Multiple micronutrient powder

Section: 27. Vitamins and minerals

EMLc | ATC codes: A11AA01

Indication	Iron deficiency anaemia ICD11 code: 3A00.Z
Medicine type	Chemical agent
List type	Core
Formulations	Sachets containing: - iron (elemental) 12.5 mg (as coated ferrous fumarate) - zinc (elemental) 5 mg - vitamin A 300 micrograms - with or without other micronutrients at recommended daily values
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Children (1 month - 12 years)
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Multiple micronutrient powder

Expert Committee recommendation

The Committee recommended the addition of multiple micronutrient powders to the core list of the EMLc for the prevention of anaemia in infants and children in populations where anaemia is a public health problem. Use should be in line with the recommendations in current WHO guidelines for point-of-use fortification of foods.

Background

The application requested the inclusion of multiple micronutrient powders (MNP) for the prevention of anaemia in infants and children on the core list of the EMLc. Multiple micronutrient powders had not previously been considered for inclusion on the EMLc.

Public health relevance

The global prevalence of anaemia worldwide for pre-school children in 2011 was 43% or an estimated 273 children, of which about 42% is attributable to iron deficiency (1). Anaemia in early childhood reduces cognitive ability and causes developmental delays and disability (1). Currently, epidemiological and experimental data suggest that in order to minimize these risks, prevention of anaemia is preferred over treatment because the physiological impairments due to deficiency start at an early age and they may be irreversible, even after repletion of iron stores (2). There are no direct estimates for prevalence of zinc deficiency; however, it is believed to be as prevalent as iron deficiency affecting approximately 293 million children under five and is responsible for 13% of lower respiratory tract infections (primarily pneumonia and influenza) (3). Amongst children under 5 years of age globally, an estimated 190 million have vitamin A deficiency. The prevalence of vitamin A deficiency is about 44% amongst children in Africa and about 50% in children in South-East Asia. Vitamin A deficiency associated with prevalence of night blindness is around 2% in African children, and about 0.5% in children in parts

of South-East Asia (3). Deficiencies of vitamins and minerals such as iron, zinc, vitamin A and others, often occur simultaneously in children due to factors such as poor nutritional status (3). The effects of these deficiencies in neonates can result in serious adverse events including mortality. Furthermore, the effects of these deficiencies in childhood may result in long-term, life-long irreversible physical and cognitive problems that lead to negative consequences for health and economic opportunities. Mineral and vitamin deficiencies particularly in iron, zinc and vitamin A, among other nutritional risk factors, are determined to be responsible for 3.9 million deaths (35% of total deaths) in children under the age of 5 years annually. These deficiencies are also responsible for 144 million disability-adjusted life years in the same population (3).

Benefits

Evidence for the effectiveness of MNP comes from two systematic reviews that informed the development of the 2016 WHO Guidelines for use of multiple micronutrient powders for point-of-use fortification of foods consumed by infants and young children 6 to 23 months and children 2 to 12 years (4). A 2011 Cochrane systematic review of 15 randomized and quasirandomized trials (12 239 participants) evaluated the effects and safety of point-of-use fortification of foods with MNP for infants and young children from 6 to 23 months of age. The trials were conducted in low- and middle-income countries (LMICs) in Asia, Africa and the Americas. Six studies were conducted in malaria-endemic areas. Most trials were assessed as having a low risk of bias (5). The Guideline Development Group reported that infants and young children from 6 to 23 months of age who consumed foods fortified at the point-of-use with multiple micronutrients powders had a lower risk for the critical outcome of anaemia, with a 26% reduction compared to placebo or no intervention (risk ratio (RR) 0.74, 95%CI 0.66 to 0.83; 10 studies; 2802 participants, high quality evidence). They also had a lower risk for the critical outcome of iron deficiency, with a 52% reduction (RR: 0.48, 95%CI 0.36 to 0.62; five studies; 796 participants, moderate quality evidence). Compared to no treatment or placebo, children receiving multiple micronutrient powders had a 5.12 g/L higher haemoglobin concentration at follow-up (mean difference (MD) 5.12 g/L, 95%CI 2.70 to 7.54; 12 studies; 3565 participants, low quality evidence). With respect to iron status, compared to no treatment or placebo, children receiving multiple micronutrient powders had an average increase in serum ferritin concentration of 16.47 µg/L at follow up (MD: 16.47 µg/L, 95%CI 3.03 to 29.91; three studies; 694 participants, very low quality evidence). Regarding weight-for-age z-score, the mean difference was minimal (MD: 0.04 in z-score, 95%CI –0.13 to 0.21; four studies; 606 participants, low quality evidence) (4). A second Cochrane systematic review of 12 randomized and quasirandomized trials (5720 participants) assessed the effects and safety of point-of-use fortification of foods with MNP for children aged from 2 to 12 years. The trials were conducted in low- and middle-income countries in Asia, Africa and the Americas. Most trials were assessed as having a low risk of bias (6). The Guideline Development Group reported that children aged 2 to 12 years receiving iron-containing multiple micronutrient powders for point-of-use fortification of foods were significantly less likely to have anaemia at follow-up than those children receiving no intervention or a placebo (prevalence ratio (PR) 0.66, 95%CI 0.49 to 0.88; 10 studies, 2448 participants, moderate quality evidence). These children also had a 3.37 g/L higher haemoglobin concentration at follow-up (MD 3.37 g/L, 95%CI 0.94 to 5.80; 11 studies; 2746 participants, low quality evidence). Also, children receiving iron-containing multiple micronutrient powders for point-of-use fortification of foods were significantly less likely to have iron deficiency at follow up than those children receiving no intervention or a placebo (PR 0.35, 95%CI 0.27 to 0.47; five studies; 1364 participants, moderate quality evidence). With respect to ferritin concentrations, children receiving iron-containing multiple micronutrient powders had, on average, 0.42 µg of ferritin more per litre at follow-up than those children receiving no intervention or a placebo (standardized mean difference (SMD): 0.42 µg/L, 95%CI –4.36 to 5.19; three studies; 1066 participants, very low quality evidence) (4).

