Ferrous salt + folic acid

Essential medicine status

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

ATC codes: B03AD03 B03AD02 B03AD05

Indication	Spina bifida ICD11 code: LA02
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > tablet:** 60 mg elemental iron + 400 µg tablet ; 60 mg elemental iron + 2.8 mg
EML status history	First added in 1982 (TRS 685) Changed in 1984 (TRS 722) Changed in 1987 (TRS 770) Changed in 1997 (TRS 882) Changed in 2015 (TRS 994) Changed in 2023 (TRS 1049)
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

Expert Committee recommendation

The Expert Committee noted the public health relevance of iron and folic acid supplementation in the prevention of anaemia in women of reproductive age and for reducing the risk of pregnancies affected by neural tube defects. The Committee also noted the global target of a 50% reduction of anaemia in adolescent girls and women by 2025, and that intermittent iron and folic acid supplementation is a recommended intervention in various WHO guidelines. The Committee noted that the evidence presented in the application supported weekly intermittent supplementation being associated with similar efficacy outcomes to daily iron and folic acid supplementation, with potentially fewer adverse effects. The Committee also considered that it was likely that weekly iron and folic acid supplementation would be associated with better adherence. The Expert Committee therefore recommended the inclusion of a new strength formulation of ferrous salt + folic acid (60 mg elemental iron + 2.8 mg folic acid) on the core list of the EML as a weekly administered supplement for preventing anaemia in menstruating women and adolescent girls, and reducing the risk of pregnancies affected by neural tube defects.

Background

Applications requesting inclusion of this formulation of ferrous salt + folic acid for prevention of anaemia have been considered on two previous occasions by the Expert Committee. In 2013, the Expert Committee recognized the programmatic needs for appropriate supplementation in pregnancy, but did not recommend listing of the formulation at that time because the available data did not show the intermittent (weekly) regimen to be at least equivalent to the daily regimen of 60 mg elemental iron + 0.4 mg folic acid (the formulation currently included on the EML) (1). Following a resubmission in 2015, the Expert Committee once again did not recommend listing, considering that the evidence presented for efficacy of intermittent supplementation was insufficient. The overall quality of the evidence for outcomes of iron supplementation, intermittent or daily, with or without folic acid, ranged from low to moderate. The Committee also noted that evidence for better adherence with the intermittent regimen had not been adequately reported, and that commercial availability of the proposed fixed-dose combination product

was limited to one country (2).

Public health relevance

Anaemia is a public health problem widely prevalent in several low- and middle-income countries. Despite a World Health Assembly target (2012–2025) of a 50% reduction in anaemia in adolescent girls and women 15–49 years of age, the most recent data from WHO's Global Health Observatory indicate little progress has been made in reducing the prevalence of anaemia in the past decade (3). For 2019, data show that, globally, 29% of non-pregnant women of reproductive age (15–49 years) suffer from anaemia. The burden is highest in South-east Asia (46%) and Africa (40%). Although data specific to adolescents aged 10–19 years are lacking globally, about 30% are estimated to be anaemic (4). Anaemia impairs resistance to infection and reduces physical capacity and work performance in all age groups; for adolescents, it can also have consequences for academic performance and energy to participate as an active member of the community. In addition, adolescent girls and women with anaemia who become pregnant are at higher risk of negative maternal and neonatal outcomes (5). Low haemoglobin concentrations can be caused by: inherited red blood cell disorders, such as sickle-cell disease and thalassaemia; dietary inadequacy; malaria; schistosomiasis; hookworm infection; HIV infection; and some noncommunicable diseases. The proportion of all anaemia associated with iron deficiency is estimated at about 50% in non-pregnant and pregnant women and 42% in children (6). Iron-deficiency anaemia occurs as a result of inadequate intakes and poor bioavailability of dietary iron. This, in turn, causes decreased concentrations iron in the blood, leading to iron deficiency and lower haemoglobin concentrations (7). Inadequate folate status can lead to adverse health consequences of public health significance, such as megaloblastic anaemia (folate-deficiency anaemia) and in adolescent girls and women an increased risk of pregnancies affected by neural tube defects (folate insufficiency) (8). Neural tube defects are associated with substantial mortality, morbidity, disability, and psychological and economic costs. Many are preventable with folic acid supplementation. Recent estimates, however, suggest that neural tube defects are still prevalent worldwide with 260 100 births with neural tube defects worldwide (prevalence 18.6/10 000 live births) occurring in 2015 alone (9).

