Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Konakion MM Paediatric Ampoules 2 mg/ 0.2 ml oral solution or solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 2 mg phytomenadione in 0.2 ml.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution or solution for injection.
A clear to slightly opalescent pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Konakion MM Paediatric is indicated for the prophylaxis and treatment of vitamin K deficiency bleeding (VKDB) in neonates and infants.

Konakion MM Paediatric is further indicated for the treatment of overdoses with anticoagulants of the coumarin type in adults and older children (1 to 18 years) where small quantities of vitamin K are required. This may also include the treatment of haemorrhage or threatened haemorrhage, associated with a low blood level of prothrombin or factor VII.

4.2 Posology and method of administration

Prevention and treatment of vitamin K deficiency bleeding (VKDB) in neonates and infants

Prophylaxis of vitamin K deficiency bleeding
Healthyneonates of 36 weeks gestation and older: Either:
- 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 4 - 7 days of age. A further 2 mg oral dose should be given at 1 month after birth. In exclusively formula fed infants the third oral dose can be omitted.

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 by intramuscular or intravenous injection 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) by intramuscular or intravenous injection 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.

There is evidence that oral prophylaxis is insufficient in patients with underlying cholestatic liver disease and malabsorption (see section 5.1).

CAUTION: care is required when calculating and measuring the dose in relation to the baby's weight (10 times dosing errors are common).

Dosing information for preterm babies at birth for the prophylaxis of Vitamin K deficiency bleeding

Weight of the baby	Dose of vitamin K at birth	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

Further oral doses in breast-fed infants have been advised, but safety or efficacy data for these additional doses is limited (see section 5.1).

Therapy of early and/or late vitamin K deficiency bleeding
Initially 1 mg by intravenous injection and further doses as required, depending on clinical picture and coagulation status. Konakion therapy may need to be accompanied by a more immediate effective treatment, such as transfusion of whole blood or blood clotting factors to compensate for severe blood loss and delayed response to vitamin *K1*.

Treatment of coumarin anticoagulant overdose in adults and older children (1 to 18 years)

The dose selection for a specific patient should be based not only on the International Normalized Ratio (INR) value, but various other risk factors and clinical determinants such as patient characteristics, comorbid conditions and concomitant medications should also be appropriately considered. Hence the actual dose selection should be at the discretion of the treating physician.

The dosage recommendations detailed in the table below are provided for therapeutic guidance only.

Adults:

Dose recommendations for vitamin K1 therapy in patients with asymptomatic high INR with or without mild haemorrhage:

Anticoagulant	INR	Oral vitamin K1	Intravenous vitamin K1
Warfarin	5.0 - 9.0	1.0 to 2.5 mg for initial reversal 2.0 to 5.0 mg for rapid reversal (add 1.0 to 2.0 mg if INR remains high after 24 h)	0.5 to 1.0 mg
	> 9.0	2.5 to 5.0 mg (up to 10.0 mg)	1.0 mg
Acenocoumarol	5.0 – 8.0	1.0 to 2.0 mg	1.0 to 2.0 mg
	> 8.0	3.0 to 5.0 mg	1.0 to 2.0 mg
Phenprocoumon	5.0 – 9.0	2.0 to 5.0 mg	2.0 to 5.0 mg
	> 9.0	2.0 to 5.0 mg	2.0 to 5.0 mg
	> 10.0	not recommended	Individually adapted doses

For doses larger than 2 mg, Konakion MM Ampoules 10 mg/ml can be used.

Special dosage instructions

Elderly
Elderly patients tend to be more sensitive to reversal of anticoagulation with Konakion MM; dosage in this group should be at the lower end of the ranges recommended.

Elderly patients with asymptomatic highI NR with or without mild haemorrhage

For an INR of 5.0 – 9.0, small doses of 0.5 to 1 mg intravenous or oral Vitamin K1 have been shown to effectively reduce the INR to < 5.0 within 24 hours.

Children
There are few data regarding the use of Konakion MM in children over 1 year.
There have been no dose ranging studies in children with haemorrhage. The optimal dose should therefore be decided by the treating physician according to the indication, clinical situation and weight of the patient. However, based on clinical experience, the following recommendation is suggested:

Children with asymptomatic high INR with or without mild haemorrhage

Intravenous vitamin K1in doses of 30 micrograms/kg have been reported to be effective in reversing asymptomatic high (> 8.0) INR in clinically well children.

Method of administration

Konakion MM Paediatric can be administered by intravenous injection or by oral administration. Administration by intramuscular injection is only suitable for the VKDB indication in babies.

