Folic acid

Essential medicine status

Section: 10. Medicines affecting the blood > 10.1. Antianaemia medicines

ATC codes: B03BB01

Indication	Anencephaly or similar anomalies ICD11 code: LA00
INN	Folic acid
Medicine type	Chemical agent
List type	Core
Additional notes	periconceptual use for prevention of first occurence of neural tube defects
Formulations	**Oral > Solid:** 400 µg
EML status history	First added in 2015 (TRS 994)
Sex	Female
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Folic acid
DrugBank	Folic acid

Summary of evidence and Expert Committee recommendations

An application was submitted for the inclusion on the Model List of a new formulation of folic acid (400 µg tablet) for periconceptional supplementation in women of childbearing age as a public health intervention for prevention of neural tube defects (NTDs). Folic acid is the synthetic form of folate (water-soluble vitamin B9), which is used in dietary supplements and added to foods. The bioavailability of folic acid from supplements and folic acid-fortified foods appears to be substantially higher than folate bioavailability from consumption of natural folate-rich foods such as beef liver, leafy green vegetables, oranges and legumes (1). The most prevalent types of NTDs are anencephaly, encephalocele and spina bifida. 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 the six WHO regions. The overall burden calculated using the median was 1.67/1000 live births for total NTD burden, 1.13/1000 for spina bifida, 0.25/1000 for anencephaly and 0.15/1000 for encephalocele (2). It was also estimated that, in low- and middle-income countries, about 190 000 babies are born each year with an NTD. Studies have shown that the occurrence of NTDs can be significantly reduced by increasing the consumption of folic acid by women during the periconceptional period. This has led WHO to recommend that a woman who has not previously had a fetus diagnosed as affected by an NTD or given birth to a baby with an NTD should consume 400 µg of folic acid daily, from the time she begins trying to conceive until 12 weeks of gestation (3). The Expert Committee noted that the 18th EML currently includes folic acid tablets in 1 mg and 5 mg strengths, and folic acid (400 µg) in combination with iron (60 mg elemental iron) (4). The application asserted the importance for women who have difficulties in taking or who choose not to take iron supplements, or for whom iron is not recommended for other reasons, to have the option of consuming folic acid alone in the recommended dose for the prevention of first occurrence of NTDs. The application described a Cochrane systematic review of five trials involving 6,105 women that assessed the effects of periconceptual folic acid supplementation to reduce NTDs. Two of the included trials involved 299 women who received either folic acid (360 µg or 4 mg) or no treatment/placebo. Overall, there was a statistically significant reduction in risk of recurrence of NTDs (RR 0.32, 95% CI: 0.08–1.34) in patients receiving folic acid supplementation (5). Supplementation was started before pregnancy and continued throughout the first trimester. The women in both trials had a history of previous pregnancy affected

by NTD. In the trial that involved the 360 µg folic acid dose, the difference between groups was not statistically significant. The Expert Committee noted that for women with a history of NTD-affected pregnancy, the WHO-recommended dose of folic acid supplementation for prevention of recurrent NTD is 5 mg daily. Studies have demonstrated an inverse relationship between the risks of NTDs and maternal red blood cell (RBC) folate. Dose-related median increases in RBC folate concentrations have been measured in a double-blind, randomized, controlled trial of several folic acid doses (100, 200 or 400 µg), with results as follows: 100 µg folic acid/day: 67 µg/L (95% CI: 43–120); 200 µg folic acid/day: 130 µg/L (95% CI: 108–184); and 400 µg folic acid/day: 200 µg/L (95% CI: 125–312) (6). A 1995 study (7) showed that women with RBC folate values below 150 µg/L had an NTD risk of 6.6 per 1000 births. When RBC folate exceeded 400 µg/L, the risk was only 0.8 per 1000 births, and the overall population risk was 1.9 per 1000 births. A cohort study conducted in China evaluated the prevalence of NTDs in fetuses and in infants born to women taking 400 µg folic acid (n = 130 142) or receiving no treatment (n = 117 689) at any time before or during pregnancy. Supplementation with 400 µg folic acid daily led to a 79% reduction in the risk of a fetus or infant having an NTD (8). Following consideration of the available evidence, the Expert Committee recommended inclusion of 400µg folic acid tablets on the core list of the EML for periconceptional use in women of childbearing age for the prevention of the first occurrence of NTDs. The Committee noted that this recommendation was consistent with recommendations in WHO’s Standards for maternal and neonatal care. The Committee recommended listing in Section 10.1. The Expert Committee acknowledged that periconceptional daily supplementation with folic acid in women of childbearing age was an effective and clinically important public health intervention. The Committee noted that 5 mg daily remains the recommended dose of folic acid supplementation for prevention of recurrent NTDs in women who have previously had an NTD-affected pregnancy, and that this higher strength is currently included on the EML. References: 1. Hochberg L, Stone J. Folic acid supplementation in pregnancy. In: UpToDate [website]. Waltham, MA: UpToDate; 2014. 2. Congenital abnormalities. Fact sheet No. 371, updated April 2015. Geneva: World Health Organization; 2015. Available from: http://www.who.int/mediacentre/factsheets/fs370/en/. 3. Standards for maternal and neonatal care. Geneva: World Health Organization; 2007. 4. The selection and use of essential medicines. Report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2014. (WHO Technical Report Series, No. 985). 5. De-Regil LM, Fernandez-Gaxiola AC, Dowswell T, Pena-Rosas JP. Effects and safety of periconceptional folate supplementation for preventing birth defects. Cochrane Database Syst Rev. 2010(10):CD007950. 6. Daly S, Mills JL, Molloy AM, Conley M, Lee YJ, Kirke PN, et al. Minimum effective dose of folic acid for food fortification to prevent neural-tube defects. Lancet. 1997;350(9092):1666-9. 7. Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. Folate levels and neural tube defects. Implications for prevention. JAMA. 1995;274(21):1698-702. 8. Berry RJ, Li Z, Erickson JD, Li S, Moore CA, Wang H, et al. Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. N Engl J Med. 1999;341(20):1485-90.