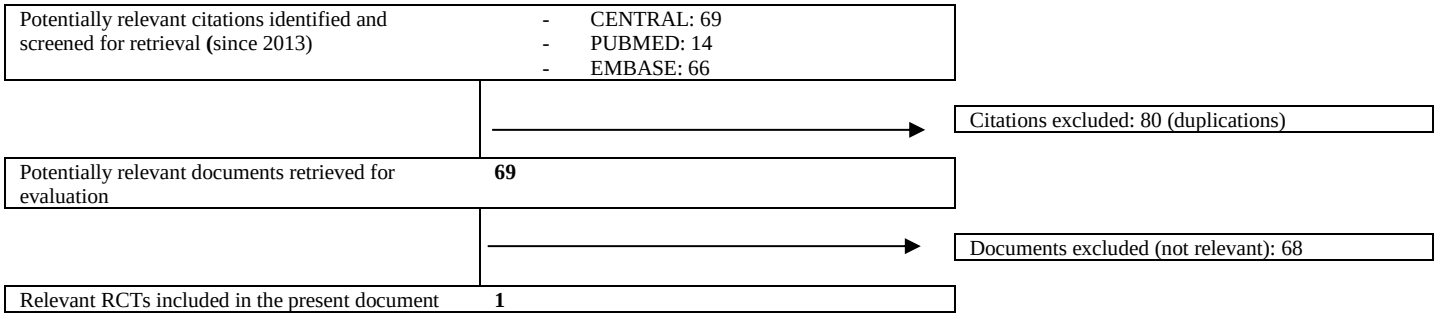
The above search strategy was re-launched on October 28, 2020, retrieving the following references:

Clinical guidelines

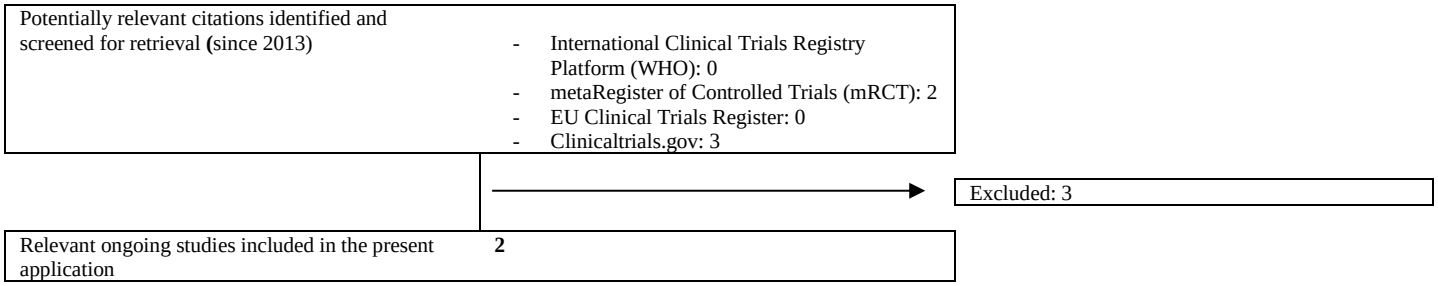
SRs



RCTs



Ongoing studies



Annex 4 - List of manufacturers that have active status in the *Drug Master File* of the Food and Drug Administration (FDA) (update September 2020)

