PROPOSAL FOR THE ADDITION OF IBUPROFEN FOR THE TREATMENT OF ACUTE MIGRAINE ATTACKS TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES

Proposed listing on the EML:

7. ANTIMIGRAINE TREATMENTS

7.1 Acute treatment of attacks

Non steroidal anti-inflammatory drugs
 ibuprofen, tablets 200 mg, 400 mg

Applicants:

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]).

The application was prepared by (in alphabetical order) Massimo Leone (Italy and Malawi), Antoinette Maassen van den Brink (the Netherlands), Christian Lampl (Osterreich), Mario Peres (Brazil), Patricia Pozo-Rosich (Spain), Francesca Puledda (UK), Simona Sacco (Italy), Timothy Steiner (UK and Norway), Cristina Tassorelli (Italy), Michela Tinelli (Italy and UK) and Derya Uluduz (Turkey).

Lead Authors:

Timothy J Steiner, MB, PhD. FRCP
t.steiner@imperial.ac.uk

Antoinette Maassen van den Brink, PhD
a.vanharen-maassenvandenbrink@erasmusmc.nl

Cristina Tassorelli, MD, PhD
Cristina.tassorelli@unipv.it it

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)*.

For the treatment of acute migraine attacks, the 23rd (2023) edition of the Essential Medicines List (EML) includes acetylsalicylic acid (aspirin), paracetamol (acetaminophen) and sumatriptan. This submission calls for the addition of ibuprofen, extending the first-line options.

Ibuprofen is already on the EML for children. It was added to address the lack of effective options available for that age group specifically. At the time, the only options listed for acute migraine in the EML were ergotamine, aspirin and paracetamol. Of these, ergotamine was unsuitable for children (and it was removed from the EML), aspirin was contraindicated, and paracetamol had relatively poor efficacy.

Ibuprofen is identified in almost all published guidelines as a first-line treatment for acute migraine in adults. It is almost universally available worldwide, at low cost. It is on the EML for other indications for adults. The case for its addition to the EML for acute migraine in adults appears indisputable.

Section 2: Consultation with WHO technical departments

During the preparation of this application there have been multiple discussions 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), the following has been consulted and supports the application:

- European Migraine and Headache Association (Mrs Elena Ruiz de la Torre), a lay organization.

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

International nonproprietary name (INN)	Ibuprofen
Anatomical Therapeutic Chemical (ATC) code	M01AE01
Indication	Treatment of acute migraine attacks in adults
ICD-11 code	**8A80** Migraine
Dosage form(s) and strength(s)	Tablet: 200 mg; 400 mg.

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

The submission proposes the individual listing of ibuprofen under section 7: “Antimigraine medicines”. Other agents listed in this section of the WHO Model List of Essential Medicines (EML) 2023 are acetylsalicylic acid (aspirin), paracetamol (acetaminophen), and sumatriptan. Ibuprofen has a different mode of action, namely non-selective inhibition of both cyclooxygenase (COX)-types.

Ibuprofen may function as the square-box representative of the pharmacological class of non-steroidal anti-inflammatory drugs (NSAIDs). This is not essential to this application. Alternatives include naproxen, which is the subject of a separate submission by the same applicants.

Justification of choice as 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. However, multiple clinical trials, systematic reviews and meta-analyses have demonstrated the efficacy of ibuprofen in improving migraine symptoms *(5-12)*. Ibuprofen is widely used for the acute treatment of migraine not only because of its efficacy, and its tolerability and good safety profile *(13-21)*, but also because of its almost universal availability at low cost around the world.

Ibuprofen is already on the EML for other indications, and on the EML for children for this indication.

6. Information supporting the public health relevance

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) *(22)*. In other words, the impact of migraine on population health is very substantial, and associated with major impairments in participation, quality of life and productivity *(2)*]. However, all of these can be reduced by appropriate treatments *(23)*. 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

Aspirin (acetylsalicylic acid) and paracetamol (acetaminophen)

These two medications are on the EML for adults, being universally available at low cost. Both have evidence of efficacy (paracetamol *(24)* less than aspirin *(25)*), but only 50-60% of users achieve headache relief (mild or no pain after 2 hours, and considerably fewer achieve the benchmark outcome of pain freedom after 2 hours.