Benefits

A 2019 Cochrane systematic review of 25 randomized or quasi-randomized trials (10 966 participants) evaluated the efficacy, effectiveness and safety of intermittent iron supplementation to reduce anaemia in adolescent and adult menstruating women (10). Overall, intermittent oral supplementation with iron in menstruating women increased haemoglobin concentration (mean difference (MD) 5.19 g/L, 95% confidence interval (CI) 3.07 to 7.32 g/L; 15 studies, 2886 participants; moderate-quality evidence) and ferritin concentration (MD 7.46 micrograms/L, 95% CI 5.02 to 9.90 micrograms/L; seven studies, 1067 participants; low-quality evidence) and reduced the risk of anaemia (risk ratio (RR) 0.65, 95% CI 0.49 to 0.87; 11 studies, 3135 participants; low-quality evidence) compared with no supplementation or placebo. For the comparison of weekly versus daily supplementation, women receiving iron supplements intermittently were as likely to have reduced anaemia at the end of the intervention as those receiving iron supplements daily (RR 1.09, 95% CI 0.93 to 1.29; eight studies, 1749 participants; moderate-quality evidence). Compared with daily supplementation, intermittent supplementation produced similar haemoglobin concentrations (MD 0.43 g/L, 95% CI −1.44 to 2.31 g/L; 10 studies, 2127 participants; low-quality evidence), lower ferritin concentrations (MD −6.07 micrograms/L, 95% CI −10.66 to −1.48 micrograms/L; four studies, 988 participants; low-quality evidence), and may reduce the risk of iron deficiency (RR 4.30, 95% CI 0.56 to 33.20; one study, 198 participants; very low-quality evidence). A secondary analysis from a randomized trial in Malaysia evaluated the effects of folic acid in weekly iron and folic acid supplements compared with iron alone on haemoglobin concentration, anaemia reduction or iron status in 311 non-pregnant women treated with 60 mg iron with no, 0.4 mg or 2.8 mg folic acid for 16 weeks (11). After 16 weeks, no significant differences were found between treatment groups for mean haemoglobin concentration or iron status. In all women, the risks of anaemia (RR 0.65, 95% CI 0.45 to 0.96) and iron deficiency based on ferritin (RR 0.30, 95% CI 0.20 to 0.44) were lower at 16 weeks than at baseline. The inclusion of folic acid in weekly iron supplementation did not reduce anaemia or improve iron status over iron supplementation alone. Data from a pre–post, longitudinal programme was used to evaluate the effectiveness of school-based weekly iron and folic acid supplementation over a 30–36 week school year in reducing anaemia and increasing haemoglobin concentrations in 1387 adolescent girls (10–19 years) in Ghana (12). A significant reduction was seen in the prevalence of anaemia over one school year of the intervention from 25.1% to 19.6%, with a corresponding increase in mean haemoglobin concentration of 0.2 g/dL. Participants consumed a mean of 16.4 tablets during the study period (range 0–36). Each additional tablet consumed over the school year was associated with a 5% reduction in the adjusted odds of anaemia at follow-up, however the relationship was non-linear. A community-based randomized trial evaluated the effect of weekly iron and folic acid supplementation for 3 months on serum ferritin, serum folate and haemoglobin concentration among 226 adolescent girls (10–19 years) in Ethiopia (13). Significant differences in haemoglobin, serum ferritin and serum folate concentrations were observed between the intervention and the control group after 3 months of supplementation. After

