

Konakion® MM**2 mg/ 0.2 ml****paediatric**

Phytomenadione

COMPOSITION

Active ingredient: phytomenadione (synthetic vitamin K₁).

One amber glass ampoule contains 0.2 ml of a clear mixed-micelle solution of 2 mg vitamin K₁ (filling volume 0.3 ml) for oral or parenteral administration.

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

PROPERTIES, EFFECTS

The presence of vitamin K₁, 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 K₁ does not readily cross the placental barrier from mother to child and is poorly excreted in breast milk.

Lack of vitamin K₁ leads to an increased tendency to hemorrhagic disease in the newborn. Vitamin K₁ administration, which promotes synthesis of the above-mentioned coagulation factors by the liver, can reverse an abnormal coagulation status and bleeding due to vitamin K₁ deficiency.

INDICATIONS AND USAGE*Documented indications*

Prophylaxis and treatment of haemorrhagic 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 breast-fed 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

Alternatively adjusted volumes of 1:5 or 1:10 dilutions in dextrose 5% can be administered.

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 haemorrhage control, such as transfusion of whole blood or coagulation factors, to compensate for severe blood loss and the delayed response to vitamin K₁.

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 K₁);
 - 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 ampoules are for intramuscular or intravenous injection. The ampoule solution should not be mixed with other parenteral medications, but may be injected, where appropriate, into the lower part of the 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.

INTERACTIONS

Vitamin K₁ antagonizes the effect of coumarin-type anticoagulants.

OVERDOSAGE

The following adverse events have been reported concerning overdose with use of Konakion in neonates and infants: jaundice, hyperbilirubinaemia, 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 K₁ is solubilized by means of a physiological colloidal system consisting of lecithin and bile acid.

Absorption

Vitamin K₁ is absorbed from the small intestine. Absorption is limited in the absence of bile.

Distribution

Vitamin K₁ 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 K₁ is converted to more polar metabolites, such as phytomenadione-2,3-epoxide.

Elimination

The elimination half-life of vitamin K₁ in plasma is about 70 hours. Vitamin K₁ 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 K₁ and undercarboxylated prothrombin (PIVKA-II) before and for up to 4 days after a single dose of mixed micellar vitamin K₁ 1 mg intravenously or 2 mg orally. A comparison was also made between vitamin K₁ levels 24 hours after oral vitamin K₁ administration in the above infants with those of 14 healthy newborns given the same dose.

Median serum vitamin K₁ concentrations were similar in the oral and intravenous groups at baseline (0.92 v 1.15 ng/ml) rising to approximately 100 times higher concentrations six hours after intravenous K₁ 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 K₁ compared

unfavorably 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 K₁ > 10 ng/ml.

SPECIAL REMARKS

Stability

This medicine should not be used after the expiry date (EXP) shown on the pack.

Konakion (MM) ampoule solution should not be stored above 25°C. Keep the glass ampoule(s) in the outer carton in order to protect from light.

PACKS

Ampoules, 2 mg in 0.2 ml	5
Dispenser for oral administration	1

Medicine: keep out of reach of children

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F. Hoffmann-La Roche Ltd,