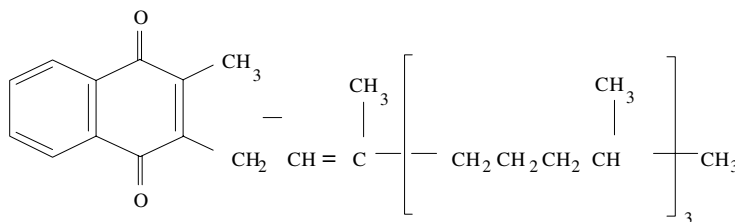


NAME OF THE MEDICINE

KONAKION[®] MM PAEDIATRIC

Phytomenadione (vitamin K₁)

CAS-84-80-0



DESCRIPTION

Konakion[®] MM Paediatric contains as the active ingredient phytomenadione (vitamin K₁) which is 2-methyl-3-phytyl-1,4-naphthaquinone. Phytomenadione is a clear, yellow, very viscous, odourless or nearly odourless oil with a molecular weight of 450.7. It is insoluble in water, soluble 1 in 70 in alcohol, more soluble in dehydrated alcohol; soluble in benzene, chloroform, ether and vegetable oils. It is stable in air but decomposes on exposure to light.

The ampoule contains the active ingredient phytomenadione 2 mg/0.2 mL in a mixed micelles (MM) solution (the micelles are composed of glycocholic acid (bile acid) and lecithin in an aqueous solution). Other excipients used in manufacture are sodium hydroxide, hydrochloric acid and water for injection. The formulation is available in two volumes, phytomenadione 10 mg/1 mL (adult) and 2 mg/0.2 mL (paediatric).

PHARMACOLOGY

As a component of an enzyme system, vitamin K₁ promotes the formation in the liver of coagulation factors II (prothrombin), VII, IX and X and of the coagulation inhibitors protein C and protein S, within the body. Anticoagulants of the coumarin and indandione series cause a reversible displacement of vitamin K₁ from this enzyme system, thereby inhibiting the synthesis of these factors. Since this is a competitive displacement, Konakion is a specific antagonist for warfarin and similar anticoagulants. It is not capable, however, of terminating the action of heparin; for this purpose a salt of protamine should be used.

Vitamin K₁ administration, which promotes synthesis of the abovementioned coagulation factors by the liver, can reverse an abnormal coagulation status or bleeding due to vitamin K₁ deficiency. Vitamin K₁ is ineffective in hereditary hypoprothrombinaemia or hypoprothrombinaemia induced by severe hepatic failure.

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 of vitamin K deficiency bleeding (VKDB). Administration of vitamin K₁ promotes synthesis of above-mentioned coagulation factors, can reverse an

abnormal coagulation status or bleeding due to vitamin K₁ deficiency and thereby reduces the risk of early, classic or late VKDB.

Pharmacokinetics

Absorption and Bioavailability

Orally ingested phytomenadione is absorbed primarily in the middle portions of the small intestine. Optimum absorption is possible only in the presence of bile and pancreatic juice. The absolute bioavailability following intramuscular (IM) administration is approximately 80%. The onset of action occurs approximately 1-3 hours after intravenous (IV) administration and 4-6 hours after oral doses.

Impaired gastrointestinal absorption may occur in conditions such as malabsorption syndromes, short bowel syndrome, biliary atresia and pancreatic insufficiency.

Distribution

The primary distribution compartment corresponds to the plasma volume. In blood plasma, 90% of vitamin K₁ is bound to lipo-proteins (VLDL portion). Vitamin K₁ plasma concentration is normally between 0.4 and 1.2 ng/L. After IV administration of 10 mg Konakion MM to adults the plasma level after 1 hour is approximately 500 ng/mL and approximately 50 ng/mL at 12 hours. Vitamin K₁ is stored in the body for only short periods of time, does not readily cross the placenta and is poorly distributed into breast milk.

Metabolism

Vitamin K₁ is rapidly converted into more polar metabolites, including an active metabolite vitamin K₁-2,3-epoxide. Some of this metabolite is reconverted into vitamin K₁. Metabolism of vitamin K₁ after birth through epoxidation may occur more rapidly in premature infants.

Elimination

The elimination half-life in plasma is 1.5-3 hours. After metabolic degradation, vitamin K₁ is excreted in the bile and urine as the glucuronide and sulphate conjugates. Less than 10% of the medicine is excreted unchanged in the urine.

INDICATIONS

Prophylaxis and treatment of vitamin K deficiency bleeding (VKDB).

CONTRAINDICATIONS

Konakion MM Paediatric is contraindicated in patients with known hypersensitivity to any of the ingredients.

PRECAUTIONS

Anticoagulant Therapy

Konakion MM Paediatric should be considered as adjunctive therapy to blood transfusions for severe haemorrhage due to anticoagulant therapy; it is not effective when heparin-like compounds have been used for anticoagulant therapy; minimal doses should be used to offset refractoriness to coumarin-like anticoagulants if long term anticoagulant therapy is intended.