DMF#	SUBMIT DATE	HOLDER	SUBJECT
15376	4/5/2001	QUIMICA SINTETICA SA	SUMATRIPTAN SUCCINATE
16279	12/2/2002	SMS PHARMACEUTICALS LTD	SUMATRIPTAN SUCCINATE
16534	3/21/2003	DR REDDYS LABORATORIES LTD	SUMATRIPTAN SUCCINATE
16930	10/23/2003	NATCO PHARMA LTD	SUMATRIPTAN SUCCINATE
17352	4/29/2004	MOEHS IBERICA SL	SUMATRIPTAN SUCCINATE
17397	5/25/2004	CIPLA LTD	SUMATRIPTAN SUCCINATE USP
19330	3/31/2006	AUROBINDO PHARMA LTD	SUMATRIPTAN SUCCINATE USP
19340	4/11/2006	ORCHID PHARMA LTD	SUMATRIPTAN SUCCINATE
19372	4/19/2006	SUN PHARMACEUTICAL INDUSTRIES LTD	SUMATRIPTAN SUCCINATE USP
20746	8/3/2007	SMS PHARMACEUTICALS LTD	SUMATRIPTAN SUCCINATE (ALTERNATIVE SYNTHESIS)
20894	10/1/2007	NATCO PHARMA LTD	SUMATRIPTAN SUCCINATE (INJECTABLE GRADE)
20906	10/3/2007	SMS PHARMACEUTICALS LTD	SUMATRIPTAN USP (ALTERNATIVE SYNTHESIS)
21711	6/3/2008	MYLAN LABORATORIES LTD	SUMATRIPTAN SUCCINATE USP
22482	2/5/2009	MSN PHARMACHEM PRIVATE LTD	SUMATRIPTAN SUCCINATE USP [ROUTE CODE - "SU"]
23442	1/8/2010	MSN PHARMACHEM PRIVATE LTD	SUMATRIPTAN USP [ROUTE CODE - "SN"]
23624	3/10/2010	DIVIS LABORATORIES LTD	SUMATRIPTAN SUCCINATE AND SUMATRIPTAN
24026	8/2/2010	MOEHS IBERICA SL	SUMATRIPTAN
28590	8/26/2014	ASYMCHEM LIFE SCIENCE TIANJIN CO LTD	SUMATRIPTAN SUCCINATE
32218	11/15/2017	AUROBINDO PHARMA LTD	SUMATRIPTAN SUCCINATE USP (PROCESS II)

https://www.fda.gov/drugs/drug-master-files-dmfs/list-drug-master-files-dmfs, accessed: November 24, 2020

