19th Expert Committee on The Selection and Use of Essential Medicines

April 8-12 2013

Expert peer review on application for the addition of Naproxen

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
Not applicable.
b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
In the recommended doses, naproxen can be considered equi-effective with ibuprofen and diclofenac.
c. Please provide any additional relevant information with reference
Not applicable.

2. Assessment of safety
a. Have all relevant studies on safety been included
Yes  No ✓

The Application is based on a published systematic review of the population-based controlled observational studies. It also refers to a drug utilization overview describing the prevalent use of the NSAIMs of higher cardiovascular risk, specifically diclofenac.

Two systematic reviews of randomized controlled trials tend to support the arguments put forward in the Application:


b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

The relative risk of a cardiovascular event in the current users versus non-users was 1.09 (95%CI 1.02 to 1.16) for naproxen and 1.18 (95%CI 1.11 to 1.259) for ibuprofen.

Naproxen was not associated with an increased risk at higher doses, whereas ibuprofen was (high dose of ibuprofen being defined as >1200mg in the majority of included studies and the relative risk of a cardiovascular event in the high dose group found to be 1.78 (95%CI 1.35 to 2.34)).
c. Please provide any additional relevant information with reference

A PD interaction of ibuprofen with ASA in healthy volunteers has been described and might be relevant for this population. Admittedly, the clinical significance of this interaction remains unclear and the suggestion that a similar interaction seen with naproxen can be avoided when the drug is dosed at least 2 hours after ASA is based on PD data only.


3. Assessment of cost and availability

a. Have all relevant data on cost and availability been provided

Yes ✓ No

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

According to the Application, based on the International Drug Price Indicator and International Dispensary Association pricing, naproxen costs $0.0378 - $0.049 per DDD (500mg) and Ibuprofen costs $0.0327 - $0.036 per DDD (1200mg).

c. Please provide any additional relevant information with reference

Not applicable.

d. Is the product available in several low and middle income countries?

Yes.

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

There is a public health need for an effective NSAIM with an optimal safety profile. Efforts have been made to develop products with better gastrointestinal tolerability and the GI risk can be partially minimized with the concomitant use of the gastro-protective medication.

More recently the cardiovascular effects of the NSAIMs, both traditional and COX-2 selective, have been extensively investigated and found to be perhaps larger than initially expected. Naproxen has consistently been shown the have the lowest CVD risk, including in comparison with the high dose ibuprofen. Thus the addition of naproxen to the EML will contribute to the CV safety of the NSAIM therapy and will also possibly increase the awareness of prescribers of the need to consider the CV risks as well as the GI risks when prescribing NSAIMs.

Addition of Naproxen
b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones?

NSAIDs are most often referred to as a group in the international guidelines (pointing out that while their efficacy is similar at large, there may be differences in the safety profile). Ibuprofen is the most common reference product in the WHO guidance documents.

5. Are there special requirements for use or training needed for safe/effective use?

No

6. Is the proposed product registered by a stringent regulatory authority?

Yes ✓ No

7. Any other comments

Not applicable.

8. What is your recommendation to the committee (please provide the rationale)

Although considerable attention in the Application has been devoted to the comparison of naproxen and diclofenac, it would be important to evaluate if the addition of naproxen to the EML (currently listing ibuprofen) would be of public health benefit.

There is little to support replacing ibuprofen as no new data have emerged on its efficacy or safety. It also has good relative GI tolerability and a wide range of pharmaceutical dosage forms available.

Considering the CV risk associated with the higher ibuprofen doses often used in clinical practice and the fact that a considerable proportion of NSAID users are of advanced age and of moderate to very high CV risk, it is recommended to approve the proposed addition of naproxen to the List.