Parenteral use: A 1 ml syringe or smaller, preferably with 0.01 ml graduations, is recommended for the administration of injection volumes of 0.04 ml (0.4 mg) to 0.1 ml (1 mg), for example, 1 ml B-D Plastipak Syringes.

Konakion MM Paediatric should not be diluted or mixed with other parenteral medications, but may be injected into the lower part of an infusion set.

Oral use:
For oral administration of 1 mg or 2 mg, oral dispensers are provided in the pack. After breaking the ampoule open, 0.2 ml of solution should be withdrawn into the oral dispenser until it reaches the mark on the dispenser (0.2 ml = 2 mg vitamin K). Drop the contents of the dispenser directly into the mouth by pressing the plunger.

Konakion MM Paediatric solution can also be given orally using a syringe (e.g. 1 ml syringe). The ampoule solution should not be diluted. The required amount should be withdrawn from the ampoule using a syringe with attached needle. The needle should then be removed from the syringe, the contents of syringe directly administered into the patient's mouth and washed down with fluid.

4.3 Contraindications

Use in patients with a known hypersensitivity to any of the constituents.

In adults and older children (1 to 18 years), Konakion MM solution should not be administered intramuscularly because the intramuscular route exhibits depot characteristics and continued release of vitamin K1 would lead to difficulties with the re-institution of anticoagulation therapy. Furthermore, intramuscular injections given to anticoagulated subjects cause a risk of haematoma formation.

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 by intramuscular or intravenous injection since oral absorption is impaired in these patients.

Care should be taken when selecting the dose of Konakion MM Paediatric to ensure that a sub-therapeutic INR is not produced as these can be associated with either thrombosis or subsequent resistance to re-initiation of anticoagulant therapy. Smaller doses of 1 mg have been found to reduce the INR effectively with less risk of over-correction than larger doses.

Konakion MM is essentially 'sodium free' as it contains less than 1 mmol sodium (2.64 mg per 1 ml).

4.5 Interaction with other medicinal products and other forms of interaction

Vitamin K1 antagonises the effect of coumarin-type anticoagulants. Anti-convulsants, such as phenobarbital and phenytoin, may cause vitamin K deficiency bleeding on the first day of life in newborns whose mothers have taken these anti-convulsants during pregnancy. The exact mechanism is still unclear.

4.6 Fertility, pregnancy and lactation

There is no specific evidence regarding the safety of Konakion MM Paediatric in pregnancy but, as with most drugs, the administration during pregnancy should only occur if the benefits outweigh the risks.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

There are only a few unconfirmed reports on the occurrence of possible anaphylactoid reactions after intravenous injection of Konakion MM. 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. Healthcare professionals are asked to report any suspected adverse reactions (see details below):

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

There is no known clinical syndrome attributable to hypervitaminosis of vitamin K1.

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 these adverse events cannot be established. The majority were, however, 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, vitamin K, ATC code B02BA01

Konakion MM is a preparation of synthetic phytomenadione (vitamin K1). The presence of vitamin K1 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 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 vitamin K deficiency bleeding. Vitamin K1 administration, which promotes synthesis of the above- mentioned coagulation factors by the liver, can reverse an abnormal coagulation status due to vitamin K1 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 K1 and undercarboxylated prothrombin (PIVKA-II) before and for up to 4 days after a single dose of mixed micellar K1 1 mg intravenously or 2 mg orally. A comparison was also made between K1 levels 24 hours after oral K1 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 K1 concentrations, indicative of subclinical vitamin K deficiency. Median serum K1 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 K1 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 K1 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 K1 > 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 K1 is solubilised by means of a physiological colloidal system consisting of lecithin and a bile acid.

Following oral administration vitamin K1 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.

A single 1 mg intramuscular dose results in comparable vitamin K1concentrations at 1 month as two 2 mg oral doses (one given at birth and the second at one week).

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

The half-life of vitamin K1 in plasma is approximately 72 hours in neonates and about 1.5 to 3 hours in adults. Vitamin K1 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

Glycocholic acid
Sodium hydroxide
Lecithin
Hydrochloric acid
Water for injection

6.2 Incompatibilities

Konakion MM paediatric ampoule solution should not be diluted or mixed with other parenteral medications. See section 4.2.

6.3 Shelf life

2 years.
Once opened, use immediately.

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

1 ml Type I amber glass ampoules containing 2 mg phytomenadione in 0.2 ml. Plastic oral dispensers. Packs of 5.

6.6 Special precautions for disposal and other handling

Konakion MM Paediatric ampoule should not be diluted.
See section 4.2 for further details.
Do not use if the solution is turbid.
For single use only.

7 MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489
Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

PA2239/002/002

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