Triptans

Sumatriptan 50 mg is also on the EML for adults. 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 *(26)*. Sumatriptan is widely

available in generic formulations, but nonetheless remains relatively expensive compared with aspirin, paracetamol or ibuprofen. It is usually recommended as second-line treatment when aspirin, paracetamol or ibuprofen are ineffective *(23)*.

Section 7. Treatment details

Dosage regimen and duration

Ibuprofen is approved by the Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) for the treatment of acute migraine *(27)*. The typical dose for adults experiencing a migraine attack is ibuprofen 200-400 mg orally administered. This can be repeated every 4-6 hours as needed, with a maximum daily dose of 1200 mg.

Requirements to ensure appropriate use of the medicine

Ibuprofen should be taken with or after food *(27)*.

Ibuprofen is contraindicated *(27)* in patients with:

- previous hypersensitivity reactions to acetylsalicylic acid or other NSAIDs;
- history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy;
- active, or history of, recurrent peptic ulcer/haemorrhage;
- severe renal failure or severe hepatic failure;
- severe heart failure (NYHA Class IV);
- last trimester of pregnancy.

Ibuprofen 200-400 mg is a very widely used over-the-counter medication for mild-to-moderate pain. Community pharmacists are well-equipped to advise on using ibuprofen for migraine therapy.

Section 8: Review of evidence for benefits and harms

Evidence of benefits

A pooled analysis of six randomized controlled trials (RCTs) showed the benefits of ibuprofen 200 mg, 400 mg and 600 mg over placebo, considering the outcome of pain freedom at 2 hours (Figure 1) *(8-12, 28)*.

