PROPOSAL FOR ADDITION TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES OF NAPROXEN AND ELETRIPTAN FOR THE ACUTE TREATMENT OF MIGRAINE ATTACKS IN ADULTS

Proposed listing on the EML (proposed additions in red):

7. ANTIMIGRAINE TREATMENTS

7.1 Acute treatment of attacks

Non steroidal anti-inflammatory drugs
- naproxen, tablet 500 mg

Triptans
□ sumatriptan, tablet 50 mg
- eletriptan, tablet 40 mg

Applicant:

The applicants are, jointly, two international scientific societies (the International Headache Society [https://ihs-headache.org/en/] and the European Headache Federation [https://www.ehf-headache.com/]), and two charities (*Lifting The Burden* [https://www.l-t-b.org/], which is in Official Relations with WHO), and Disease Relief by Excellent and Advanced Means (DREAM [https://www.dream-health.org/a-new-public-health-model/?lang=en]).

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Section 1: Summary statement of the proposal

The global migraine prevalence is estimated at 14–15%, with minor variations across regions *(1, 2)*. Reliable estimates show that migraine accounts for 4.9% of global population ill health quantified in years lived with disability (YLDs) *(1)*. Migraine manifests as recurrent and largely unpredictable attacks of head pain, often severe, accompanied by other disabling symptoms such as nausea, vomiting and intolerance to sensory stimuli (photophobia and phonophobia) *(3)*, all of which impair function and participation in life activities *(4)*. Inadequately treated, it may increase in frequency and evolve into chronic migraine, with headache on more days than not, with commensurate increases in ill-health and disability burdens, and in direct and indirect costs *(5)*.

This submission calls for the inclusion of additional options in the Model List for the acute treatment of migraine attacks in adult in order to bring adequate treatment to a greater proportion of the more than 1 billion people affected by migraine around the world.

The standard approach to the acute treatment of migraine attacks is based on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and triptans. Most guidelines recommend the use of NSAIDs as first-line choice, while triptans are considered second-line (see paragraph #9).

The rationale for adding alternatives to those already on the EML for the acute treatment of migraine attacks (acetylsalicylic acid, paracetamol and sumatriptan) lies in the limited efficacy of each individual medication, which is widely recognized. Multiple randomized controlled trials (RCTs) and everyday clinical practice show that the percentage of subjects with migraine attaining the recognised benchmark of good response to acute treatment (pain freedom 2 hours after medication intake) is far from satisfactory, with numbers needed to treat (NNTs) for NSAIDs ranging from 7 to 12 *(6)*, only marginally better for triptans (4 to 6) *(7)*. Many people with migraine cannot, therefore, be effectively managed with the medications currently on the EML.

It must be noted that there are no reliable factors to predict response to one acute drug or another, while failure of one does not predict failure of another.

Adding the options of another NSAID (naproxen), with characteristics that may make it preferable to paracetamol and acetylsalicylic acid, and another triptan (eletriptan) with proven superior efficacy to sumatriptan, will increase the therapeutic options of controlling migraine attacks in a larger number of people with migraine.

Section 2: Consultation with WHO technical departments

During the preparation of this application there have been multiple meetings with Drs Tarun Dua, Nicoline Schiess and Rodrigo Cataldi of the Brain Health Unit, Department of Mental Health & Substance Use, World Health Organization (WHO).

They have provided guidance and suggestions, and critically assessed drafts of this application.

Section 3: Other organization(s) consulted and/or supporting the submission

In addition to the four joint applicants (IHS, EHF, LTB and DREAM), we have also consulted the European Migraine and Headache Association (Mrs Elena Ruiz de la Torre), https://www.emhalliance.org/, who is in full support of this applicaton (see last page of this document).

Section 4: Key information summary for the proposed medicine(s)

Non steroidal anti-inflammatory drugs

INN	**naproxen**
ATC code	M01AE02
Indication	Acute treatment of migraine attacks in adults
ICD-11 code	8A80 1-3 Migraine, migraine with aura, chronic migraine

Dosage form	Strength	EML	EMLc
Tablets	500 mg	No	No

□ Triptans

INN	**eletriptan**
ATC code	N02CC06
Indication	Acute treatment of migraine attacks
ICD-11 code:	**8A80 1-3** Migraine, migraine with aura, chronic migraine

Dosage form	Strength	EML	EMLc
Tablets	40 mg	No	no

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

In the 23rd (2023) edition of the EML, section 7 Antimigraine medicines lists for the population acetylsalicylic acid (aspirin), paracetamol (acetaminophen) and sumatriptan.

This submission is composed of two parts: one proposjng the addition of naproxen and the other the addition of eletriptan to the EML of drugs for the acute treatment of migraine in the adult population. Both applications are aimed at providing highly needed additional options to the large share of subjects with migraine who do not benefit from or have contraindications to acetylsalicylic acid (aspirin), paracetamol (acetaminophen) and sumatriptan.

Justification of choices of the representative medicines

Many NSAIDs have similar efficacy against migraine, although, in general, the evidence from RCTs is poor and this assertion rests on decades of clinical experience and practice.

Naproxen 500 mg has wide availability and clinical studies have shown that it is more effective than placebo in relieving acute migraine headaches in adults when considering both pain freedom and headache relief at two hours (details will be presented in section 8).

Naproxen is generally well tolerated, with adverse effects rarely leading to discontinuation of treatment. Among the NSAIDs, naproxen has the best cardiac safety *(8-11)*. This is important because a sizeable minority of people with migraine use acute medication with high frequency. There are additional potential benefits of naproxen. It has a much longer half-life (12-17 hours) than ibuprofen (2-4 hours), which may confer advantage in migraine treatment since migraine attacks commonly last 12-24 hours, and may recur even after apparently successful treatment. Further, there is good evidence (unique to naproxen) that the combination of naproxen with sumatriptan is more effective than sumatriptan alone in terms of sustained (2-24 hours) pain-free response, while being well tolerated *(12, 13)*.

Among triptans, sumatriptan is not the most effective, but was the first triptan to be marketed and the first to become available in generic formulations.
Eletriptan is generally more costly than sumatriptan and most others of the class (because of their more widespread availability as generics). For this reason, it is not proposed as the representative drug of its class, but as the alternative when sumatriptan is not effective or not tolerated. There are important differences in the pharmacokinetic characteristics. Eletriptan is characterized by higher lipophilicity than other triptans, with a higher potential to cross the blood-brain barrier, which suggests central sites of action putatively able to increase treatment efficacy *(14)*. Eletriptan also has a longer half-life than all other triptans, except frovatriptan, which may explain the lower rate of attack recurrence. Eletriptan 40 mg has had higher efficacy in head-to-head studies against sumatriptan 50 and 100 mg, and a better tolerability profile (see Section 8). Eletriptan has also shown superiority to other triptans for many outcome measures, although not all data were obtained from head-to-head studies (see Section 8 for details).

Section 6: Information supporting the public health relevance

Indication

We propose the additions of naproxen and eletriptan for the acute treatment of migraine attacks with and without aura in adults.

Epidemiology and burden of migraine

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, and photophobia/phonophobia and sensitivity to external stimuli (light, noise, odours). All of these symptoms are disabling and impair participation in life activities. In about one quarter of those affected, episodes may be preceded by transient focal neurological symptoms (most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits). The global prevalence of migraine is estimated at 14-15% (more than one billion people worldwide), 2-3 times higher in women than men *(2)*. The disorder is ubiquitous, despite regional variations *(1)*.

Migraine contributes significantly to the global disease burden *(1, 2)*. In the Global Burden of Disease (GBD) study 2021 *(1)*, migraine was the fourth highest cause of years lived with disability (YLDs) at level 4. In the detailed analysis of GBD2016, migraine accounted for 45.1 million disability-adjusted life years (DALYs) *(15)*.

There is evidence that, every year, 2-3% of people with episodic migraine (headache on fewer than 15 days/month transition to the much more disabling chronic migraine (headache on ≥15 days/month of which a majority are with symptoms of migraine)*(16)*. One of the main risk factors for the transition to chronic migraine is the overuse of the poorly managed acute treatment and the overuse of acute medications *(17)*.

Therefore, the impact of migraine on population health is very substantial, and associated with major impairments in participation, quality of life and productivity *(18)*. However, all of these can be reduced by appropriate treatments. These include preventative treatments to reduce attack frequency, but the effectiveness of these is limited. Treatments to abort (or mitigate) acute attacks, in the shortest time possible, remain the mainstay of management for most people. These also are far from always effective; hence it is necessary to have available a range of options.

Alternative medicines currently included on the Model Lists for the proposed indication

<u>Aspirin (acetylsalicylic acid) and paracetamol (acetaminophen)</u>

These two medications are also on the EML for use in adult populations. Both have evidence of efficacy (paracetamol less than aspirin, but again this is limited *(19, 20)*.

<u>Triptans</u>

Sumatriptan 50 mg is already included in the EML. Sumatriptan was the first triptan to be marketed, followed by a further six triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan), which exhibit different pharmacokinetic properties *(7)*. Sumatriptan is widely available in generic formulations, but nonetheless remains relatively expensive compared with NSAIDs. It is usually recommended as second-line treatment when NSAIDs are ineffective.

Section 7: Treatment details

Naproxen

Naproxen is indicated for the acute treatment of migraine headaches in adults and adolescents aged 16 years and older and should be orally administered at the first symptoms. The recommended initial dose is 500 mg taken orally at the onset of migraine symptoms *(21)*. This can be repeated after 4-6 hours but the total dosage should not exceed 1000 mg within a 24-hour period *(22)*. Naproxen is intended for short-term use; over-frequent usage is not recommended since it does not prevent future migraine attacks, it may be associated to a paradoxical worsening of migraine frequency and may induce undesirable effects.

Naproxen is widely available and accessible in most countries. It can be self-administered at home, with no monitoring or testing required. General practitioners and community pharmacists are well-equipped to advise on use of naproxen for migraine since no specialised training is required beyond standard medical and pharmaceutical education.

Specific Patient Populations

Paediatric population: Naproxen is not recommended for use in children and adolescents under 16 years.

Elderly population: The dose should be reduced in elderly patients and the lowest effective dose should be used for the shortest possible duration, since they have an increased risk of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal.

Subjects with renal and/or hepatic insufficiency: In patients with mild or moderate renal or hepatic failure, the dosage of 500 mg, should be reduced and the lowest effective dose should be used for the shortest possible duration.
In particular, naproxen is not recommended in patients with severe renal disease (baseline creatinine clearance lower than 30 ml/min), since an accumulation of naproxen metabolites has been observed in patients with severe kidney failure and patients in dialysis. Also, naproxen is not recommended for patients with severe hepatic impairment due to the increased risk of adverse effects related to reduced drug metabolism by the enzymes CYP2C9 and CYP1A2 and drug clearance.

Pregnancy: Naproxen may adversely affect the pregnancy and/or foetal development. Clinical studies suggest an increased risk of miscarriage and/or cardiac malformation and gastroschisis after the use of a NSAID in early pregnancy. Its administration is therefore not recommended. If accepted, the listing should include information similar to what is provided for sodium valproate: *avoid use in pregnancy and in women and girls of childbearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.

Breastfeeding: The naproxen anion has been detected in the milk of breastfeeding mothers at a concentration of approximately 1% of the plasma concentration. Considering the possible side

effects of NSAIDs on newborns, its administration to breastfeeding mothers is not recommended.

Contraindications: the following contraindications exist for naproxen:

- Hypersensitivity to the active substance in naproxen;
- History of bronchospasm, asthma, rhinitis or urticaria associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAID);
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding) and/or history of gastrointestinal bleeding or perforation, related to previous NSAID therapy;
- Severe heart failure;
- Pregnancy (caution against use in 1st trimester, absolute contraindication at 30 weeks gestation;
- Severe liver or kidney failure;
- Ulcerative colitis;
- Concurrent use of other non-steroidal anti-inflammatory drugs.

Eletriptan

Eletriptan is indicated in adults (≥18 years). It is administered orally in a single dose of 40 mg, preferably at the onset of a migraine attack to improve efficacy *(23)*. In migraine with aura, it should be taken early in the headache phase since (like sumatriptan) it is ineffective when taken during the aura phase before headache onset *(24)*. If the initial dose proves ineffective, a second dose can be taken within 12 to 24 hours of the first dose, with a maximum recommended dose of 80 mg within a 24-hour period *(25)*. As with all triptans, eletriptan should not be used regularly more than twice weekly: to do so risks the development of medication overuse headache.

No monitoring or testing is required for eletriptan. It can be self-administered at home, with no monitoring or testing required. General practitioners and community pharmacists are well-equipped to advise on use of eletriptan for migraine since no specialised training is required beyond standard medical and pharmaceutical education.

Specific Patient Populations

Pediatric population: Eletriptan has not been studied in children younger than 18, and thus, it is not approved for use in pediatric patients due to a lack of safety and efficacy studies in this population.

Elderly population: Eletriptan has not demonstrated specific issues limiting its use in older patients. However, caution may be warranted in older individuals, among whom there is a higher prevalence of cardiovascular risk factors and age-related kidney disorders.

Hepatic impairment: No dosage adjustment of eletriptan is necessary for mild-to-moderate hepatic impairment. However, the use of eletriptan is not recommended in patients with severe hepatic impairment. Eletriptan undergoes extensive metabolism mediated by the liver enzyme CYP3A4, and its clearance may be diminished in individuals with hepatic impairment. Some experts recommend considering a lower dose of 20 mg for patients with moderate hepatic impairment.

Renal impairment: Eletriptan does not appear to be significantly affected by renal function, and no dosage adjustment is recommended for patients with mild, moderate, or severe renal impairment. However, as patients with renal impairment may have an increased risk of hypertension, it is advisable to monitor their blood pressure levels after the administration of eletriptan.

Pregnancy: Triptans as a class are not the preferred first-line treatment for pregnant patients with migraine. Limited data exist on the safety and efficacy of eletriptan in pregnancy. Animal studies have shown some evidence of developmental toxicity at high doses. Eletriptan is categorized as "pregnancy category C" by the FDA and as "category B1" by the Australian Therapeutic Goods Administration (TGA), indicating that there may be situations where the potential benefits outweigh the potential risks. However, most guidelines recommend avoiding the use of eletriptan during pregnancy unless deemed necessary and following careful a careful evaluation of the risk/benefit ratio

Breastfeeding: Eletriptan is excreted into human milk in small amounts, and the concentration of its active metabolite is unknown. The relative infant dose of eletriptan is significantly lower than the maternal dose, estimated to be less than 1%, making it unlikely to cause adverse effects in breastfed infants. Among triptans, eletriptan may, theoretically, be less likely to be transferred into breastmilk owing to its high protein binding compared to other triptans. Nevertheless, to minimize infant exposure, it is advisable to avoid breastfeeding for 12-24 hours after taking eletriptan.

Contraindications

Eletriptan is contraindicated in people with coronary artery vasospasm, ischaemic coronary artery disease, uncontrolled hypertension, peripheral vascular disease, and ischaemic bowel disease. Additional cardiovascular contraindications include Wolff-Parkinson-White syndrome or cardiac accessory conduction pathway disorders.

Eletriptan is metabolized by CYP3A4 enzymes and is contraindicated within 72 hours of recent use of potent CYP3A4 inhibitors. As with other triptans, serotonin syndrome may occur during the use of eletriptan. Therefore, it is not recommended for use concurrently with drugs that enhance its serotonergic effect, and is contraindicated if another 5-HT_1 agonist, ergotamine-containing or ergot-type medication has been taken within the last 72 hours.

Section 8: Review of evidence for benefits and harms

We conducted a systematic analysis of the literature together with a large group of headache experts from several countries, including some contributors to this application, and strictly based on the use of the GRADE methodology.

Search of available evidence was performed according to the Cochrane guidelines for systematic reviews of interventions and overviews of reviews (Appendices 1 and 2). Cochrane guidelines were also followed for study selection, data extraction and synthesis. Reporting was performed according to relevant items of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.
Three scientific databases were searched, namely PubMed, Scopus, and Cochrane Database, since the beginning of indexing, utilizing the PICOM (Patients – Intervention – Comparison – Outcome – Methods) methodology. To ensure a broad coverage of available literature, when building search strings, only Participants (i.e., migraine patients) and Interventions (i.e., drugs) were considered for each topic.
A literature search for systematic reviews and meta-analyses and the RCTs published after the reviews and the meta-analyses was performed in 2022. As the process of literature search and analysis took more than 12 months, search strings were re-launched in May 2023 and November 2023 to update the search to the RCTs published from February 2022.
Search of available evidence was performed according to the Cochrane guidelines for systematic reviews of interventions *(26)* and overviews of reviews *(27)*. Cochrane guidelines were also followed for study selection, data extraction and synthesis. Reporting was performed according to relevant items of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement *(28)*.
The literature search was performed for each pharmacological class of acute treatments – namely, non-steroidal anti-inflammatory drugs, triptans, paracetamol, combination analgesics, antiemetics, opioids, ditans, and gepants. Three scientific databases were searched, namely PubMed, Scopus, and Cochrane Database, since the beginning of indexing, utilizing the PICOM (Patients – Intervention – Comparison – Outcome – Methods) methodology. To ensure a broad coverage of available literature, when building search strings, only Participants (i.e., migraine patients) and Interventions (i.e., drugs) were considered for each topic. The same search strings were launched in two separate searches. In search 1, we looked for systematic reviews and meta-analyses, while in search 2 we looked for RCTs published after the reviews and the meta-analyses retrieved in search 1. If Search 1 did not allow to retrieve any systematic review or meta-analysis, Search 2 was considered for RCT inclusion since the beginning of indexing of each database. Search 1 was performed at the beginning of search, while Search 2 was performed at the beginning and repeated in May 2023 and November 2023. Only published literature was considered for searches. Reference management and duplicate removal were performed with EndNote X6®.

Study selection
The selection process was performed in two stages. In stage 1, systematic reviews and meta-analysis covering the topic of interest were screened to identify eligible studies. In stage 2, additional RCTs, published after the selected systematic review and meta-analyses were

considered for inclusion. In case no systematic reviews and meta-analyses were available, only RCTs were selected.

Stage 1. Each module working subgroup initially received from the coordination supporting group an .xlsx file containing authors, publication year, title, abstract, and DOI of references retrieved during Search 1 (systematic reviews and meta-analyses) after duplicates were removed. Any further duplicates identified during the study selection process were accounted for in the study selection flow-chart. Module subgroups performed the study selection process in two phases, first evaluating titles and abstracts for eligibility, and then evaluating the full text of eligible references for inclusion. Inclusion and exclusion criteria for both phases are reported in Appendix 1. The evaluation process was performed by one rater, with a second rater consulted in case of uncertainty.