Annex 5 - International availability and proprietary names of sumatriptan *

Medicine	Country, trade name and pharmaceutical industry
International availability and proprietary names of sumatriptan	**AFRICA** **SOUTH AFRICAN REPUBLIC: Imigen® | Mylan; Imigran® | Aspen; Migrex ® | Sandoz; Triptam® | Aspen** **AMERICAS** **ARGENTINA: Imigran® | GSK; Micranil® | Pharmadorf; Migraneitor® | Lafedar; Migratriptan® | Craveri; Rontadol® | Lafedar. BRASIL: Imigran® | GSK; Sumax® | Libbs Sutriptan® | Actavis. CANADA: Imitrex® | GSK. CHILE: Somatran® | Andromaco. MEXICO: Fermig® | Raam; Imigran® | GSK; Sumitrex® | Bajamed; Tebegran® | Collins.** **usa: Imitrex® | GSK; Onzetra® | Avanir; Zembrace® | Reddy.** **VENEZUELA: Imigran® | GSK; Migraval® | Giempi.** **ASIA** **PHILIPPINES: Imigran® | GSK; Sumig® | XL; Sumigran® | InnoGen. JAPAN: Imigran® | GSK. HONG KONG: Imigran® | GSK; Sumacta® | Actavis. INDIA: Migratan® | Dabur Suminat® | Sun. INDONESIA: Triptagic® | Tempo Scan Pacific. MALAYSIA: Imigran® | GSK; Sumitran® | Reddy. SINGAPORE: Imigran® | GSK; Sumatran® | Sandoz; Sumitran® | Reddy. THAILAND: Imigran® | GSK** **OCEANIA** **AUSTRALIA: Clustran® | Sun; Imigran® | Aspen; Iptam® | Alphapharm; Sumagran® | Arrow Sumatab® | Alphapharm; Sumatran® | Arrow. NEW ZEALAND: Imigran® | GSK; MyGran ® | Actavis; Sumagran® | Mylan.** **EUROPEAN UNION** **AUSTRIA: Imigran® | Glaxosmithkline Pharma Gmbh; Sumatriptan 1a Pharma® | 1a Pharma Gmbh; Sumatriptan Hexal® | Hexal Pharma Gmbh; Sumatriptan Sandoz® | Sandoz Gmbh; Sumatriptan Stada® | Stada Arzneimittel Gmbh BELGIUM: Imitrex Instant® | Glaxosmithkline Pharmaceuticals Sa; Imitrex Sc® | Glaxosmithkline Pharmaceuticals Sa Imitrex® | Glaxosmithkline Pharmaceuticals Sa; Sumatriptan Eg® | Eurogenerics N.V./S.A.; Sumatriptan Mylan® | Mylan Bvba/Sprl; Sumatriptan Sandoz® | Sandoz N.V.; Sumatriptan Teva® | Teva Pharma Belgium N.V./S.A BULGARIA: Амигрен® | Adipharm Ead; Имигран® | Glaxosmithkline Eood; Хедан® | Actavis Group Ptc Ehf. CIPRO: Imigran® | Glaxosmithkline (Ireland) Limited CROATIA: Imigran® | Glaxosmithkline D.O.O.; Sumigra® | Sandoz D.O.O. DENMARK: Imigran Sprint® | Glaxosmithkline Pharma A/S; Imigran® | Glaxosmithkline Pharma A/S; Sumatriptan Accord® | Accord Healthcare B.V. Sumatriptan Aurobindo® | Aurobindo Pharma (Malta) Limited; Sumatriptan Bluefish® | Bluefish Pharmaceuticals Ab; Sumatriptan Gsk® | Glaxosmithkline Pharma A/S; Sumatriptan Mylan® | Mylan Ab; Sumatriptan Sandoz® | Sandoz A/S; Sumatriptan Sun® | Sun Pharmaceutical Industries Europe B.V.; Sumatriptan Teva® | Teva B.V ESTONIA: Cinie® | Zentiva, K.S.; Imigran Fdt® | Glaxosmithkline (Ireland) Limited; Migriptan® | Stada Arzneimittel Ag; Sumatriptan Actavis® | Actavis Group Ptc Ehf. FINLAND: Imigran Radis® | Glaxosmithkline Oy; Imigran® | Glaxosmithkline (Ireland) Limited; Imigran® | Glaxosmithkline Oy; Oriptan® | Orion Corporation; Sumatriptan Accord® | Accord Healthcare B.V.; Sumatriptan Sandoz® | Sandoz A/S; Sumatriptan Teva® | Teva Sweden Ab FRANCE: Imigrane® | Laboratoire Glaxosmithkline; Imiject® | Laboratoires Paucourt; Sumatriptan Sun® | Sun Pharmaceutical Industries Europe B.V.; Sumatriptan Teva® | Teva Santé GERMANY: Imigran® | Glaxosmithkline Gmbh & Co. Kg; Imigran-Inject® | Glaxosmithkline Gmbh & Co. Kg; Imigran-T® | Glaxosmithkline Gmbh & Co. Kg; Sumatriptan 1 A Pharma® | 1 A Pharma Gmbh; Sumatriptan Abz® | Abz-Pharma Gmbh; Sumatriptan Aiwa® | T&d Pharma Gmbh; Sumatriptan Al® | Aliud Pharma Gmbh; Sumatriptan Aurobindo® | Aurobindo Pharma Gmbh; Sumatriptan Beta® | Betapharm**

