20th Expert Committee on Selection and Use of Essential Medicines

Peer Review Report #2

[Folic acid]

(1) Does the application adequately address the issue of the public health need for the medicine?

Yes.

Congenital anomalies affect an estimated 1 in 33 infants. For approximately half of these cases there is no known cause. Amongst the known causes like infections, environmental factors and maternal nutritional factors, maternal folate deficiency has been linked to Neural Tube Defects (NTDs) and supplementation of folate before conception and during the first trimester of pregnancy is effective in reducing the risk of NTD.

(2) Have all important studies that you are aware of been included in the application?

Yes.

This specific dose (0.4mg) in the specified time interval (2 months before pregnancy and continued up to 12 weeks after conception), has not been adequately studied with scientific rigour.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes.

There is adequate information regarding the folic acid supplementation and decrease in the incidence of NTD. However, the application states that 0.4mg of folic acid alone is for women “who have difficulties taking iron supplements, those who choose not to, or where iron is not recommended for other reasons”. This narrows the population who will actually need this drug. The application does not elaborate on actual estimates of how many women will fit this profile. Hence it is difficult to estimate the real need for 0.4mg of folic acid alone as this may be a small subset of women.

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

No.

A cohort study conducted in China and studies done in Irish population show similar outcome. However, there is no other evidence for this.
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?

No.

At the dose being recommended, folic acid is safe. However, there are concerns about larger doses having effects on the foetus. The application has not adequately considered the safety and adverse effect of the medicine perhaps because folic acid is available in higher strengths in the WHO EML.

ADDITIONAL CONSIDERATIONS:

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

No.

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

No.

This strength is not available in many countries. This could be a real limitation as the strength will not be available. Manufacturers may not see the need to include this strength as other strengths are available.

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

The WHO Guideline which came out in 2012, “Daily iron and folic acid supplementation in pregnant women” only recommended 0.4 mg folic acid along with iron.

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

Folic acid is cheap and cost effective. In table 3, none of the 20 countries listed have folic acid in the 0.4mg strength. The table states that none of the three strengths are available in India. This is not true. 1 mg and 5 mg folic acid is available and the cost is also very low. 10 tablets of folic acid (1 mg) costs one rupee only.

Any additional comments?

Currently the WHO EML includes folic acid with iron (400 μg folic acid plus 60 mg elemental iron) and high dose folic acid (1000 μg and 5000 μg), but does not include the 400 μg (0.4 mg) folic acid dose without iron. There is no evidence for the superiority of 0.4mg of folic acid versus 0.4mg folic acid +60 mg
elemental iron. Adding more strengths of folic acid may also pose a problem at the ground level in primary care facilities as health care systems without much sophistication may not be able manage the supply chain.

(11) Please summarise the action you propose the Expert Committee takes.

I do not recommend that 0.4 mg of folic acid should be added to the EML for the following reasons.
(a) The need for folic acid alone (0.4mg) is for a very small subset of women who have not been well defined in terms of numbers in this proposal.
(b) Even in USA (according to CDC) more than 50% of pregnancies are unplanned.\(^1\) In LMICs this may be a larger proportion. Hence giving folic acid 2 months before the pregnancy will not be a tenable option.
(c) This formulation (folic acid 0.4mg alone) is not available in most countries.
(d) There is no evidence that this is superior to folic acid with iron.

References:
1. Folic acid. CDC, USA. 

2. WHO Guideline 2012: Daily iron and folic acid supplementation in pregnant women