Stage 2. Module working subgroups received from the coordination supporting group an .xlsx file that contained the authors, publication year, title, abstract, and DOI of references retrieved during Search 2 (RCTs) after removing duplicates. To review all the literature that was not included in the selected systematic reviews and meta-analyses, the module working subgroups identified the most recent and comprehensive systematic review or meta-analysis on each pharmacological class and extracted the temporal limit (i.e., the 'until date') of the search. They then evaluated only the studies published after the identified 'until date' following the same evaluation procedure described in stage 1. The inclusion and exclusion criteria for eligibility and inclusion in phase 2 are presented in Appendix 2.

If duplicates were identified during study selection, they were considered and accounted for in the study selection flow-chart. Full texts of all RCTs identified in all systematic reviews and meta-analyses included in stage 1 were evaluated according to the same criteria. Therefore, module subgroups selected the final number of RCTs included in the review. This final number was revised if needed after the literature search updates performed in May 2023 and November 2023.

For the analysis of the efficacy of drugs for the acute treatment of migraine, the outcomes considered were:

- pain freedom at 2 hours from intake;
- pain relief at 2 hours from intake.

Both outcome measures are recommended by the guidelines of the International Headache Society for clinical trials for the acute treatment of migraine *(29)*.

Methodological notes

Main evidence: Our review includes results from RCTs with measurable outcomes of interest and reporting a sample size calculation and a study hypothesis for superiority or non-inferiority in the case of comparison between two active principles or an active principle and placebo. For each comparison, data included in this section were meta-analyzed separately for each outcome, introducing, when needed, subgroup analyses to describe the effect of different dosages. Analyses referring to outcomes of interest were considered among main evidence also if those outcomes were secondary outcomes in the included studies, provided that they were pre-specified. To describe all data retrieved in a homogenous way, meta-analyses were conducted also when only one study was available for a comparison and outcome.

Additional evidence: We also assessed data from RCTs lacking a clear study hypothesis for superiority or non-inferiority or a sample size calculation related to the comparison that is being considered (or, if performed, minimum sample size was not achieved). Data were meta-analyzed with the same procedure adopted for the previous section. This section also includes summaries of data from studies reporting considered outcomes and expressed through indexes not allowing to perform meta-analyses (e.g., medians or mean without SD).

Meta-analyses were performed using RevMan®, version 5.3. Computed effect sizes were Standardized Mean Difference (SMD) for continuous outcomes and Relative Risk (RR) for categorical outcomes. Pooled effect sizes were computed using the random effect model and expressed with a 95% Confidence Interval (95% CI).

In the following paragraphs we will illustrate separately the benefits and harms of naproxen and eletriptan in this order.

1) NAPROXEN

From the literature search update performed in May and November 2023, 572 additional references were retrieved. Only one study was included from this updated search, which was however not relevant for the scopes of this application. Only three trials were relevant and used for assessing the efficacy of naproxen versus placebo.

The literature search for systematic reviews and meta-analyses on the drugs for the acute treatment of migraine identified 1346 references from searching. After duplicate removal and screening stages, 7 systematic reviews and meta-analyses were included *(20, 30-35)* and were considered as sources of RCTs. After analyzing the full texts of these RCTs, 17 of them were included in this synthesis *(36-52)* (Figure 1). From the search of RCTs we included 2 additional RCTs *(53, 54)* and from the literature search update performed in May 2023, we included one study *(55)* (Figure 2).

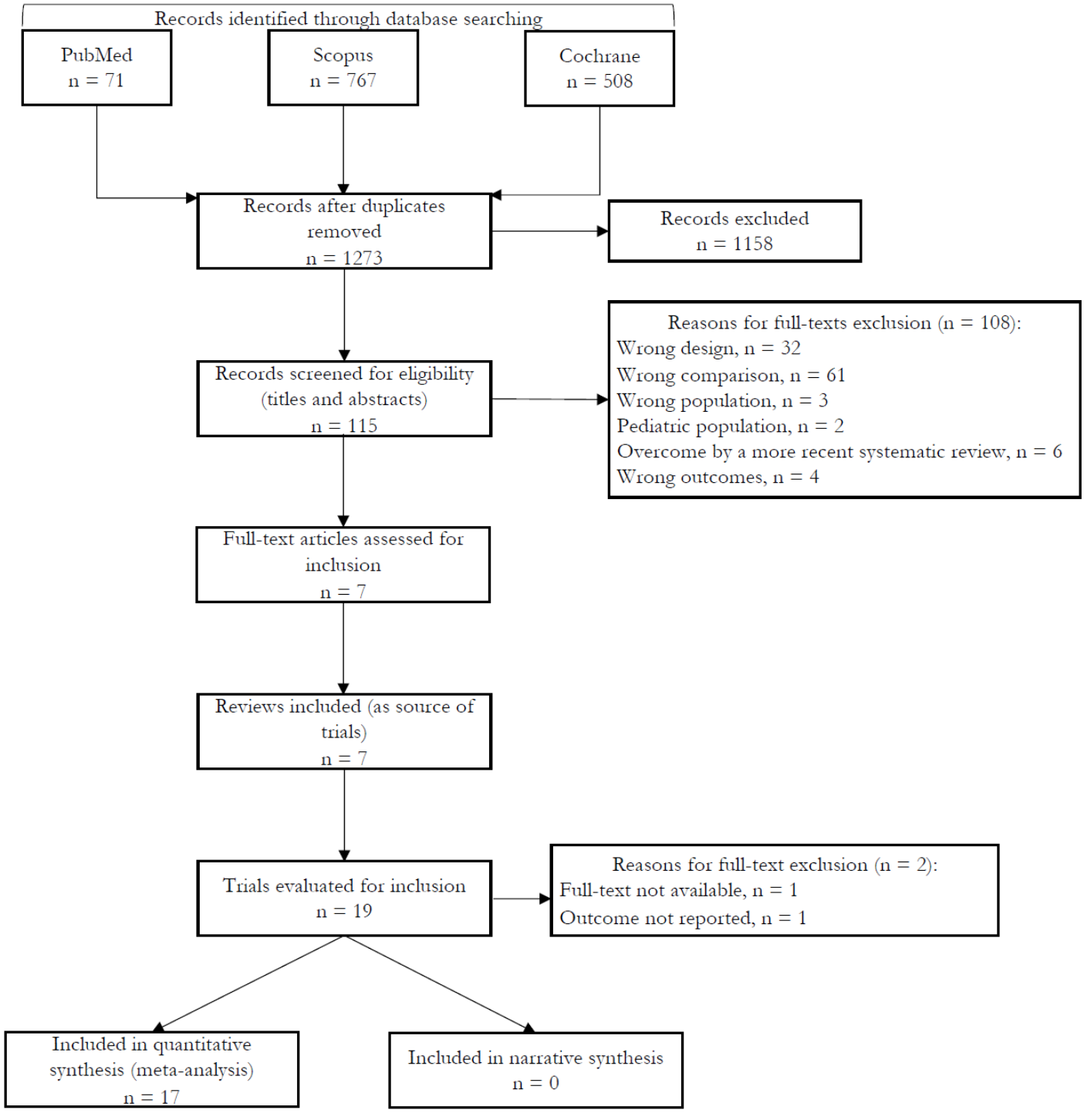


Figure 1 *- Flow-chart of the selection of meta-analyses and systematic reviews.*

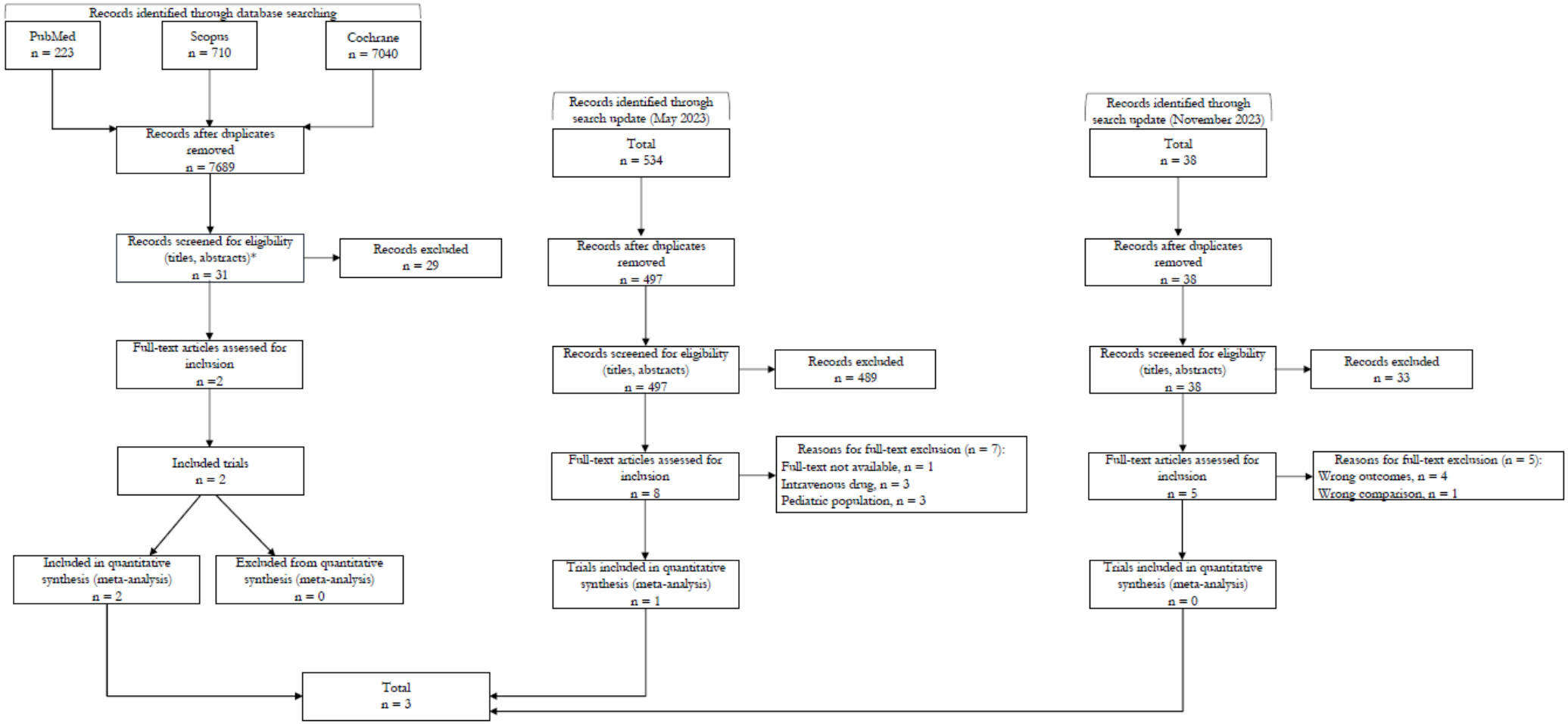


Figure 2 - Flow-chart of the selection of randomized controlled trials published since 2010.

Evidence for naproxen vs placebo

Main evidence: none.

Additional evidence was derived from a total of 3 RCTs, addressing oral naproxen 500-825 mg as compared to placebo in the treatment of acute migraine attacks *(37, 51, 56)*. One RCT *(37)* reported data from two different studies. The overall risk of bias was considered unclear and the quality of evidence very low. The pooled analysis showed benefits of naproxen 500 mg and 825 mg over placebo considering the outcomes of pain freedom at 2h (Figure 3) and pain relief at 2h (Figure 4).

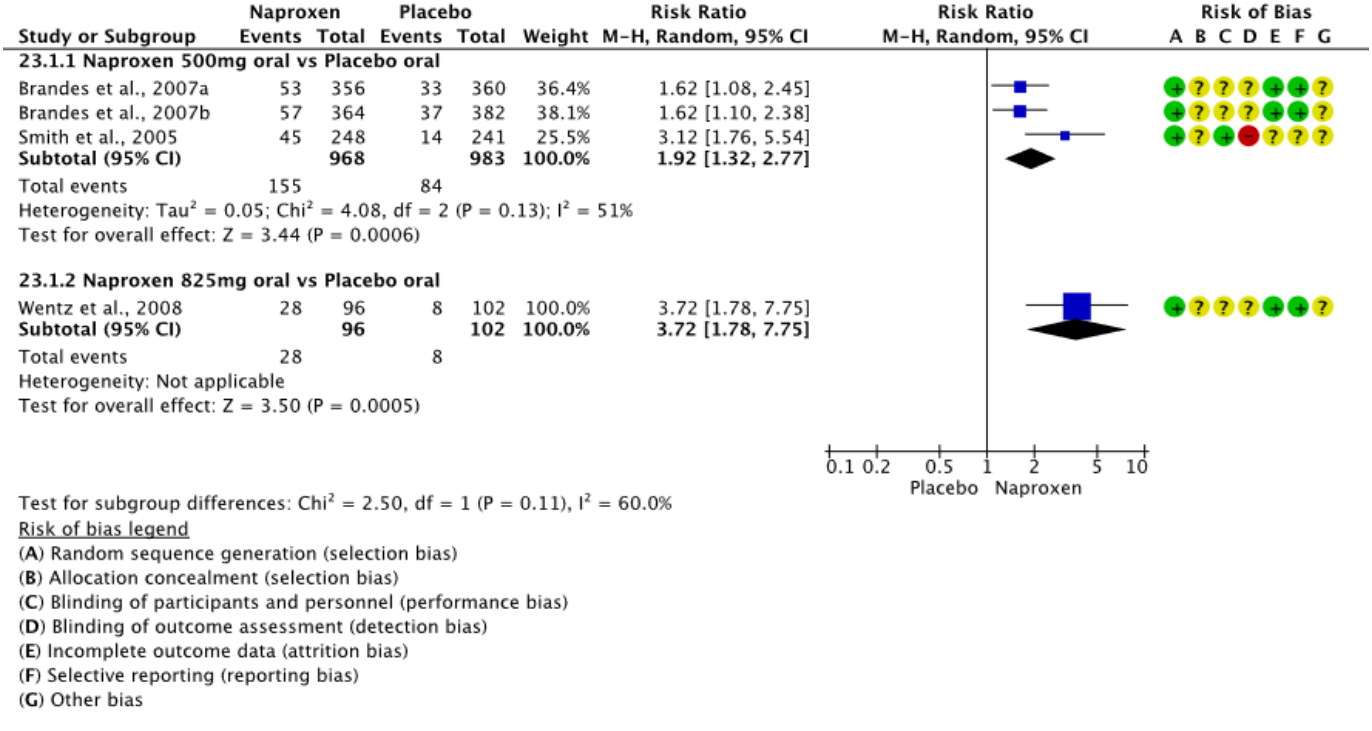


Figure 3. Forest plot showing the comparison between naproxen 500 mg or naproxen 825 mg and placebo for the outcome pain freedom at 2 hours.

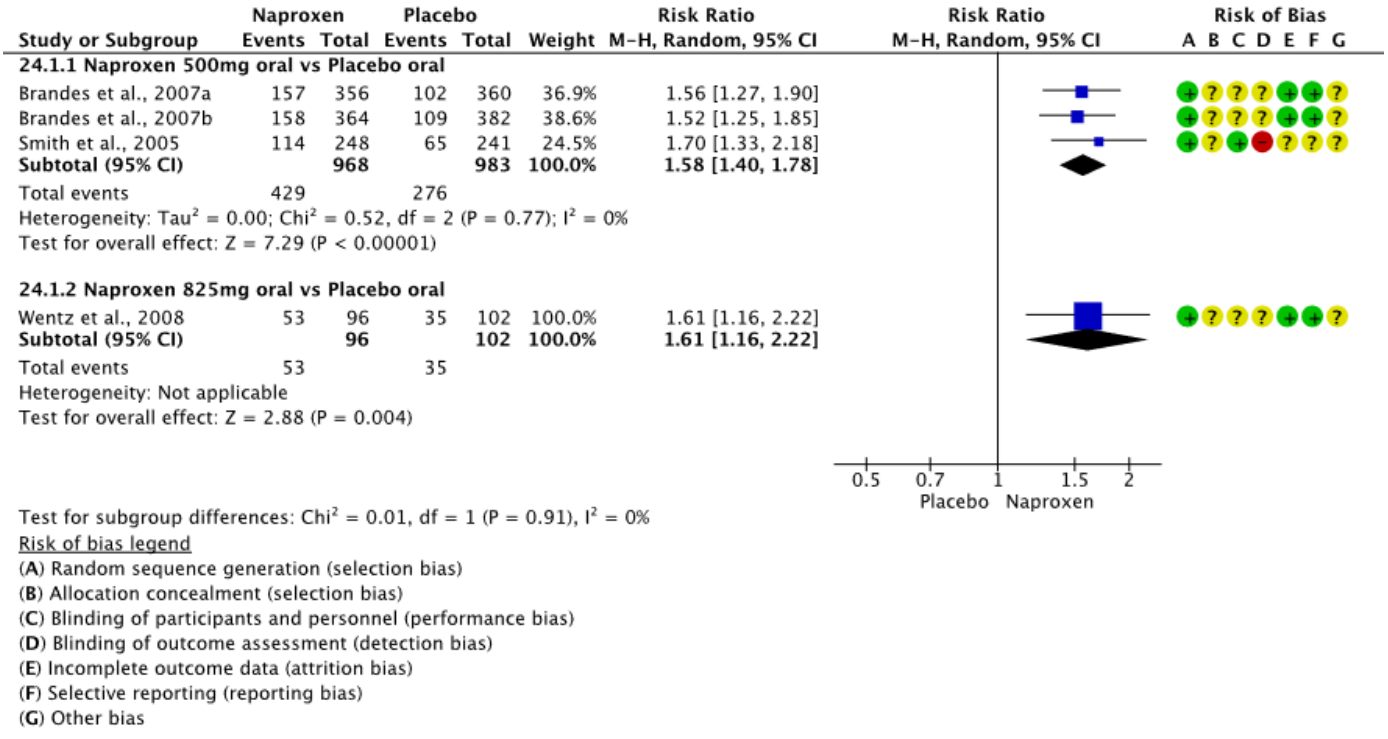


Figure 4. Forest plot showing the comparison between naproxen 500 mg or naproxen 825 mg and placebo for the outcome pain relief at 2 hours.

On this evidence, oral naproxen 500 mg is superior to placebo for the acute treatment of migraine attacks.

Evidence for the comparative efficacy of naproxen

Figure 5 illustrates the output of our literature search for comparative studies involving naproxen.

