

I.7 Ibuprofen for migraine - EML

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Applicants are the International Headache Society, the European Headache Federation, and Disease Relief by Excellent and Advanced Means. It was prepared by 11 experts from nine countries and received 20 letters of support from various organizations. European Migraine and Headache Association supports the application. The global migraine prevalence is estimated at 14–15% and estimates show that migraine accounts for 4.9% of global population ill health quantified in years lived with disability (YLDs). 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). Treatments to stop or mitigate acute attacks, in the shortest time possible, are needed. Making it necessary to have available a range of options. The submission proposes the addition of ibuprofen (M01AE01) tablets 200 mg, 400 mg, as a first-line option for acute migraine attacks in adults, but suggests it may be listed as a square box. Ibuprofen is already listed on the EMLc. The typical dose for adults is ibuprofen 200-400 mg orally and repeated every 4-6 hours as needed, with a maximum daily dose of 1200 mg. There is sufficient evidence of effectiveness, from several RCTs, even if total abortion of symptoms happens for a small portion of individuals suffering from migraine attacks. The medicine is considered generally very safe, with some precautions and contraindications. The overall benefit to harm balance is positive. 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. I support the addition of ibuprofen 200mg and 400mg as treatment for acute migraine in section 7.1 of the EML.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? 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. Ibuprofen is on the EML for other indications for adults. (https://list.essentialmeds.org/)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? Multiple clinical trials, systematic reviews and meta-analyses have demonstrated the efficacy of ibuprofen in pain, and also in migraine ¹ . Ibuprofen is an effective treatment for acute migraine headaches, providing pain relief in about 50% of those treated; complete relief from pain and associated symptoms occur for only a minority. NNTs for all efficacy outcomes were better with 400 mg than 200 mg in comparisons with placebo, and soluble formulations provided more rapid relief ² . A SR and network metanalysis compared several drugs in various classes and showed that for sustained pain freedom, the most efficacious interventions were eletriptan and ibuprofen ³ . The application shows 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. Additionally, two RCTs compared different dosages of ibuprofen (200, 400 and 600 mg) for pain and the pooled analyses showed no significant differences between these dosages.	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? Ibuprofen is an NSAID associated with occasional adverse events of upper gastrointestinal bleeding, large intestinal ulcers, bleeding and perforation. About 0.5% of individuals using NSAIDs on long term use have been reported to have an upper gastrointestinal bleed	☒ Yes ☐ No ☐ Not applicable

annually. Factors that enhance the risk are older age, the presence of <i>Helicobacter pylori</i> infection, a history of bleeding and anticoagulant drug use. Of all NSAIDs, ibuprofen appears to have one of the best gastrointestinal tolerability profiles. Adverse events were mostly mild and transient, occurring at the same rate as with placebo¹. 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 pregnancy⁴. Due to its very low levels in breastmilk, short half-life and safe usage in infants, ibuprofen is considered an ideal analgesic or anti-inflammatory option during breastfeeding.	
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? Ibuprofen is widely used for the acute treatment of migraine not only because of its efficacy, and its tolerability and good safety profile, but also because of its almost universal availability at low cost around the world. Years of clinical experience also are a meaningful source in the positive balance.	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? Ibuprofen can be taken with or after food. Contraindicated when there are previous hypersensitivity reactions to acetylsalicylic acid or other NSAIDs; history of gastrointestinal bleeding or perforation, recurrent peptic ulcer/haemorrhage; severe renal failure or severe hepatic failure; severe heart failure (NYHA Class IV); last trimester of pregnancy⁴. An emerging problem is inadequate pain management, which may cause inappropriate use, usually by continuous use of pain-relieving agents. This may generate a secondary headache known as medication overuse headache (MOH)⁵. Ibuprofen 200-400 mg is a very widely used OTC for mild-to-moderate pain. Community pharmacists are well-equipped to advise on using ibuprofen for migraine therapy.	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? There are no economic studies of ibuprofen for the treatment of migraine. The medicine is affordable; approximately 3x cheaper than dispersible aspirin (400mg ibuprofen x 900 mg aspirin). Additionally, effectiveness of ibuprofen (measured as 'success rate' after single dose) was higher. Modeling for Cost/HLY of 400mg ibuprofen gained was also favorable showing cost-effectiveness. There was no ICER modeling.	☒ Yes ☒ No ☐ Not applicable
Is the medicine available and accessible across countries? Ibuprofen is available in almost all countries with many brands and generics.	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval? Ibuprofen is approved for the treatment of mild-to-moderate pain in most countries. Ibuprofen is listed in various pharmacopoeias, including the European Pharmacopoeia the British Pharmacopoeia and the USP.	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable

Additional References

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3. Karlsson WK, Ostinelli EG, Zhuang ZA, Kokoti L, Christensen RH, Al-Khazali HM, Deligianni CI, Tomlinson A, Ashina H, Ruiz de la Torre E, Diener HC, Cipriani A, Ashina M. Comparative effects of drug interventions for the acute

management of migraine episodes in adults: systematic review and network meta-analysis. *BMJ*. 2024 Sep 18;386:e080107. doi: 10.1136/bmj-2024-080107.

4. Marhofer D, Jaksch W, Aigmüller T, Jochberger S, Urlesberger B, Pils K, Maier B, Likar R, Kayer B, Wallner R, Fink P, Grögl G. Schmerztherapie in der Schwangerschaft : Eine expertInnenbasierte interdisziplinäre Konsensus-Empfehlung [Pain management during pregnancy : An expert-based interdisciplinary consensus recommendation]. *Schmerz*. 2021 Dec;35(6):382-390. German. doi: 10.1007/s00482-021-00571-4.

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