Konakion® MM Paediatric 2mg/0.2ml
Phytomenadione

Composition
Active ingredient: phytomenadione (synthetic vitamin K_1).
One amber glass ampoule contains 0.2 ml of a clear mixed-micelle solution of 2 mg vitamin K_1 (filling volume 0.3 ml) for oral or parenteral administration.

Excipients: glycocholic acid, sodium hydroxide, lecithin, hydrochloric acid, water for injection.

Properties and effects
Presence of vitamin K_1, the active ingredient of Konakion MM paediatric, is essential for the formation of prothrombin, factors VII, IX and X, and the coagulation inhibitors protein C and protein S in the body.
Vitamin K_1 does not readily cross the placental barrier from mother to child and is poorly excreted in breast milk.
Lack of vitamin K_1 leads to an increased tendency to hemorrhagic disease in the newborn. Vitamin K_1 administration, which promotes synthesis of the above-mentioned coagulation factors by the liver, can reverse an abnormal coagulation status and bleeding due to vitamin K_1 deficiency.

Indications and usage
Documented indications
Prophylaxis and treatment of hemorrhagic disease of the newborn.

Dosage and administration
Prophylaxis
For all healthy neonates of 36 weeks gestation and older:
1 mg administered by intramuscular injection at birth or soon after birth
or
2 mg orally at birth or soon after birth; the oral dose should be followed by a further dose of 2 mg at four to seven days of age. A further 2 mg oral dose should be given 1 month after birth. In exclusively formula-fed infants the third oral dose can be omitted.

A single 1 mg (0.1 ml) dose intramuscularly is recommended in children who are not assured of receiving a second oral dose or, in the case of breastfed children, who are not assured of receiving a third oral dose.

Preterm neonates of less than 36 weeks gestation, weighing 2.5 kg or greater, and term neonates at special risk (e.g. prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics): 1 mg intramuscularly or intravenously at birth or soon after birth. The amount and frequency of further doses should be based on coagulation status.

Preterm neonates of less than 36 weeks gestation, weighing less than 2.5 kg: 0.4 mg/kg (equivalent to 0.04 ml/kg) intramuscularly or intravenously at birth or soon after birth. This parenteral dose should not be exceeded. The amount and frequency of further doses should be based on coagulation status.

Table 1 Dose calculation based on body weight for healthy and preterm neonates
It is important to check the calculation and measurement for the dose in relation to the baby's weight (10-fold dosing errors are often made).

Table 1

Body weight	Dose of vitamin K (i.m or i.v)	Injection volume
1 kg	0.4 mg	0.04 ml
1.5 kg	0.6 mg	0.06 ml
2 kg	0.8 mg	0.08 ml
2.5 kg	1 mg	0.1 ml
Over 2.5 kg	1 mg	0.1 ml

There is evidence that oral prophylaxis is insufficient in patients with underlying cholestatic liver disease and malabsorption. Therefore oral vitamin K administration is not recommended in this category of patients (see section Pharmacokinetics).

Therapy
Initially, 1 mg by intravenous injection, with further doses as required, based on the clinical picture and coagulation status. In certain circumstances, treatment with Konakion MM paediatric may need to be accompanied by more direct forms of effective hemorrhage control, such as transfusion of whole blood or coagulation factors, to compensate for severe blood loss and the delayed response to vitamin K_1.

Administration
Oral use:
- With the dispenser included in the package:
  - after breaking the ampoule, place the dispenser vertically into the ampoule;
  - withdraw the solution from the ampoule into the dispenser until the solution reaches the marking of the dispenser (= 2 mg vitamin K_1);
  - administer the contents of the dispenser directly into the newborn's mouth.

- If no dispenser is available an alternative method of oral administration is the use of a syringe as follows:
  - the required volume should be withdrawn from the ampoule with a syringe and needle;
  - after removal of the needle the content of the syringe should be administered directly from the syringe into the newborn's mouth.