	Arzneimittel Gmbh; Sumatriptan Bluefish® | Bluefish Pharmaceuticals Ab; Sumatriptan Dura® | Mylan Germany Gmbh; Sumatriptan Hexal® | Hexal Ag; Sumatriptan Hormosan® | Hormosan Pharma Gmbh; Sumatriptan Puren® | Puren Pharma Gmbh & Co. Kg; Sumatriptan Ratiopharm® | Ratiopharm Gmbh; Sumatriptan Stada® | Stada Arzneimittel Ag; Sumatriptan Stada® | Stadapharm Gmbh; Sumatriptan-Hexal N® | Hexal Ag; Sumy® | Hexal Ag; Tempil® | Hormosan Pharma Gmbh; Tripti Hexal® | 1 A Pharma Gmbh GREECE: Forcet® | Target Pharma Single Member Private Ltd; Imigran® | Glaxosmithkline Aebe; Sumatriptan Generics® | Generics Pharma Hellas Ltd; Sutriptan® | Verisfield S.M.S.A ITALY: Imigran® | Glaxosmithkline; Sumatriptan Accord | Accord Healthcare Italia; Sumatriptan Aurobindo | Aurobindo Pharma Italia; Sumatriptan DOC | DOC Generici; Sumatriptan EG | EG; Sumatriptan MYLAN | MYLAN; Sumatriptan SANDOZ | SANDOZ; Sumatriptan SUN | SUN Pharma Italia; Sumatriptan TEVA | TEVA Italia; Sumatriptan ZENTIVA | ZENTIVA Italia; IRELAND: Imigran Ftab® | Glaxosmithkline (Ireland) Limited; Imigran® | Glaxosmithkline (Ireland) Limited; Sumatran Relief® | Rowex Ltd; Sumatran® | Rowex Ltd; Sumatriptan Accord Healthcare Ireland® | Accord Healthcare Ireland Limited ICELAND: Imigran Juvenil® | Glaxosmithkline Pharma A/S; Imigran Radis® | Glaxosmithkline Pharma A/S; **Imigran® | Glaxosmithkline Pharma A/S; Sumatriptan Apofri® | Apofri Ab; Sumatriptan Bluefish® | Bluefish Pharmaceuticals Ab LATVIA: Cinie® | Zentiva, K.S. LITHUANIA: Cinie® | Zentiva, K.S.; Imigran T® | Glaxosmithkline Lietuva Uab; Imigran® | Glaxosmithkline Lietuva Uab; Migriptan® | Stada Arzneimittel Ag; Sumatriptan Actavis® | Actavis Group Ptc Ehf. LUXEMBOURG: Imitrex Instant® | Glaxosmithkline Pharmaceuticals Sa; Imitrex Sc® | Glaxosmithkline Pharmaceuticals Sa; Imitrex® | Glaxosmithkline Pharmaceuticals Sa; Sumatriptan Eg® | Eurogenerics N.V./S.A. MALTA: Imigran® | Glaxosmithkline (Ireland) Limited; Sumatriptan Aurobindo® | Aurobindo Pharma (Malta) Limited NORWAY: Imigran Juvenil® | Glaxosmithkline As; Imigran Radis® | Glaxosmithkline As; Imigran® | Glaxosmithkline As; Sumatriptan Aristo® | Aristo Pharma Gmbh (Art 57); Sumatriptan Aurobindo® | Aurobindo Pharma (Malta) Limited; Sumatriptan Bluefish® | Bluefish Pharmaceuticals Ab; Sumatriptan Sandoz® | Sandoz A/S; Sumatriptan Sun® | Sun Pharmaceutical Industries Europe B.V.; Sumatriptan Teva® | Teva Sweden Ab NETHERLANDS: Imigran Ftab® | Glaxosmithkline B.V.; Imigran S.C.