Harms

In the systematic review on MNP in infants and young children, data on morbidity, other indicators of vitamin and mineral status and side-effects were scarce due to a lack of standardization; however, none of the trials reported deaths attributable to the intervention and there was no difference regarding the patterns of morbidity between children receiving placebo or no intervention and the ones receiving MNP. Only one of the studies conducted in

malaria-endemic areas reported results related to malaria and found no difference in the presence of positive malaria smears between the groups (RR 0.24, 95%CI 0.05 to 1.12; 194 children). None of the trials reported on the outcome of all-cause mortality (5). In the systematic review on MNP in older children, only one trial reported on the outcome of all-cause mortality and there were no deaths reported during this trial (MD 0, 95%CI –0.03 to 0.03; one study; 115 participants, low quality evidence). Finally, diarrhoea (three liquid stools or more per day) was reported by two trials and children receiving iron-containing MNP were as likely to have diarrhoea at follow-up as those children receiving no intervention or a placebo (RR 0.97, 95%CI 0.53 to 1.78; two studies; 366 participants, moderate quality evidence) (6). A 2016 Cochrane systematic review evaluated the effects and safety of iron supplementation (including MNP), with or without folic acid, in children living in areas with hyperendemic or holoendemic malaria transmission. The review found that overall, iron does not cause an excess of clinical malaria (RR 0.93, 95%CI 0.87 to 1.00; 14 trials, 7168 children, high quality evidence). Iron probably does not cause an excess of clinical malaria in both populations where anaemia is common and those in which anaemia is uncommon. In areas where there are prevention and management services for malaria, iron (with or without folic acid) may reduce clinical malaria (RR 0.91, 95%CI 0.84 to 0.97; seven trials, 5586 participants, low quality evidence), while in areas where such services are unavailable, iron (with or without folic acid) may increase the incidence of malaria, although the lower CIs indicate no difference (RR 1.16, 95%CI 1.02 to 1.31; nine trials, 19 086 participants, low quality evidence). Iron supplementation does not cause an excess of severe malaria (RR 0.90, 95%CI 0.81 to 0.98; 6 trials, 3421 children, high quality evidence). Iron resulted in fewer anaemic children at follow up, and the end average change in haemoglobin from base line was higher with iron (7).

Cost / cost effectiveness

The current listed price of the MNP provided by UNICEF Supply Catalogue website is US$ 0.62 to US$ 0.65 per pack (30 sachets) (8). The composition of the UNICEF supplied product differs from the composition of MNP proposed for inclusion on the EMLc with regard to the amount of iron, vitamin A and zinc, and the inclusion of 12 additional micronutrients. The World Bank estimated the annual cost of MNP intervention at US$ 3.60 per child aged 12 to 23 months (9). A Copenhagen Consensus review found that micronutrient interventions were cost-effective in general (10). It has also been estimated that iron-containing MNP recover US$ 37 for every US$ 1 invested due to the positive effects of addressing childhood anaemia among children aged 6 to 23 months (11).

WHO guidelines

The 2016 WHO Use of multiple micronutrient powders for point-of-use fortification of foods consumed by infants and young children 6–23 months and children 2–12 years (4) make the following recommendations with regard to MNP: – In populations where anaemia is a public health problem, point-of-use fortification of complementary foods with iron-containing micronutrient powders in infants and young children aged 6 to 23 months is recommended, to improve iron status and reduce anaemia (strong recommendation, moderate quality evidence). – In populations where anaemia is a public health problem, point-of-use fortification of foods with iron containing micronutrient powders in children aged 2 to 12 years is recommended, to improve iron status and reduce anaemia (strong recommendation, moderate quality evidence).

Availability

The following manufacturers were identified in 2016 by UNICEF Supply Division’s Multiple Micronutrient Powder Supply & Market Outlook as meeting standards (i.e. good manufacturing practice) and having the capacity to provide suitable, age-appropriate dose forms and strengths of multiple micronutrient powders for administration to infants and children (12): 1. DSM Europe (Switzerland) 2. DSM (Malaysia) – formerly Fortitech 3. Renata (Bangladesh) 4. Piramal (India) 5. DSM (South Africa)

Other considerations

The Committee noted the information provided in the application regarding the submission for MNP to be included in the United States Pharmacopoeia (USP), including a draft of the approved product monograph, which will take

effect in May 2019.

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