

Konakion[®]MM

Phytomenadione

COMPOSITION

Active substance:

phytomenadione (synthetic vitamin K₁)

Excipients:

Ampoules: glycocholic acid, sodium hydroxide, lecithin (produced from genetically modified soya oil), hydrochloric acid, water for injection

GALENICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

MM ampoules (1 ml) containing 10 mg.

Solution for injection, oral solution: Each amber-glass ampoule contains 1 ml of a clear mixed micelle solution with 10 mg vitamin K₁ (filling volume 1.15 ml) for oral and parenteral administration.

INDICATIONS AND POTENTIAL USES

Hemorrhage or risk of hemorrhage as a result of severe “hypoprothrombinemia” (i.e. deficiency of clotting factors II, VII, IX and X) due, among other things, to overdosage of coumarin-based anticoagulants or their combination with phenylbutazone or to other forms of hypovitaminosis K (e.g. in obstructive jaundice, liver and intestinal disorders, prolonged administration of antibiotics, sulfonamides or salicylic acid derivatives).

DOSAGE AND ADMINISTRATION

The route of administration (oral, intravenous), dose, dosage interval and duration of treatment depend on the severity of the patient’s hypoprothrombinemia and his or her response. An intravenous (i.v.) injection of Konakion MM should generally be given slowly (over at least 30 seconds) and may be repeated as required. Onset of action occurs approximately 1–3 hours after i.v. Konakion MM administration and 4–6 hours after oral doses.

Intravenous administration guarantees more rapid onset of action than oral dosing. Oral administration of Konakion MM is therefore not recommended in severe or life-threatening hemorrhage.

Konakion MM should not be diluted or mixed with other parenteral medications, but where appropriate may be injected into the lower chamber of an i.v. giving set during continuous infusion of 0.9% sodium chloride or 5% glucose.

Konakion MM can be given orally with a syringe as follows: Attach the needle to the syringe and withdraw the required volume from the ampoule. Remove the needle from the syringe and administer the contents of the syringe directly into the patient's mouth. Wash down with fluid.

Acute intoxication with oral anticoagulants

10–20 mg vitamin K₁ (one to two 10 mg Konakion MM ampoules) daily by i.v. injection, followed by oral treatment and continuous monitoring of prothrombin time until the patient's coagulation status normalises.

Should surgical intervention be necessary in a patient receiving coumarin-type anticoagulants, Konakion MM can be used to reverse their anticoagulant action (provided anticoagulant protection is not desired). If thrombosis recurs on treatment with Konakion MM, anticoagulant treatment must be continued initially with i.v. heparin.

When referring patients to another physician for further care, inform the latter that Konakion MM has been prescribed. In life-threatening intracranial or gastrointestinal hemorrhage, institute clotting factor replacement as a first-line measure and administer Konakion MM concurrently.

Emergency operations

Interrupt anticoagulation.

Phenprocoumon (or *warfarin*): Konakion MM 10 mg i.v. plus prothrombin complex concentrate (PCC) 60 IU/kg body weight i.v.

Acenocoumarol: Konakion MM 5 mg i.v. plus fresh frozen plasma (FFP) 15 ml/kg body weight i.v. or PCC 35–50 IU/kg body weight together with factor VII concentrate 20 IU/kg body weight i.v.

Severe or life-threatening hemorrhage during oral anticoagulant therapy

Treatment with the coumarin anticoagulant should first be interrupted.

Phenprocoumon (e.g. Marcoumar[®]) or *warfarin* (not approved in Switzerland): Konakion MM 5.0–10.0 mg i.v. plus PCC or FFP.

Acenocoumarol (e.g. Sintrom[®]): Single dose of Konakion MM 5.0 mg i.v. plus FFP or PCC.

Elevated International Normalised Ratio (INR) with or without mild to moderate hemorrhage

Phenprocoumon (*warfarin*): INR $\geq$ 9: Konakion MM 10.0 mg i.v. INR <9: Konakion MM 2.0–5.0 mg orally or i.v.

Acenocoumarol: Temporary dose reduction is often sufficient. For moderate hemorrhage: Konakion MM 2.0–5.0 mg orally.

Konakion MM paediatric ampoules (2 mg/0.2 ml; same concentration as 10.0 mg/1.0 ml ampoules) are available for small dosages.

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. Low 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 under 1 year of age

The mixed micelle ampoules containing 10 mg/ml must not be administered to infants under one year of age or to neonates. Konakion paediatric MM is available for this purpose.

CONTRAINDICATIONS

Hypersensitivity to phytomenadione or any of the constituent excipients.

WARNINGS AND PRECAUTIONS

The mixed micelle solution in the ampoule must be clear at the time of administration. Incorrect storage can result in turbidity or phase separation. In such cases the ampoule must not be used.

Careful monitoring of the INR is necessary after administration of Konakion MM in patients with severely impaired liver function.

INTERACTIONS

Dicoumarol and its derivatives antagonise the effect of vitamin K₁ on postribosomal carboxylation of certain clotting factors and inhibitors. Coadministration of anticonvulsants can impair the action of phytomenadione.

PREGNANCY AND LACTATION

No controlled studies of Konakion MM have been performed in animals or pregnant women.

Based on many years' experience, however, it is safe to assume that neither phytomenadione nor the excipients contained in the various Konakion MM formulations have any reproductive toxicological effects at the applicable dosages. Attention is nevertheless drawn to the principle that medicines should be used in pregnancy only if strictly indicated.

Since only a small fraction of administered vitamin K₁ enters breast milk, no adverse effects on the infant need be expected when Konakion MM is administered in therapeutic doses to nursing mothers.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Konakion MM does not affect driving ability or the ability to use machines.

UNDESIRABLE EFFECTS

There are reports of anaphylactic-type reactions after intravenous injection of Konakion MM.

Local irritation may occur at the injection site. In rare cases, potentially severe reactions such as inflammation, atrophy and necrosis may occur at the injection site.

Immune system

Rare: Anaphylactoid reactions after i.v. injection of Konakion MM.

Administration site reactions

Very rare: Venous irritation or phlebitis in association with i.v. injection of Konakion MM.

OVERDOSAGE

Hypervitaminosis K₁ is unknown.

PROPERTIES/EFFECTS

ATC code: B02BA01

Mechanism of action

Vitamin K₁ (phytomenadione), the active ingredient of Konakion MM, is a procoagulant factor. As a component of a hepatic carboxylase system, phytomenadione is involved in carboxylation of clotting factors II (prothrombin), VII, IX and X, and of clotting inhibitors protein C and protein S in the postribosomal phase. Coumarins inhibit the reduction of phytomenadione (quinone form) to phytomenadione hydroquinone and also prevent the phytomenadione epoxide arising after the carboxylation reaction from being reduced to the quinone form.

Pharmacodynamics

Vitamin K₁ is an antagonist of phenprocoumon (Marcoumar[®]) and similar anticoagulants. It does not, however, neutralise the activity of heparin; protamine is used for this purpose.

Vitamin K₁ is ineffective in hereditary hypoprothrombinemia or hypoprothrombinemia induced by severe hepatic failure.

In Konakion MM, phytomenadione is solubilised using the colloidal system of bile acid-lecithin micelles, a physiological carrier principle also employed in the human body.

PHARMACOKINETICS

Absorption

Orally ingested phytomenadione is absorbed primarily in the middle portions of the small intestine. Systemic availability after oral dosing is approximately 50%, with large interindividual differences.

Distribution

The primary distribution compartment corresponds to the plasma volume. In blood plasma, 90% of phytomenadione is bound to lipoproteins (VLDL fraction). The normal plasma concentration of phytomenadione is between 0.4 and 1.2 µg per litre. Placental transfer of phytomenadione and its passage into breast milk are low.

Metabolism

Phytomenadione is rapidly converted to more polar metabolites, including phytomenadione-2,3-epoxide, some of which is reconverted to phytomenadione.

Elimination

After metabolic degradation, phytomenadione is conjugated with glucuronic acid and sulphuric acid and excreted in the bile and urine. The terminal half-life in adults is 14±6 hours after i.v. administration and 10±6 hours after oral administration. The fraction excreted unchanged in the urine is less than 10%.

Pharmacokinetics in special patient populations

Clinical situations associated with impaired phytomenadione (vitamin K₁) absorption include malabsorption, short bowel syndrome, biliary atresia and pancreatic insufficiency. The dosage for this patient group should therefore be at the lower end of the recommended range (see *Dosage and administration*).

PRECLINICAL DATA

No mutagenic or carcinogenic effects have been reported to date.

Injection of vitamin K₁ from day 6 to day 11 of gestation produced teratogenic effects in mice.

SPECIAL REMARKS

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the container.

For stability reasons, contents remaining in opened ampoules cannot be stored and must be discarded.

Special precautions for storage

Konakion ampoule solution should be protected from light and not stored above 25°C.

Keep out of reach of children.

PACKS

10 mg MM ampoules (1 ml):

5

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at August 2015

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland by CENEXI SAS, Fontenay-sous-Bois, France