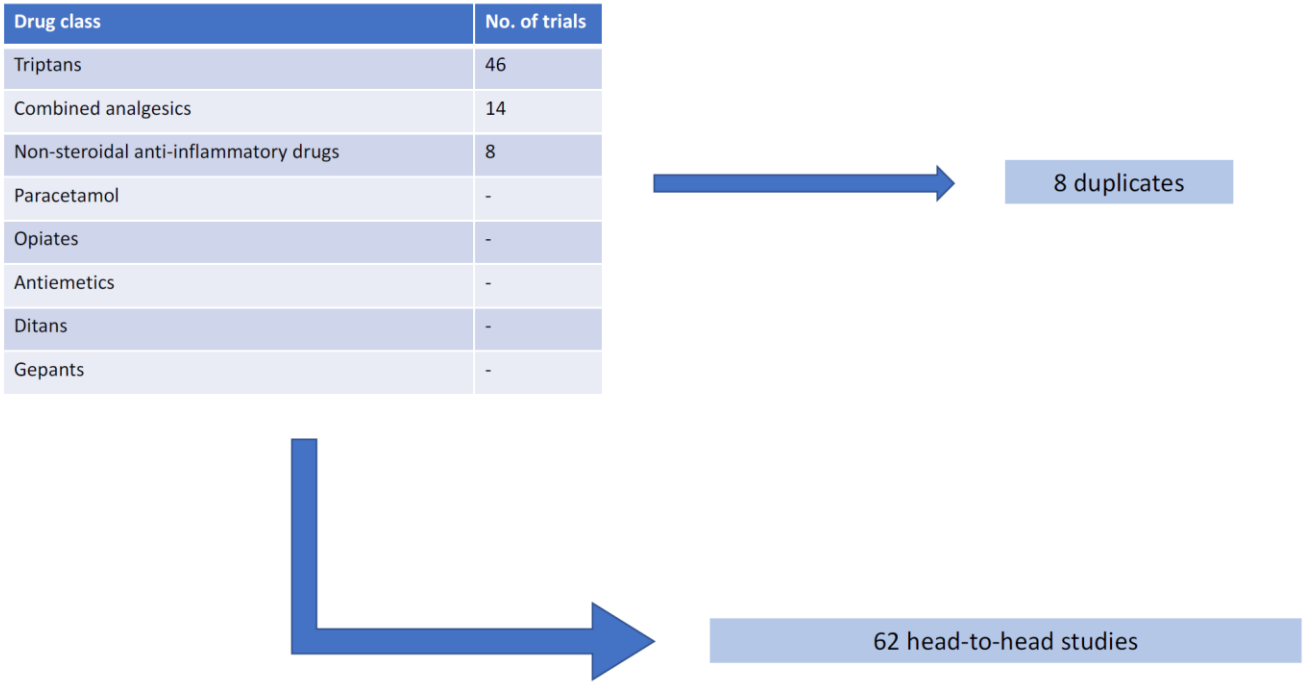


Figure 5 – Flowchart for selected comparative RCTs

Comparison with sumatriptan

Three RCTS compared oral naproxen 500 mg with oral sumatriptan 50 or 85 mg *(37, 51, 57)*. The quality of evidence of these studies is considered low (see below), but the two drugs were rated equivalent in terms of efficacy.

Main evidence: One RCT comparing oral sumatriptan 100 mg with oral naproxen 500 mg *(57)* met the criteria for main evidence. The risk of bias was unclear. The RCT showed no difference between oral sumatriptan 100 mg and oral naproxen 500 mg considering the outcome pain freedom at 2 hours (Figure 6). The quality of evidence was considered low.

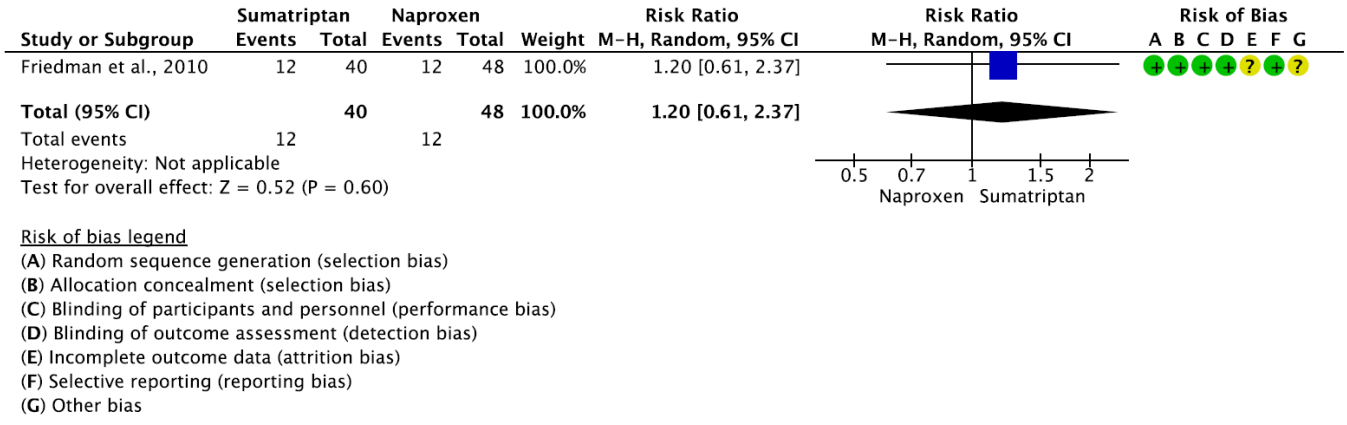


Figure 6 - Forest plot showing the comparison between oral sumatriptan 100 mg and oral naproxen 500 mg for the outcome pain freedom at 2 hours in patients with migraine.

Additional evidence: Two RCTs compared oral sumatriptan 50 mg or 85 mg with oral naproxen 500 mg *(37, 51)*. These RCTs did not meet the criteria for main evidence as they did not report criteria for sample size calculation. The risk of bias was unclear (Figures 7 and 8). Overall, the RCTs showed that the 85 mg dose of oral sumatriptan was superior to oral naproxen 500 mg considering the outcomes pain freedom at 2 hours and pain relief at 2 hours, while the 50 mg dose of oral sumatriptan was not more effective than oral naproxen 500 mg. The quality of evidence was considered very low due to the availability of RCTs with unclear risk of bias.

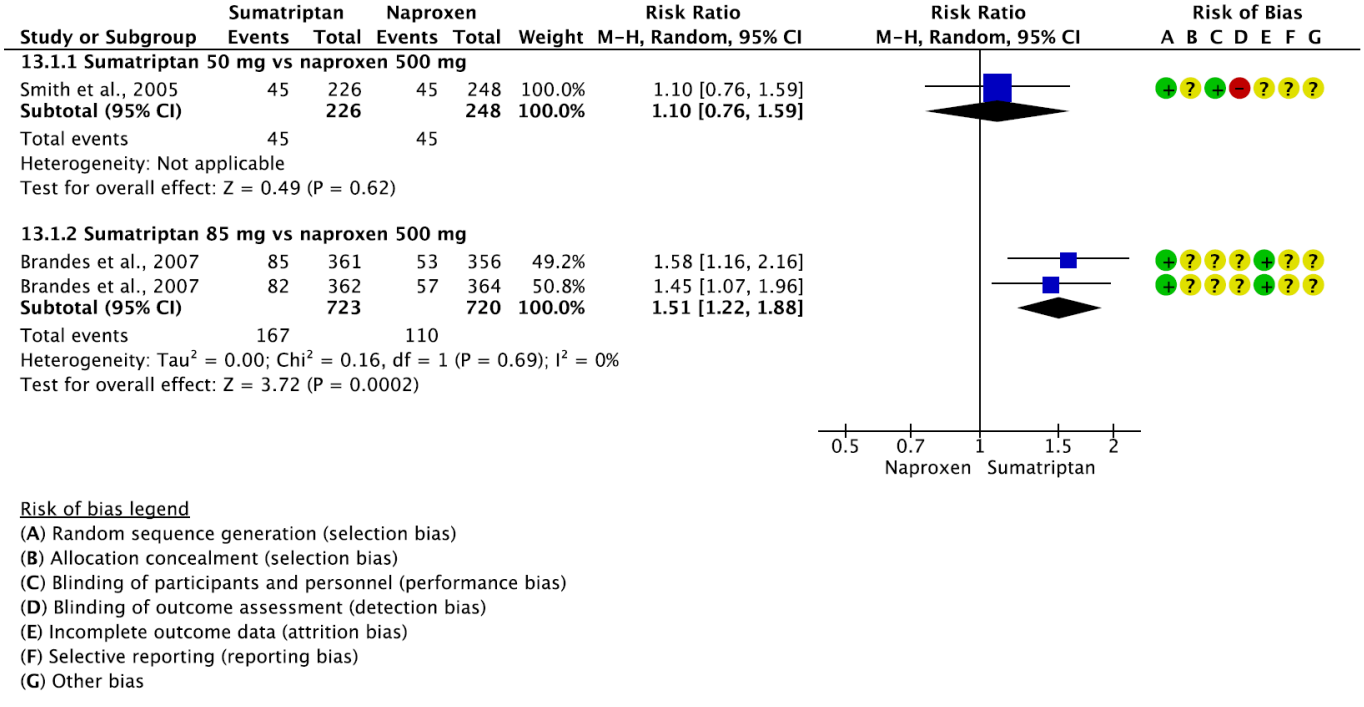
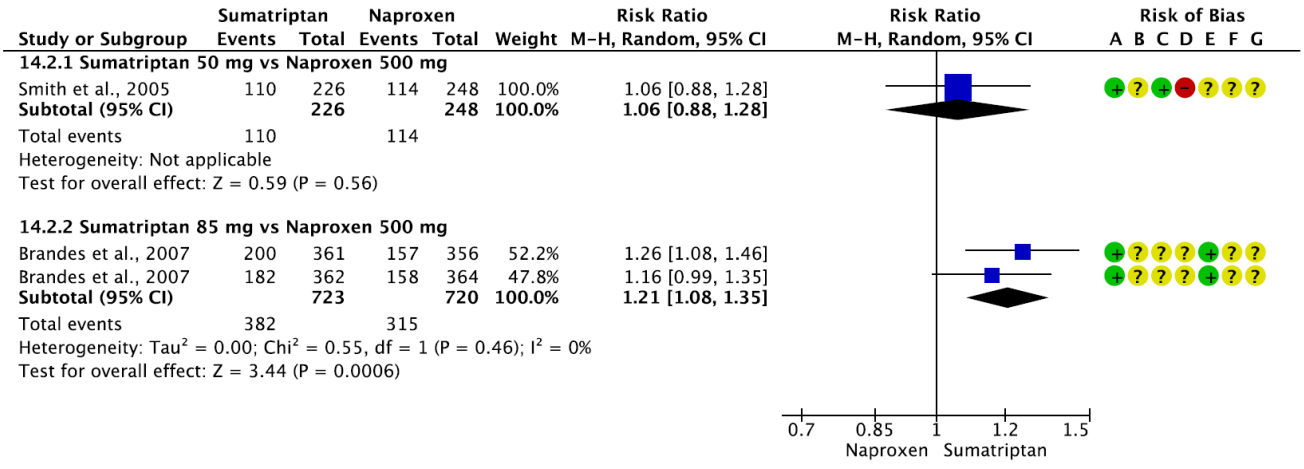


Figure 7 - Forest plots showing the comparison between oral sumatriptan (50 mg or 85 mg) and oral naproxen 500 mg for the outcome pain freedom at 2 hours in patients with migraine.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 8 - Forest plot showing the comparison between oral sumatriptan (50 mg or 85 mg) and oral naproxen 500 mg for the outcome pain relief at 2 hours in patients with migraine.

On this evidence, oral naproxen 500 mg is not inferior to oral sumatriptan 50 mg for the acute treatment of migraine attacks.

Naproxen versus other NSAIDs

No head-to-head RCTs have assessed the efficacy of naproxen versus aspirin, paracetamol ibuprofen or other NSAIDs. We were able to derive some indirect evidence from a recent systematic review and meta-analysis, which reported a pain-free rate at 2 hours of 22% for naproxen, 23% for acetyl salicylic acid, 20% for ibuprofen and 19% for paracetamol. Pain response at 2 hours was achieved in 44% of subjects with naproxen, 42% with acetyl salicylic acid, 43% with ibuprofen and 46% with paracetamol *(58)*.

In conclusion, naproxen is as effective as sumatriptan, acetyl salicylic acid, paracetamol and ibuprofen in the acute treatment of migraine.

Evidence for naproxen combined with sumatriptan

The search of systematic reviews and metanalyses on analgesics in combination yielded 249 references (Figure 9). After duplicate removal and screening, 19 systematic reviews and meta-analyses *(30, 31, 59-75)* were included as source of randomized controlled trials (RCTs). These latter corresponded to 655 references, which were reduced to 33 after screening stages and full text analysis *(36, 37, 51, 73, 76-104)*.
From the literature search update performed in 2023, 85 additional references were retrieved, but no further studies were included.
Of the above trials, seven evaluated the combination sumatriptan-naproxen: four were assessed for main evidence *(73, 86, 100, 105)* and 3 for additional evidence *(37, 51, 80)* as additional evidence.

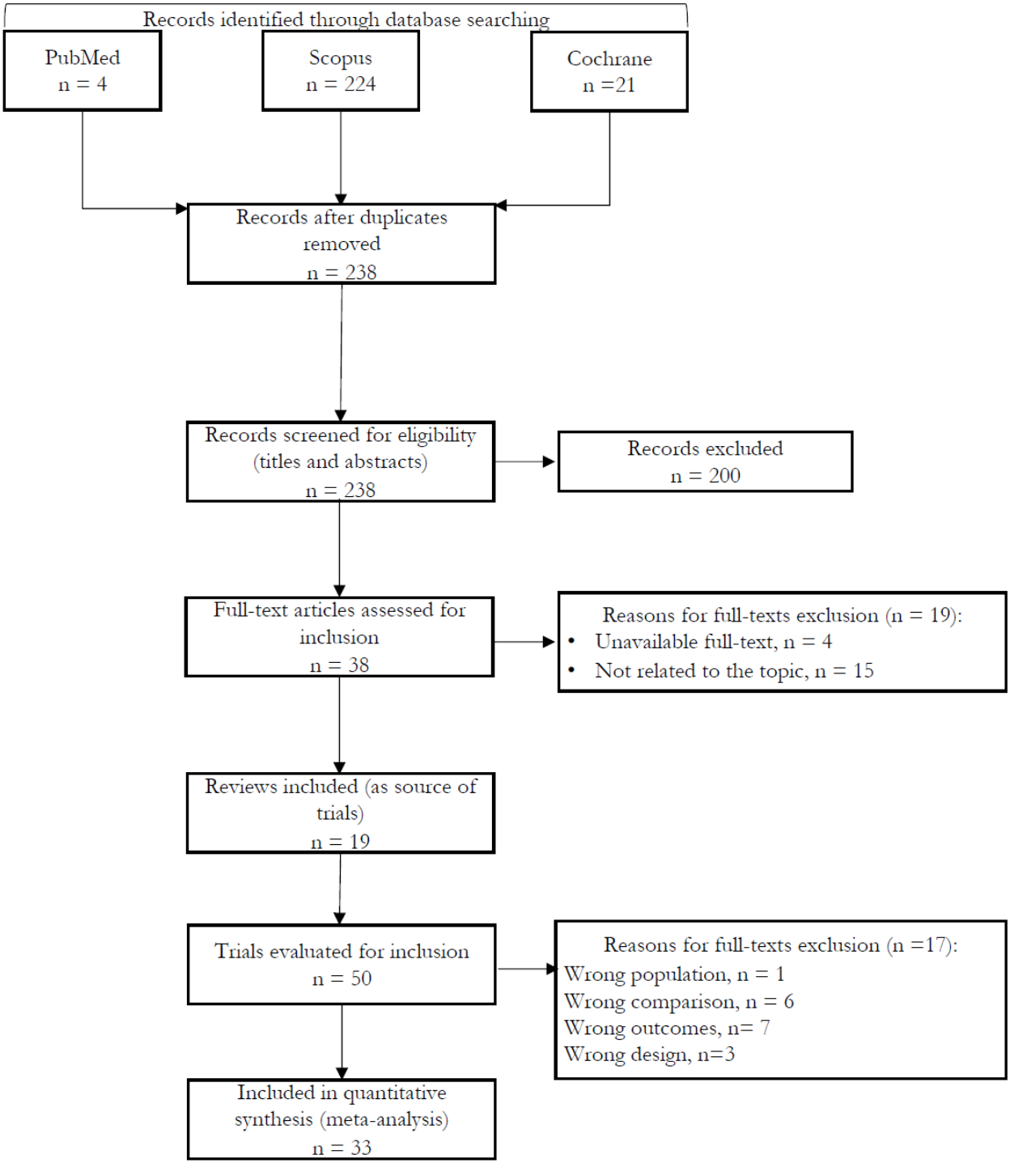


Figure 9 - Flowchart of the selection of meta-analyses and systematic reviews for the use of combinations of drugs for the acute treatment of migraine.

Main evidence: Four RCTs *(73, 86, 100, 105)* addressed oral sumatriptan-naproxen compared to placebo in the acute treatment of migraine attacks.

The pooled analysis showed benefits of oral sumatriptan 85 mg + naproxen 500 mg versus placebo considering the outcome of pain freedom at 2h (Figure 10); more limited evidence coming from Brandes et al. (2007) *(37)* and Silberstein et al. (2014) *(73)* did not show benefits considering the outcome of pain response at 2h (Figure 11). The quality of evidence for both outcomes was considered low (Table 2).

