A.22 (item number)	**Multiple micronutrient supplement - antenatal supplement** (application title)
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Many women of reproductive age in LMIC experience micronutrients deficiency. Each micronutrient components of the MMS have important role individually or in-synergy in pregnancy and foetal growth and development; deficiency of each component is associated with some negative effect on the maternal and infant.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Most of the micronutrients were already included individually in the model list with indication for deficiency; iron and folic acid are currently the only components indicated for nutritional anaemia complicating pregnancy, childbirth and puerperium in the EML. Vitamin C also provides a positive effect on iron metabolism Vitamin D supports the absorption of calcium, which is essential for foetal bone development and growth. When combined with folic acid, B12 supplementation can reduce the risk of spina bifida and other central nervous system defects
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable *Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).* The evidence included a 2019 Cochrane Systematic Review involving 19 trials and an Individual Patient Data Meta-analysis involving 15 trials. The Cochrane SR reported that MMS reduced the risk of small-for-gestational age and low birth weight, while the IPD Meta-analysis reported that MMS reduces the risk of stillbirth, mortality among 6-month infants, low birth weight (<2500g), preterm (<37 weeks) birth, and the risk of being born small-for-gestational age. However, from 19 trials involved in the two meta-analyses, only 10 used the UNIMMAP formulation as proposed in this application. *Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?* All the 21 trials were conducted in LMIC. The Cochrane review suggests the effect on SGA and low birth weight was only observed in populations with better nutritional status. The IPD Meta-analysis revealed the evidence of larger benefits of MMS among women who were anaemic.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Data on safety and adverse effects were based on the 2019 Cochrane Systematic Review and two trials that were statistically powered to analyse the effect on early infant mortality.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable since the benefit is high with very minimal adverse effects.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	High quality of evidence that MMS reduce the risk of low-birth-weight dan doesn't affect the risk of perinatal mortality, neonatal mortality and still birth. Moderate quality of evidence that MMC reduce the risk of small for gestational age dan doesn't affect the risk of preterm birth. Kaets EC et al. Cochrane Systematic Review 2019.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments:
Are you aware of 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: All the 15 nutrient components are widely available and used globally either individually or in combination. However, the regulation is differed from country to country either as food supplement or therapeutic product.

Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: MMS is currently recommended for use in pregnant women in four World Health Organization (WHO) guidelines: • The guidelines for pregnant women in emergency settings in Preventing and controlling micronutrient deficiencies in populations affected by an emergency • For pregnant women with tuberculosis in Micronutrient supplementation in individuals with active tuberculosis. • For pregnant women who are in food insecure areas by UNICEF and the World Food Programme (WFP) in their guidance on Protecting Maternal Diets and Nutrition Services and Practices in the Context of COVID-19. • In the recent update to the WHO antenatal care recommendations for a positive pregnancy experience.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	It is highly cost-effective as proven in a study which model the intervention in 3 South Asian LMIC (India, Pakistan, Bangladesh) and additional modelling has been done in 29 countries. Also in another study which analysed its implementation in Bangladesh and Burkina Faso.
Any additional comments	

Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	It is strongly recommended to be included in the model list since it has been proven to be very cost effective with minimal adverse effects and could affecting a large number of population in LMIC.
References (if required)	Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database Syst Rev. 2019;3:CD004905