

Justification of “Long lasting – pain relief up to 12h” claim for gastro-resistant naproxen 250mg

I. Introduction – pharmacokinetic parameters

A non-steroidal anti-inflammatory drug (NSAID) with a long elimination half-life such as naproxen (~10 – 15 hours), has a long duration of action. In contrast, NSAIDs such as ibuprofen, with a shorter half-life (half-life ~ 1 – 2 hours) have a relatively shorter duration of action. [1,2]

II. Clinical studies confirming “long lasting pain relief up to 12 hours” by naproxen

Napralief 250mg gastro-resistant tablets contain the NSAID naproxen as the active ingredient. Naproxen has been shown to provide long-lasting pain relief from mild to moderate acute pain for up to 12 hours [1-3].

The clinical evidence for long lasting pain relief up to 12 hours has been demonstrated in clinical studies as detailed below:

- Naproxen provided significantly ($p < 0.001$) greater total pain relief over 12 h investigated as primary endpoint [1]
- The sum of pain intensity difference (SPID_{0-12h}) and total pain relief scores throughout 12 h (between 6 – 12 h) were significantly ($p < 0.001$) higher compared to paracetamol [1]
Source: Daniels SE, et al. Significant, long-lasting pain relief in primary dysmenorrhea with low-dose naproxen sodium compared with acetaminophen: a double-blind, randomized, single-dose, crossover study. *Curr Med Res Opin.* 2019;35(12):2139-47
- Naproxen significantly prolonged the time to rescue medication ($p < 0.001$) and reduced the need for its use compared to ibuprofen or placebo, as assessed by the primary endpoint [2].
- The sum of pain intensity difference (SPID_{0-24h}) and total pain relief over 24 hours were significantly ($p < 0.05$) higher compared to paracetamol [2]
Source: Cooper SA, Desjardins P, Brain P, et al. Longer analgesic effect with naproxen sodium than ibuprofen in post-surgical dental pain: a randomized, double-blind, placebo-controlled, single-dose trial. *Curr Med Res Opin.* 2019;35(12):2149-58.

III. **Comparative aspects of the clinical studies confirming “longer lasting” than ibuprofen or paracetamol**

In addition to its long-lasting benefits as confirmed by Daniels et al., a single dose of naproxen 440 mg (notably lower than the initial Napralief dose of 500 mg*) was compared to the maximum dose of paracetamol 1000 mg in a dental pain study. The results demonstrated that naproxen provided superior total pain relief over a 12-hour period, compared to paracetamol [1]

A comparative single-dose study in acute dental pain conducted by Cooper et al., evaluated the same 440 mg naproxen dose against the maximum over-the-counter dose of ibuprofen (400 mg). The study found that naproxen provided significantly longer-lasting pain relief. [2]

[*SmPC Napralief]

IV. **Extrapolation of “long-lasting pain relief” to other types of pain**

The dental impaction pain model used in Cooper et al., is a well-validated acute pain model and has been used in several successful analgesic efficacy studies. The model has excellent assay sensitivity because surgical removal of impacted third molars can be easily standardized and the target population is homogeneous in healthy patients, with isolated pain. Most importantly, the post-surgical pain described has the following features:

- its severity can be adjusted by choosing a relevant pain model
- it is typically persistent and often lasts for 24h or longer
- it offers suitable sensitivity, allowing for the comparison of analgesic efficacy
- It provides reliable estimates of various endpoints such as onset of analgesia, peak effects, Pain Intensity Differences (PIDs) over a defined period, and duration of pain relief as defined by the time to rescue medication or a second dose of the same study drug. [4,5]

Other types of pain like joint or muscle pain, are not suitable for investigating pain relief in clinical studies, since the pain intensity can vary from constant to sporadic and be influenced by movement or psychological factors. [6]

Naproxen is an analgesic drug of the NSAID group with a well-known mode of action. Naproxen and other NSAIDs inhibit the enzymes cyclooxygenase (COX)-1 and -2, involved in prostaglandin synthesis (which is released during cell damage) and is involved in the development of pain and inflammation. It is valid to conclude that the dental impaction pain model is particularly amenable to evaluating the NSAID-class of drugs. There is a plethora of dental impaction pain model articles in the literature that describe the efficacy of just about every NSAID and selective

COX-2 **inhibitor**. [4] Thus, the efficacy and duration of pain relief of naproxen shown in the studies above [1,2] can be translated/ extrapolated to other types of inflammatory pain, in which prostaglandin is involved as a messenger as seen in period, joint and muscle pain.

V. Differences between maximal duration of pain relief and investigation of recommended dose interval

Maximal duration of pain relief

In clinical studies, the offset of analgesia is typically assessed by either recording the time at which pain intensity returns to baseline or, more commonly, measuring the elapsed time from dosing to when rescue medication is requested. These data are often presented as a Kaplan-Meier curve, showing the cumulative probability of taking rescue analgesic over time. [4]

The **maximum effective duration of pain relief** can be determined by measuring the time until rescue or **when re-medication is required**. Patients who do not require re-medication were removed from the analysis. [4] Studies have found that naproxen provides pain relief for up to 12 h before a rescue medication is needed [1,2]

Investigation of recommended dose interval

Nevertheless, appropriate dosing intervals and regimens are guided by publications reporting the **median time until rescue or re-medication** is needed [4]. For naproxen, a dosing interval of 6 – 8 h is recommended.

References:

1. Daniels SE, Paredes-Diaz A, An R, et al. Significant, long-lasting pain relief in primary dysmenorrhea with low-dose naproxen sodium compared with acetaminophen: a double-blind, randomized, single-dose, crossover study. *Curr Med Res Opin*. 2019;35(12):2139-47
2. Cooper SA, Desjardins P, Brain P, et al. Longer analgesic effect with naproxen sodium than ibuprofen in post-surgical dental pain: a randomized, double-blind, placebo-controlled, single-dose trial. *Curr Med Res Opin*. 2019;35(12):2149-58.
3. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Naproxen. [Updated 2020 Mar 20]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548159/>
4. Cooper SA, Desjardins PJ, Turk DC, et al. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. *Pain*. 2016;157(2):288-301.

5. Cooper SA, Desjardins PJ. The value of the dental impaction pain model in drug development. *Methods Mol Biol.* 2010;617:175-190.
6. Cooper SA. Models for clinical assessment of oral analgesics. *Am J Med.* 1983;75(5A):24-9.