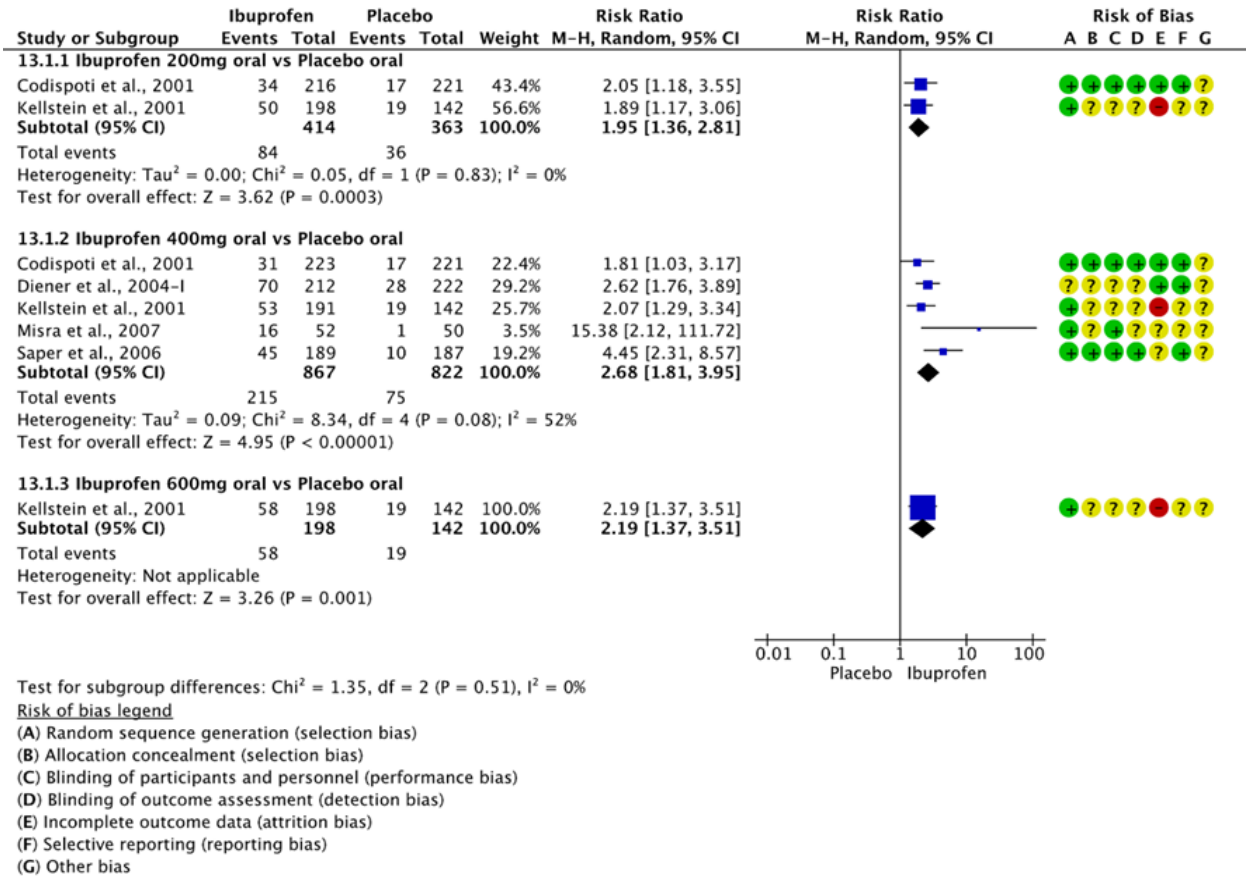

Figure 1: Forest plot showing the comparison between oral ibuprofen 200, 400 and 600 mg and placebo for the outcome pain freedom at 2 hours.

Two RCTs compared different dosages of ibuprofen (200, 400 and 600 mg) for the same outcome *(8, 10)*. The pooled analyses showed no significant differences between these dosages (Figures 2 and 3).

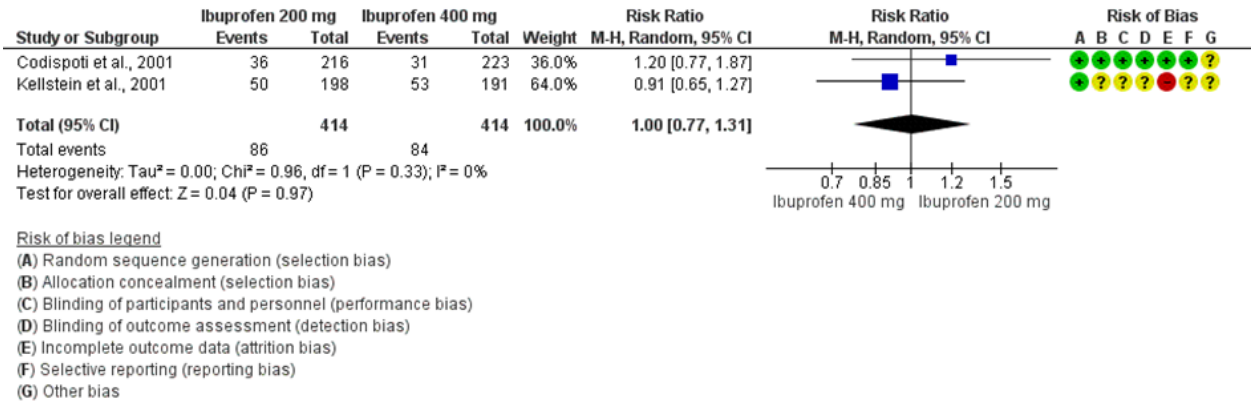

Figure 2. Forest plot showing the comparison between oral ibuprofen 200 mg and 400 mg for the outcome pain freedom at 2 hours

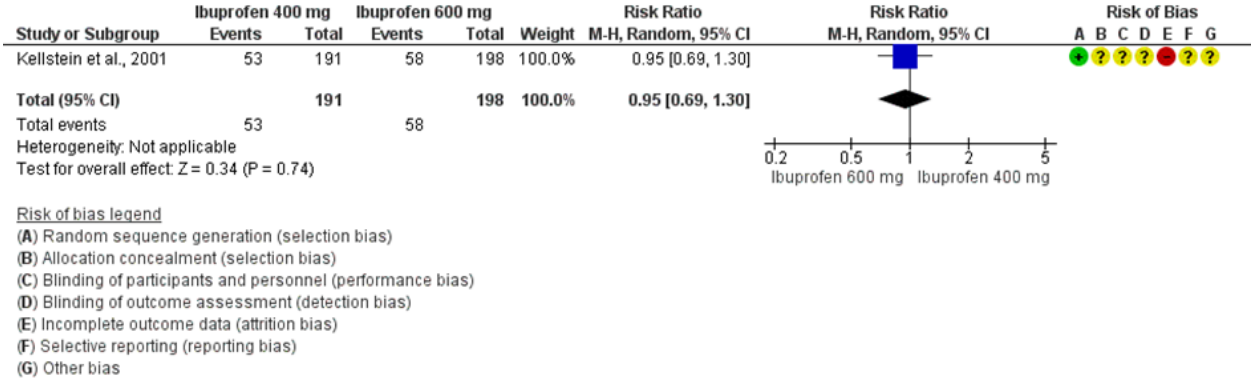

Figure 3. Forest plot showing the comparison between oral ibuprofen 400 and 600 mg for the outcome pain freedom at 2 hours

