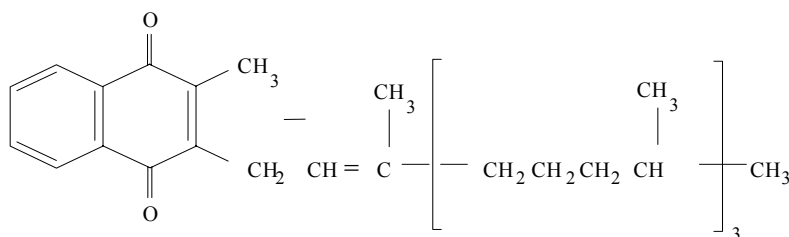


NAME OF THE MEDICINE

KONAKION®

Phytomenadione (Vitamin K₁)

CAS-84-80-0



DESCRIPTION

KONAKION 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.

KONAKION is available in ampoules. The ampoule contains the active ingredient phytomenadione 10mg/mL in a mixed micelles (MM) solution (the micelles are composed of glycocholic acid and lecithin in an aqueous solution). The MM ampoule also contains sodium hydroxide, hydrochloric acid and water for injection.

PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

Absorption and Bioavailability

A pharmacokinetic study indicated that the MM solution of vitamin K₁ administered orally is rapidly and effectively absorbed. Orally ingested phytomenadione is absorbed primarily in the middle portions of the small intestine. Systemic availability after oral administration is about 50%, with a wide range of interindividual variability. Onset of action occurs approximately 1-3 hours after intravenous (i.v.) 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. The oral dosage for this patient group should therefore be at the higher end of the recommended range (see DOSAGE AND ADMINISTRATION).

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 i.v. administration of 10mg KONAKION MM the plasma level after 1 hour is approximately 500 ng/mL and approximately 50 ng/mL at 12 hours. Vitamin K₁ 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 K_{1-2,3}-epoxide. Some of this metabolite is reconverted into vitamin K₁.

Elimination

After metabolic degradation, vitamin K₁ is excreted in the bile and urine as the glucuronide and sulphate conjugates. In one pharmacokinetic study of patients on phenprocoumon (another coumarin), which used a sensitive assay, the terminal half-life in adults was 14 ± 6 hours after i.v. administration of KONAKION MM. Less than 10% of the medicine is excreted unchanged in the urine.

INDICATIONS

Haemorrhage or threatened haemorrhage as a result of severe "hypo-prothrombinaemia" (i.e. deficiency of coagulation factors II, VII, IX and X) due, for instance, to overdosage of anticoagulants of the dicoumarol type, or to other forms of hypovitaminosis K (e.g. obstructive jaundice, liver and intestinal disorders, or prolonged administration of antibiotics, sulfonamides or salicylates).

CONTRAINDICATIONS

KONAKION is contraindicated in patients with known hypersensitivity to any of its constituents.

KONAKION should not be used for patients with pronounced allergic diathesis.

KONAKION MM ampoules should not be administered intramuscularly as this route of administration exhibits depot characteristics which may cause difficulties in the re-institution of anticoagulant therapy. Furthermore i.m. administration of medications to anticoagulated patients cause a risk of haematoma formation.

PRECAUTIONS

KONAKION 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.

Use in Impaired Liver and Renal Function

Careful monitoring of the INR (International Normalized Ratio) is necessary after administration of KONAKION in patients with severely impaired liver function. In severe liver disease, KONAKION should be discontinued if no significant effect is noted within 1-2 days after the initial dose.

Thromboembolism

Vitamin K inhibits the therapeutic effect of coumarin anticoagulants and hence creates a risk of thrombosis. In patients in whom KONAKION MM is being used to reverse the effect of coumarin anticoagulation,

careful consideration must be given to the fact that restoring the blood's clotting ability restores the risk of thrombosis, possibly even to an increased extent.

Effects on Fertility

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

Use in Pregnancy

Vitamin K₁ does not readily cross the placental barrier. There are no specific studies regarding the safety of KONAKION in pregnancy and no reproductive studies have been performed in animals. KONAKION is contraindicated in pregnant women.

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 the Elderly

Elderly patients tend to be more sensitive to reversal of anticoagulation with KONAKION. Dosage in this group should be at the lower end of the range.

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

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

Vitamin K₁ antagonises the effects of coumarin-type anticoagulants. Coumarins inhibit epoxide reductase in the vitamin K cycle and hence the cofactor function of vitamin K in the carboxylation reaction. Aspirin and other salicylates also attenuate the effect of vitamin K by inhibiting the carboxylase reductase system.

Cephalosporins with the N methylthiotetrazole group inhibit vitamin K epoxide reductase and hence the effect of vitamin K.

Co-administration of anticonvulsants can impair the action of vitamin K₁. Anticonvulsants such as phenobarbital and phenytoin, as well as the antituberculosis drugs isoniazid and rifampicin, may cause vitamin K deficiency bleeding on the first day of life in newborns whose mothers have taken these drugs during pregnancy. The exact mechanism is still unclear.

Vitamin K inhibits the therapeutic effect of coumarin anticoagulants and hence creates a risk of thrombosis (see PRECAUTIONS).

ADVERSE EFFECTS

Should an anaphylactoid reaction occur, the usual measures must be taken (administration of adrenaline and supportive measures as required).

