F.4	Ferrous salt + folic acid – tablet containing 60 mg elemental iron + 2.8 mg folic acid – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Both interventions have a body of evidence that suggests that these will provide several desirable benefits in the target populations, with low costs, feasibility, and minimal burden to the health systems as well as none / trivial harms.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Globally, 29% of non-pregnant women of reproductive age (WRA) (age 15-49 years) suffer from anaemia. WRA in Southeast Asia and Africa suffer the highest burden (46% and 40% respectively). The prevalence of folate deficiency is estimated to be greater than 20% in many countries with lower income economies. Neural tube defects (NTDs) remain prevalent worldwide with 260,100 NTD- affected birth outcomes worldwide (prevalence 18.6 (15.3-23.0)/10,000 live births) occurring in 2015 alone.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: One Cochrane review (2019) including 25 RCTs and 10,996 participants found that for the prevention and reduction of anaemia in menstruating women, compared with daily supplementation, data shows that intermittent weekly iron supplementation has a similar effect in reducing the prevalence of anaemia and increasing haemoglobin levels (low to moderate certainty). For the use of folic acid, when comparing weekly doses specifically, women taking 2.8 mg of folic acid per week, compared to 0.4 mg of folic acid per week, were 7.3 times more likely to have RBC folate concentrations above a level associated with lower risk of NTDs. This was based on two RCTs and one pre-post study assessed in the WHO submission.

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The body of evidence suggest that there are no harms concerns from WIFAS. There are some side effects associated with taking WIFAS related to iron. These can include black stools, nausea, constipation, abdominal cramping, and vomiting. However, these side effects are typically reported only in the first few weeks of use and normally decrease over time. The 2019 Cochrane review on intermittent iron supplementation reported that women receiving iron supplements intermittently were less likely to have any adverse side effects than those receiving iron supplements daily (RR 0.41, 95% CI 0.21 to 0.82; 6 studies, 1166 participants; moderate-quality evidence).
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: There is a concern with very low certainty that treatment with folic acid might interfere with anti-malarial treatment, but there is currently no evidence that an IFA supplement containing 2.8 mg/folic acid given once weekly to non-pregnant adolescent girls or women would interfere with the efficacy of anti-malarial treatment.
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments: No special needs were detected to the administration of these interventions other than the adequate distribution in remote or difficult areas. No specific health training is required.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: Existing data shows that WIFAS is a low-cost and cost-effective intervention for addressing anaemia, particularly when programmes are taken to scale to cover a larger number of beneficiaries, and are built on existing health, education, or outreach programmes. For instance, in Viet Nam in 2011 it was achieved with an annual cost of US$ 0.76 per woman.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Both iron and folic acid supplements are currently on the EML for adults. In some countries, manufacturers of supplements must be registered entities and certified to adhere to good manufacturing practices.

Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: The proposed medicine of 60 mg iron and 2.8 mg folic acid is in the current WHO Guideline: "Guideline: Intermittent iron and folic acid supplementation in menstruating women" (2011); and in "Guideline: Implementing effective actions for improving adolescent nutrition" (2018). This guidance reads: "Intermittent iron and folic acid supplementation is recommended as a public health intervention in menstruating adolescent girls and women living in settings where anaemia is highly prevalent, to improve haemoglobin concentration and iron status and reduce the risk of anaemia in populations where the prevalence of anaemia among non-pregnant adolescent girls and women (15-49 years of age) is 20% or higher"