A Cochrane systematic review compared symptom-relieving migraine medications, including ibuprofen, with placebo *(29)*. Although restricted by the quality and number of trials, ibuprofen was found superior to placebo for the outcome headache relief at 2 hours (RR 2.50, 95% CI 1.02-6.10).

Evidence of harms

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) associated with known yet occasional adverse events of upper gastrointestinal bleeding, large intestinal ulcers, bleeding and perforation. The risk of bleeding increases with older age, the presence of Helicobacter pylori infection, a history of bleeding and anticoagulant drug use. About 0.5% of individuals using NSAIDs have been reported to have an upper gastrointestinal bleed annually *(15, 16)*. However, these adverse events are typically associated with long-term use. Of all NSAIDs, ibuprofen appears to have one of the best gastrointestinal tolerability profiles *(17)*.

In the Cochrane systematic review, ibuprofen was not linked to an increase in adverse events overall *(29)*. Further, a meta-analysis and qualitative review evaluated the efficacy and safety of ibuprofen in children and adults, comparing it to acetaminophen *(30)*. While ibuprofen was more efficacious than acetaminophen in both children and adults, both drugs were demonstrated to be equally safe, with no significant differences between them in adverse event incidence.

Special populations: pregnancy and lactation

Since ibuprofen is a prostaglandin synthetase inhibitor, the risk for premature closure of the ductus arteriosus is high when it is used during the third trimester of pregnancy. While being contraindicated during that period, it has been shown to be safe during pregnancy in the first trimester *(31, 32)*.

Furthermore, due to its very low levels in breastmilk *(33, 34)*, short half-life and safe usage in infants at much higher doses than those found in breastmilk, ibuprofen is considered an ideal analgesic or anti-inflammatory option for breastfeeding mothers *(35)*.

Section 9: Summary of recommendations in current clinical guidelines

Almost all published guidelines recommend ibuprofen among the first-line treatment options for acute migraine [eg, *(23, 36-41)*].

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

The literature is unhelpful: there are no economic studies of ibuprofen for the treatment of migraine.

Comparative cost-effectiveness versus aspirin

In 2015, a study by Linde, Steiner and Chisholm, using WHO-CHOICE, examined the cost-effectiveness of first-line medications (including aspirin 1 g, but not ibuprofen) used within hypothesized structured headache services in three of the large, middle-income BRIC countries, China, Russian Federation and India (not Brazil, for which there were insufficient data), and one lower middle-income country, Zambia, for comparison *(42)*. For aspirin 1 g, the estimated costs per healthy life year (HLY) gained were US$ 34 for China, US$ 73 for India, US$ 53 for Russia and US$ 24 for Zambia (all 2015 values).

Therefore, aspirin is a very highly cost-effective comparator.

For comparative costs, we factored in only medication costs, assuming other healthcare costs such as consultations to be constant across the alternatives. For aspirin, dispersible tablets were used in all RCTs, but, because these are not universally available, costs worldwide were not a reliable indicator for this analysis. We therefore used the lowest costs for ibuprofen 400 mg tablets (GBP 0.78 for 24 tablets) and aspirin 3*300 mg tablets (GBP 0.97 for 32 dispersible tablets) in the UK NHS drug tariff, and converted these to US$/dose at GBP 1.00=US$ 1.31 (US$ 0.043 for ibuprofen 400 mg and US$ 0.119 for aspirin 900 mg.

Thus cost/dose for aspirin (dispersible) is almost 3 times that of ibuprofen.

