Phytomenadione

Section: 10. Medicines affecting the blood > 10.2. Medicines affecting coagulation

EMLc | Codes ATC: B02BA01

Indication	Haemorrhagic or haematological disorders of fetus or newborn Code ICD11: KA8Z
INN	Phytomenadione
Type de médicament	Chemical agent
Type de liste	Liste de base
Formulations	**Parenteral > General injections > IV:** 10 mg per mL in ampoule (EMLc) ; 1 mg per mL in ampoule (EMLc) ; 2 mg per 0.2 mL in ampoule mixed micelle solution (EMLc) ; 10 mg per mL in ampoule mixed micelle solution (EMLc) ; 1 mg per 0.5 mL in ampoule (EMLc)
Historique des statuts LME	Ajouté pour la première fois en 1977 (TRS 615) Modifié en 1979 (TRS 641) Modifié en 2007 (TRS 950) Modifié en 2025 (TRS 1064)
Sexe	Tous
Âge	Nouveau-né (< 1 mois)
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Wikipédia	Phytomenadione
DrugBank	Phytomenadione (Phylloquinone)

Recommandation du comité d'experts

The Expert Committee noted that phytomenadione is currently included in the Model Lists as oral and injectable formulations as an essential medicine for prophylaxis and treatment of haemorrhagic disease of newborns and for treatment and prophylaxis of haemorrhage due to severe hypoprothrombinaemia. The proposed new formulation is a mixed micelle solution formulation that can be administered intravenously, intramuscularly or orally. It has enhanced solubility and bioavailability, and faster and more reliable onset. The Committee considered that the proposed formulation represents an additional effective treatment option that offers flexibility for administration with evidence of comparable efficacy and safety to currently listed formulations. In the case of haemorrhagic disease of newborns, it allows single-dose intramuscular injection at birth, which is crucial in settings where follow-up for multi-dose oral regimens is unreliable. The Expert Committee therefore recommended the inclusion of the proposed mixed micelle formulation of phytomenadione on the EML and EMLc for the same indications for which the existing formulations are currently listed. Following the review of the age-appropriateness of formulations on the EMLc, the Expert Committee recommended the addition of phytomenadione (standard) injection 1 mg/0.5 mL and phytomenadione 5 mg tablets to the EMLc. Due to unavailability, the Expert Committee also recommended the deletion of phytomenadione 10 mg tablets from the EML and EMLc.

Contexte

The proposed formulation of phytomenadione had not been previously evaluated for inclusion on the Model Lists. The Model Lists currently include standard injection and oral dosage forms of phytomenadione.

Pertinence pour la santé publique

The public health relevance of phytomenadione in the prevention and treatment of vitamin K deficiency bleeding in newborns, and for prevention and treatment of haemorrhage due to severe hypoprothrombinaemia due to various causes is well established. Phytomenadione has been included on the Model Lists for these indications since the first list was published in 1977.

