Konakion® MM 10 mg/ml
Phytomenadione

Composition
Active ingredient: phytomenadione (synthetic vitamin K_1).

Ampoule MM 10 mg/ml in a bile acid/lecithin mixed-micelle (MM) solution. One amber glass ampoule contains 1 ml of the clear mixed-micelle solution of 10 mg vitamin K_1 (filling volume 1.15 ml) for oral or parenteral administration.

Excipients:
Ampoules: glycocholic acid, sodium hydroxide, lecithin, hydrochloric acid, water for injections.

Properties and effects
Vitamin K_1 (phytomenadione), the active ingredient of Konakion, is a procoagulant factor. As a component of a hepatic carboxylase system, vitamin K_1 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. Coumarins inhibit the reduction of vitamin K_1 (quinone form) to vitamin K_1 hydroquinone and also prevent the vitamin K_1 epoxide arising after carboxylation from being reduced to the quinone form.
Vitamin K_1 is an antagonist of coumarin-type anticoagulants, e.g. phenprocoumon (active ingredient of Marcoumar®). It does not, however, neutralize the activity of heparin (active ingredient of Liquemin®); protamine is the antagonist of heparin.
Vitamin K_1 is ineffective in hereditary hypoprothrombinemia or hypoprothrombinemia induced by severe hepatic failure.
In the MM ampoules, vitamin K_1 is solubilized by means of a physiological colloid system of bile acid- lecithin micelles, a transport medium also found in the body.

Pharmacokinetics
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).

Indications and usage
Hemorrhage or risk of hemorrhage as a result of severe 'hypoprothrombinemia' (i.e. deficiency of clotting factors II, VII, IX and X) of various etiologies, including overdosage of coumarin-type anticoagulants, their combination with phenylbutazone and other forms of hypovitaminosis K (e.g. in obstructive jaundice as well as liver and intestinal disorders, and after prolonged treatment with antibiotics, sulfonamides or salicylates).
For prophylaxis and treatment of hemorrhagic disease in the newborn, Konakion MM paediatric ampoules (2 mg/0.2 ml) should be used.

Dosage and administration
Konakion MM 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 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 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 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. 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 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 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 should be used.

Oral use
Either with a Konakion MM dispenser or a syringe.

Syringe
Konakion MM 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.

Restrictions on use

Contraindications
Konakion is contraindicated in patients with known hypersensitivity to any of its constituents. Konakion MM ampoules should not be administered intramuscularly because the i.m. route exhibits depot characteristics and continued release of vitamin K_1 would lead to difficulties with the re-institution of anticoagulation therapy. Furthermore, i.m. injections given to anticoagulated subjects cause a risk of haematoma formation.

Precautions
At the time of use, the mixed-micelle ampoule solution must be clear. Following incorrect storage, the solution may become turbid or a phase separation may occur. 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.

Pregnancy, nursing mothers
No controlled studies of Konakion have been performed in animals or pregnant women. On the basis of many years' clinical experience, however, it is safe to assume that neither vitamin K_1 nor the excipients contained in the Konakion formulations have any reproductive toxicological effects when the drug is given at the recommended dosages. As with all medications, however, Konakion should be given to pregnant women only if the benefit to the mother outweighs the risk to the fetus.
As vitamin K_1 does not readily cross the placental barrier, it is not recommended that Konakion be given to expectant mothers as prophylaxis of hemorrhagic disease in the newborn.
Only a small fraction of administered vitamin K_1 enters the breast milk. At therapeutic doses, administration of Konakion to nursing mothers accordingly does not pose a risk to their infants.
However, Konakion is not recommended for nursing mothers as prophylaxis of hemorrhagic disease in the newborn.

Undesirable effects
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) and 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.

Reporting 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
In addition, you may report suspected adverse reactions by sending an e-mail message to safety@tzamal-medical.co.il
or by visiting the "Contact Us" webpage at:
http://www.tzamal-medical.co.il/69601.html
or by phone: +972-73-7151107.

Interactions
Vitamin K_1 antagonizes the effect of coumarin-type anticoagulants. Coadministration of anticonvulsants can impair the action of vitamin K_1.

Overdosage
There is no known clinical syndrome attributable to hypervitaminosis of vitamin K_1. Reintroduction of anti-coagulation may be affected.

Special remarks
Shelf-life
The expiry date of the product is indicated on the packaging materials.

Stability
This medicine should not be used after the expiry date (EXP) shown on the pack.
Konakion MM ampoule solution should be protected from light and should not be stored above 25ºC. It should not be frozen.
For stability reasons, the unused contents of open ampoules cannot be used and should be discarded.

Packs
Ampoules MM 10 mg/ml

Manufacturer
Cheplapharm Arzneimittel GmbH, Greifswald, Germany

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

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