For the preferred outcome measure Ppf (proportion of those treated who are reported to be pain-free [PF] at 2-hours), ibuprofen had a success rate of 215/867 (24.8%) in five trials (see section 8) or of 334/1303=25.6% according to the metanalysis of Suthisisang *(7)*, from which we derived a weighted mean 25.3%. For the same measure, aspirin had a success rate of 20.3% among N=1112 in 6 trials summarized by Lampl *(43)*. For the more pragmatic outcome measure Phr (proportion of those treated who report headache relief [mild or no pain; HR] at 2-hours, which assumes HR allows normal function *(42)*, ibuprofen had a success rate of 349/674=51.8% according to the metanalysis of Suthisisang *(7)*. For the same measure, aspirin had a success rate of 50.8% among N=1112 in the 6 trials summarized by Lampl *(43)*.

Table 1: Input data for economic modelling, comparing aspirin with ibuprofen

	Cost/attack (US$ 2024 values)	D = mean attack duration (hr) from N=8,363 in 14 countries	Ppf = proportion of those treated who are reported to be pain-free (PF) at 2-hours	Phr = proportion of those treated who report headache relief at 2-hours (includes Ppf)
Ibuprofen (400 mg single dose)	0.043	20.6 hours	25.3%	51.8%
Aspirin (900 mg single dose)	0.119	20.6 hours	20.3%	50.8%

The input data are summarised in Table 1.

On this assessment, ibuprofen is the preferred option: the two treatments have similar efficacy but ibuprofen, at lower cost, is more cost-effective.

For this reason, we did not conduct an incremental cost-effectiveness analysis.

Cost/HLY gained

To calculate cost/HLY gained for ibuprofen, we made the same assumptions as in Linde *(42)*. 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 by *Lifting The Burden* 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) [unpublished data available to LTB].

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 ibuprofen 400 mg, cost/HLY gained is:

$0.043/\{[(20.6-2.5)/(24*365)]*0.441*0.248\}$ = US$ 190.28 (for PF)

0.043/{[(20.6-2.5)/(24*365)]*0.441*0.518} = US$ 91.10 (for HR)

On this assessment, ibuprofen 400 mg is very highly cost-effective.

Allowing for the US$ inflation of 33% over the period 2015 to 2024 *(44)*, this cost/HLY gained is of the same order, but somewhat higher, than the cost estimated for aspirin by Linde *(42)*. In that analysis, aspirin costs, for 2*500 mg tablets, a slightly higher dose, but not necessarily dispersible, were lower.

Section 11: Regulatory status, market availability and pharmacopoeial standards

Ibuprofen is approved for the treatment of mild-to-moderate pain and is available in almost all countries.

https://pheur.edqm.eu/internal/4d98149498f2451884665a2575c26a36/11-5/11-5/page/0727E.pdf

