

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

April 8-12 2013

Expert peer review on application for Ferrous salt + folic acid (New formulation) -- Adults

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
   Yes
b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences):
   1. Already listed in the EML are:
      a. Ferrous salt + Folic acid Tablet equivalent to 60 mg iron + 400 micrograms folic acid (Nutritional supplement for use during pregnancy). combination is already listed in the EML
      b. Ferrous salt Oral liquid: equivalent to 25 mg iron (as sulfate)/ml. Tablet: equivalent to 60 mg iron.
      c. Folic acid (tablet, 1 mg, 5 mg)
   2. New application is for “Add 60 mg elemental iron in a ferrous form plus folic acid 2.8 mg tablet/capsule formulation for the prevention of anaemia in menstruating women and adolescent girls” (Intermittent use)
   3. No data on efficacy (in the applications and in the literature) comparing already existing “ferrous 60 mg + Folic acid 400 micrograms” versus “ferrous 60 mg plus folic acid 2.8 mg” in preventing anaemia
   4. The difference is folic acid dose only (400 micrograms to be replaced with 2.8 mg). But the Cochrane review (1) and WHO guidelines (2) have commented that the “evidence for the effective dose of folic acid for intermittent supplementation is very limited, the current recommendation is based on the rationale of providing seven times the recommended daily dose to prevent NTDs”
   5. Even the dose of Ferrous 60 mg has no strong evidence (1) “Overall, whether the supplements were given once or twice weekly, for less or more than three months, contained less or more than 60 mg of elemental iron per week, or to populations with different degrees of anaemia at baseline did not seem to affect the findings.
   c. Please provide any additional relevant information with reference

2. Assessment of safety
a. Have all relevant studies on safety been included
   No — Evidence is emerging that high folate status promotes tumour progression. Suggests that folate may play a dual role in the risks of colorectal cancers and other cancer depending on the dosage and timing of exposure. A modest dose taken before establishment of pre-neoplastic lesion may suppress development of cancer in normal tissues, in contrast if taken in high doses after establishment of pre-neoplastic lesions may promote development and progression of cancer. It is recommended that high doses of folic acid for supplementation purpose have to be used with caution (3-19)

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

c. Please provide any additional relevant information with reference -- Because of this safety issue we recently replaced the folic acid 5 mg with folic acid 1 mg in our national procurement list

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3. Assessment of cost and availability
   a. Have all relevant data on cost and availability provided
      No (See below)
   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) – Since this is a new formulation no data on cost and availability. All the existing data are for Ferrous 60 plus 400 micrograms folic acid
   c. Please provide any additional relevant information with reference
   d. Is the product available in several low and middle income countries? – No (See 3.b)

4. Assessment of public health need
   a. Please provide the public health need for this product (1-2 sentences). With the evidence available unable to see a public health need for a product with 2.8 mg folic acid over a product with 0.4 mg folic acid
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable – WHO (Yes)

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? – No

7. Any other comments

8. What is your recommendation to the committee (please provide the rationale)
   Not recommended
      1. No evidence on superior efficacy of ferrous 60 + folic acid 2.8 mg over already existing ferrous 60 + folic acid 0.4 mg
      2. Emerging concerns regarding the association between “high doses of folic acid and development and progression of cancers”

Reference

Folate, Vitamins B6 and B12, and/or Omega-3 Fatty Acids (SU.FOL.OM3) Randomized Trial. Arch Intern Med 172(7): 540-547. [PubMed abstract]