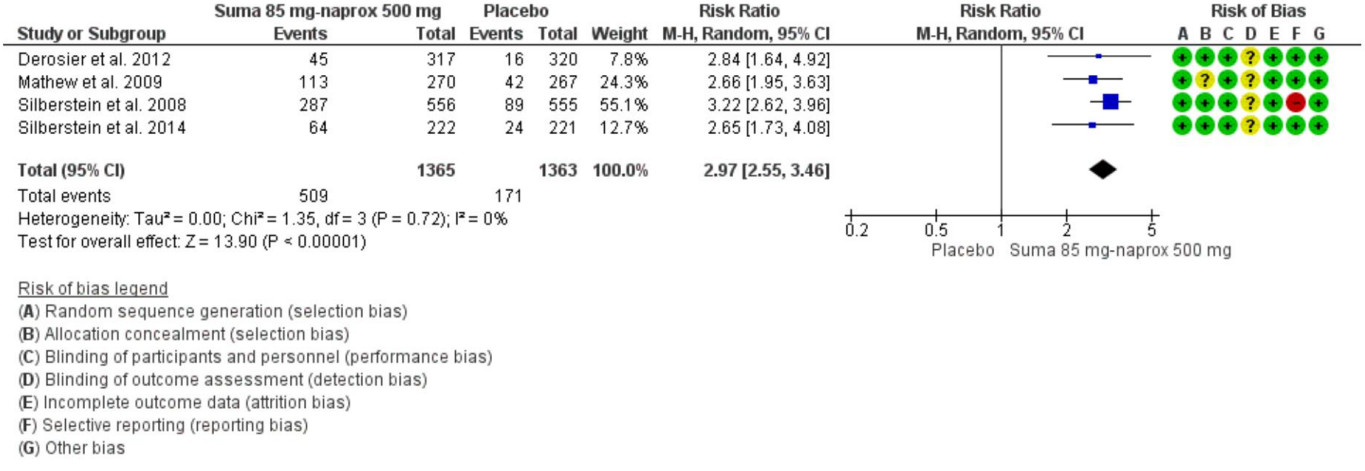


Figure 10 - Forest plot showing the comparison between oral sumatriptan 85 mg + naproxen 500 mg and placebo for the outcome pain freedom at 2h in patients with migraine.

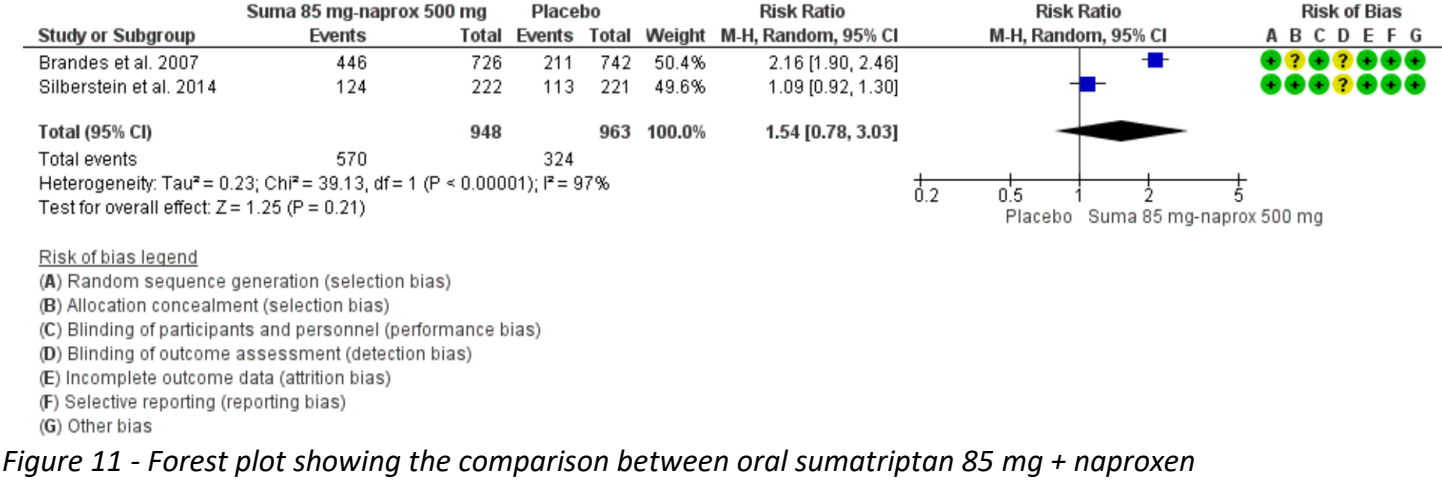


Figure 11 - Forest plot showing the comparison between oral sumatriptan 85 mg + naproxen 500 mg and placebo for the outcome pain response at 2h in patients with migraine.

Certainty assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sumatriptan 85 mg + naproxen 500 mg os	Placebo	Relative (95% CI)	Absolute (95% CI)		
Pain freedom at 2 hours – Sumatriptan 85 mg + Naproxen 500 mg oral vs Placebo												
4	RCTs	Low	Not serious	Not serious	Not serious	None	509/1365 (37.3%)	171/1363 (12.5%)	**RR 2.97** (2.55 to 3.46)	**247 more per 1.000** (from 194 more to 309 more)	⊕⊕⊕⊕ High	Critical
Pain relief at 2 hours – Sumatriptan 85 mg + Naproxen 500 mg oral vs Placebo												
2	RCTs	Low	Serious[1]	Not serious	Serious[2]	None	570/948 (60.1%)	324/963 (33.6%)	**RR 1.54** (0.78 to 3.03)	**182 more per 1.000** (from 74 fewer to 683 more)	⊕⊕⊖⊖ Low	Critical

[1]Very different results across trials; [2]confidence interval included the threshold for clinical decision

Table 2 - GRADE evidence profile table for oral sumatriptan 85 mg + naproxen 500 mg versus placebo in the acute treatment of migraine.

Additional evidence: Three RCTs *(37, 51, 80)* compared sumatriptan-naproxen to placebo, but the studies did not meet the criteria to be included in the main evidence. The overall risk of bias was considered unclear, and the quality of evidence was considered very low.
One RCT showed benefits of oral sumatriptan 50 mg + naproxen 500 mg over placebo considering the outcomes pain freedom and pain relief at 2h; the other two RCTs showed benefits of oral sumatriptan 85 mg + naproxen 500 mg versus placebo in the outcomes pain freedom and pain relief at 2 hours (Figures 12 and 13).

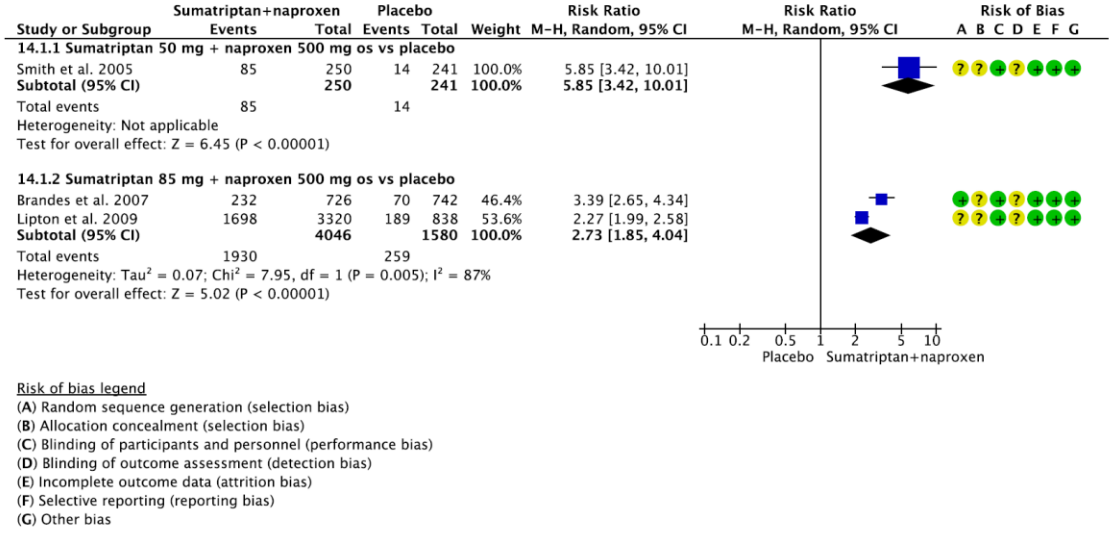


Figure 12 - Forest plot showing the comparison between oral sumatriptan 50 mg + naproxen 500 mg and placebo, or sumatriptan 85 mg + naproxen 500 mg and placebo for the outcome pain freedom at 2 hours in patients with migraine.

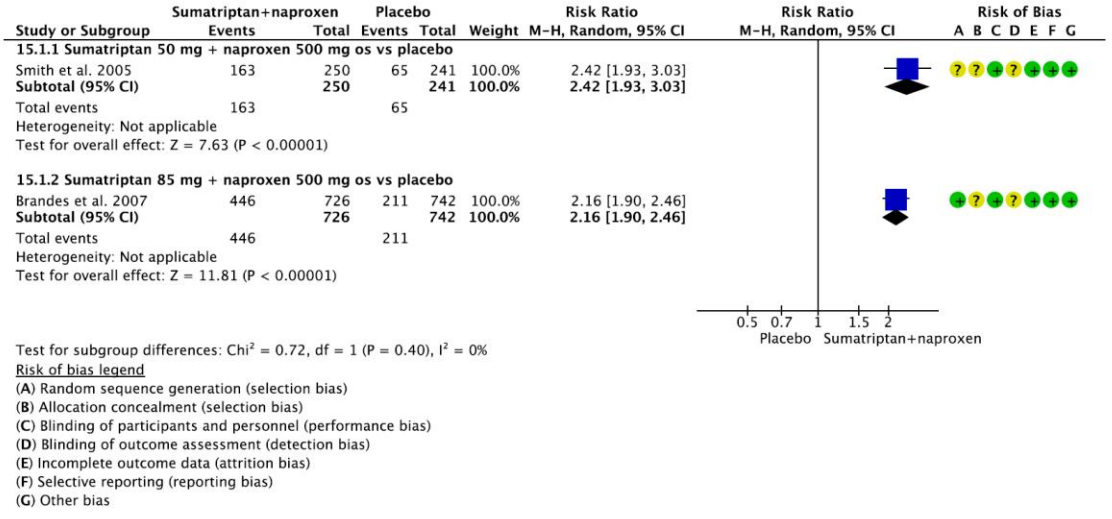


Figure 13 - Forest plot showing the comparison between oral sumatriptan 50 mg + naproxen 500 mg versus placebo, or sumatriptan 85 mg + naproxen 500 mg versus placebo for the outcome pain relief at 2 hours in patients with migraine.

Of note, the paper by Brandes et al. (2007) and the paper by Smith et al. (2005), who were considered among the 'additional evidence' in our systematic analysis, had been previously analysed by Larry et al. (2016) in a Cochrane review that showed that in all efficacy analyses, the combination naproxen-sumatriptan was superior to monotherapy with either sumatriptan or naproxen alone.

Limited data exist on the comparisons of sumatriptan-naproxen with other acute migraine therapies. In our search we found one RCT comparing oral sumatriptan 85 mg + naproxen 500 mg with oral paracetamol 325 mg + butalbital 50 mg + caffeine 40 mg *(86)* that met the criteria for main evidence. The risk of bias was considered low.
A total of 442 participants were enrolled and treated three migraine attacks with either placebo, sumatriptan-naproxen sodium or the BCM combination. No differences were observed in the primary outcome measure (sustained pain-free response rates 2–24 h post-dose) between sumatriptan-naproxen and BCM, although both interventions were superior to placebo. Sumatriptan-naproxen sodium showed superior efficacy to both BCM and placebo for pain-free responses observed at 2, 4, 6, 8, 24 and 48 h ($p < 0.05$ vs. both placebo and BCM, respectively).
The quality of evidence was considered moderate due to the availability of only one RCT.

On this evidence the oral combination of sumatriptan (50 or 80 mg)-naproxen 500 mg is superior to placebo in the acute treatment of migraine attacks, is superior to the individual drugs used alone. No direct comparative data of efficacy is available for the combination versus acetyl salicylic acid, ibuprofen or other NSAIDs. It is unclear whether the combination sumatriptan-naproxen is superior to a combination of paracetamol+butalbital+caffeine.

2) ELETRIPTAN

Evidence of efficacy for eletriptan vs placebo

The search of the literature for systematic reviews and meta-analyses of the efficacy of triptans in the acute treatment of migraine yielded 2445 references (Figure 14). After duplicate removal and screening, we included 21 systematic reviews and meta-analyses *(60, 106-125)* as sources of randomized controlled trials (RCTs). After reviewing the full texts of these RCTs, we included 119 in the quantitative synthesis *(37, 39, 48, 51, 54, 57, 76-82, 126-230)* . Two additional RCTs were included from searching RCTs *(76, 231)* and none from the search updates. Of these 121 studies, 11 assessed eletriptan efficacy *(78, 131-140)*.

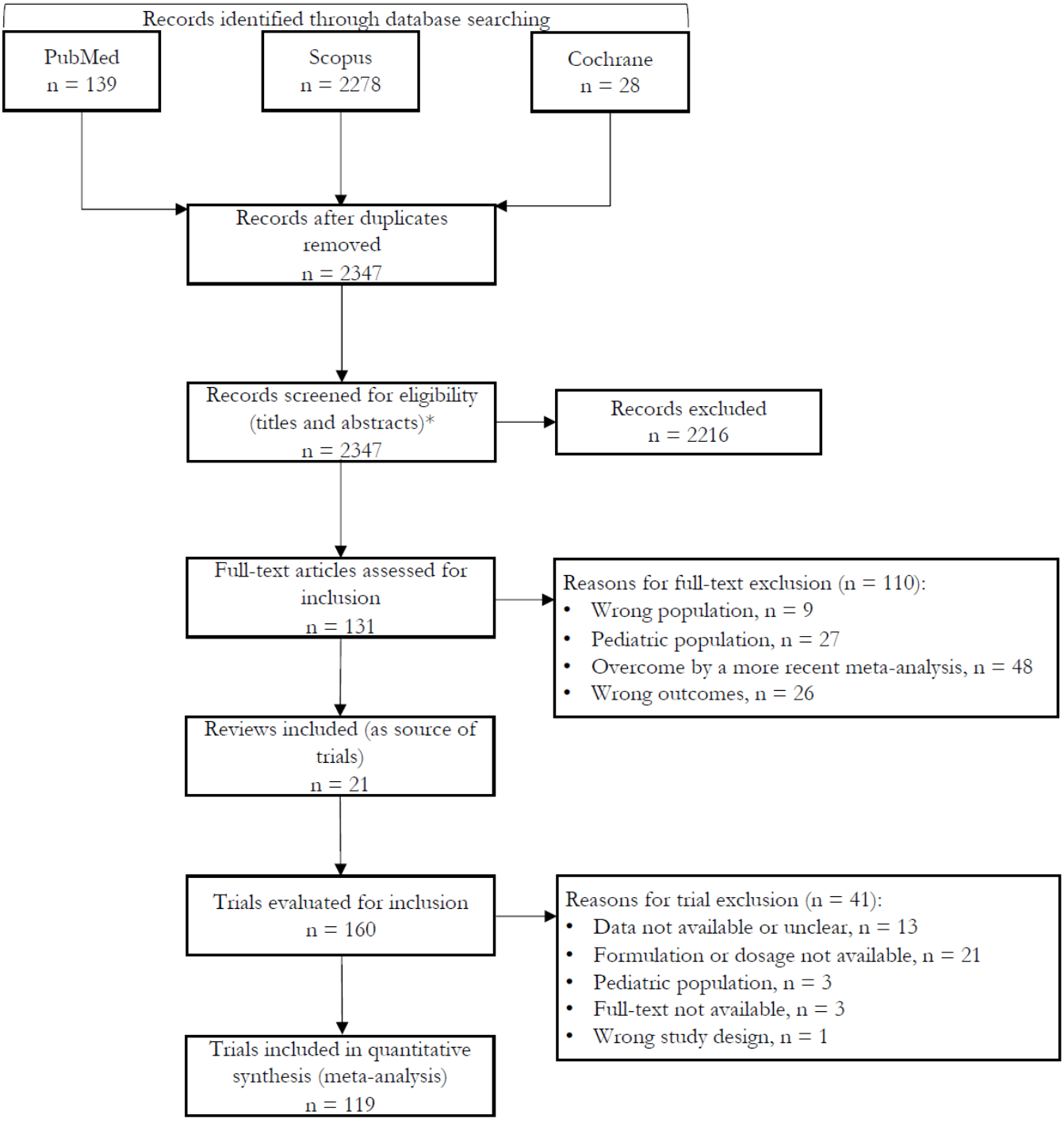


Figure 14 – Selection flowchart for meta-analyses and systematic reviews on the efficacy of triptans in the acute treatment of migraine

There was high-quality evidence to recommend the use of eletriptan 20 and 40 mg, as well as oral almotriptan 12.5 mg, frovatriptan 2.5 mg, naratriptan 2.5 mg, rizatriptan 5 and 10 mg, sumatriptan 50 and 100 mg and zolmitriptan 2.5 mg, and subcutaneous sumatriptan 6 mg for

the acute treatment of migraine attacks. Additionally, there was moderate quality of evidence to recommend oral naratriptan 1 mg and sumatriptan nasal spray 10 and 20 mg.

On this literature, eletriptan has a high level of quality of evidence of efficacy in the acute treatment of migraine, with a strong recommendation for its use.

Evidence of comparative efficacy for eletriptan vs other triptans

In comparative RCTs, eletriptan tablet 40 mg proved more effective than sumatriptan 100 mg, and naratriptan 2.5 mg, slightly superior to rizatriptan and equivalent to zolmitriptan 2.5 mg *(78, 132, 135-137, 139)*. More specifically, eletriptan 40 mg was superior to both sumatriptan 100 mg and naratriptan 2.5 mg for both pain freedom and pain relief at 2 hours (Tables 3 and 4 and Figures 15-18), to rizatriptan for pain relief at 2 hours (Figures 19 and 20), while it was equivalent to zolmitriptan for both outcome measures (data not shown). The quality of evidence and the strength of recommendations in favour of eletriptan over naratriptan, rizatriptan and sumatriptan is illustrated in Table 5.

In a network meta-analysis that was published very recently, eletriptan was rated superior to naratriptan, sumatriptan and zolmitriptan for the efficacy measures pain freedom at 2 hours, pain relief at 2 hours and sustained pain freedom from two to 24 hours: OR 2.73 (1.35 to 5.52) vs naratriptan, 1.41 (1.02 to 1.93) versus sumatriptan and 1.47 (1.03 to 2.11) versus zolmitriptan with a low or very low level of certainty of evidence *(58)*.

On this evidence, eletriptan is more effective than sumatriptan, and should be used when the latter proves ineffective.

Certainty assessment				№ of patients		Effect			
Risk of bias	Inconsistency	Indirectness	Imprecision	Eletriptan	Sumatriptan	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain freedom at 2 hours – Eletriptan 40 mg oral vs Sumatriptan 100 mg oral									
Not serious	Not serious	Not serious	Not serious	386/1118 (34.5%)	268/1139 (23.5%)	RR 1.36 (1.20-1.55)	85 [47-129] more per 1,000	⨁⨁⨁⨁ High	Critical
Pain relief at 2 hours – Eletriptan 40 mg oral vs Sumatriptan 100 mg oral									
Not serious	Not serious	Not serious	Not serious	741/1118 (66.3%)	651/1139 (57.2%)	RR 1.16 (1.08-1.23)	91 [46-131] more per 1,000	⨁⨁⨁⨁ High	Critical

Table 3 - GRADE evidence profile table for oral eletriptan 40 mg vs oral sumatriptan 100 mg from three RCTs for the outcomes pain freedom and pain relief at 2 hours.