Section 12: Reference list

1. GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol. 2024;23(4):344-81 (https://doi.org/10.1016/s1474-4422(24)00038-3).
2. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. The Journal of Headache and Pain. 2022;23(1):34 (https://doi.org/10.1186/s10194-022-01402-2).
3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211 (https://doi.org/10.1177/0333102417738202).
4. Ashina M, Katsarava Z, Do TP, Buse DC, Pozo-Rosich P, Özge A et al. Migraine: epidemiology and systems of care. The Lancet. 2021;397(10283):1485-95 (https://doi.org/https://doi.org/10.1016/S0140-6736(20)32160-7).
5. Xu H, Han W, Wang J, Li M. Network meta-analysis of migraine disorder treatment by NSAIDs and triptans. J Headache Pain. 2016;17(1):113 (https://doi.org/10.1186/s10194-016-0703-0).
6. Rabbie R, Derry S, Moore RA, McQuay HJ. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev. 2010(10):Cd008039 (https://doi.org/10.1002/14651858.CD008039.pub2). Licence: EMS58704.
7. Suthisisang C, Poolsup N, Kittikulsuth W, Pudchakan P, Wiwatpanich P. Efficacy of low-dose ibuprofen in acute migraine treatment: systematic review and meta-analysis. Ann Pharmacother. 2007;41(11):1782-91 (https://doi.org/10.1345/aph.1K121).
8. Codispoti JR, Prior MJ, Fu M, Harte CM, Nelson EB. Efficacy of nonprescription doses of ibuprofen for treating migraine headache. a randomized controlled trial. Headache. 2001;41(7):665-79 (https://doi.org/10.1046/j.1526-4610.2001.041007665.x).
9. Diener HC, Bussone G, de Liano H, Eikermann A, Englert R, Floeter T et al. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. Cephalalgia. 2004;24(11):947-54 (https://doi.org/10.1111/j.1468-2982.2004.00783.x).
10. Kellstein DE, Lipton RB, Geetha R, Koronkiewicz K, Evans FT, Stewart WF et al. Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, double-blind, placebo-controlled, dose-ranging study. Cephalalgia. 2000;20(4):233-43 (https://doi.org/10.1046/j.1468-2982.2000.00055.x).
11. Misra UK, Jose M, Kalita J. Rofecoxib versus ibuprofen for acute treatment of migraine: a randomised placebo controlled trial. Postgrad Med J. 2004;80(950):720-3 (https://doi.org/10.1136/pgmj.2003.012393).
12. Misra UK, Kalita J, Yadav RK. Rizatriptan vs. ibuprofen in migraine: a randomised placebo-controlled trial. Journal of Headache and Pain. 2007;8(3):175-9 (https://doi.org/10.1007/s10194-007-0386-7).
13. Adams SS, McCullough KF, Nicholson JS. The pharmacological properties of ibuprofen, an anti-inflammatory, analgesic and antipyretic agent. Arch Int Pharmacodyn Ther. 1969;178(1):115-29 (
14. Bjarnason I, Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. Gastroenterology. 1993;104(6):1832-47 (https://doi.org/10.1016/0016-5085(93)90667-2).
15. Bjarnason I. Gastrointestinal safety of NSAIDs and over-the-counter analgesics. Int J Clin Pract Suppl. 2013(178):37-42 (https://doi.org/10.1111/ijcp.12048).

16. Fenn GC. Review article: controversies in NSAID-induced gastroduodenal damage--do they matter? Aliment Pharmacol Ther. 1994;8(1):15-26 (https://doi.org/10.1111/j.1365-2036.1994.tb00156.x).
17. Rampal P, Moore N, Van Ganse E, Le Parc JM, Wall R, Schneid H et al. Gastrointestinal tolerability of ibuprofen compared with paracetamol and aspirin at over-the-counter doses. J Int Med Res. 2002;30(3):301-8 (https://doi.org/10.1177/147323000203000311).
18. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011;342:c7086 (https://doi.org/10.1136/bmj.c7086).
19. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med. 2011;8(9):e1001098 (https://doi.org/10.1371/journal.pmed.1001098).
20. Harbin M, Turgeon RD, Kolber MR. Cardiovascular safety of NSAIDs. Can Fam Physician. 2014;60(3):e166 (
21. Shao QH, Yin XD, Liu HX, Zhao B, Huang JQ, Li ZL. Kidney Injury Following Ibuprofen and Acetaminophen: A Real-World Analysis of Post-Marketing Surveillance Data. Front Pharmacol. 2021;12:750108 (https://doi.org/10.3389/fphar.2021.750108).
22. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(11):954-76 (https://doi.org/10.1016/s1474-4422(18)30322-3).
23. Steiner TJ, Jensen R, Katsarava Z, Linde M, MacGregor EA, Osipova V et al. Aids to management of headache disorders in primary care (2nd edition) : on behalf of the European Headache Federation and Lifting The Burden: the Global Campaign against Headache. J Headache Pain. 2019;20(1):57 (https://doi.org/10.1186/s10194-018-0899-2).
24. Derry S, Moore RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev. 2013;2013(4):Cd008040 (https://doi.org/10.1002/14651858.CD008040.pub3).
25. Kirthi V, Derry S, Moore RA. Aspirin with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev. 2013;2013(4):CD008041 (https://doi.org/10.1002/14651858.CD008041.pub3).
26. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia. 2002;22(8):633-58 (
27. Ibuprofen 400 mg film-coated tablets (PL 16363/0523) - Summary of Product Characteristics (SmPC). [website]. (https://www.medicines.org.uk/emc/product/7020/smpc.).
28. Saper J, Dahlof C, So Y, Tfelt-Hansen P, Malbecq W, Loeys T et al. Rofecoxib in the acute treatment of migraine: a randomized controlled clinical trial. Headache. 2006;46(2):264-75 (https://doi.org/10.1111/j.1526-4610.2006.00334.x).
29. Richer L, Billinghurst L, Linsdell MA, Russell K, Vandermeer B, Crumley ET et al. Drugs for the acute treatment of migraine in children and adolescents. Cochrane Database Syst Rev. 2016;4(4):Cd005220 (https://doi.org/10.1002/14651858.CD005220.pub2).
30. Pierce CA, Voss B. Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. Ann Pharmacother. 2010;44(3):489-506 (https://doi.org/10.1345/aph.1M332).
31. Parikh SK. Unique Populations with Episodic Migraine: Pregnant and Lactating Women. Curr Pain Headache Rep. 2018;22(12):80 (https://doi.org/10.1007/s11916-018-0737-x).
32. Dathe K, Fietz AK, Pritchard LW, Padberg S, Hultzsch S, Meixner K et al. No evidence of adverse pregnancy outcome after exposure to ibuprofen in the first trimester -

