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

Yes [ ] No [ ]

Please provide brief details:
Congenital anomalies (also referred as birth defects) affect an estimated 1 in 33 infants and result in approximately 3.2 million birth defect-related disabilities every year. The NTD burden was recently assessed in 18 countries in 6 WHO regions. It was estimated that about 190,000 neonates were born each year with a NTD in low- and middle-income countries. In 2010, an estimated 270,000 deaths globally were attributable to congenital anomalies during the first 28 days of life, with NTDs being one of the most serious and most common of these anomalies. Folic acid supplementation before conception and during the first trimester of pregnancy is one of the few public health interventions effective in reducing the risk of NTD. The 400 μg (0.4 mg) dose of folic acid alone is missing in several National Essential Medicines List (NEML), especially in low and middle income countries that use the WHO EML/EMLc to build their respective national formularies.

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:

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

Yes [ ] No [ ]

Briefly summarise the reported outcomes (e.g. clinical, surrogate, other) and comment, where possible, on the magnitude of clinical benefit associated with use of the medicine:
Cochrane systematic review included two trials with 299 women. The prevalence of NTDs was lower in the women who received folic acid alone compared with women who received no treatment or placebo (RR 0.32, 95% CI 0.08 to 1.34).
The effect of supplementation in women with 100 μg, 200 μg or 400 μg folic acid provided
in tablet form on RBC folate concentrations and the prevalence of NTDs was assessed. Supplementation with 400 μg folic acid daily lead to a higher RBC folate concentration compared to the placebo group (MD 260 μg/L; 95% CI 103.81 to 416.19). And a 47% reduction in NTD risk.

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

Yes □ No □

Please provide brief details:
Several African countries and China.

(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 □

Please provide brief details:

ADDITIONAL CONSIDERATIONS:

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

Yes □ No □

Please provide brief details:

(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 □

Please provide brief details:
Currently the Essential Medicine’s List includes folic acid with iron (400 μg folic acid plus 60 mg iron) and high dose folic acid (1 mg and 5 mg), but does not include the 400 μg folic acid dose without iron

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

Yes □ No □

Please provide brief details:
WHO currently recommends all women, from the moment they being trying to conceive until 12 weeks of gestation, take a daily supplement of 400 μg (0.4 mg) folic acid to prevent NTDs (occurrent NTDs) and women who have previously had a fetus diagnosed as affected by a NTD, or have given birth to a baby with a NTD, should take a daily supplement of 5mg folic
acid to prevent recurrent NTDs.

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

The most recent International Drug Price Indicator Guide 2013 and the UNICEF Supply Catalogue were reviewed. Supplements containing 400 μg (0.4 mg) folic acid alone (without other micronutrients) were not found.

(10) **Any additional comments?**

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

Add 400 μg (0.4 mg) folic acid tablet/capsule formulation for the prevention of NTD’s during periconceptional period.

a. **Dose**
   i. 400 μg (0.4 mg) folic acid.

b. **Frequency and duration of the supplementation**
   iv. One tablet per day
   v. Start two months before the planned pregnancy and continue 12 weeks after the pregnancy
   vi. This dose does not concern pregnant women who have previously had a baby with NTD or who have diabetes or who are under anticonvulsant treatment. A higher dose as 5000 μg (5 mg) is recommended for these cases.