® | Glaxosmithkline B.V.; Imigran® | Glaxosmithkline B.V.; Sumatriptan Accord® | Accord Healthcare B.V.; Sumatriptan Apotex® | Apotex Europe B.V.; Sumatriptan Aurobindo® | Aurobindo Pharma B.V.; Sumatriptan Ipca® | Ipca Productos Farmaceuticos Unipessoal Lda; Sumatriptan Mylan® | Mylan B.V.; Sumatriptan Pch® | Pharmachemie B.V; Sumatriptan Pch® | Teva Nederland B.V.; Sumatriptan Sandoz B.V.® | Sandoz B.V.; Sumatriptan Sandoz® | Sandoz B.V. Sumatriptan Sun® | Sun Pharmaceutical Industries Europe B.V.; Sumatriptan Teva® | Teva Nederland B.V. POLONIA: Amigrenex® | Exeltis Poland Sp. Z O.O.; Cinie 100® | Zentiva, K.S.; Cinie® | Zentiva, K.S.; Frimig® | Orion Corporation; Imigran Fdt® | Glaxosmithkline (Ireland) Limited; Imigran® | Glaxosmithkline (Ireland) Limited; Sumamigren Control® | Medana Pharma Spolka Akcyjna; Sumamigren® | Zaklady Farmaceutyczne "polpharma" Spolka Akcyjna; Sumatriptan Apotex® | Apotex Europe B.V.; Sumatriptan Aurovitas® | Aurovitas Pharma Polska Sp. Z O.O; Sumatriptan Medical Valley® | Medical Valley Invest Ab Sumatriptan Sun® | Sun Pharmaceutical Industries Europe B.V.; Sumigra 100® | Sandoz Gmbh; Sumigra® | Sandoz Gmbh PORTUGAL: Imigran® | Glaxo Wellcome Farmacêutica, Lda UNITED KINGDOM: Imigran Radis® | Glaxosmithkline Uk Limited; Imigran Recovery® | Accord Healthcare Limited; Imigran Subject® | Glaxo Wellcome Uk Limited Imigran® | Glaxo Wellcome Uk Ltd; Imigran® | Glaxo Wellcome Uk Ltd Trading As Glaxosmithkline Uk; Migraine Recovery® | Teva Uk Limited; Migraine Relief® | Teva Uk Limited; Migraitan® | Bristol Laboratories Ltd (Berkhamsted); Numark Migraine Relief® | Teva Uk Limited; Sumatriptan Accord Healthcare® | Accord Healthcare Limited; Sumatriptan Activase Pharmaceuticals® | Activase Pharmaceuticals Limited; Sumatriptan Almus® | Teva Uk Limited; Sumatriptan Bristol Laboratories® | Bristol Laboratories Ltd (Berkhamsted); Sumatriptan Consilient Health® | Consilient Health Ltd; Sumatriptan Crescent Pharma® | Crescent Pharma Limited; Sumatriptan Dexcel Pharma® | Dexcel Pharma Ltd; Sumatriptan Dr. Reddy's Laboratories (Uk)® | Dr. Reddy's Laboratories (Uk) Ltd.; Sumatriptan Generics [uk]® | Generics [uk] Limited; Sumatriptan Generics® | Generics [uk] Limited; Sumatriptan Milpharm Limited® | Milpharm Limited; Sumatriptan Relonchem® | Relon Chem Limited; Sumatriptan Sandoz Ltd® | Sandoz Ltd; Sumatriptan Sun Pharmaceutical Industries Europe® | Sun Pharmaceutical Industries Europe B.V.; Sumatriptan Sun® | Sun Pharmaceutical Industries Europe B.V.; Sumatriptan Teva Uk® | Teva Uk Limited; Sumatriptan Torrent Pharma (Uk)® | Torrent Pharma (Uk) Ltd.; Sumibril® | Bristol Laboratories Ltd (Berkhamsted CZECH REPBLIC: Frimig® | Orion Corporation; Imigran® | Glaxosmithkline (Ireland)**

