Konakion® MM Paediatric 2 mg/0.2 ml

Prescribing Information

1 NAME OF THE MEDICINAL PRODUCT

Konakion MM Paediatric 2 mg/0.2 ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 2 mg phytomenadione (vitamin K_1) in 0.2 ml.

3 PHARMACEUTICAL FORM

Solution
The ampoule solution is clear to slightly opalescent and contains the active constituent in a mixed micelles vehicle of glycocholic acid and lecithin.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis and treatment of hemorrhagic disease of the newborn.

4.2 Posology and method of 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 5.2 Pharmacokinetic Properties).

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.

Method of 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 2 mg/0.2 ml should not be diluted or mixed with other parenteral medications. It may however be injected into the lower part of an infusion set.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

At the time of use, the ampoule contents should be clear. Following incorrect storage, the contents may become turbid or present a phase-separation. In this case the ampoule must no longer be used.
Parenteral administration to premature babies weighing less than 2.5 kg may increase the risk for the development of kernicterus (bilirubin encephalopathy).
Infants with cholestatic disease must receive Konakion MM Paediatric 2 mg/0.2 ml by intramuscular or intravenous injection since oral absorption is impaired in these patients.

4.5 Interaction with other medicinal products and other forms of interaction

No significant interactions are known other than antagonism of coumarin anticoagulants.

4.6 Fertility, pregnancy and lactation

Not applicable

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

There have been reports of anaphylactoid reactions after intravenous injections of this medicine. Local irritation may occur at the injection site but is unlikely due to the small injection volume. Rarely, injection site reactions may occur which may be severe, including inflammation, atrophy and necrosis.

Reporting of 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

4.9 Overdose

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 MM Paediatric 2 mg/0.2 ml in neonates and infants: jaundice, hyperbilirubinaemia, increase 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics (vitamins), ATC code B02BA01.

Konakion MM Paediatric 2 mg/0.2 ml is a preparation of synthetic phytomenadione (vitamin K_1). The presence of vitamin K_1 is essential for the formation within the body of prothrombin, factor VII, factor IX and factor X, and of the coagulation inhibitors, protein C and protein S.

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 haemorrhagic 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 due to vitamin K_1 deficiency.

Paediatric population
A prospective randomised controlled study included 44 infants (1-26 weeks of age) with conjugated hyperbilirubinaemia (idiopathic neonatal hepatitis - 17 patients, biliary atresia - 13, total parenteral nutrition cholestasis - 3, Alagille's syndrome - 2, alpha 1 antitrypsin deficiency - 2, inspissated bile syndrome - 2, and 5 miscellaneous diagnoses (fructosaemia, galactosaemia, choledochal cyst, necrotising enterocolitis, cytomegalovirus hepatitis). The pharmacokinetics and efficacy of oral versus intravenous mixed micellar vitamin K prophylaxis in infants with cholestatic liver disease was compared.
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 K_1 1 mg intravenously or 2 mg orally. A comparison was also made between K_1 levels 24 hours after oral K_1 administration with those of 14 healthy newborns given the same dose.
Results: At admission, 18 infants (41%) had elevated levels of serum PIVKA-II and eight (18%) had low K_1 concentrations, indicative of subclinical vitamin K deficiency. Median serum K_1 concentrations were similar in the oral and intravenous groups at baseline (0.92 v 1.15 ng/ml), rising to 139 ng/ml six hours after intravenous K_1 but to only 1.4 ng/ml after oral administration. In the latter group, the low median value (0.95 ng/ml) and wide range (< 0.15–111 ng/ml) of serum K_1 compared unfavourably with the much higher levels (median 77, range 11–263 ng/ml) observed in healthy infants given the same oral dose, and suggested impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 4/24 (17%) achieved an incremental rise in serum $K_1 > 10$ ng/ml.

The data from a retrospective study indicate that weekly oral prophylaxis was effective in the prevention of VKDB. A total of 507 850 live babies were born during the study period, November 1992 to June 2000. Of these infants, 78% and 22% received oral and intra-muscular prophylaxis, respectively; i.e. about 396000 neonates received oral prophylaxis at birth. Weekly oral prophylaxis was recommended for all infants as long as they were mainly breastfed. Oral vitamin K prophylaxis at birth 2 mg phytomenadione, followed by weekly oral vitamin K prophylaxis; 1 mg was administered by the parents until 3 months of age. No cases of VKDB were revealed, i.e. the incidence was 0-0.9:100000 (95% CI).

5.2 Pharmacokinetic properties

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

Following oral administration vitamin K_1 is absorbed from the small intestine. The systemic availability following oral dosing is approximately 50%, with a wide range of interindividual variability. Absorption is limited in the absence of bile.

After intramuscular administration vitamin K_1 release into the circulation is prolonged, i.e. the IM route acts as a depot. A single 1 mg IM dose results in comparable vitamin K_1 concentrations at 1 month as two 2 mg doses (one given at birth and the other at one week).

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

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

The half-life of vitamin K_1 in plasma is approximately 72 hours in neonates and about 1.5 to 3 hours in adults. Vitamin K_1 is excreted in bile and urine as the glucuronide and sulfate conjugates.

5.3 Preclinical safety data

None applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lecithin for mixed micelles, Glycocholic acid, Sodium hydroxide, Hydrochloric acid, Water for injections

6.2 Incompatibilities

Incompatibilities have been observed with diluted Konakion MM Paediatric 2 mg/0.2 ml solution and certain siliconised syringes, therefore, Konakion MM Paediatric 2 mg/0.2 ml must not be diluted before injection.
Do not dilute with sodium chloride containing solutions as precipitation may occur, see section 4.2 Posology and Method of Administration.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton to protect from light.
The solution should not be frozen.
Do not use if the solution is turbid.
For single use.

6.5 Nature and contents of container

Amber glass ampoules containing 2 mg phytomenadione in 0.2 ml. Plastic oral dispensers

Pack sizes: 5 ampoules with or without dispensers.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

See section 4.2 *Posology and method of administration,* section 4.4 *Special warnings and precautions for use* and section 6.2 *Incompatibilities* for advice regarding the administration of this medicine.

7 MANUFACTURER

Cheplapharm Arzneimittel GmbH, Greifswald, Germany

8 LICENSE HOLDER

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

8 LICENSE NUMBER

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