adjusting for confounding factors, 3-month weekly iron and folic acid supplementation was associated with significant improvements of 4.10 ng/mL in serum folate, 39.1 micrograms/L in serum ferritin and 1.2 g/dL in haemoglobin concentrations relative to the control group. Two studies compared a weekly folic acid dose (2.8 mg (14) and 4 mg (15)) with a daily dose of 0.4 mg. In both studies, the larger weekly dose was not as effective as the daily dose in raising blood folate levels above a level associated with a lower risk of neural tube defects. Another study comparing weekly folic acid doses of 2.8 mg and 0.4 mg (plus iron) found that women who received the higher folic acid dose were 7.3 times more likely to have red blood cell folate concentrations higher than the level associated with lower risk of neural tube defects (16). Adherence and compliance The 2019 Cochrane systematic review included four studies (507 participants) that examined adherence (defined as percentage of participants who consumed ≥ 70% of the prescribed dosage) to intermittent versus daily supplementation (10). Pooled meta-analysis of these studies found no difference in adherence between treatment groups (RR 1.04, 95% CI 0.99 to 1.09). Compliance outcomes for 4417 menstruating women were reported from a double-blind randomized trial in Viet Nam in which 78% of women consumed more than 80% of the preconception supplements. Women of minority ethnicity (odds ratio (OR) 0.78, 95% CI 0.67 to 0.91) and farmers (OR 0.71, 95% CI 0.58 to 0.88) were less likely to consume more than 80% of the preconception supplements. Socioeconomic status was positively associated with more than 80% adherence (OR 2.71 highest versus lowest quintile, 95% CI 2.10 to 3.52) (17). A prospective cohort study in Ghana evaluated the effectiveness of school-based weekly iron and folic acid supplementation in reducing anaemia and increasing haemoglobin concentrations in 1387 girls aged 10–19 years (12). In this study, 90% of the girls had ever consumed the tablet, and 56% had consumed at least 15 weekly tablets. The average intake adherence was about half of the available tablets. Among ever consumers, 88% of the girls liked the tablet and 27% reported undesirable changes (primarily heavy menstrual flow). A prospective cohort study in Viet Nam in 2017 followed up a cohort of 389 women of childbearing age from baseline until 6 years after the introduction of a weekly iron and folic acid (200 mg + 0.4 mg) and deworming (400 mg albendazole twice yearly) programme (18). Reduced but reasonable adherence with weekly iron and folic acid was reported after 54 and 72 months, respectively (76% and 72%), suggesting that the programme remained popular with the target population over time and adherence to once weekly supplements was maintained. Impediments to participating in the programme included interruption of supply and inadequate training of new health staff over the 6 years of implementation. Limitations of this study included a reduced participation rate in the later surveys. The study reported that this reduced participation was most likely due to the long follow-up period and the movement of some families out of the area. The relatively high loss to follow-up was acknowledged as a possible bias to estimates of adherence and effectiveness, as non-adherent women may have chosen not to take part, while healthier adherent women may have remained engaged. Adherence rates of 89% and higher have been reported in programmes supported by Nutritional International in Ethiopia, Indonesia, Kenya, Pakistan, Senegal and United Republic of Tanzania.

Harms

There are no recorded safety concerns linked to weekly iron and folic acid supplementation. Gastrointestinal side-effects from iron are well known and include black stools, nausea, constipation, abdominal cramping and vomiting. The 2019 Cochrane review reported that women receiving iron supplements intermittently were less likely to have any adverse effects than those receiving iron supplements daily (RR 0.41, 95% CI 0.21 to 0.82; six studies, 1166 participants; moderate-quality evidence) (10). Some concerns are emerging about potential interactions with antimalarial drugs and folic acid supplementation. A protocol for a Cochrane review to examine the effects of folic acid supplementation, at various doses, on the risk of malaria infection and severity in people living in areas with various degrees of malaria endemicity has been published (19). Currently available evidence focuses on sulfadoxine + pyrimethamine, which is frequently used to prevent and treat malaria in endemic malarial areas and works by inhibiting folate synthesis in the parasite (20). Evidence has shown that Plasmodium parasites can use exogenous folic acid salvaged from the host (21). At higher intakes, folic acid passes into the circulation unmetabolized and may reduce the efficacy of antifolate drugs, such as sulfadoxine + pyrimethamine. The effect of folic acid on the therapeutic efficacy of sulfadoxine + pyrimethamine against Plasmodium infection has been examined in many studies in sub-Saharan Africa. In two studies of children aged 6 months to 9 years (22,23), folic acid supplementation at doses ranging from 1 mg to 10 mg daily increased the risk of parasitological failure with sulfadoxine + pyrimethamine. In a study of all age groups, folic acid reduced the time to treatment failure as assessed by parasitological examination (24). In a study of pregnant women in Kenya with Plasmodium infection, daily supplementation with 5 mg folic acid doubled the risk of treatment failure with sulfadoxine + pyrimethamine at 14 days, while a dose of 0.4 mg a day did not increase the risk of treatment failure (25). Another study of pregnant women in the Gambia found that folic acid supplementation in doses of 0.5 mg to 1.5 mg a day did not affect the efficacy of intermittent sulfadoxine + pyrimethamine in preventing malaria (26).

