[Ferrous salt + folic acid] (Section 10.1) (60 mg iron + 2.8 mg folic acid)

(1) Does the application adequately address the issue of the public health need for the medicine?
   Yes [ ] No [ ]

Please provide brief details:
The application provided the prevalence of anaemia in menstruating women (＞40%), the currently standard approach for anaemia prevention (daily iron and folic acid supplementation), and the introduction and rationale of intermittent supplementation of iron and folic acid.
However, no information on the formulation of “60 mg iron + 2.8 mg folic acid” was mentioned.

(2) Have all important studies that you are aware of been included in the application?
   Yes [ ] No [ ]

Please provide brief comments on any relevant studies that have not been included:
The application provided two important evidences: a Cochrane systematic review and a WHO guideline, as well as some other studies.
However, some important publications were missed. For efficacy evaluation, there was an ongoing study on the formulation of “60 mg iron + 2.8 mg folic acid” (Nguyen, PH, et al. Rationale, design, methodology and sample characteristics for the Vietnam pre-conceptual micronutrient supplementation trial (PRECONCEPT): a randomized controlled study. BMC Public Health, 2012) . For safety evaluation, the relationship between folic acid and cancer are still in argument (Miller JW, Ulrich CM. Folic acid and cancer--where are we today? Lancet. 2013, 23; 381 (9871) : 974-6) .

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
   Yes [ ] No [ ]

Briefly summarize the reported outcomes (e.g. clinical, surrogate, other) and comment, where possible, on the magnitude of clinical benefit associated with use of the medicine:
The Cochrane systematic review, which this application mainly based on, concluded “Interruption iron supplementation in menstruating women is a feasible intervention in settings where daily supplementation is likely to be unsuccessful or not possible. In comparison with daily supplementation, the
provision of iron supplements intermittently is less effective in preventing or controlling anaemia.” And the application dosage was evidence limited.

There was no any results on “60 mg iron + 2.8 mg folic acid, weekly” for prevention or treatment of anemia of menstruating women and adolescent girls. The only one study is ongoing. (Nguyen, PH, et al. Rationale, design, methodology and sample characteristics for the Vietnam pre-conceptual micronutrient supplementation trial (PRECONCEPT) : a randomized controlled study. BMC Public Health, 2012.)

(4) Is there evidence of efficacy in diverse settings and/or populations?

Yes [ ] No [x]

Please provide brief details:

There was few studies on “60 mg iron + 2.8 mg folic acid”. The only study was ongoing. This study recruited 5011 women of reproductive age in rural Vietnam and randomly assigned them to receive weekly supplements containing either: 1) 2.8 mg folic acid, 2) 60 mg iron and 2.8 mg folic acid, or 3) multiple micronutrient.

(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes [ ] No [x]

Please provide brief details:

The application provided the most common side-effects of iron supplementation include nausea, constipation, dark stools and metallic taste.

However, it is still in argument about the impaction of folic acid on cancer. Miller discussed that “Folate has a putative two-faced relationship with cancer: it can protect against initiation, but promote proliferation”. (Miller JW, Ulrich CM. Folic acid and cancer--where are we today? Lancet. 2013, 23; 381 (9871) : 974-6.)

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes [ ] No [x]

Please provide brief details:

No special requirements.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes [ ] No [x]
Please provide brief details:

There is no new registration, indications, nor off-label use on iron plus folic acid, except the formulation of “60 mg iron + 2.8 mg folic acid” is new.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☑ No ☐

Please provide brief details:

The application provided a WHO Guideline on intermittent iron and folic acid supplementation in menstruating women published in 2011. The guideline recommend a scheme for intermittent iron and folic acid supplementation in menstruating women: 60 mg iron and 2.8 mg folic acid, one supplement per week, 3 months of supplementation followed by 3 months of no supplementation after which the provision of supplements should restart.

However, the guideline was based on a Cochrane systematic review, which concluded that "Intermittent iron supplementation in menstruating women is a feasible intervention in settings where daily supplementation is likely to be unsuccessful or not possible. In comparison with daily supplementation, the provision of iron supplements intermittently is less effective in preventing or controlling anaemia." Moreover, no information on the dosage of iron or folic acid was recommended.

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

The application provided cost information of single nutrient formulations and the “60 mg iron + 0.4 mg folic acid” tablets instead of the “60 mg iron + 2.8 mg folic acid” formulation.

Although the “60 mg iron + 2.8 mg folic acid” has been recommended by the WHO guideline, this formulation was not available in the market and no economic information was available so far.

(10) Any additional comments?

In the section of 10.1 Antianaemia medicines in the 18th WHO/EML in 2013, the following medicines were already listed:

1) ferrous salt: Oral liquid: equivalent to 25 mg iron (as sulfate) /ml. Tablet: equivalent to 60 mg iron;
2) folic acid: Tablet: 1 mg; 5 mg;
3) ferrous salt + folic acid: Tablet equivalent to 60 mg iron + 0.4 mg folic acid.

But there was no direct evidence indicated “60 mg iron + 2.8 mg folic acid, weekly” for the prevention of anaemia in menstruating women and adolescent girls so far.
(11) Please summarise the action you propose the Expert Committee takes.

This reviewer doesn’t recommend ‘Add 60 mg elemental iron in a ferrous form plus 2.8 mg folic acid tablet/capsule formulation for the prevention of anaemia in menstruating women’, due to:

● The current evidence for efficacy and safety is insufficient.