F.2 Phytomenadione – mixed micelle formulation – EML and EMLc

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Vitamin K is well known as an essential factor in blood coagulation. Vitamin K is indicated for the prevention of hemorrhagic disease in newborns or as an antidote to correct vitamin K antagonist overshooting or poisoning, since vitamin K antagonists are also used as rodenticides. In newborns, there is a risk of hypovitaminosis, as they have low vitamin K reserves (vitamin K is not efficiently transported across the placenta), vitamin K levels are low in breast milk and gastrointestinal absorption is immature. Formula-fed infants are protected from VKDB, because vitamin K content of milk formula is typically 50-fold higher than human milk, providing average daily intakes of approximately 50 µg of vitamin K. In line with these findings, exclusively breast-fed infants are more susceptible to the development of vitamin K hypovitaminosis than formula-fed children. The human infant is therefore exposed to a small but potentially life-threatening risk of vitamin K deficiency bleeding (VKDB). It presents as unexpected bleeding, often with gastrointestinal hemorrhage, ecchymosis and, in many cases, intracranial hemorrhage. Early VKDB has been associated with mothers on anticonvulsants or other vitamin K interfering substances, and incidence without vitamin K supplementation has been reported as high as 12 %. It has been suggested that preterm infants have an even greater risk of vitamin K deficiency. Prophylaxis with vitamin K markedly decreased the vitamin K deficiency in new-born babies. Importantly, the effect of vitamin K administration on coagulation normalization is very rapid. VKDB is rare after intramuscular prophylaxis, with a reported incident in epidemiological surveillance studies of ~1/100.000 births. Oral administration is preferred in most cases. Phytonadione (vitamin K1) has a black box warning due to severe anaphylaxis when given IV that may cause shock, respiratory arrest, and cardiac arrest. Phytomenadione is already classified as essential medicine. The difference between the new formula and the old one lies mainly in the composition of the solution, notably the nature of the excipients used. The previous formulation of phytomenadione used different excipients, such as polysorbate 80 and propylene glycol, which have been associated with adverse effects, including allergic reactions and increased blood viscosity. The current “new” version (mixed micellar solution - MM) is formulated as a mixed micellar solution, where the phytomenadione is solubilized in a combination of sodium glycocholate and lecithin in an aqueous solution, with formulation without preservatives or potentially problematic excipients. The benefits of the new formula, improved absorption of vitamin K_1, particularly orally and is suitable for infants and young children. A significant/major advantage of MM solution as a dosage form is that it can also be administered orally like tablets but allows more precise and flexible adjustment of the dose to be administered. When MM phytomenadione was administered orally to fully breast-fed neonates, it was absorbed more rapidly than the comparator formulation and was well tolerated. Intramuscular injection of phytomenadione MM is a simple, fast and safe alternative for neonatal prophylaxis, especially in world regions with limited health care systems, where there is a risk of incomplete oral prophylaxis. Phytomenadione MM is safer than the comparator formulation when injected intravenously.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**) Phytomenadione	☒ Yes ☐ No ☐ Not applicable

25th WHO Expert Committee on Selection and Use of Essential Medicines
Expert review

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
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
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☐ Yes ☒ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval?	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable