

SCHEDULING STATUS

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PROPRIETARY NAME AND DOSAGE FORM

KONAKION® MM 10 mg/1 mL Ampoule

COMPOSITION

Synthetic Vitamin K₁ (phytomenadione). Each ampoule contains 10 mg phytomenadione in a mixed micelles vehicle of glycocholic acid and lecithin.

Ampoule excipients: glycocholic acid, sodium hydroxide, lecithin, hydrochloric acid, water for injections.

PHARMACOLOGICAL CLASSIFICATION

A 22.1.4 Vitamin.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Vitamin K₁ (phytomenadione), is a procoagulant factor. As a component of a hepatic carboxylase system, Vitamin K₁ is involved in the post-translational carboxylation of clotting factors II (prothrombin), VII, IX and X and the clotting inhibitors, protein C and protein S.

Pharmacokinetic properties

Absorption:

A pharmacokinetic study indicated that the MM solution of vitamin K₁ administered orally is well absorbed. Oral doses of Vitamin K₁ are absorbed primarily from the middle portions of the small intestine. Bile acids and pancreatic lipase are required for absorption, due to its lipid solubility.

Distribution:

The primary distribution compartment corresponds to the plasma volume. In blood plasma, 90 % of Vitamin K₁ is bound to lipoproteins (VLDL fraction). Normal plasma concentrations of Vitamin K₁ range from 0,4 to 1,2 ng/mL. 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 Vitamin K_{1-2,3}-epoxide. Some of this metabolite is reconverted to Vitamin K₁.

Elimination:

Following metabolic degradation, Vitamin K₁ is excreted in the bile and urine as glucuronide and sulfate conjugates. The terminal half-life in adults is 14 ± 6 hours after i.v. administration and 10 ± 6 hours after oral administration.

Pharmacokinetics in special clinical situations:

Intestinal absorption of Vitamin K₁ is impaired by various conditions, including malabsorption syndromes, short bowel syndrome, biliary atresia and pancreatic insufficiency. In the elderly, the dosage should be at the lower end of the recommended range. See DOSAGE AND DIRECTIONS FOR USE.

INDICATIONS

Haemorrhage or threatened haemorrhage associated with Vitamin K deficiency of coagulation factors II, VII, IX and X due, for instance, to overdosage of anticoagulants of the coumarin-type, or their combination with phenylbutazone, or to other forms of hypovitaminoses K (e.g. obstructive jaundice, liver and intestinal disorders, or prolonged administration of antibiotics, sulfonamides or salicylates).

For prophylaxis and treatment of haemorrhagic disease in the newborn, KONAKION MM paediatric ampoules (2 mg/0,2 ml) should be used

CONTRAINDICATIONS

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

WARNINGS AND SPECIAL PRECAUTIONS

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. Careful monitoring of the INR is necessary after administration of KONAKION MM in patients with severely impaired liver function. In potentially fatal and severe haemorrhage due to overdosage of coumarin anticoagulants, intravenous injections of KONAKION MM (maximum of 40 mg in 24 hours) should be accompanied by a more immediately effective treatment such as transfusion of whole blood or blood clotting factors. When patients with prosthetic heart valves

are given transfusions for the treatment of severe or potentially fatal haemorrhage, fresh frozen plasma should be used.

Large doses of KONAKION should be avoided if it is intended to continue with anticoagulant therapy. Vitamin K₁ is not an antidote to heparin.

INTERACTIONS

Vitamin K₁ antagonises the effects of coumarin-type anticoagulants. Co-administration of anticonvulsants can impair the action of Vitamin K₁.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

KONAKION MM ampoules are for intravenous injection or oral use. KONAKION MM ampoule solution should not be diluted or mixed with other injectables, but may be injected, where appropriate into the lower part of an infusion set, during continuous infusion of sodium chloride 0,9 % or dextrose 5 %. For neonates and infants under one year, KONAKION MM Paediatric should be used because of the lower doses required

Standard dosage

Severe or life-threatening haemorrhage e.g. during anticoagulant therapy:

The coumarin anticoagulant should be withdrawn and an intravenous (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) or prothrombin complex concentrate (PCC). The dose of Vitamin K₁ can be repeated as needed.

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

Anticoagulant	INR	Oral vitamin K ₁	Intravenous vitamin K ₁
Warfarin	5 – 9	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 hours)	0,5 to 1,0 mg 0,5 to 1,0 mg
	> 9	2,5 to 5,0 mg (up to 10,0 mg)	1,0 mg
Acenocoumarol	5 – 8	1,0 to 2,0 mg	1,0 to 2,0 mg
	> 8	3,0 to 5,0 mg	1,0 to 2,0 mg

Phenprocoumon	5 – 9	2,0 to 5,0 mg	2,0 to 5,0 mg
	> 9	2,0 to 5,0 mg	2,0 to 5,0 mg
	> 10	Not recommended	Individually adapted doses

For small doses one or more ampoules of KONAKION MM Paediatric (2 mg/0,2 ml; same solution) can be used.

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

Anticoagulant	Condition	Intravenous vitamin K₁	Concomitant therapy
Warfarin	Major bleeding	5,0 to 10,0 mg	FFP or PCC
	Life-threatening bleeding	10,0 mg	FFP, PCC, or recombinant factor VIIa
Acenocoumarol	Major bleeding	5,0 mg	FFP, PCC, or prothrombin concentrates and factor VII
Phenprocoumon	Major bleeding with INR < 5,0	5,0 mg	PCC
	Major bleeding with INR > 5,0	10,0 mg	PCC
FFP: fresh frozen plasma PCC: prothrombin complex concentrate			

Special dosage instructions

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 ranges recommended. Small doses of 0,5 to 1,0 mg i.v. or oral Vitamin K₁ have 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 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.

Haemorrhage or threatened haemorrhage in the newborn and infants under one year of age:

Refer to the KONAKION MM Paediatric package insert for details.

Oral use

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

SIDE-EFFECTS

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* $\geq 1/1\ 000$, $< 1/100$;

Rare $\geq 1/10\ 000$, $< 1/1\ 000$; *Very rare* $< 1/10\ 000$, including isolated reports

Immune system disorders

Very rare: Anaphylactoid reactions after intravenous administration of KONAKION MM.

General disorders and administration site conditions

Very rare: Venous irritation or phlebitis in association with intravenous administration of KONAKION MM.

If surgical intervention should be necessary in a patient receiving anticoagulants of the coumarin or indandione series, their anticoagulant action, if not required for the purpose of the operation, may be counteracted by means of KONAKION. If there is a recurrence of thrombosis while KONAKION is being used, i.v. administration of heparin is recommended as a first measure.

Note: When a patient on KONAKION is referred to another doctor, it is particularly important to notify the latter that KONAKION has been prescribed.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See "WARNINGS AND SPECIAL PRECAUTIONS". Treatment is symptomatic and supportive.

Re-introduction of anti-coagulation may be affected.

IDENTIFICATION

Injection: The ampoule solution is clear to slightly opalescent, pale yellow in colour and contains the active constituent in a mixed micelle vehicle of glycocholic acid and lecithin.

PRESENTATION

KONAKION MM 10 mg/1 mL: 10 ampoules

STORAGE INSTRUCTIONS

KONAKION injection: The ampoules should be protected from light.

The recommended maximum storage temperature is 25 °C and the solution should not be frozen.

Keep out of reach of children.

REFERENCE NUMBER

KONAKION MM 10 mg/1 ml Ampoules: H2250 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

Registration: 4 March 1975

Last revision: 30 September 2011, 20 July 2018