Parenteral use:
Konakion MM paediatric should not be diluted or mixed with other parenteral medications. It may however be injected into the lower part of an infusion set.

Contraindications
The use of Konakion MM paediatric is contraindicated in cases of known hypersensitivity to any of the ingredients.

Precautions
At the time of use, the mixed-micelle ampoule solution must be clear in appearance. Parenteral administration may be associated with an increased risk of kernicterus in premature infants weighing less than 2.5 kg.

Undesirable effects
In rare cases, anaphylactoid reactions have been reported after parenteral use of Konakion MM paediatric. Local irritation may occur at the injection site.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
In addition, you may report suspected adverse reactions by sending an e-mail message to safety@tzamal-medical.co.il
or by visiting the "Contact Us" webpage at:
http://www.tzamal-medical.co.il/69601.html
or by phone: +972-73-7151107.

Interactions
Vitamin K_1 antagonizes the effect of coumarin-type anticoagulants.

Overdosage
There is no known clinical syndrome attributable to hypervitaminosis of vitamin K_1. The following adverse events have been reported concerning overdose with use of Konakion in neonates and infants: jaundice, hyperbilirubinemia, increased GOT and GGT, abdominal pain, constipation, soft stools, malaise, agitation and cutaneous eruption. The causality of those cannot be established. The majority of these adverse events were considered non-serious and resolved without any treatment.
Treatment of suspected overdose should be aimed at alleviating symptoms.

Pharmacokinetics
In the mixed-micelle solution, vitamin K_1 is solubilized by means of a physiological colloidal system consisting of lecithin and bile acid.

Absorption
Vitamin K_1 is absorbed from the small intestine. Absorption is limited in the absence of bile.

Distribution
Vitamin K_1 accumulates predominantly in the liver. It is up to 90% bound to lipoproteins in the plasma and is stored in the body only for short periods of time.

Metabolism
Vitamin K_1 is converted to more polar metabolites, such as phytomenadione-2,3-epoxide.

Elimination
The half-life of vitamin K_1 in plasma is about 70 hours. Vitamin K_1 is excreted in the bile and urine as glucuronide and sulphate conjugates.

Pharmacokinetic of oral vs. iv mixed micellar vitamin K prophylaxis in special populations
Infants with cholestatic liver disease
A randomized study with 44 cholestatic infants of up to 26 weeks of age compared the pharmacokinetics of 2 mg oral versus 1 mg intravenous mixed micellar vitamin K prophylaxis.

The main outcome measures were serum concentrations of vitamin K_1 and undercarboxylated prothrombin (PIVKA-II) before and for up to 4 days after a single dose of mixed micellar vitamin K_1 1 mg intravenously or 2 mg orally. A comparison was also made between vitamin K_1 levels 24 hours after oral vitamin K_1 administration in the above infants with those of 14 healthy newborns given the same dose.
Median serum vitamin K_1 concentrations were similar in the oral and intravenous groups at baseline (0.92 vs. 1.15 ng/ml) rising to approximately 100 times higher concentrations six hours after intravenous K_1 compared to oral administration (139 ng/ml vs. 1.4 ng/ml). Moreover in the oral group the low median value and wide range of serum K_1 compared unfavourably with the much higher levels observed in healthy infants given the same oral dose.

The study suggested an impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 17% achieved an incremental rise in serum vitamin K_1 > 10 ng/ml.

Special remarks
Shelf-life
The expiry date of the product is indicated on the packaging materials.

Stability
This medicine should not be used after the expiry date (EXP) shown on the pack.
Konakion ampoule should be protected from light and should not be stored above 25°C.

Packs
Ampoules, 2 mg in 0.2 ml
Dispenser for oral administration

Manufacturer
Cheplapharm Arzneimittel GmbH, Greifswald, Germany

License Holder
Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Kiryat Matalon, Petah-Tikva

License Number
105.47.28944.00

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