Konakion® MM 10 mg/ml

Prescribing Information

1 NAME OF THE MEDICINAL PRODUCT

Konakion MM 10 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 10 mg phytomenadione (vitamin K_1) in 1 ml.

3 PHARMACEUTICAL FORM

Solution
Amber glass ampoules containing 10 mg phytomenadione in 1 ml. The ampoule solution is clear to slightly opalescent, pale yellow in colour and contains the active constituent in a mixed micelles vehicle of glycocholic acid and lecithin.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment and prophylaxis of hemorrhage.

For prophylaxis and treatment of hemorrhagic disease in the newborn, Konakion MM paediatric 2 mg/0.2 ml ampoules should be used.

4.2 Posology and method of administration

Konakion MM 10 mg/ml ampoules are for I.V. injection or oral use. The ampoule solution should not be diluted or mixed with other injectables, but may be injected, where appropriate, into the lower part of the infusion set, during continuous infusion of sodium chloride 0.9% or dextrose 5%.

Because of the lower doses required, Konakion MM paediatric 2 mg/0.2 ml should be used in neonates and infants under one year of age.

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The coumarin anticoagulant should be withdrawn and an I.V. injection of Konakion MM 10 mg/ml given slowly (in at least 30 seconds) at a dose of 5-10 mg together with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). The dose of Vitamin K_1 can be repeated as needed.

Dose recommendations for vitamin K_1 therapy in patients with asymptomatic high International Normalized 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 h)	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 K_1 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 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 MM 10 mg/ml. 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 K_1 have shown to effectively reduce the INR to <5.0 within 24 hours (see section 5.2 Pharmacokinetic Properties).

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 K_1 has been reported to be effective in reversing asymptomatic high (> 8) INR in clinically well children.

Infants under one year of age:

For this patient group, Konakion MM paediatric 2 mg/0.2 ml should be used.

Oral use
Either with a Konakion MM 10 mg/ml dispenser or a syringe.

Syringe
Konakion MM 10 mg/ml solution can 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

This medicine should not be administered intramuscularly because the IM route exhibits depot characteristics and continued release of vitamin K_1 would lead to difficulties with the re-institution of anticoagulation therapy. Furthermore, IM injections given to anticoagulated subjects cause a risk of haematoma formation.

4.4 Special warnings and precautions for use

When treating patients with severely impaired liver function, it should be borne in mind that one 1 ml ampoule of Konakion MM 10 mg/ml contains 54.6 mg glycocholic acid and this may have a bilirubin displacing effect. Careful monitoring of the INR is necessary after administration of this medicine in patients with severely impaired liver function.

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.

In potentially fatal and severe haemorrhage due to overdosage of coumarin anticoagulants, intravenous injections of Konakion MM 10 mg/ml must be administered slowly and not more than 40 mg should be given during a period of 24 hours. Konakion MM 10 mg/ml therapy should be accompanied by a more immediate 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. The use of vitamin K_1 in patients with mechanical heart valves is generally to be avoided, unless there is major bleeding.

Large doses of Konakion MM 10 mg/ml (not more than 40 mg per day) should be avoided if it is intended to continue with anticoagulant therapy because there is no experience with doses above this maximum of 40 mg per day and higher doses may give rise to unexpected adverse events. Clinical studies have shown a sufficient decrease in the INR with the recommended dosage. If haemorrhage is severe, a transfusion of fresh whole blood may be necessary whilst awaiting the effect of the vitamin K_1.

Vitamin K_1 is not an antidote to heparin.

4.5 Interaction with other medicinal products and other forms of interaction

No significant interactions are known other than antagonism of coumarin anticoagulants.

4.6 Fertility, pregnancy and lactation

There is no specific evidence regarding the safety of Konakion MM 10 mg/ml in pregnancy but, as with most drugs, the administration during pregnancy should only occur if the benefits outweigh the risks.

This medicine is not recommended for pregnant women as prophylaxis of vitamin K deficiency bleeding in the newborn.

4.7 Effects on ability to drive and use machines

None

4.8 Undesirable effects

There have been reports of anaphylactoid reactions after intravenous injections of this medicine. Very rarely, venous irritation or phlebitis has been reported in association with intravenous administration of Konakion MM 10 mg/ml mixed micelles solution.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

Hypervitaminosis of vitamin K_1 is unknown.

Reintroduction of anti-coagulation may be affected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics (vitamins), ATC code B02BA01.

Konakion MM 10 mg/ml is a synthetic preparation of vitamin K. The presence of vitamin K (i.e. vitamin K or substances with vitamin K activity) is essential for the formation within the body of prothrombin, factor VII, factor IX and factor X. Lack of vitamin K leads to an

increased tendency to haemorrhage. When an antidote to an anticoagulant is necessary it is essential to use vitamin K_1 itself, as vitamin K analogues are much less effective.
In the mixed micelles solution, vitamin K_1 is solubilised by means of a physiological colloidal system, also found in the human body, consisting of lecithin and bile acid. Owing to the absence of organic solvents, Konakion MM 10 mg/ml mixed micelles solution is well tolerated on intravenous administration.

5.2 Pharmacokinetic properties

Absorption
A pharmacokinetic study indicated that the MM solution of vitamin K_1 given orally is rapidly and effectively absorbed.
Oral doses of vitamin K_1 are absorbed primarily from the middle portions of the small intestine. Systemic availability following oral dosing is approximately 50%, with a wide range of interindividual variability. Onset of action occurs approximately 1–3 hours after intravenous administration and 4–6 hours after oral doses.
Distribution
The primary distribution compartment corresponds to the plasma volume. In blood plasma 90% of vitamin K_1 is bound to lipoproteins (VLDL fraction). Normal plasma concentrations of vitamin K_1 range from 0.4 to 1.2 ng/ml. After i.v. administration of 10 mg vitamin K_1 (Konakion MM), the plasma level after 1 hour is about 500 ng/ml and about 50 ng/ml at 12 hours. Vitamin K_1 does not readily cross the placenta and is poorly distributed into breast milk.
Metabolism
Vitamin K_1 is rapidly converted into more polar metabolites, including vitamin K_1-2,3-epoxide. Some of this metabolite is reconverted into vitamin K_1.
Elimination
Following metabolic degradation, vitamin K_1 is excreted in the bile and urine as glucuronide and sulfate conjugates. The terminal half-life in adults is 14 ± 6 h after i.v. administration and 10 ± 6 h after oral administration. Less than 10% of a dose is excreted unchanged in the urine.
Pharmacokinetics in special clinical situations
Intestinal absorption of vitamin K_1 is impaired by various conditions, including malabsorption syndromes, 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 section Dosage and administration).

5.3 Preclinical safety data

None applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lecithin for mixed micelles, Glycocholic acid, Sodium hydroxide, Hydrochloric acid, Water for injection

6.2 Incompatibilities

None

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton to protect from light.
Do not use if the solution is turbid.
For single use.

6.5 Nature and contents of container

Konakion MM 10 mg/ml is supplied in amber glass ampoules with breaking neck, containing 10 mg phytomenadione in 1 ml. The ampoule solution is clear to slightly opalescent, and contains the active constituent in a mixed micelles vehicle of glycocholic acid and lecithin.

Pack sizes: 5 or 25 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

See Section 4.2 Posology and method of administration.

7 MANUFACTURER

Cheplapharm Arzneimittel GmbH, Greifswald, Germany

8 LICENSE HOLDER

Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Kiryat Matalon, Petah-Tikva

8 LICENSE NUMBER

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