Evaluation of the national Embryotox cohort. Reprod Toxicol. 2018;79:32-8 (https://doi.org/10.1016/j.reprotox.2018.05.003).
33. Townsend RJ, Benedetti TJ, Erickson SH, Cengiz C, Gillespie WR, Gschwend J et al. Excretion of ibuprofen into breast milk. Am J Obstet Gynecol. 1984;149(2):184-6 (https://doi.org/10.1016/0002-9378(84)90195-9).
34. Rigourd V, de Villepin B, Amirouche A, Bruneau A, Seraissol P, Florent A et al. Ibuprofen Concentrations in Human Mature Milk—First Data About Pharmacokinetics Study in Breast Milk With AOR-10127 “Antalait” Study. Therapeutic Drug Monitoring. 2014;36(5) (https://journals.lww.com/drug-monitoring/fulltext/2014/10000/ibuprofen_concentrations_in_human_mature.6.aspx).
35. Bethesda (MD): National Institute of Child Health and Human Development. Drugs and Lactation Database (LactMed®) [Internet] [website]. 2006 (https://www.ncbi.nlm.nih.gov/books/NBK501922/).
36. Oskoui M, Pringsheim T, Holler-Managan Y, Potrebic S, Billinghurst L, Gloss D et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2019;93(11):487-99 (https://doi.org/10.1212/wnl.0000000000008095).
37. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E et al. Canadian Headache Society Guideline: Acute Drug Therapy for Migraine Headache. Canadian Journal of Neurological Sciences. 2013;40(5):S1-S3 (<Go to ISI>://WOS:000330267900001).
38. Diener HC, Förderreuther S, Kropp P. Treatment of migraine attacks and preventive treatment of migraine (English) [website]. Deutsche Gesellschaft für Neurologie (Hrsg.); 2022 (https://ihs-headache.org/wp-content/uploads/2023/06/DMKG_Treatment-of-migraine-attacks-and-preventive-treatment-of-migraine-2022.pdf).
39. Ducros A, de Gaalon S, Roos C, Donnet A, Giraud P, Guegan-Massardier E et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment. Rev Neurol (Paris). 2021;177(7):734-52 (https://doi.org/10.1016/j.neurol.2021.07.006).
40. British Association for the Study of Headache - Headache Management System for Adults [website]. 2019 (https://www.bash.org.uk/downloads/guidelines2019/02_BASHNationalHeadache_Management_SystemforAdults_2019_guideline_versi1.pdf).
41. Demarquay G, Moisset X, Lantéri-Minet M, de Gaalon S, Donnet A, Giraud P et al. Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 1: Diagnosis and assessment. Rev Neurol (Paris). 2021;177(7):725-33 (https://doi.org/10.1016/j.neurol.2021.07.001).
42. Linde M, Steiner TJ, Chisholm D. Cost-effectiveness analysis of interventions for migraine in four low- and middle-income countries. J Headache Pain. 2015;16:15 (https://doi.org/10.1186/s10194-015-0496-6).
43. Lampl C, Voelker M, Steiner TJ. Aspirin is first-line treatment for migraine and episodic tension-type headache regardless of headache intensity. Headache. 2012;52(1):48-56 (https://doi.org/10.1111/j.1526-4610.2011.01974.x).
44. [website]. (https://www.in2013dollars.com/us/inflation/2015?amount=1).