Bénéfices

The application presented summaries of four published reports in which phytomenadione mixed micelle solution was compared with existing phytomenadione formulations in paediatric patients. A 1998 randomized controlled trial compared orally administered phytomenadione MM with a standard intramuscular preparation during the first 8 weeks of life in 156 exclusively breastfed infants (1). Participants were randomized to receive 2 mg oral phytomenadione (n = 79) or 1 mg intramuscular phytomenadione (n = 77) at birth, with additional oral doses at 7 and 30 days. Prothrombin time, plasma vitamin K1 and protein induced by vitamin K absence/antagonism-II (PIVKA-II) were monitored at 14, 30 and 56 days. Prothrombin times did not differ between the two groups. Plasma vitamin K1 levels were higher in the oral group at 14 days and 56 days. PIVKA-II levels were raised in 47% of infants at birth but normalized by 14 days in both groups, with no raised values at 30 days and only three raised values in the intramuscular group at 56 days. A 1997 randomized study examined the pharmacokinetics of two orally administered phytomenadione preparations in 30 exclusively breastfed newborns (2). Concentrations of vitamin K, PIVKA-II and total bound bilirubin were measured at 24 hours, 4 days and 24 days after birth. Median plasma vitamin K1 levels were higher in the MM group at all time points but was only significantly different at 4 days. PIVKA-II was detectable in fewer infants in the MM group at 24 hours (21% versus 75%) and 4 days (14% versus 50%). No infants had detectable PIVKA-II at 24 days. A 1992 study evaluated the pharmacokinetics and safety phytomenadione MM and standard phytomenadione administered parenterally in 71 infants with chronic cholestasis (3). The study found no significant differences between treatment groups in blood parameters, including total and conjugated bilirubin, transaminases, gamma-glutamyl transferase and alkaline phosphatase. Both formulations were well tolerated. Among nine infants with biliary atresia randomized to receive a single oral dose of 20 mg phytomenadione (n = 3) or 20 mg phytomenadione MM (n = 3) or 10 mg of phytomenadione MM administered intramuscularly. (n = 3), low serum vitamin K1 levels of were observed after oral phytomenadione. However, the same dose of oral phytomenadione MM or 10 mg intramuscular phytomenadione MM both resulted in very high serum vitamin K1 levels. No adverse events were reported. Long-term administration was also investigated in this study: 22 infants and children received 10 mg phytomenadione intramuscularly twice a week for 6 months, followed by 10 mg oral or intramuscular phytomenadione MM for an additional 3 months. The highest vitamin K levels were observed in the intramuscular group. A 2003 surveillance study in Germany assessed the efficacy of oral phytomenadione MM versus other oral phytomenadione preparations in preventing late vitamin K deficiency bleeding (4). Between 1997 and 2000, about 1.8 million and 1.3 million newborns were exposed to phytomenadione MM and other phytomenadione formulations, respectively. In total, 29 infants had confirmed vitamin K deficiency bleeding, of whom 17 had been given recommended doses of phytomenadione: seven received the MM formulation, nine received other formulations and one received both. The rate of late vitamin K deficiency bleeding was 0.44 per 100 000 (95% confidence intervale (CI) 0.19 to 0.87 per 100 000) in children given the MM formulation compared with 0.76 per 100 000 (95% CI 0.36 to 1.39 per 100 000) in children given other preparations. No significant differences were seen between the formulations. However, the MM formulation was effective in maintaining adequate vitamin K levels and preventing vitamin K deficiency bleeding. The application also presented summaries of nine unpublished clinical studies conducted by F. Hoffman-LA Roche that included 182 infants treated with oral, intramuscular or intravenous phytomenadione MM compared with existing phytomenadione formulations. The application presented a summary of one published report in which phytomenadione MM solution was compared with existing phytomenadione formulations in adults. The pharmacokinetics and tolerance of intravenous and intramuscular phytomenadione MM were evaluated in 30

healthy adult volunteers in a 1996 study using an open randomized crossover design (5). Participants received phytomenadione 10 mg via intravenous or intramuscular injection, and blood samples were collected up to 12 hours after intravenous injection and up to 72 hours after intramuscular injection. Phytomenadione MM was well tolerated after both routes of administration. Systemic availability following intramuscular administration was less than 65% in 20% of participants, indicating irregular and unpredictable absorption from the depot site.

Torts

Adverse events associated with phytomenadione formulations were evaluated in a worldwide post-marketing surveillance programme (6). Data were collected from spontaneous reports, clinical trials, and post-marketing surveillance. Between 1974 and 1995, an estimated 635 million adults and 728 million children were prescribed phytomenadione formulations. A total of 404 adverse events were reported in 286 individuals, 387 of which were associated with standard phytomenadione formulations. Most of the serious adverse events (117/120) were associated with standard formulations, including 85 probable anaphylactoid reactions (six fatal). Most of the adverse events with phytomenadione MM were minor injection-site reactions (13/17). The application also presented summaries of various unpublished clinical studies conducted by F. Hoffman-LA Roche in adults and children that suggested an acceptable safety profile for phytomenadione MM.

