Ferrous salt + folic acid

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

ATC codes: B03AD02 B03AD03 B03AD05

Indication	Iron deficiency anaemia ICD11 code: 3A00.Z
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid: 60 mg iron + 2.8 mg
EML status history	Application rejected in 2015 (TRS 994)
Sex	All
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	Ferrous salt + folic acid
DrugBank	Ferrous salt (Ferrous sulfate), Folic acid

Summary of evidence and Expert Committee recommendations

An application was submitted by Ms Hala Boukerdenna, Dr Juan Pablo Pena- Rosas and Dr Maria Nieves Garcia-Casal, on behalf of the WHO Department of Nutrition for Health and Development, for the inclusion on the Model List of a new formulation of iron (60 mg elemental iron) plus folic acid (2.8 mg) for use in menstruating women and adolescent girls as a public health intervention in areas where anaemia is 20% or higher and no interventions are in place to control anaemia. Reviews of the application were prepared by two members of the Expert Committee. No public comments were received in relation to this application. Doses of 60 mg elemental iron and 2.8 mg folic acid taken once a week are recommended in the 2011 WHO guideline Intermittent iron and folic acid supplementation in menstruating women (1) (strong recommendation) to improve haemoglobin concentrations and iron status and reduce the risk of anaemia in menstruating women living in settings where anaemia is highly prevalent. It is recommended that supplements be taken for three months, followed by no supplementation for three months, after which supplementation should be restarted. The Expert Committee noted that the 18th EML currently includes a ferrous salt plus folic acid formulation (iron equivalent to 60 mg plus 400 µg folic acid) as a nutritional supplement for use during pregnancy (2). This application proposed the addition of a different strength preparation (iron equivalent to 60 mg plus 2.8 mg folic acid) for prevention of anaemia in menstruating women, consistent with recommendations in the WHO guidelines. This application was a resubmission of an application from 2013 and provided additional data on the efficacy of weekly folic acid regimen in improving red blood cell (RBC) folate concentration and preventing neural tube defects (NTDs). In 2013, the Expert Committee recognized the programmatic needs for appropriate supplementation in pregnancy but, after careful consideration, decided not to include the proposed combination in the EML because the data did not show the intermittent regimen to be at least equivalent to the listed fixed- dose combination (ferrous salt + folic acid tablet, equivalent to 60 mg iron + 400µg folic acid), taken once daily (2). While daily supplementation with iron and folic acid for a period of 3 months has been the standard approach for the prevention and treatment of iron-deficiency anaemia among women of reproductive age, its success in public health programmes has been limited; this is in

part due to low coverage rates, insufficient tablet distribution and low adherence because of side-effects (e.g. constipation, dark stools, metallic taste) (1). The current application argued that intermittent regimens may increase acceptability and adherence, while improvements in iron and folate status before pregnancy may also help to prevent NTDs. A Cochrane systematic review (3) undertaken as part of the 2011 guideline development compared intermittent iron supplementation (alone or with folic acid or other micronutrients) with no supplementation, and daily with intermittent administration schedules. Compared with no supplements or placebo, women taking intermittent iron supplements (alone or in combination with folic acid or other micronutrients) had higher haemoglobin (mean difference 4.58 g/L; 95% CI: 2.56–6.59; 13 studies) and ferritin concentrations (mean difference 8.32 µg/L; 95% CI: 4.97–11.66; six studies) and were less likely to develop anaemia (average risk ratio (RR) 0.73; 95% CI 0.56–0.95; 10 studies). Compared with daily iron supplements, women receiving intermittent supplements were more likely to be anaemic (RR 1.26; 95% CI: 1.04–1.51; six studies), have lower ferritin concentrations (mean difference –11.32 µg/L; 95% CI: –22.61 to –0.02; three studies), with no difference in haemoglobin (mean difference –0.15 g/L; 95%: CI –2.20 to 1.91; eight studies). With regard to safety, the Cochrane review found no evidence to suggest a significant difference in adverse effects between once-weekly intermittent iron supplementation and daily iron supplementation (RR 0.36; 95% CI 0.10–1.31). The Committee noted the conclusion of the Cochrane review that "intermittent iron supplementation in menstruating women is a feasible intervention in settings where daily supplementation is likely to be unsuccessful or not possible". Intermittent supplementation was found to be less effective than daily supplementation with regard to prevention and control of anaemia. Two clinical trials that were included in the application examined the prevention of NTDs and showed that weekly folic acid supplementation (2.8 mg or 4 mg) was not equivalent to daily supplementation with 0.4 mg (4,5). Compared with daily supplementation, 12 weeks of weekly supplementation resulted in a lower plasma folate concentration (mean difference –12.5; 95% CI: 1.04-1.51) and a lower RBC folate concentration (mean difference –136.04; 95% CI: 185.24–6.83). Both studies showed that the rise in RBC folate was linear and did not plateau during the studies; a er 12 weeks of weekly supplementation with 2.8 mg folic acid, RBC folate concentration had reached 900 nmol/L (95% CI: 828– 978), which approaches 906nmol/L – defined as the threshold for optimal RBC folate concentration to prevent NTDs. In all the studies listed above, compliance among menstruating women and adolescent girls was also taken into account in identifying the most effective regimen in terms of public health intervention. The Committee noted that the proposed fixed-dose combination formulation is not widely commercially available. Concern about this lack of commercial availability was also expressed by the Expert Committee in 2013 (2). Following consideration of the available evidence, the Expert Committee did not recommend addition of the new fixed-dose combination formulation of ferrous salt plus folic acid (60 mg + 2.8 mg) to the Model List. The Committee considered that the evidence presented for effcacy of intermittent supplementation was insufficient to support such a recommendation. The overall quality of evidence for outcomes of iron supplementation, intermittent or daily, with or without folic acid, ranged from low to moderate. The Committee considered that, although claimed as an advantage of an intermittent supplementation regimen, adherence has yet to be adequately reported. The Committee also noted that commercial availability of the proposed fixed-dose combination product was limited to one country. References: 1. Guideline: intermittent iron and folic acid supplementation in menstruating women. Geneva: World Health Organization; 2011. 2. 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). 3. Fernández-Gaxiola AC, De-Regil LM. Intermittent iron supplementation for reducing anaemia and its associated impairments in menstruating women. Cochrane Database Syst Rev. 2011(12):CD009218. 4. Norsworthy B, Skea CM, Adank C, Green TJ. E ects of once-a-week or daily folic acid supplementation on red blood cell folate concentrations in women. Eur J Clin Nutr. 2004;58(3):548-54. 5. Hao L, Yang QH, Li Z, Bailey LB, Zhu JH, Hu DJ, et al. Folate status and homocysteine response to folic acid doses and withdrawal among young Chinese women in a large-scale randomized double-blind trial. Am J Clin Nutr. 2008;88(2):448-57.