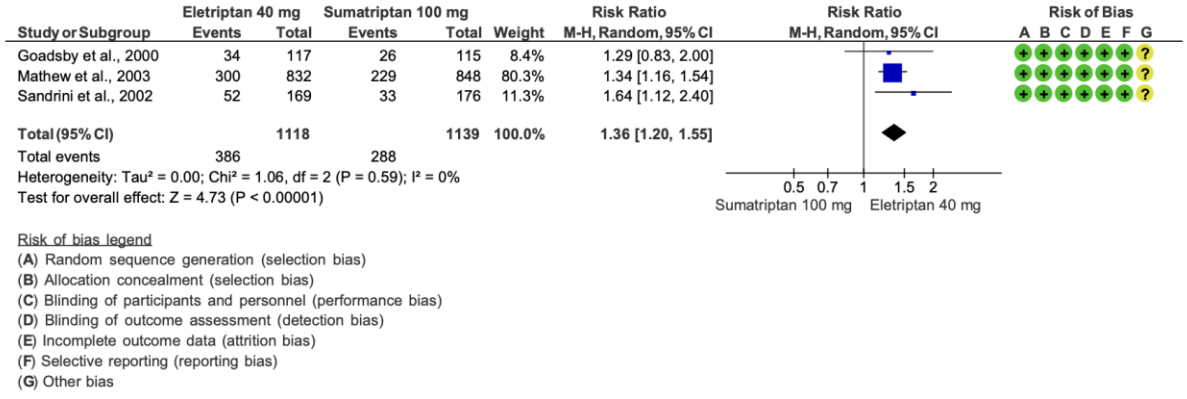


Figure 15 - Forest plot showing the comparison between oral eletriptan 40 mg and oral sumatriptan 100 mg for the outcome pain freedom at 2 hours in patients with migraine.

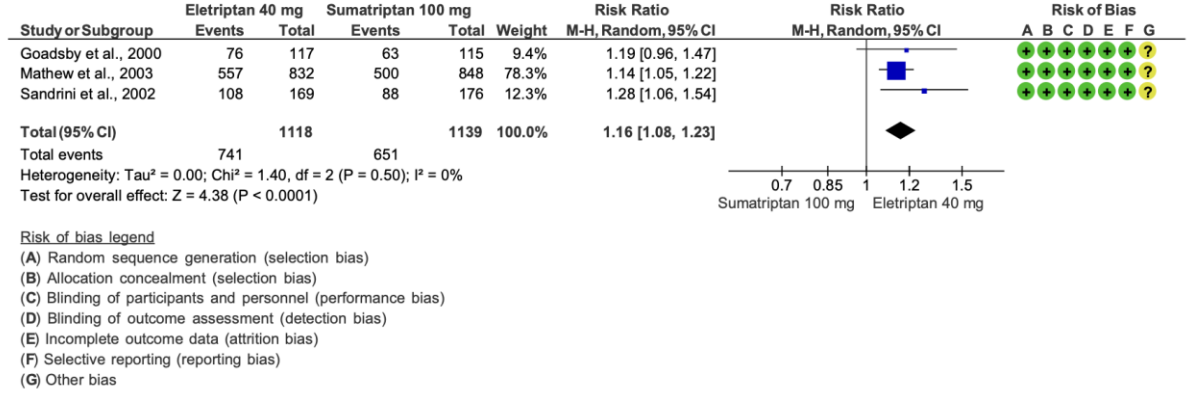


Figure 16 - Forest plot showing the comparison between oral eletriptan 40 mg and oral sumatriptan 100 mg for the outcome pain relief at 2 hours in patients with migraine.

Certainty assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Eletriptan	Naratriptan	Relative (95% CI)	Absolute (95% CI)		
Pain freedom at 2 hours – Eletriptan 40 mg oral vs naratriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[1]	Not serious	Not serious	None	67/192 (34.9%)	36/199 (18.1%)	**RR 1.93** (1.36 to 2.75)	**168 more per 1,000** (from 65 more to 317 more)	⨁⨁⨁⨀ Moderate	Critical
Pain relief at 2 hours – Eletriptan 40 mg oral vs naratriptan 2.5 mg oral												
1	RCT	Not serious	Not applicable[1]	Not serious	Not serious	None	108/192 (56.3%)	84/199 (42.2%)	**RR 1.33** (1.09 to 1.64)	**139 more per 1,000** (from 38 more to 270 more)	⨁⨁⨁⨀ Moderate	Critical

[1]Only one trial

Table 4 - GRADE evidence profile table for oral eletriptan 40 mg vs oral naratriptan 2.5 mg in people with migraine for the outcomes pain freedom and pain relief at 2 hours.

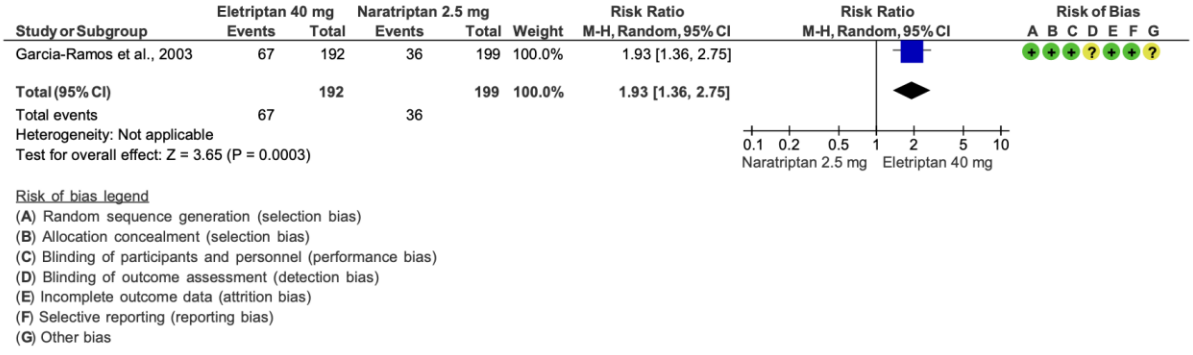


Figure 17 - Forest plot showing the comparison between oral eletriptan 40 mg and oral naratriptan 2.5 mg for the outcome pain freedom at 2 hours in patients with migraine.

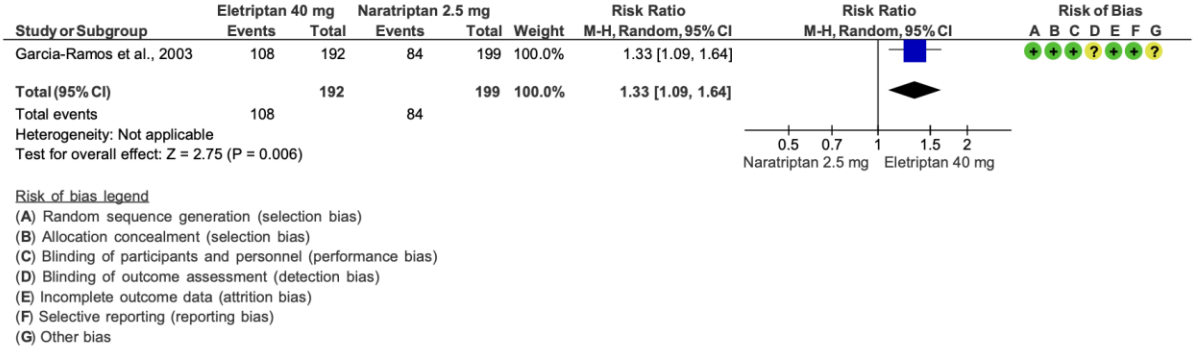


Figure 18 - Forest plot showing the comparison between oral eletriptan 40 mg and oral naratriptan 2.5 mg for the outcome pain relief at 2 hours in patients with migraine.

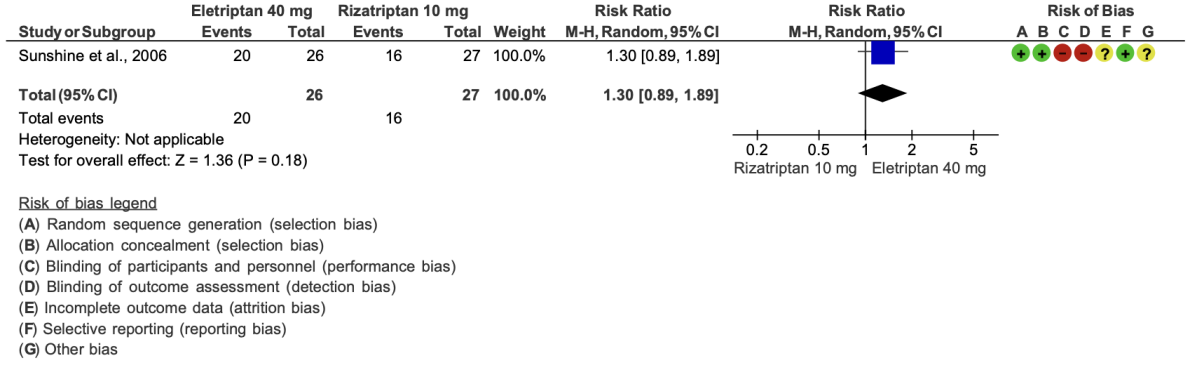


Figure 19 - Forest plot showing the comparison between eletriptan 40 mg and rizatriptan 10 mg for the outcome pain freedom at 2 hours in patients with migraine.

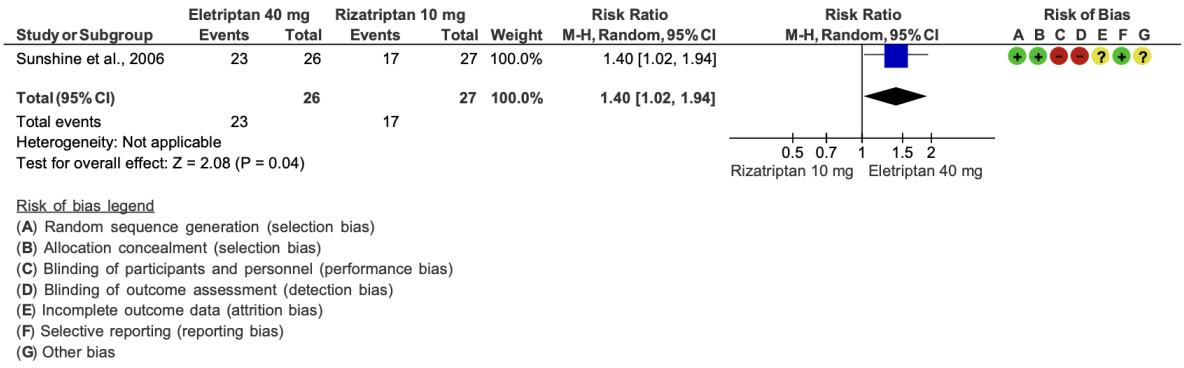


Figure 20 - Forest plot showing the comparison between eletriptan 40 mg and rizatriptan 10 mg for the outcome pain relief at 2 hours in patients with migraine.

The table below summarizes the evidence from head-to-head comparisons between eletriptan and other triptans for the acute treatment of migraine attacks.

Comparator	**Quality of evidence**	**Strength of recommendation (eletriptan over comparator)**
Naratriptan	⊕⊕⊕⊖	↑
Rizatriptan	⊕⊖⊖⊖	↑
Sumatriptan	⊕⊕⊕⊕	↑↑
Zolmitriptan	⊕⊕⊕⊖	=

Table 5 – Summary evidence from head-to-head trial assessing the efficacy of eletriptan.

Safety and tolerability of naproxen

Safety and Tolerability: In the trials assessed in this review with the 500 mg dose of naproxen, no differences were detected as regards side effects versus placebo. No difference was detected also when comparing the combination naproxen-sumatriptan versus sumatriptan alone, while the occurrence of side effect was lower in the subjects treated with naproxen alone when compared to the group treated with the combinations naproxen-sumatriptan. Gastrointestinal (GI) complaints were the most frequently reported event, including nausea, diarrhoea and dyspepsia. Other reported adverse events were dizziness, dry mouth, paraesthesia, somnolence, chest tightness and tinnitus.

Serious safety concerns: No serious adverse events were reported in the available RCTs.

Warnings and Contraindications: Non serious adverse events emerged from the studies assessed in our systematic review. In general, naproxen bears the same contraindications as other NSAIDs *(232)*, like NSAID hypersensitivity or salicylate hypersensitivity, subjects who have experienced an allergic reaction (urticaria, asthma, etc.) after taking NSAIDs; subjects who have undergone coronary artery bypass graft surgery and during the third trimester of pregnancy.

Overall, while naproxen is effective for pain relief, the use of naproxen is relatively safe as no serious adverse events are reported in available RCTS. However, it is important to monitor for potential GI side effects, particularly in patients with a history of GI issues and renal side effects in subjects with frequent use.

Safety and tolerability of triptans

Serious safety concerns: the presence of $5HT_{1B}$ receptors in the coronary arteries has arisen several concerns about the risk of triptan-induced coronary arterial narrowing, further supported by individual cases of acute myocardial infarction in close temporal relationship with triptans intake. Contrariwise, incidence of triptan-induced serious cardiovascular adverse events in both clinical trials and clinical practice appears to be extremely low and limited to migraine patients with significant cardiovascular risks or with overt cardiovascular diseases. In line with these observations, analyses of FDA reports, observational studies, and general practice research databases failed to reveal an increased risk of cardiovascular or cerebrovascular incidents in triptan users in the absence of vascular risk factors *(233)*.

Safety and Tolerability: Triptans are associated with a statistically significant increase in odds of any adverse events or treatment-related adverse events compared with placebo, although usually mild to moderate in intensity, transient and spontaneously resolving. Among the most frequent triptan AEs nausea, tingling, paresthesia, as well as flushing and warm sensations in the head, neck, chest, and limbs should be mentioned.

'Chest-related AEs', also known as "triptan sensation", are not related to myocardial ischemia according to aggregated data from trials, real world experiences and pharmacodynamic instrumental assessments (by electrocardiogram, myocardial scintigraphy and angiography). Therefore, "chest-related AEs" characterized by chest pressure, chest pain, shortness of breath, palpitations, and anxiety, should be considered non-serious AEs. Although rare, it is worth mentioning 'central nervous system AEs' (asthenia, abnormal dreams, agitation, aphasia, ataxia, confusion, dizziness, somnolence, headache, speech disorder, thinking abnormal, tremor, vertigo, and other focal neurological symptoms). The "central nervous system AEs" rates of incidence largely overlap among triptans with higher values for eletriptan 80 mg and lower values for almotriptan 12.5 mg.

Warnings and Contraindications: the vasoconstrictive potential of triptans has led to the exclusion of patients over 65 years with vascular diseases from phase III studies. Therefore, eletriptan, like the other triptans, is contraindicated in patients with coronary artery disease or coronary artery vasospasm, history of stroke, transient ischemic attack, hemiplegic or basilar migraine, intracerebral or subarachnoid hemorrhage, hypertensive crisis, Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders or arrhythmias, peripheral vascular disease, ischemic bowel disease and severe hepatic impairment. Moreover, sumatriptan and other triptans are not recommended in patients over 65 years. Nevertheless, several studies reported the use of triptans as safe in patients with stable vascular diseases, including people beyond the age of 65 years.

Comparative safety and tolerability of naproxen and eletriptan versus other drugs for the acute treatment of migraine

In a systematic literature review and Bayesian network meta-analysis of treatments for migraine for comparative tolerability, naproxen and eletriptan showed favourable profiles (Tables 6 and 7) *(234)*. More specifically, naproxen showed a profile similar to placebo, while eletriptan had a better tolerability profile than those of other triptans when considering the outcomes 'any side effect', 'treatment-related side effects' and 'serious side effects' (Figures 21-23).

Comparison	Any adverse events, OR (95% CrI)	Treatment-related adverse events, OR (95% CrI)	Serious adverse events, OR (95% CrI)
Pooled placebo proportion	16.8%	10.8%	0.1%
Triptan placebo comparisons			
Sumatriptan vs. placebo	**1.79 (1.57–2.05)**	**2.23 (1.83–2.73)**	2.20 (0.73–6.33)
Almotriptan vs. placebo	1.28 (0.95–1.72)	1.15 (0.81–1.61)	0.90 (0.11–7.49)
Eletriptan vs. placebo	1.33 (0.95–1.81)	**1.95 (1.45–2.68)**	1.24 (0.23–5.30)
Frovatriptan vs. placebo	1.40 (0.82–2.36)	1.13 (0.53–2.34)	—
Naratriptan vs. placebo	1.11 (0.84–1.43)	0.86 (0.51–1.55)	**11.8 (1.25–106)**
Rizatriptan vs. placebo	**1.80 (1.54–2.12)**	**1.93 (1.51–2.45)**	1.66 (0.50–4.97)
Zolmitriptan vs. placebo	**2.22 (1.82–2.72)**	**1.75 (1.18–2.58)**	1.49 (0.47–4.31)
Sumatriptan+naproxen vs. placebo	**1.77 (1.34–2.30)**	**2.44 (1.66–3.59)**	0.10 (0.00–1.30)

Table 6 - Network meta-analysis results for triptans. Note: OR, odds ratio; CrI, credibility interval; —, no evidence in the network. COX-2: cyclooxygenase-2; statistically significant values are highlighted in bold. Serious adverse event outcomes do not include trials with zero counts (from Thorlund et al., 2017).

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Comparison	Any adverse events, OR (95% CrI)	Treatment-related adverse events, OR (95% CrI)	Serious adverse events, OR (95% CrI)
Non-triptan placebo comparisons			
Acetaminophen vs. placebo	1.33 (0.98–1.84)	**1.48 (1.05–2.11)**	1.28 (0.06–13.40)
COX-2 inhibitor vs. placebo	0.78 (0.53–1.13)	1.18 (0.79–1.73)	0.99 (0.07–9.80)
Diclofenac vs. placebo	—	0.38 (0.01–10.0)	—
Ergotamine vs. placebo	**1.60 (1.14–2.29)**	1.94 (0.96–3.93)	0.12 (0.00–1.72)
Ibuprofen vs. placebo	0.75 (0.36–1.59)	—	—
Naproxen vs. placebo	0.95 (0.69–1.33)	1.07 (0.72–1.58)	0.77 (0.02–10.34)

Table 7 - Network meta-analysis results for non-triptans. Note: OR, odds ratio; CrI, credibility interval; —, no evidence in the network. COX-2: cyclooxygenase-2; statistically significant values are highlighted in bold. Serious adverse event outcomes do not include trials with zero counts (from Thorlund et al., 2017 (234)).