Rapport coût/efficacité

The application reported that the price per ampoule of phytomenadione MM ranges from 0.26 United States dollars (US$) to US$ 3.00 (mean US$ 1.63) for the 2 mg/0.2 mL strength, and from US$ 0.35 to US$ 4.00 (mean US$ 2.18) for the 10 mg/mL strength. Average treatment costs were reported in the application as US$ 3.26 per dose in paediatric patients and US$ 2.18 per dose in adults.

Directives de l'OMS

The WHO recommendations on newborn health include a strong recommendation (moderate-quality evidence) for all newborns to be given 1 mg of vitamin K intramuscularly after birth (after the first hour during which the infant should be in skin-to-skin contact with the mother and breastfeeding should be initiated). The guidelines also include a strong recommendation (moderate-quality evidence) for neonates at especially high risk of bleeding, e.g. requiring surgical procedures, those with birth trauma, preterm newborns and those exposed in utero to maternal medication known to interfere with vitamin K, to be given 1 mg vitamin K intramuscularly (7).

Disponibilité

Phytomenadione MM formulation has wide global regulatory approval. It is actively marketed in more than 40 countries, with ongoing registration processes reported in additional countries. The application reported that it is provided to non-profit organizations such as United Nations Children’s Fund and Médecins Sans Frontières.

Autres considérations

Changes to the listing of phytomenadione were also considered as part of the review of the age-appropriateness of formulations for children.

1. Greer FR, Marshall SP, Severson RR, Smith DA, Shearer MJ, Pace DG et al. A new mixed micellar preparation for or al vitamin K prophylaxis: randomised controlled comparison with an intramuscular formulation in breast fed infants. Arch Dis Child. 1998;79(4):300–5 (https://doi.org/10.1136/adc.79.4.300).
2. Schubiger G, Grüter J, Shearer MJ. Plasma vitamin K1 and PIVKA-II after oral administration of mixed-micellar or cr emophor EL-solubilized preparations of vitamin K1 to normal breast-fed newborns. J Pediatr Gastroenterol Nutr. 199 7;24(3):280–4 (https://doi.org/10.1097/00005176-199703000-00009).
3. Amédée-Manesme O, Lambert WE, Alagille D, De Leenheer AP. Pharmacokinetics and safety of a new solution of vitamin K1(20) in children with cholestasis. J Pediatr Gastroenterol Nutr. 1992;14(2):160–5 (https://doi.org/10.1097/ 00005176-199202000-00007).
4. von Kries R, Hachmeister A, Göbel U. Oral mixed micellar vitamin K for prevention of late vitamin K deficiency ble eding. Arch Dis Child Fetal Neonatal Ed. 2003;88(2):F109–12 (https://doi.org/10.1136/fn.88.2.f109).
5. Soedirman JR, De Bruijn EA, Maes RA, Hanck A, Grüter J. Pharmacokinetics and tolerance of intravenous and intra muscular phylloquinone (vitamin K1) mixed micelles formulation. Br J Clin Pharmacol. 1996;41(6):517–23 (https://do

i.org/10.1046/j.1365-2125.1996.03847.x).
6. Pereira SP, Williams R. Adverse events associated with vitamin K1: results of a worldwide post-marketing surveillance programme. Pharmacoepidemiol Drug Saf. 1998;7(3):173–82 (https://doi.org/10.1002/(sici)1099-1557(199805/06)7:3<173::Aid-pds343>3.0.Co;2-8).
7. WHO recommendations on newborn health: guidelines approved by the WHO Guidelines Review Committee. Geneva: World Health Organization, 2017 (https://iris.who.int/handle/10665/259269). Licence: CC BY-NC-SA 3.0 IGO.