Cost / cost effectiveness

Cost–effectiveness data for weekly iron and folic acid supplementation using the proposed formulation are not currently

available. The United Nations Children's Fund (UNICEF) supply catalogue currently lists the 60 mg + 2.8 mg formulation at an indicative price of US$ 1.56 for a bottle of 100 tablets. In comparison the UNICEF supply catalogue indicative price for the 60 mg + 0.4 mg formulation is US$ 0.84 for a bottle of 100 tablets (30).

WHO guidelines

The 2011 WHO guidelines for intermittent iron and folic acid supplementation include a strong recommendation for use of this supplementation as a public health intervention in menstruating women living in areas where anaemia is highly prevalent, to improve their haemoglobin concentrations and iron status and reduce the risk of anaemia (27). The suggested dose is 60 mg elemental iron plus 2.8 mg folic acid, once a week for 3 months, followed by 3 months of no supplementation. The 2016 WHO guidelines on antenatal care for a positive pregnancy experience include a context-specific recommendation for use of intermittent oral iron and folic acid supplementation (120 mg of elemental iron plus 2.8 mg folic acid) once a week for pregnant women to improve maternal and neonatal outcomes, if daily iron is not acceptable due to side-effects and in populations with an anaemia prevalence in pregnant women of less than 20% (28). In 2018, WHO published guidance that summarized the global evidence-informed recommendations that address malnutrition in all its forms in adolescents with the aim of ensuring healthy lives and well-being in this group. In this guidance, intermittent iron and folic acid supplementation is included as one of eight evidence-based nutrition interventions and policies that could affect adolescent nutrition. This guidance draws on the recommendation made by the 2011 guidance described above for menstruating adolescent girls and women (29).

Availability

Market availability of the 60 mg + 2.8 mg formulation of iron and folic acid has been limited but has recently improved. There are currently two approved suppliers of the formulation supplied by UNICEF, who have provided nearly 1.2 million bottles of the supplement since 2019.

1. 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; 2013. (WHO Technical Report Series, No. 985; https://apps.who.int/iris/handle/10665/112729, accessed 6 October 2023).
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015 (WHO Technical Report Series, No. 994; https://apps.who.int/iris/handle/10665/189763, accessed 6 October 2023).
3. Global Health Observatory. Prevalence of anaemia in non-pregnant women (aged 15-49) (%) [internet]. Geneva: World Health Organization; –2021 (https://www.who.int/data/gho/data/indicators/indicator-details/GHO/anaemia-in-non-pregnant-women-prevalence-(-) , accessed 6 October 2023).
4. Yang F, Liu X, Zha P. Trends in socioeconomic inequalities and prevalence of anemia among children and nonpregnant women in low- and middle-income countries. JAMA Netw Open. 2018;1(5):e182899.
5. James PT, Wrottesley SV, Lelijveld N, Brennan E, Fenn B, Menezes R, et al. Women's nutrition: a summary of evidence, policy and practice including adolescent and maternal life stages. Oxford: Emergency Nutrition Network; 2022 (https://www.ennonline.net/womensnutritionasummarytechnicalbriefingpaper, accessed 6 October 2023).
6. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. Lancet Glob Health. 2013;1(1):e16–25.
7. Stoltzfus RJ. Iron interventions for women and children in low-income countries. J Nutr. 2011;141(4):756s–62s.
8. Rogers LM, Cordero AM, Pfeiffer CM, Hausman DB, Tsang BL, De-Regil LM, et al. Global folate status in women of reproductive age: a systematic review with emphasis on methodological issues. Ann N Y Acad Sci. 2018;1431(1):35–57.
9. Blencowe H, Kancherla V, Moorthie S, Darlison MW, Modell B. Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis. Ann N Y Acad Sci. 2018;1414(1):31–46.
10. Fernández-Gaxiola AC, De-Regil LM. Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women. Cochrane Database Syst Rev. 2019;1(1):CD009218.
11. Samson KLI, Loh SP, Lee SS, Sulistyoningrum DC, Khor GL, Mohd Shariff ZB, et al. The inclusion of folic acid in weekly iron–folic acid supplements confers no additional benefit on anemia reduction in nonpregnant women: a randomized controlled trial in Malaysia. J Nutr. 2021;151(8):2264–70.
12. Gosdin L, Sharma AJ, Tripp K, Amoaful EF, Mahama AB, Selenje L, et al. A school-based weekly iron and folic acid supplementation program effectively reduces anemia in a prospective cohort of Ghanaian adolescent girls. J Nutr. 2021;151(6):1646–55.
13. Handiso YH, Belachew T, Abuye C, Workicho A, Baye K. A community-based randomized controlled trial providing weekly iron-folic acid supplementation increased serum-ferritin,-folate and hemoglobin concentration of adolescent girls in southern Ethiopia. Sci Rep. 2021;11(1):1–7.
14. Norsworthy B, Skeaff CM, Adank C, Green TJ. Effects 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.
15. Hao L, Yang Q-H, Li Z, Bailey LB, Zhu J-H, 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.
16. Samson KLI, Loh SP, Lee SS, Sulistyoningrum DC, Khor GL, Shariff ZBM, et al. Weekly iron–folic acid supplements containing 2.8 mg folic acid are associated with a lower risk of neural tube defects than the current practice of 0.4 mg: a randomised controlled trial in Malaysia. BMJ Glob Health. 2020;5(12):e003897.
17. Gonzalez-Casanova I, Nguyen PH, Young MF, Harding KB, Reinhart G, Nguyen H, et al. Predictors of adherence to micronutrient supplementation before and during pregnancy in Vietnam. BMC Public Health. 2017;17(1):1–9.
18. Casey GJ, Tinh TT, Tien NT, Hanieh S, Cavalli-Sforza LT, Montresor A, et al. Sustained effectiveness of weekly iron-folic acid supplementation and regular deworming over 6 years in women in rural Vietnam. PLoS Negl Trop Dis. 2017;11(4):e0005446.
19. Crider K, Williams J, Qi YP, Gutman J, Yeung L, Mai C, et al. Folic acid supplementation and malaria susceptibility and severity among people taking antifolate antimalarial drugs in endemic areas. Cochrane Database Syst Rev. 2022(2):CD01421.