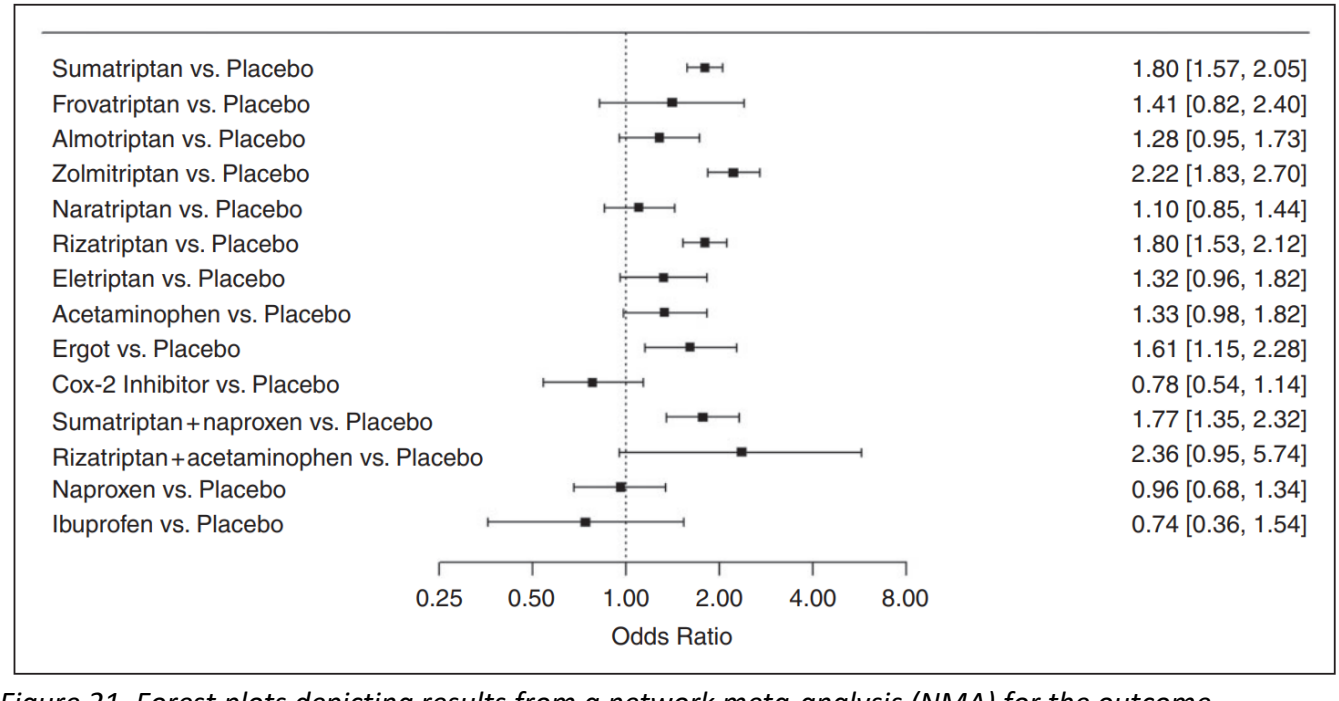


Figure 21. Forest plots depicting results from a network meta-analysis (NMA) for the outcome any adverse event. Comparative effects are presented as odds ratios with 95% credibility

intervals. Odds ratios smaller than 1.00 favour the active treatments, odds ratios larger than 1.00 favour placebo (from Thorlund et al., 2017 (234)).

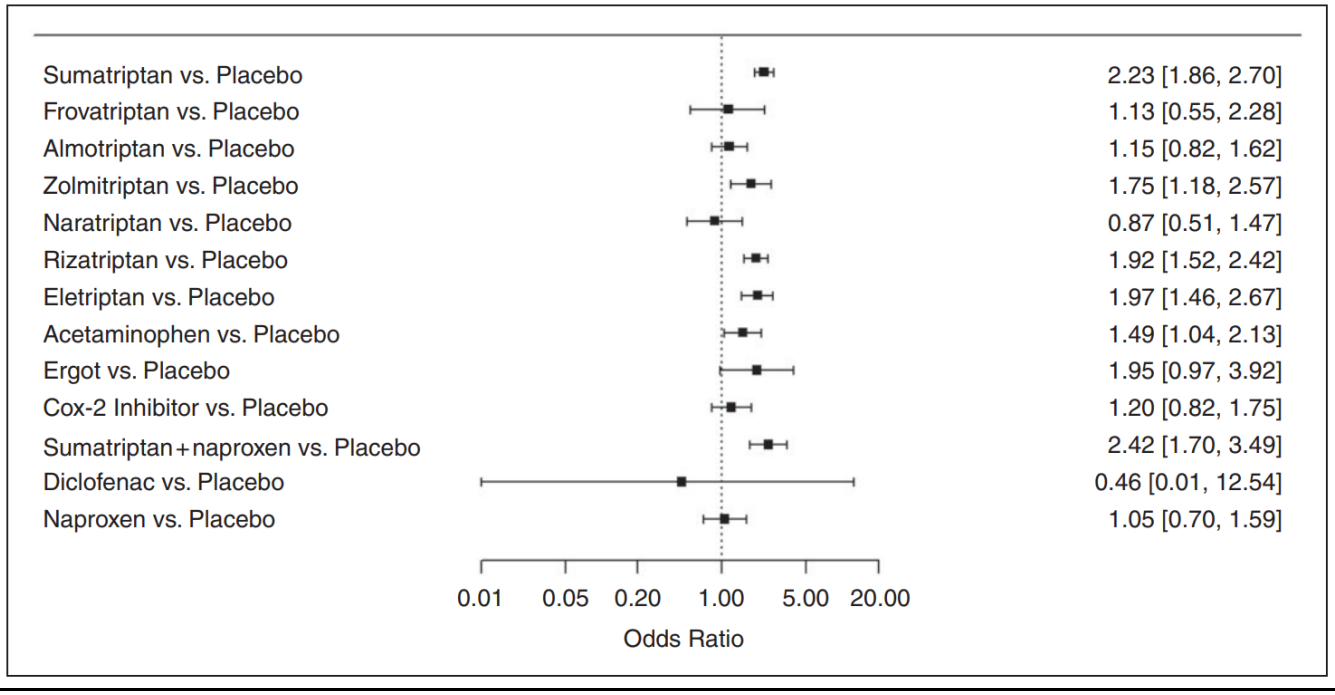


Figure 22. Forest plots depicting results from a network meta-analysis (NMA) for the outcome treatment-related adverse events. Comparative effects are presented as odds ratios with 95% credibility intervals. Odds ratios smaller than 1.00 favour the active treatments, odds ratios larger than 1.00 favour placebo (from Thorlund et al., 2017 (234)).

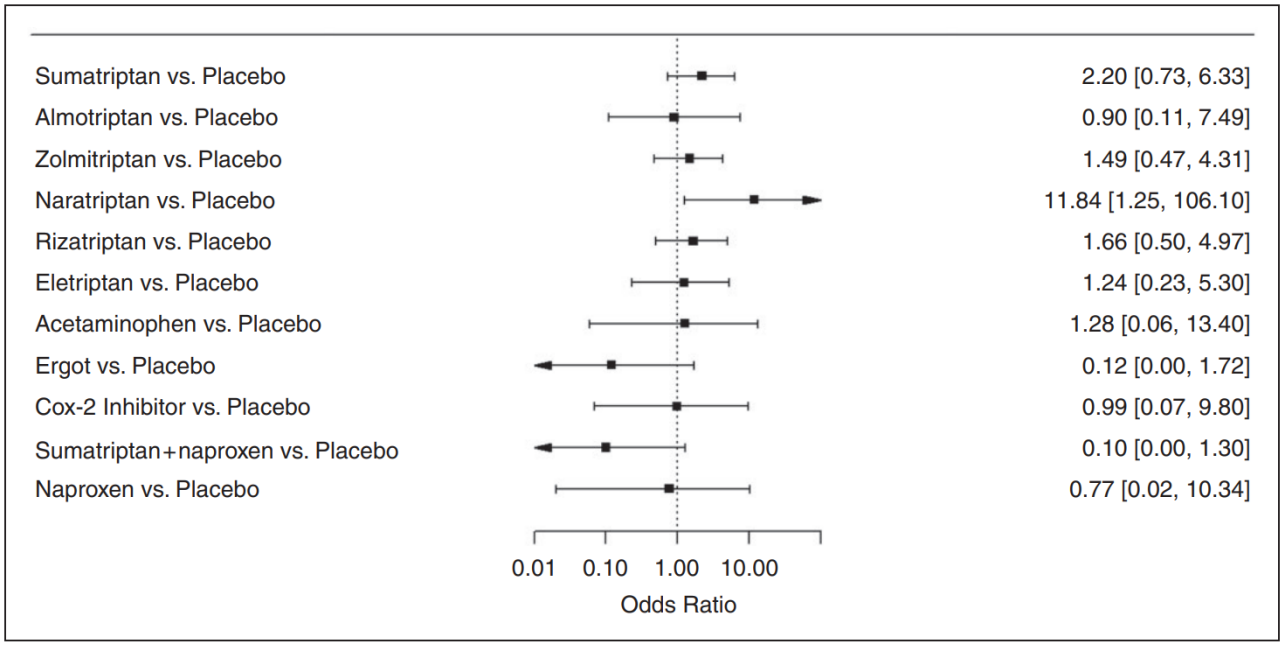


Figure 23. Forest plots depicting results from a network meta-analysis (NMA) for the outcome serious adverse events. Comparative effects are presented as odds ratios with 95% credibility

intervals. Odds ratios smaller than 1.00 favour the active treatments, odds ratios larger than 1.00 favour placebo (from Thorlund et al., 2017(234)).

Another network meta-analysis designed to compare the relative efficacies and tolerability of triptans and NSAIDs suggested that eletriptan was the preferable therapy for migraine from a comprehensive perspective combining efficacy and tolerability *(125)* (Figure 24).

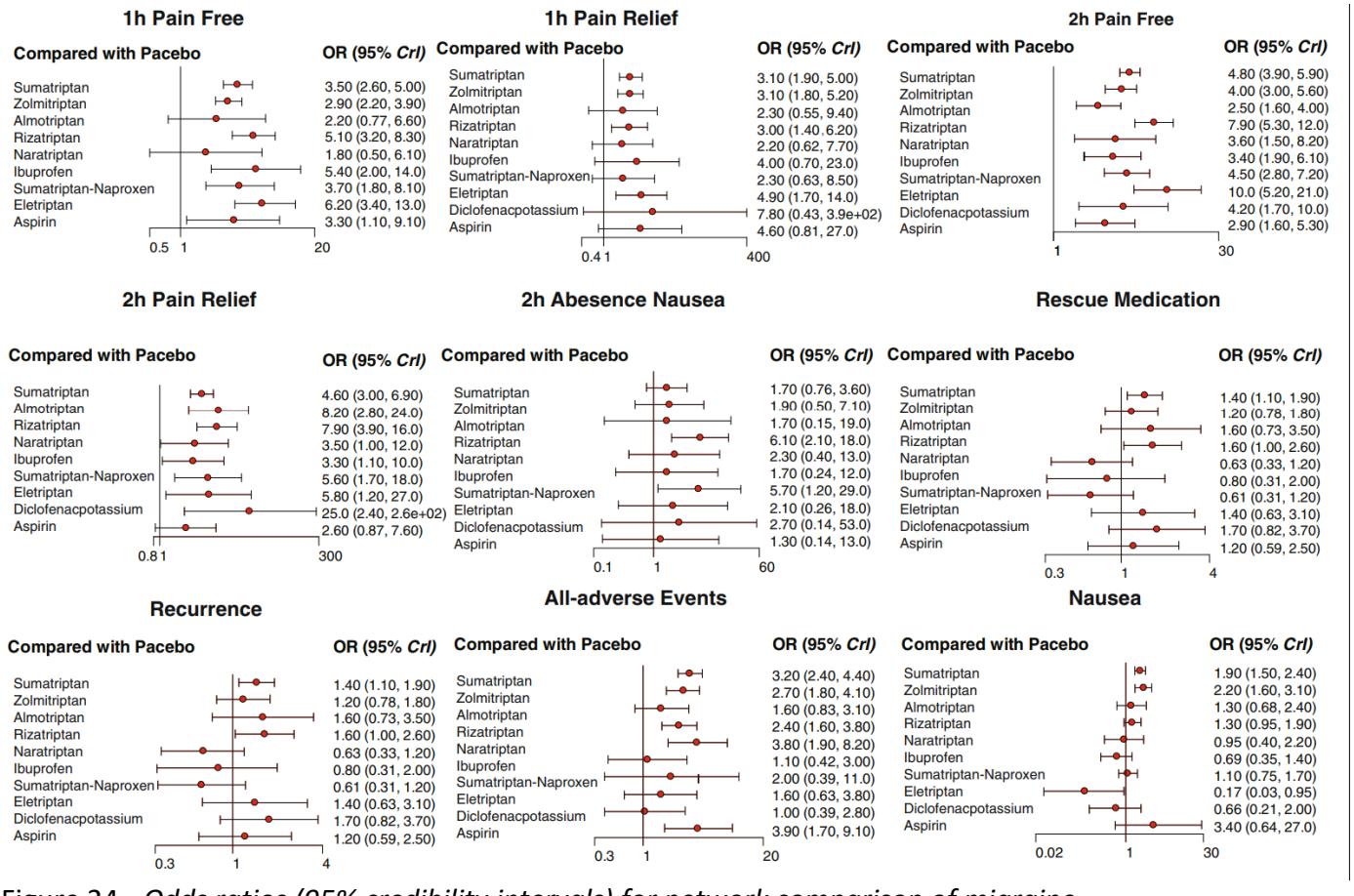


Figure 24 - *Odds ratios (95% credibility intervals) for network comparison of migraine treatments (from Xu et al. 2016*)

No data comparing directly the safety of naproxen with the other drugs listed in the EML for the acute treatment of migraine are available in the literature. Data from other areas suggests that naproxen has better safety profile as compared to ibuprofen for hypertension, cardiovascular events and renal events, while it may be associated more frequently to oedema *(235)*. Asthma and bronchospasm may be more frequent with acetyl salicylic acid as compared with other NSAIDs *(236)*.

A recent systematic review of the literature on tension type headache can offer interesting insights due to the similarity with migraine for the recurrent intake of acute medications, no substantial differences emerged in occurrence and severity of adverse events with naproxen 375 mg, acetyl salicylic acid 1000 mg and paracetamol 1000 mg (Figure 25, panels a and b) *(237)*.

Panel a)

Body system Adverse event	Aspirin 1000 mg	Acetaminophen 1000 mg	Diclofenac-K 12.5/25 mg	Ibuprofen 400 mg	Ketoprofen 12.5/25 mg	Lumiracoxib 200/400 mg	Metamizol 500/1000 mg	Naproxen 375 mg	Placebo	Total
N	314	605	316	331	466	120	178	300	1018	3648
Aes	46	57	10	4	60	0	12	35	91	315
Deaths	0	0	0	0	0	0	0	0	0	0
Serious Aes	0	0	0	0	0	0	0	0	0	0
Digestive system	[a]	20	4	4	14		[a]	20	17[a]	98[a]
Nausea	5	8			3		2	9	19	46
Dyspepsia	4[b]	6					[b]	11	6[b]	43[b]
Dry mouth		4						2	0	6
Vomiting	0						0		1	1
Nervous system	24	20			10			11	20	85
Somnolence	11	4					1	5	11	32
Dizziness	11	6						3	3	23
Dry mouth	2								8	10
Musculoskeletal		0			4				1	5
Cardiovascular		1			3				0	4
Urogenital		1			3				0	4
Respiratory		0			3				0	3
As a whole		6			14			6	9	35
Asthenia		1						4	1	6
Urticaria	0						0		1	1
Abdominal pain		1								1

AEs: adverse events.
[a]Nineteen cases (including metamizol, aspirin and placebo) involving the gastrointestinal tract (digestive system).
[b]Dyspepsia was reported in 16 patients (including metamizol, aspirin and placebo).

Panel b)

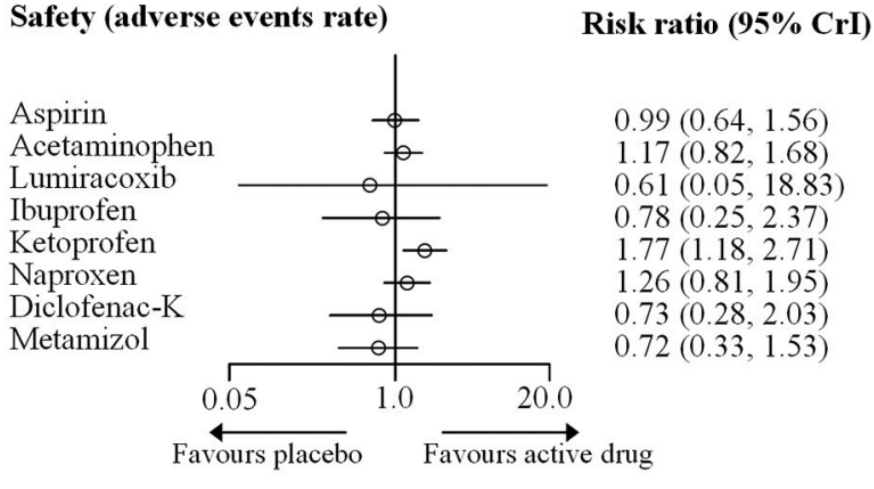


Figure 25 – Panel a) Summary of adverse event included in the network meta-analysis by Xie et al., 2024; Panel b) forest plot for the outcome of safety of simple analgesics compared with placebo, which was the reference compound. (Both panels are taken from Xie et al., 2024 (237).

Section 9: Summary of recommendations in current clinical guidelines

Recommendations in existing WHO guidelines

N.A.

Recommendations in other current clinical guidelines

A summary of recommendations in current guidelines mentioning naproxen and eletriptan as acute migraine treatments is provided in the table below (Table 8).

Guideline	**Year**	**Recommendation**
Lifting The Burden (1st edition) *(238)*	2007	• Ibuprofen 400-800 mg and naproxen 500-1000 mg are indicated as step one treatment for attacks.
European Federation of Neurological Societies (EFNS) Guidelines *(239)*	2009	Drugs of first choice for mild or moderate migraine attacks are analgesics. • Level A recommendation for ibuprofen 200–800 mg and Naproxen 500–1000 mg In about 60% of non-responders to NSAIDs, triptans are effective • Level A recommendation for eletriptan 20, 40 mg
NICE Guidelines (National Institute of Health and Care Excellence, available online) *(240)*	2012	• Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. • For people who prefer to take only one drug, consider monotherapy with an oral triptan, NSAID, aspirin (900 mg) or paracetamol for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. • 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.