Venous irritation or phlebitis has been reported in association with i.v. administration of KONAKION MM. Facial flushing and sweating and unusual taste have been reported.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100, <1/10$), uncommon ($\geq 1/1000, <1/100$), rare ($\geq 1/10,000, <1/1000$) and very rare ($<1/10,000$) including isolated reports.

Immune system disorders

Very rare: Anaphylactoid reactions after i.v. administration of KONAKION MM. Should an anaphylactoid reaction occur, the usual measures must be taken (e.g. administration of adrenaline and supportive measures as required).

General disorders and administration site conditions

Very rare: Venous irritation or phlebitis in association with i.v. administration of KONAKION MM. Facial flushing and sweating and unusual taste have been reported.

DOSAGE AND ADMINISTRATION

KONAKION MM ampoules are for i.v. injection or oral use.

This product has a shelf-life of 2 years. During that time 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.

Slow i.v. injection must be reserved for potentially fatal haemorrhage due to overdosage of anticoagulants of the coumarin and indandione series. There is currently no data to advise on the appropriate vitamin K₁ dosage in the event of an indandione overdose.

Excessive doses of KONAKION impede the resumption of anticoagulant therapy without offering any advantages.

If there is a recurrence of thrombosis while KONAKION is being used, i.v. administration of heparin is recommended as a first measure.

KONAKION MM should not be diluted or mixed with other injectables except, where appropriate, into the lower part of the infusion set during continuous infusion of sodium chloride 0.9 % or dextrose 5 %.

Standard Dosage

Severe or life-threatening haemorrhage, e.g. during anticoagulant therapy: The coumarin anticoagulant should be withdrawn and an i.v. injection of KONAKION MM given slowly (in at least 30 seconds) in a dose of 5-10 mg together with fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC). Vitamin K₁ is essential for sustaining the reversal achieved by FFP or PCC. The prothrombin level should be estimated 3 hours later and, if the response has been inadequate, the dose of vitamin K₁ can be repeated as needed.

Dose recommendations for vitamin K₁ therapy in patients with major and life-threatening bleeding:

Anticoagulant	Condition	Intravenous vitamin K ₁	Concomitant therapy
Warfarin	Major bleeding	5.0 to 10.0 mg	*FFP and PCC
	Life-threatening bleeding	10.0 mg	*FFP and PCC

FFP, fresh frozen plasma

PCC, prothrombin complex concentrate

*FFP should be added to PCC as a source of factor VII when used for warfarin reversal.

Close monitoring of all patients with frequent review of INR (International Normalized Ratio) is recommended.

Oral administration of vitamin K₁ is not recommended for patients with major or life-threatening bleeding.

Dose recommendations for vitamin K₁ therapy in patients with asymptomatic high International Normalized Ratio (INR) with or without mild haemorrhage:

Warfarin should be withdrawn prior to administration of vitamin K₁.

Anticoagulant	INR	Oral vitamin K ₁ *	Intravenous vitamin K ₁
Warfarin	5-9	1.0 to 2.5 mg for initial reversal (add. 1.0 to 2.0 mg if INR remains high after 24 h)	0.5 to 1.0 mg
	>9	2.5 to 5.0 mg	1.0 mg

* Oral vitamin K₁ dosing instructions refer to oral dosing of ampoules only.

KONAKION MM may be administered orally with a syringe. Administration with a syringe can be performed as follows: withdraw the required amount from the ampoule using a syringe with a needle attached. Remove the needle from the syringe and administer the contents of the syringe directly into the patient's mouth. Wash down with fluid.

For small doses one or more ampoules of KONAKION MM paediatric (2 mg/0.2 ml; same solution) can be used.

Special dosage instructions

Use in the elderly: Elderly patients tend to be more sensitive to reversal of anticoagulation with KONAKION MM. The dosage for this patient group should therefore be at the lower end of the ranges recommended. Small doses of 0.5 to 1.0 mg i.v. or oral vitamin K₁ have been shown to effectively reduce the INR to < 5.0 within 24 hours (see Pharmacokinetics).

Children over one year of age: The optimal dose should be decided by the treating physician according to the indication and weight of the patient. A single dose of 30 mcg/kg or one tenth of the full i.v. adult dose of vitamin K₁ has been reported to be effective in reversing asymptomatic high (> 8) INR in clinically well children. KONAKION MM must not be injected intramuscularly to children on oral anticoagulant.

Infants under one year of age: For this patient group, KONAKION MM paediatric should be used.

OVERDOSAGE

There is no known clinical syndrome attributable to hypervitaminosis of vitamin K₁. Reintroduction of anticoagulation may be affected.

Treatment of suspected overdose should consist of general supportive measures.

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



PRESENTATION AND STORAGE CONDITIONS

MM Ampoules 10 mg/1mL, IV, 5s.
Store below 25 °C. Protect from light.

At the time of use, the ampoule solution should be clear. Following incorrect storage, the solution may become turbid or present a phase separation. In this case the ampoule must not be used. KONAKION MM ampoules should be used early in the shelf-life wherever possible (see DOSAGE AND ADMINISTRATION).

POISON SCHEDULE OF THE MEDICINE

Unscheduled

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
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Date of Latest Amendment: 4 June 2010