20. Verhoef H, Veenemans J, Mwangi MN, Prentice AM. Safety and benefits of interventions to increase folate status in malaria-endemic areas. Br J Haematol. 2017;177(6):905–18.
21. Nzila A, Ward SA, Marsh K, Sims PFG, Hyde JE. Comparative folate metabolism in humans and malaria parasites (part I): pointers for malaria treatment from cancer chemotherapy. Trends Parasitol. 2005;21(6):292–8.
22. Mulenga M, Malunga P, Bennett S, Thuma P, Shulman C, Fielding K, et al. Folic acid treatment of Zambian children with moderate to severe malaria anemia. Am J Trop Med Hyg. 2006;74(6):986–90.
23. Van Hensbroek MB, Morris-Jones S, Meisner S, Jaffar S, Bayo L, Dackour R, et al. Iron, but not folic acid, combined with effective antimalarial therapy promotes haematological recovery in African children after acute falciparum malaria. Trans R Soc Trop Med Hyg. 1995;89(6):672–6.
24. Carter JY, Loolpapit MP, Lema OE, Tome JL, Nagelkerke NJD, Watkins WM. Reduction of the efficacy of antifolate antimalarial therapy by folic acid supplementation. Am J Trop Med Hyg. 2005;73(1):166–70.
25. Ouma P, Parise ME, Hamel MJ, Kuile FOt, Otieno K, Ayisi JG, et al. A randomized controlled trial of folate supplementation when treating malaria in pregnancy with sulfadoxine-pyrimethamine. PLoS Clin Trials. 2006;1(6):e28.
26. Mbaye A, Richardson K, Balajo B, Dunyo S, Shulman C, Milligan P, et al. Lack of inhibition of the anti-malarial action of sulfadoxine-pyrimethamine by folic acid supplementation when used for intermittent preventive treatment in Gambian primigravidae. Am J Trop Med Hyg. 2006;74(6):960–4.
27. Guideline: intermittent iron and folic acid supplementation in menstruating women. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/handle/10665/44649, accessed 6 October 2023).
28. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250796, accessed 6 October 2023).
29. Guideline: Implementing effective actions for improving adolescent nutrition. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/260297, accessed 6 October 2023).
30. UNICEF Supply Catalogue [internet]. Copenhagen: UNICEF Supply Division; 2023 (https://supply.unicef.org/all-materials.html, accessed 6 October 20