	Limited; Rosemig Sprintab® | Glaxosmithkline (Ireland) Limited; Rosemig® | Glaxosmithkline (Ireland) Limited; Sumamigren® | Zaklady Farmaceutyczne "polpharma" Spolka Akcyjna Sumatriptan Actavis® | Actavis Group Ptc Ehf.; Sumatriptan Aurovitas® | Aurovitas, Spol. S R.O.; Sumatriptan Mylan® | Mylan Ireland Limited; Sumigra® | Sandoz Gmbh. ROMANIA: Imigran Dr® | Glaxosmithkline (Ireland) Limited; Sumacta® | Actavis Group Ptc Ehf.; Sumatriptan Sun® | Sun Pharmaceutical Industries Europe B.V.; Xibimer® | Dr. Reddy's Laboratories Romania Srl SOLVAKIA: Cinie® | Zentiva, A.S.; Imigran® | Glaxosmithkline (Ireland) Limited; Imigran® | Glaxosmithkline Slovakia S.R.O.; Sumamigren® | Zaklady Farmaceutyczne "polpharma" Spolka Akcyjna; Sumatriptan Sandoz® | Sandoz Pharmaceuticals D.D. SLOVENIA: Imigran Sprint® | Glaxosmithkline D.O.O.; Imigran® | Glaxosmithkline D.O.O. SPAIN: Imigran Neo® | Glaxosmithkline S.A.; Imigran® | Glaxosmithkline S.A.; Sumatriptán Aurobindo® | Laboratorios Aurobindo S.L.U.; Sumatriptán Bluefish® | Bluefish Pharmaceuticals Ab; Sumatriptán Bluepharma® | Onedose Pharma; Sumatriptán Sandoz® | Sandoz Farmacéutica, S.A.; Sumatriptán Sun® | Sun Pharmaceutical Industries Europe B.V.; Sumatriptán Teva® | Teva Pharma S.L.U.,; Sumatriptán Ur® | Aristo Pharma Iberia, S.L.; Sumatriptán® | Mylan Pharmaceuticals S.L SWEDEN: Imigran Novum® | Glaxosmithkline Ab; Imigran® | Glaxosmithkline Ab; Oriptan® | Orion Corporation Sumatriptan Abece® | Evolan Pharma Ab; Sumatriptan Accord® | Accord Healthcare B.V.; Sumatriptan Actavis® | Actavis Group Ptc Ehf.; Sumatriptan Apofri® | Apofri Ab; Sumatriptan Aristo® | Aristo Pharma Gmbh (Art 57); Sumatriptan Aurobindo® | Aurobindo Pharma (Malta) Limited; Sumatriptan Bluefish® | Bluefish Pharmaceuticals Ab; Sumatriptan Mylan® | Mylan Ab; Sumatriptan Sandoz® | Sandoz A/S; Sumatriptan Sun® | Sun Pharmaceutical Industries Europe B.V.; Sumatriptan Teva® | Teva Sweden Ab HUNGARY: Cinie® | Zentiva, K.S.; Imigran Sprint® | Glaxosmithkline Kft.; Imigran® | Glaxosmithkline Kft.; Sumatriptan Orion® | Orion Corporation; Sumatriptan Polpharma® | Zaklady Farmaceutyczne "polpharma" Spolka Akcyjna; Triptagram® | Actavis Group Ptc Ehf. **RUSSIA: Amigrenin® | Veropharm; Imigran® | GSK; Mygrepam® | Obolenskoe; Rapimed® | Actavis; Sumamigren® | Polpharma; Sumarin® | Ranbaxy; Sumitran® | Reddy; Trimigren® | Nizhpharm.** **ISRAEL: Imitrex® | GSK; Sumatridex® | Dexcel; Sumavel® | Tzamal.** **SWITZERLAND: Imigran® | GSK. TURKEY: Imigran® | GSK. UKRAIN: Amigren® | Astrafarm; Antimigren ® | Zdorovje; Stopmigren® | KVZ; Sumamigren® | Polpharma.**

* Codifa – L'Informatore farmaceutico. https://www.codifa.it/ (European Union: accessed November 25, 2020; Africa, Americas, Asia, Switzerland, Oceania accessed December 3, 2018)

Annex 6 – List of studies excluded after full text evaluation (reasons for exclusion)

Study	Study type	Reasons for exclusion
Allais 2018	Review	Non systematic methodology
Asadollahi 2014	RCT	Control arm: promethazine
Friedman 2017	Review	Non systematic methodology
Law 2016	SR	Three studies with oral sumatriptan in the control arm, already included in Derry 2012
Maasumi 2017	Review	Non systematic methodology
Macone 2017	Review	Non systematic methodology
Menshawy 2018	SR	No oral sumatriptan
Messali 2014	SR	No data on sumatriptan
Patniyot 2016	Qualitative SR	3 open-label studies + 4 studies included in the SR by Richer et al.
Pini 2012	RCT	Number of patients with outcomes not available. Results expressed as number of attacks.
Silberstein 2014	Review	Non systematic methodology
Tabeeva 2019	RCT	Results presented as before-after estimates, without comparison between arms. Estimates expressed as averaged VAS scores
Tsu 2016	SR	Search date not stated