Effects on Fertility

There have been no studies investigating the effect of phytomenadione on reproductive fertility.

Use in Pregnancy

Not applicable, please refer to the Konakion MM 10 mg/1 mL Product Information

Use in Lactation

Vitamin K₁ is poorly excreted into breast milk. Konakion is not recommended for nursing mothers as prophylaxis of haemorrhagic disease in the newborn.

Use in Premature Infants

Parenteral administration is associated with a possible risk of kernicterus in premature infants weighing less than 2.5 kg.

Use in the Elderly

Please refer to the Konakion MM 10 mg/1 mL Product Information for recommendations for this group.

Carcinogenicity

No studies on the potential carcinogenic activity of phytomenadione have been conducted.

Mutagenesis

Neither phytomenadione nor phytomenadione in the mixed micellar formulation showed evidence of mutagenic activity in *Salmonella typhimurium*. No evidence of chromosomal aberration in human lymphocytes was demonstrated *in vitro* for phytomenadione, but no tests of potential for DNA damage have been conducted.

Interactions with Other Medicines

Vitamin K₁ antagonises the effects of coumarin and indanedione-type anticoagulants (e.g. warfarin, phenindione).

Co-administration of anticonvulsants can impair the action of vitamin K₁.

Konakion MM Paediatric should not be mixed with infusion solutions (see DOSAGE AND ADMINISTRATION).

ADVERSE EFFECTS

In rare cases anaphylactoid reactions have been reported after parenteral use of Konakion MM Paediatric. Should an anaphylactoid reaction occur, the usual measures must be taken (e.g. administration of adrenaline and supportive measures as required).

Very rarely, injection site reaction, venous irritation or phlebitis has been reported in association with parenteral administration of Konakion MM solution to adults. This reaction is unlikely in neonates due to the small injection volume (0.2 mL). Rarely, injection site reactions may occur which may be severe, including inflammation, atrophy and necrosis.

Facial flushing and sweating, and unusual taste have been reported.

DOSAGE AND ADMINISTRATION

Konakion MM Paediatric may be given by intramuscular, oral or intravenous routes. Care should be taken to ensure the correct dose is given for the chosen route of administration.

Prophylaxis

All healthy neonates

1 mg (0.1 mL) IM at birth is recommended.

Alternatively, 2 mg (0.2 mL) orally at birth, at the time of newborn screening (3-5 days of age) and at 4 weeks.

For predominately formula fed neonates the last oral dose may be omitted.

Neonates with special risk factors

1 mg IM at birth is recommended in neonates with special risk factors. If the neonate has special risk factors and weighs less than 1.5 kg, then 0.5 mg (0.05 mL) is recommended (see PRECAUTIONS).

The size and frequency of further doses should be based on clinical grounds and coagulation status.

Clotting and PIVKA-II (Proteins Induced in Vitamin K Absence) tests are not to be relied upon as indications of deficiency as the relationship between biochemical evidence of deficiency and late VKDB is not clear.

Special Risk Factors

Early and/or classical VKDB

Risk factors include: prematurity, birth asphyxia, delay in establishment of oral feeding, maternal use of anticoagulants, antiepileptics or tuberculostatics and antibiotic treatment.

Late VKDB

Risk factors include liver dysfunction including obstructive jaundice, malabsorption and prolonged use of antibiotics.

Therapy

Initially, 1 mg by intravenous injection, with further doses as required, based on the clinical grounds 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.

VKDB should be suspected with any minor bleed in infants less than 6 months of age, even if coagulation tests are within normal limits. Clotting and PIVKA-II tests are not to be relied upon as indications of deficiency as the relationship between biochemical evidence of deficiency and late VKDB is not clear.

Administration

Parenteral use

Konakion MM Paediatric should not be diluted or mixed with other parenteral medications.

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 on the dispenser (= 2 mg vitamin K₁);



- administer the contents of the dispenser directly into the infant's mouth.
- repeated doses are advised if the infant spits out or vomits an oral dose or alternatively diarrhoea occurs within 24 hours of administration.

OVERDOSAGE

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 glutamine-oxaloacetic transferase and gamma-glutamyl transferase, 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 and consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Konakion MM Paediatric ampoules 2 mg/0.2 mL (filling volume 0.3 mL): pack of five amber glass ampoules and 5 dispensers (graduated oral plastic syringes).

Store below 25°C. Protect from light.

At the time of use, the MM ampoule solution should be clear. Following incorrect storage, the solution may become turbid or phase-separation may occur. In this case the ampoule must not be used.

During the shelf-life of KONAKION it is known that impurities will develop. Although there has been no definite evidence of a safety problem due to these impurities, there are also no adequate safety and toxicity data in relation to the impurities. In order to minimise the amount of impurities, prescribers are encouraged to use the product early in the shelf-life wherever possible.

POISON SCHEDULE OF THE MEDICINE

Unscheduled

NAME AND ADDRESS OF THE SPONSOR

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