TOP Primary care management of headache in adults (Toward Optimized Practice, 2016) *(241)*	2016	NSAIDs, acetaminophen, and triptans are the primary drugs for treating acute migraine. • Ibuprofen 400 mg and naproxen sodium 500 mg are recommended for acute treatment in patients with migraine of all severities • The response of a patient with migraine to medications is individual and idiosyncratic. Although all triptans have a similar molecular structure, the differences between them are sufficient that one patient will find better efficacy and/or fewer side effects with one particular triptan compared with another, while a second patient will find the opposite.
Scottish (SIGN) Guidelines *(242)*	2018	• Ibuprofen (400 mg) is recommended as first-line treatment for patients with acute migraine. If ineffective, the dose should be increased to 600 mg. • Triptans are recommended as first-line treatment for patients with acute migraine. The first choice is sumatriptan (50–100 mg), but others should be offered if sumatriptan fails.
British Association for the Study of Headache (BASH) Guidelines *(243)*	2019	When prescribing acute treatments […] start with simple analgesics and if ineffective step-up to a triptan • Ibuprofen 400-600 mg, naproxen 250 mg and eletriptan 40 mg are among recommended acute treatments
Japanese Headache Society Guidelines *(244)*	2019	The mainstays of acute treatment […] include NSAIDs, […] and triptans. Use NSAIDs such as […] naproxen for mild-to-moderate headache, and use triptans for moderate-to-severe headache, or even mild-to-moderate headache when NSAIDs were ineffective in the past. • Level A recommendation for ibuprofen 100-600 mg and Naproxen 100-600 mg • Level A recommendation for eletriptan 20-40 mg
Lifting the Burden (2nd edition) *(245)*		• Efficacy of sumatriptan may be increased by combination with naproxen 500–1000 mg (there are no data on combinations of other triptans and NSAIDs).

Danish Headache Society Guidelines *(246)*	2021	• Simple analgesics, and in particular ibuprofen 400–600 mg and naproxen 500 mg, are recommended as a first step in the acute treatment of the migraine attack. • Triptans, including eletriptan 40 mg, are recommended as a second step
American Headache Society Guidelines *(247)*	2021	• NSAIDs (including ibuprofen and naproxen) are recommended for mild-to-moderate attacks and triptans (including eletriptan) are recommended for moderate or severe attacks and mild-to-moderate attacks that respond poorly to nonspecific therapy
French Headache Society Guidelines *(248)*	2021	• Strong level of recommendation for both ibuprofen 200-400 mg and naproxen 550-1000 mg as non-specific acute migraine treatment • Strong level of recommendation for eletriptan 20 or 40 mg as specific acute migraine treatment
German Headache Society Guidelines *(249)*	2022	• Ibuprofen 200 mg/400 mg/600 mg and naproxen 500 mg are recommended for treatment of migraine attack • Eletriptan 40 mg (as well as 20 and 80 mg) is recommended for moderate-severe attacks and lack of response to analgesics
SISC-IHS Guidelines *(250)*	2024 (in press)	In people with migraine not responding to analgesics or non-steroidal anti-inflammatory drugs taken at appropriate doses and early during the attack, we suggest switching to a triptan for the next attack. • Based on the evidence, eletriptan, rizatriptan, sumatriptan and zolmitriptan are at least equally or more effective than simple analgesics and NSAIDs.

Table 8 – Summary of recommendations dealing with naproxen or eletriptan in current guidelines for migraine treatment.

Section 10: Summary of available data on comparative cost and cost-effectiveness

Naproxen

No studies have reported comparative cost or cost-effectiveness of naproxen in the treatment of acute migraine.

In the following estimates comparing naproxen with ibuprofen (the subject of a separate proposal), we factored in only medication costs, assuming other healthcare costs such as consultations to be constant across the alternatives. We ascertained medication costs in nine countries (data provided by clinical experts in eight, and from the UK NHS drug tariff) (see Table 9). Across these countries, with Argentina a clear outlier, the cost of naproxen 500 mg (median US$ 0.155) is almost three times that of ibuprofen 400 mg (US$ 0.056).

Cost per treatment success

The analysis was conducted against ibuprofen as an example of NSAID that is proposed in many guidelines for the acute treatment of migraine.

We took efficacy data for ibuprofen from Suthisisang et al. (2010) *(251)* and for naproxen from Law et al. (2013) *(252)*. Proportions of those treated reporting pain freedom at 2 hours (Ppf: the preferred outcome measure) are 25.6% for ibuprofen, 17.0% for naproxen; proportions of those treated reporting headache relief at 2 hours (Phr: the more pragmatic outcome measure) are 51.8% for ibuprofen, 45.0% for naproxen. Thus, for pain freedom, naproxen 500 mg is 4.2 ([0.155/0.056]*[25.6/17.0]) times more expensive per treatment success, and for headache relief 3.2 ([0.155/0.056]*[51.8/45.0]) times more expensive, than ibuprofen 400 mg.

However, naproxen is proposed here not on the basis of cost but for a better cardiac safety and a longer duration of action than other (see Section 5).

For comparison of naproxen with sumatriptan (the alternative in most guidelines when ibuprofen is inadequate), we found the cost of sumatriptan to be highly variable worldwide. Therefore, we used the cheapest prices listed in the NHS drug tariff: for sumatriptan 50 mg, GBP 0.97 for 6 tablets (USD 0.21 per tablet); for sumatriptan 100 mg (the dose for which efficacy data were available) GBP 1.22 for 6 tablets (USD 0.27 per tablet); for naproxen, GBP 1.33 for 28 tablets (USD 0.06 per tablet). The cost of sumatriptan 50 mg is therefore 3.5 times, and the cost of sumatriptan 100 mg is 4.5 times, that of naproxen 500 mg.

The proportion of those treated reporting pain freedom (PF) at 2 hours (Ppf) is 25.3% for sumatriptan 100 mg and the proportion reporting headache relief (HR) at 2 hours (Phr) is 57.2% (see section 8). Thus, for pain freedom, sumatriptan 100 mg is 3.0 (4.5*[17.0/25.3]) times more expensive per treatment success, and for headache relief 3.5 (4.5*[45.0/57.2]) times more expensive, than naproxen 500 mg.

			Ibuprofen 400 mg					Naproxen 500 mg			
Country	**Exchange**		**Cost local**	**Quantity**	**Cost per 400 mg local**	**Cost per 400 mg $**		**Cost local**	**Quantity**	**Cost per 500 mg local**	**Cost per 500 mg $**
Egypt	0.02064		51.00	30	1.700	0.035		not available			
Moldova	0.05643		31.00	10	3.100	0.175		250.00	30	8.333	0.470
Nepal	0.00737		1.13	1	1.130	0.008		90.00	10	9.000	0.066
Georgia	0.3663		7.78	10	0.778	0.285		4.33	10	0.433	0.159
Indonesia	0.00006		591.00	1	591.000	0.035		2500.00	1	2500.000	0.150
Mongolia	0.000296		19000.00	100	190.000	0.056		18000.00	10	1800.000	0.533
Argentina	0.00104		188.71	1	188.710	0.196		1570.00	1	1570.000	1.633
Brazil	0.17961		0.79	1	0.790	0.142		0.79	1	0.790	0.142
UK (NHS drug tariff)	1.31205		0.78	24	0.033	0.043		1.33	28	0.048	0.062
Median						**0.056**					**0.155**

Table 9 - Drug prices (ibuprofen and naproxen) in nine countries

Therefore, for those in whom naproxen is judged to be safer than other NSAIDs, naproxen 500 mg is a cost-effective option compared with sumatriptan 100 mg (or sumatriptan 50 mg even if this has the same efficacy as 100 mg), the next alternative to NSAIDs in most guidelines.

It should be noted that this analysis did not include the additional healthcare costs associated with prescriptions of sumatriptan. In many countries, naproxen is also prescription-only.

Cost per healthy life year gained

To estimate effectiveness in terms of healthy life years (HLYs) gained, we assumed treatment is administered 0.5 hours after the onset of symptoms. We assumed untreated attack duration (D) would be reduced to 2 hours after treatment (ie, to 2.5 hours) with probabilities Ppf or Phr. We established D (20.6 hours) from population-based studies conducted among N=8,363 in 14 countries (China, Mongolia, Nepal, India, Pakistan, Saudi Arabia, Morocco, Benin, Cameroon, Ethiopia, Zambia, Peru, Lithuania and Russian Federation, which represented a range of low- to high-income settings).

We calculated HLYs gained per treatment using the formula:

$[(D–2.5)/(24*365)]*DW*P$

where DW is the disability weight (from GBD2013) for the ictal state (0.441) and P = Ppf or Phr.

Thus, for naproxen 500 mg, using median cost across the nine countries (US$ 0.155), cost/HLY gained is:

$0.155/\{[(20.6-2.5)/(24*365)]*0.441*0.170\}$ = US$ 1,001 (for PF)

$0.155/\{[(20.6-2.5)/(24*365)]*0.441*0.450\}$ = US$ 378 (for HR)

or, using the NHS drug tariff price (US$ 0.06):

$0.06/\{[(20.6-2.5)/(24*365)]*0.441*0.170\}$ = US$ 387 (for PF)

$0.06/\{[(20.6-2.5)/(24*365)]*0.441*0.450\}$ = US$ 146 (for HR)

By all these estimates, naproxen 500 mg is highly cost-effective.

Incremental cost effectiveness (ICER) for combination of naproxen 500 mg with sumatriptan 50 mg

We undertook this analysis making the same assumptions and using the same data sources as above. We used a timeframe of 1 year. We established mean frequency (F=41 days/year) from the population-based studies in the 14 countries (N=8,363). Therefore, HLYs gained per person per year (assuming all attacks are treated) = 41*HLYs gained per treatment.

We used efficacy data from Smith et al. 2005, which made a head-to-head comparison for the outcome pain relief at 2 hours: for sumatriptan 50 mg, Phr = 110/226 (48.7%); for sumatriptan 50 mg + naproxen 500 mg, Phr = 163/250 (65.2%). Thus:

HLYs gained per person per year:

for sumatriptan:

{[(20.6–2.5)/(24*365)]*0.441}*41*0.487 = 0.0182

for sumatriptan + naproxen:

{[(20.6–2.5)/(24*365)]*0.441}*41*0.652 = 0.0244.

We assumed one dose per attack. We used the median cost of naproxen 500 mg (US$ 0.155: see above), and assumed this to be the difference in cost per treatment. Therefore, incremental cost per person per year for the combination would be US$ 0.155*41 = US$ 6.36.

Thus, ICER (extra US$ to be invested per HLY gained) = 6.36/(0.0244-0.0182) = US$ 1,026.

On this evidence, the addition of naproxen 500 mg to sumatriptan 50 mg is cost-effective.

Eletriptan

Several studies have assessed the pharmacoeconomics of eletriptan, all summarised in 2015 by Bhambri et al., although it must be noted that the paper was funded by drug company *(253)*. This overview found "a consistent pattern [in which] eletriptan 40 mg, rizatriptan 10 mg and almotriptan 2.5 mg were shown to be more cost-effective than other triptans". This conclusion was based on costs at the time of publication of each included study, when generics were less widely available, and pricing was less competitive.

For comparison of eletriptan 40 mg with sumatriptan 50 mg (currently on the EML), we found the cost of sumatriptan to be highly variable worldwide. The price of eletriptan, ascertained in five countries (data provided by clinical experts in four, and from the UK NHS drug tariff) was even more so (Table 10), reflecting the difference between generic and branded formulations and that, at present, generics are currently available in only a minority of countries. In the following estimates comparing these triptans, we factored in only medication costs, assuming other healthcare costs such as consultations to be constant across the alternatives.

Country	Exchange	Cost per tablet local	Cost per tablet $
Nepal	0.00737	130.20	0.960
India	0.01189	81.50	0.979
Georgia	0.3663	15.60	5.716
Brazil	0.17961	19.20	3.449
UK (NHS drug tariff)	1.31205	3.75	4.920
Median			**3.449**

Table 10 - Drug prices (eletriptan 40 mg) in five countries

Cost per treatment success

On the basis of today's costs from the UK NHS drug tariff (sumatriptan 100 mg US$ 0.27 per tablet, eletriptan 40 mg US$ 4.92 per tablet, 18 times that of sumatriptan 100

mg), the above conclusion that “eletriptan 40 mg [was] … more cost-effective than other triptans” does not hold for the comparison of eletriptan with sumatriptan. The proportions of those treated reporting pain freedom at 2 hours (Ppf) are 34.5% for eletriptan 40 mg, 25.3% for sumatriptan 100 mg, and the proportions reporting headache relief at 2 hours (Phr) are 66.3% for eletriptan, 57.2% for sumatriptan. Thus, for pain freedom, eletriptan 40 mg is 13.2 (18*[25.3/34.5]) times more expensive per treatment success, and for headache relief 15.5 (18*[57.2/66.3]) times more expensive, than sumatriptan 100 mg.

However, eletriptan is proposed not as a substitute for sumatriptan but as second-line triptan when sumatriptan proves ineffective or not tolerated.

Applying UK prices, the marginal cost of using eletriptan 40 mg rather than sumatriptan 100 mg is US$ 4.65 (4.92-0.27) for increased probabilities of treatment success of 9.2% (34.5-25.3%) for pain freedom and 9.1% (66.3-57.2%) for headache relief, in patients for whom other options are limited.

Cost-effectiveness (US$/HLY gained)

To calculate cost/HLY gained for eletriptan, we used the median cost from five countries (Table 10). We assumed one dose per attack, administered 0.5 hours after the onset of symptoms. We assumed untreated attack duration (D) would be reduced to 2 hours after treatment (ie, to 2.5 hours) with probabilities Ppf or Phr. We established D (20.6 hours) from population-based studies conducted among N=8,363 in 14 countries (China, Mongolia, Nepal, India, Pakistan, Saudi Arabia, Morocco, Benin, Cameroon, Ethiopia, Zambia, Peru, Lithuania and Russian Federation, which represented a range of low- to high-income settings).

We calculated HLYs gained per treatment using the formula:

$[(D–2.5)/(24*365)]*DW*P$

where DW is the disability weight (from GBD2013) for the ictal state (0.441) and P = Ppf or Phr.

Thus, for eletriptan 40 mg, cost/HLY gained is:

3.449/{[(20.6-2.5)/(24*365)]*0.441*0.345} = US$ 10,971 (for PF)

3.449/{[(20.6-2.5)/(24*365)]*0.441*0.663} = US$ 5,709 (for HR)

Eletriptan 40 mg is therefore cost-effective by most thresholds at its current price. This is likely to fall substantially with marketing of generics if eletriptan is included in the EML.

Incremental cost effectiveness (ICER)

We made this analysis against sumatriptan 100 mg, adapting the analytical model presented by Tinelli et al. (2021). For sumatriptan 100 mg, we used the NHS drug tariff price of US$ 0.27 per tablet and for eletriptan the median cost from five countries of US$ 3.45 per tablet (Table 10).

We assumed one dose per attack, administered 0.5 hours after the onset of symptoms. We assumed untreated attack duration (D=20.6 hours) would be reduced to 2 hours after treatment (ie, to 2.5 hours) with probabilities Ppf or Phr. We calculated HLYs gained per treatment at the individual level as above.

Accordingly, the incremental cost/HLY gained of using eletriptan 40 mg rather than sumatriptan 100 mg is:

US$ (3.45-0.27)/{[(20.6-2.5)/(24*365)]*0.441*0.092} = US$ 37,993 (for PF)

US$ (3.45-0.27)/{[(20.6-2.5)/(24*365)]*0.441*0.091} = US$ 38,350 (for HR)

Eletriptan is therefore not cost-effective by most thresholds at its current price, if used as first-line triptan. This analysis confirms that it should be reserved for non-responders to sumatriptan who may have no other treatment options.

Section 11: Regulatory status, market availability and pharmacopoeial standards

Naproxen

Naproxen was first marketed in 1976 by the company Syntex, as the prescription drug Naprosyn. The US FDA approved it as an over-the-counter (OTC) drug in 1994, but it became available OTC only in 2007 in many European countries and is prescription-only in others.

It remains unavailable in many countries elsewhere, but multiple generic formulations are available and its addition to the EML would be likely to extend its availability and widen access to it.

Appendix 6 reports the availability of naproxen in numerous Countries across the world as a result of a survey conducted among IHS members by Francesca Puledda.

Eletriptan

Eletriptan is a prescription drug. It was granted US FDA and Europe EMA approvals under the trade name Relpax manufactured by Upjohn and later by Pfizer. It has been approved for use in the acute treatment of migraine in 51 countries under the trade names Relpax or Relert, and is available in generic formulations in 17 countries, including Canada, Mexico, Italy, France and Japan.

It is not available in all countries. Its addition to the EML would be likely to encourage the development of generic formulations with competitive pricing, extend its availability and widen access to the most effective treatment for acute migraine.

Appendix 7 reports the availability of eletriptan in numerous Countries across the wolrd as a result of a survey conducted among IHS members by Francesca Puledda.

Pharmacopoieal standards

Eletriptan: not included in European Pharmacopoeia (version 11.5)

Naproxen:
https://pheur.edqm.eu/internal/4d98149498f2451884665a2575c26a36/11-5/11-5/page/0731E.pdf

Sumatriptan:
https://pheur.edqm.eu/internal/4d98149498f2451884665a2575c26a36/11-5/11-5/page/1573E.pdf

Appendix 1

Inclusion and exclusion criteria for evaluation of references in eligibility and inclusion phases for stage 1.

Phase	Inclusion criteria	Exclusion criteria
Eligibility (evaluation of titles and abstracts)	1) Studies meeting all of the following criteria: - Systematic review and meta-analysis - Including randomized controlled trials - Trials performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs 2) Abstract not available 3) Abstract not allowing to fully assess eligibility	1) Study design was not a systematic review and meta-analysis 2) The systematic review/meta-analysis did not include studies on migraine 3) The systematic review/meta-analysis did not include studies assessing the outcome of a pharmacological therapy versus placebo or other drugs
Inclusion (evaluation of full texts)	1) Studies meeting all of the following criteria: - Systematic review and meta-analysis - Including randomized controlled trials - Performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs	1) Full text not available (e.g., conference abstracts, conference proceedings) 2) Wrong design (not a systematic review or meta-analysis) 3) Wrong comparison (the systematic review/meta-analysis did not include studies assessing the outcome of a pharmacological therapy versus placebo or other drugs) 4) Wrong population (the systematic review/meta-analysis included studies on other types of headache apart from migraine and did not report separate findings for patients with migraine) 5) Pediatric population (0–18-year-old subjects) 6) Overcome by a more recent systematic review and meta-analysis (i.e., all RCTs included in the systematic review/meta-analysis were also included in another included systematic review/meta-analysis) 7) Wrong outcomes (i.e. the systematic review/meta-analysis did not evaluate any of the outcomes considered for the present guidelines)

Appendix 2

Inclusion and exclusion criteria for evaluation of references in eligibility and inclusion phases for stage 2.

