Expert peer review on application for the inclusion of naproxen

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes  No (if no, please provide reference and information)

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

      n/a

   c. Please provide any additional relevant information with reference

      n/a

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes  No (if no, please provide reference and information)

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

      The data presented are from an update of the cardiovascular safety of various NSAIDs based on meta-analysis of results from observational studies (case-control and controlled cohort studies). The relative risk of a cardiovascular event in users versus non-users (or uses at a remote time point) was 1.18 (95%CI 1.11, 1.25) with ibuprofen, 1.18 (1.11, 1.25) and 1.09 (1.02, 1.16) with naproxen. In a pair-wise comparison, the ratio of relative risks for naproxen was just significantly lower than for ibuprofen: RRR = 0.92 (99% CI 0.87, 0.99). However, when dose were taken into account, only high-dose ibuprofen (>1200mg/day) was associated with higher risk. Naproxen was risk neutral at all doses.

   c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
   a. Have all relevant data on cost and availability provided
      Yes  Yes  No (if no, please provide reference and information)

   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)
Comparable median procurement prices per DDD were shown for naproxen and ibuprofen: naproxen cost $0.0378 - $0.049 per DDD (500mg) and ibuprofen cost $0.0327 - $0.036 per DDD (1200mg).

c. Please provide any additional relevant information with reference

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

4. Assessment of public health need

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

The public health need for an effective NSAIM is already established.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

Ibuprofen has traditionally been referred to in WHO guidelines.

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

If yes, please provide details in 1-2 sentences

No.

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

Yes ✓ No

7. Any other comments

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

Although the text of the unpublished manuscript on sales volumes has not been provided publically, the text of the proposal makes mention of high use of diclofenac in many countries. Given the risk profile demonstrated by this review, the need for regulatory action, particularly around the non-prescription status of diclofenac, is clear. However, the data on utilisation are of limited relevance for this particular decision, as ibuprofen is listed in the WHO EML without a square box symbol. WHO has therefore not promoted the use of diclofenac by means of its inclusion in the List or by allowing for local choice within the NSAIM class. Where diclofenac has been included in country EMLs, this has been a local decision, not in line with the Model EML. It appears from the proposal that the request is not to remove ibuprofen, but to add naproxen. Accordingly, it is proposed that the entry into the WHO Model Formulary list naproxen with a note to the effect that it represents an “optimal choice for individuals with underlying cardiovascular risks”. Further, it is proposed that the note state: “use lowest effective dose for shortest duration possible”. Given the modest differences in cardiovascular risk demonstrated between ibuprofen and naproxen, which barely reached statistical significance, the lack of markedly increased risk when ibuprofen is used at doses not exceeding 1200mg/day, as well as the availability of a wide range of dosage forms of ibuprofen (including for paediatric use), it is recommended that the proposed addition of naproxen to the List not be approved, and that ibuprofen be retained as the NSAIM of choice. Further it is recommended that the text of the WHO Model Formulary be amended, if necessary, to reflect these data, and to emphasise that NSAIMs be used at the lowest effective dose for the shortest duration possible.