Phase	Inclusion criteria	Exclusion criteria
Eligibility (evaluatlion of titles and abstracts)	1) Studies meeting all of the following criteria: - RCT - Performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs 1) Abstract not available 2) Abstract not allowing to fully assess eligibility	1) Study design was not RCT 2) The RCT was not performed in patients with migraine 3) The RCT did not assess the outcome of a pharmacological therapy versus placebo or other drugs
Inclusion (evaluation of full)	1) Studies meeting all the following criteria: - RCT - Performed in patients with migraine - Addressing a pharmacological therapy versus placebo or other drugs	1) Full text not available (e.g., conference abstracts, conference proceedings) 2) Wrong design (not a RCT) 3) Wrong comparison (the RCT did not assess the outcome of a pharmacological therapy versus placebo or other drugs) 4) Wrong population (the RCT included patients with headache other than migraine, or included mixed samples and no separate findings were reported for patients with migraine) 5) Pediatric population (0–18-year-old subjects) 6) The RCT included only patients with menstrual migraine 7) The RCT only assessed non-commercial and non-approved doses of the selected drugs 8) The RCT tested an intravenous drug for acute treatment 10) Wrong outcomes (i.e. the systematic review/meta-analysis did not evaluate any of the outcomes considered for the present guidelines)

Appendix 3

Search strings for all databases to retrieve systematic review/meta-analysis and additional RCTs for NSAIDs.

Database	Search 1 – systematic review/meta-analysis	Search 2 – RCTs
PubMed	("migrain*"[All Fields] AND ("anti inflammatory agents non steroidal"[All Fields] OR "nsaid*"[All Fields])) AND (meta-analysis[Filter] OR systematicreview[Filter])	("migrain*"[All Fields] AND ("anti inflammatory agents non steroidal"[All Fields] OR "nsaid*"[All Fields])) AND (randomizedcontrolledtrial[Filter])
Scopus	ALL (migrain* AND ("Anti- Inflammatory Agents, Non- Steroidal" OR nsaid*) AND ("systematic review" OR "meta-analysis")) AND (LIMIT-TO (DOCTYPE , "re"))	ALL(migrain* AND ("Anti-Inflammatory Agents, Non-Steroidal" OR NSAID*) AND ("randomized controlled trial" OR RCT)) AND (EXCLUDE (DOCTYPE,"le")) AND (EXCLUDE (DOCTYPE,"re") OR EXCLUDE (DOCTYPE,"ch") OR EXCLUDE (DOCTYPE,"bk") OR EXCLUDE (DOCTYPE,"cp") OR EXCLUDE (DOCTYPE,"no") OR EXCLUDE (DOCTYPE,"sh") OR EXCLUDE (DOCTYPE,"ed"))
Cochrane	(migrain* AND (“Anti- Inflammatory Agents, Non- Steroidal” OR NSAID*)) Limit To review	(migrain* AND (“Anti-Inflammatory Agents, Non-Steroidal” OR NSAID*)) Limit To trial

Appendix 4

Search strings for all databases to retrieve systematic review/meta-analysis and additional RCTs for combined analgesics.

Database	Search 1	Search 2
PubMed	("migrain*"[All Fields] AND ("drug combination"[All Fields] OR "combination analgesics"[All Fields])) AND (meta-analysis[Filter] OR systematicreview[Filter])	("migrain*"[All Fields] AND ("drug combination"[All Fields] OR "combination analgesics"[All Fields])) AND (randomizedcontrolledtrial[Filter])
Scopus	ALL (migrain* AND ("drug combination" OR "combination analgesics") AND ("systematic review" OR "meta-analysis")) AND (LIMIT-TO (DOCTYPE , "re"))	ALL (migrain* AND ("drug combination" OR "combination analgesics") AND ("randomized controlled trial" OR rct)) AND (EXCLUDE (DOCTYPE , "re")) AND (EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "bk") OR EXCLUDE (DOCTYPE , "cp") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "ed") OR EXCLUDE (DOCTYPE , "Undefined"))
Cochrane	migrain* AND ("drug combination" OR "combination analgesics") Limit to review	migrain* AND ("drug combination" OR "combination analgesics") Limit to trial

Appendix 5

Search strings for all databases to retrieve systematic review/meta-analysis and additional RCTs for triptans.

Database	Search 1	Search 2
PubMed	(“migrain*”[All Fields] AND (“almotriptan”[Supplementary Concept] OR “almotriptan”[All Fields] OR (“eletriptan”[Supplementary Concept] OR “eletriptan”[All Fields]) OR (“frovatriptan”[Supplementary Concept] OR “frovatriptan”[All Fields]) OR (“naratriptan”[Supplementary Concept] OR “naratriptan”[All Fields]) OR (“rizatriptan”[Supplementary Concept] OR “rizatriptan”[All Fields]) OR (“sumatriptan”[MeSH Terms] OR “sumatriptan”[All Fields] OR “sumatriptans”[All Fields]) OR (“zolmitriptan”[Supplementary Concept] OR “zolmitriptan”[All Fields]) OR “triptan*”[All Fields])) AND (meta-analysis[Filter] OR systematicreview[Filter])	(“migrain*”[All Fields] AND (“almotriptan”[Supplementary Concept] OR “almotriptan”[All Fields] OR (“eletriptan”[Supplementary Concept] OR “eletriptan”[All Fields]) OR (“frovatriptan”[Supplementary Concept] OR “frovatriptan”[All Fields]) OR (“naratriptan”[Supplementary Concept] OR “naratriptan”[All Fields]) OR (“rizatriptan”[Supplementary Concept] OR “rizatriptan”[All Fields]) OR (“sumatriptan”[MeSH Terms] OR “sumatriptan”[All Fields] OR “sumatriptans”[All Fields]) OR (“zolmitriptan”[Supplementary Concept] OR “zolmitriptan”[All Fields]) OR “triptan*”[All Fields])) AND (randomizedcontrolledtrial[Filter])
Scopus	ALL (migrain* AND (almotriptan OR eletriptan OR frovatriptan OR naratriptan OR rizatriptan OR sumatriptan OR zolmitriptan OR triptan*)) AND (“systematic review” OR “meta-analysis”) AND (LIMIT-TO (DOCTYPE , “re”))	ALL (migrain* AND (almotriptan OR eletriptan OR frovatriptan OR naratriptan OR rizatriptan OR sumatriptan OR zolmitriptan OR triptan*)) AND (“randomized controlled trial” OR rct) AND (EXCLUDE (DOCTYPE , “re”)) AND (EXCLUDE (DOCTYPE , “ch”) OR EXCLUDE (DOCTYPE , “cp”) OR EXCLUDE (DOCTYPE , “bk”) OR EXCLUDE (DOCTYPE , “no”) OR EXCLUDE (DOCTYPE , “le”) OR EXCLUDE (

		DOCTYPE , “sh”) OR EXCLUDE (DOCTYPE , “ed”) OR EXCLUDE (DOCTYPE , “er”))
Cochrane	migrain* AND (Almotriptan OR Eletriptan OR Frovatriptan OR Naratriptan OR Rizatriptan OR Sumatriptan OR Zolmitriptan OR triptan*) Limit to Cochrane reviews	migrain* AND (Almotriptan OR Eletriptan OR Frovatriptan OR Naratriptan OR Rizatriptan OR Sumatriptan OR Zolmitriptan OR triptan*) Limit to Trials

Appendix 6

Availability of naproxen across the World (International Headache Society internal survey coordinated by Dr Francesca Puledda)

Naproxen				
Country	**Available**	**Prescription**	**Reimbursement**	**Within country differences**
Algeria	Yes	Prescription – GP	Full reimbursement	No
Argentina	Yes			No
Armenia	Yes	Pharmacy	No reimbursement	No
Australia	Yes	Pharmacy	No reimbursement	No
Austria	Yes	Prescription – GP	Full reimbursement	No
Azerbaijan	Yes	Pharmacy	No reimbursement	No
Belgium	Yes	Prescription – GP	No reimbursement	No
Bolivia (Plurinational State of)				Unknown
Bosnia and Herzegovina	Yes	Pharmacy	No reimbursement	No
Brazil	Yes	Pharmacy	No reimbursement	No
Brunei Darussalam	Yes	General sales list		No
Bulgaria	Yes			No
Burkina Faso	Yes			Yes
Burundi	Yes			Yes
Cabo Verde	Yes	Prescription – GP	Partial reimbursement	No
Cameroon	Yes	Prescription – GP	No reimbursement	Yes
Canada	Yes	Prescription – GP	Partial reimbursement	No
Chad				No
Chile	Yes	Pharmacy	Full reimbursement	No
China	No			Unknown
Colombia	Yes	General sales list	Full reimbursement	No
Côte D'Ivoire	Yes			Yes
Czech Republic	Yes	Prescription – GP	Partial reimbursement	No
Denmark	Yes	Prescription – GP	Partial reimbursement	No
Djibouti	Yes	Prescription – GP		No
Dominican Republic	Yes			No
Ecuador	Yes	Pharmacy	Full reimbursement	No
Egypt	Yes	Pharmacy		No
El Salvador	Yes	General sales list	Full reimbursement	No
Ethiopia	No			Unknown
Finland	Yes	Prescription – GP	Partial reimbursement	No
France	Yes	Prescription – GP	Full reimbursement	No
Gabon	Yes	Prescription – specialist only	No reimbursement	No
Georgia	Yes	Pharmacy	Full reimbursement	No
Germany	Yes	Pharmacy	Full reimbursement	No

Ghana	Yes	Prescription – GP	No reimbursement	Yes
Greece	Yes	Pharmacy	Partial reimbursement	No
Guinea				Unknown
India	Yes	General sales list	No reimbursement	No
Iran (Islamic Republic of)	Yes			No
Italy	Yes	Pharmacy	Full reimbursement	No
Latvia	Yes	Pharmacy	No reimbursement	No
Libya				No
Lithuania	Yes	Pharmacy	No reimbursement	No
Madagascar				No
Mali	Yes	Prescription – specialist only	Partial reimbursement	Yes
Mexico	Yes	Pharmacy	No reimbursement	No
Mongolia	Yes	Pharmacy		No
Nepal	Yes	Pharmacy		No
Netherlands	Yes	Pharmacy	Full reimbursement	No
New Zealand	Yes	Prescription – specialist only	No reimbursement	No
Niger	Yes	Prescription – GP		Yes
Nigeria	Yes	Prescription – GP	No reimbursement	Yes
Norway	Yes	Prescription – GP	Full reimbursement	No
Pakistan	Yes			No
Panama	Yes	Pharmacy		No
Peru	Yes	General sales list	Partial reimbursement	No
Poland	Yes	General sales list	Partial reimbursement	No
Portugal	Yes	Prescription – GP	Partial reimbursement	No
Republic of Korea	Yes	Prescription – GP	Partial reimbursement	No
Republic of Moldova	Yes	Pharmacy	No reimbursement	No
Romania	Yes	Pharmacy	No reimbursement	No
Russian Federation	Yes	Pharmacy	No reimbursement	Yes
Rwanda	Yes	Prescription – specialist only	No reimbursement	Yes
Senegal				Unknown
Singapore	Yes			Unknown
Slovenia	Yes	Prescription – GP	Full reimbursement	No
South Africa	Yes			Yes
Spain	Yes	Pharmacy	Full reimbursement	No
Sudan	Yes			No
Switzerland	Yes	Prescription – GP	Full reimbursement	No
Thailand	Yes	Prescription – GP		No
Togo				No
Tunisia	Yes	Prescription – GP	Full reimbursement	No
Turkey	Yes	Pharmacy	Full reimbursement	No
Uganda	Don't know			No
Ukraine	Yes	Prescription – GP	No reimbursement	Yes

United Kingdom of Great Britain and Northern Ireland	Yes	Prescription – GP	Partial reimbursement	No
United Republic of Tanzania	Yes			Yes
United States of America	Yes	General sales list	No reimbursement	No
Uruguay	Yes	Pharmacy	No reimbursement	Yes
Vietnam	Yes	Prescription – specialist only	Partial reimbursement	Unknown
Zambia	No			No
Zimbabwe	Yes	Prescription – GP	Full reimbursement	Yes

GP= General practitioner

Appendix 7

Availability of eletriptan across the World (International Headache Society internal survey coordinated by Dr Francesca Puledda)

Eletriptan				
Country	**Available**	**Prescription**	**Reimbursement**	**Within country differences**
Algeria	Yes	Prescription – specialist only	Full reimbursement	Unknown
Argentina	Yes			Yes
Armenia	Yes	Pharmacy	No reimbursement	No
Australia	Yes	Prescription – GP	Partial reimbursement	No
Austria	Yes	Prescription – specialist only	Full reimbursement	No
Azerbaijan	Yes	Pharmacy	No reimbursement	No
Belgium	Yes	Prescription – GP	No reimbursement	No
Bolivia (Plurinational State of)	No			No
Bosnia and Herzegovina	No			No
Brazil	No			No
Brunei Darussalam	No			Unknown
Bulgaria	Yes			No
Burkina Faso				Unknown
Burundi				Unknown
Cabo Verde	No			No
Cameroon	No			No
Canada	Yes	Prescription – GP	Partial reimbursement	No
Chad				No
Chile	Yes	Pharmacy	Full reimbursement	No
China	No			Unknown
Colombia	Yes	Prescription – specialist only	Full reimbursement	No
Côte D'Ivoire	No			Yes
Czech Republic	Yes	Prescription – GP	No reimbursement	No
Denmark	Yes	Prescription – GP	Partial reimbursement	No
Djibouti	No			No
Dominican Republic	Yes			Yes
Ecuador	Yes	Prescription – specialist only	Full reimbursement	Yes
Egypt	Yes	Pharmacy	No reimbursement	No
El Salvador	No			No
Ethiopia	No			Unknown
Finland	Yes	Prescription – GP	Partial reimbursement	No
France	Yes	Prescription – GP	Full reimbursement	No
Gabon	Don't know	Prescription – specialist only	Partial reimbursement	No

Georgia	Yes	Prescription – GP	Full reimbursement	No
Germany	Yes	Prescription – GP	Full reimbursement	No
Ghana	No			Unknown
Greece	Yes	Prescription – specialist only	Partial reimbursement	No
Guinea				Unknown
India				Unknown
Iran (Islamic Republic of)	No			No
Italy	Yes	Prescription – GP	Full reimbursement	No
Latvia	Yes	Prescription – GP	No reimbursement	No
Libya				No
Lithuania	No			Unknown
Madagascar				Unknown
Mali	No			Unknown
Mexico	Yes	Pharmacy	Full reimbursement	Yes
Mongolia	No			Unknown
Nepal	No			Unknown
Netherlands	Yes	Prescription – GP	Full reimbursement	No
New Zealand	No	Other	No reimbursement	No
Niger	No			Unknown
Nigeria	No			Yes
Norway	Yes	Prescription – GP	Full reimbursement	No
Pakistan				No
Panama	Yes	Pharmacy		No
Peru	Yes	Prescription – specialist only	Partial reimbursement	Yes
Poland	Yes	Prescription – GP	No reimbursement	No
Portugal	Yes	Prescription – GP	Partial reimbursement	No
Republic of Korea	No			No
Republic of Moldova	No			No
Romania	No			No
Russian Federation	Yes	Prescription – GP	No reimbursement	Yes
Rwanda	No			Unknown
Senegal				Unknown
Singapore				Unknown
Slovenia	Yes	Prescription – GP	Full reimbursement	No
South Africa	Don't know			No
Spain	Yes	Prescription – GP	Full reimbursement	No
Sudan				No
Switzerland	Yes	Prescription – GP	Full reimbursement	Unknown
Thailand	Yes	Prescription – specialist only	Partial reimbursement	Yes
Togo	No			Unknown
Tunisia	Yes	Prescription – GP	No reimbursement	No
Turkey	Yes	Prescription – specialist only	Full reimbursement	No
Uganda	Don't know			No

Ukraine	Yes	Prescription – GP	No reimbursement	No
United Kingdom of Great Britain and Northern Ireland	Yes	Prescription – GP	Full reimbursement	No
United Republic of Tanzania				Unknown
United States of America	Yes	Prescription – GP	Partial reimbursement	No
Uruguay	No			Unknown
Vietnam	No	Prescription – GP	No reimbursement	No
Zambia	No			No
Zimbabwe	No			Yes

To whom it may concern

Re: Support and Endorsement for the application for the inclusion of additional drugs for the treatment of migraine in the WHO Essential Medicines List

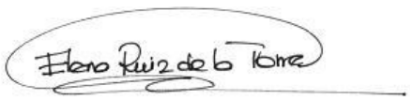
On behalf of EHMA, the leading non-profit umbrella organization of 34 patient associations for Migraine, Cluster Headache, Trigeminal Neuralgia and other headache diseases, dedicated to supporting individuals with migraine and other headache, I am writing to express our wholehearted support and endorsement for the joint application made by the International Headache Society, Lifting the Burden and European Headache Federation to include addition drugs for the acute and preventive treatment of migraine in the World Health Organization Essential Medicines List.

Migraine, characterized by their severe and debilitating nature, pose a significant challenge to those affected, impacting their quality of life and daily functioning. As a patient organization, we witness firsthand the profound suffering experienced by individuals with this condition. Despite the availability of effective treatments, many patients still face barriers to accessing these critical therapies, particularly in regions with limited healthcare resources.

The inclusion of additional treatment options, such as naproxen, eletriptan, amitriptyline, bisoprolol and fremanezumab in the WHO Essential Medicines List is a crucial step towards improving global access to these essential medications. It would ensure that effective and life-changing treatments are available to individuals regardless of their geographic or economic circumstances. This inclusion not only aligns with the WHO's mission to improve global health equity but also represents a significant advancement in the fight against a condition that affects millions worldwide.

Our organisation is committed to supporting this initiative and are available to provide any further information or assistance. We look forward to the positive impact this development will have on the global health landscape.

Sincerely,
EMHA – European Migraine and headache Alliance



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