Phytomenadione

**Composition**

*Active ingredient:* phytomenadione (synthetic vitamin K<sub>1</sub>).

Ampoules 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<sub>1</sub> (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<sub>1</sub> (phytomenadione), the active ingredient of Konakion, is a procoagulant factor. As a component of a hepatic carboxylase system, vitamin K<sub>1</sub> 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<sub>1</sub> (quinone form) to vitamin K<sub>1</sub> hydroquinone and also prevent the vitamin K<sub>1</sub> epoxide arising after carboxylation from being reduced to the quinone form.

Vitamin K<sub>1</sub> is an antagonist of coumarin-type anticoagulants, e.g. phenprocoumon (active ingredient of Marcoumar<sup>®</sup>). It does not, however, neutralize the activity of heparin (active ingredient of Liquemin<sup>®</sup>); protamine is the antagonist of heparin.

Vitamin K<sub>1</sub> is ineffective in hereditary hypoprothrombinemia or hypoprothrombinemia induced by severe hepatic failure.

In the MM ampoules, vitamin K<sub>1</sub> 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<sub>1</sub> given orally is rapidly and effectively absorbed.

Oral doses of vitamin K<sub>1</sub> 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<sub>1</sub> is bound to lipoproteins (VLDL fraction). Normal plasma concentrations of vitamin K<sub>1</sub> range from 0.4 to 1.2 ng/ml. After i.v. administration of 10 mg vitamin K<sub>1</sub> (Konakion MM), the plasma level after 1 hour is about 500 ng/ml and about 50 ng/ml at 12 hours. Vitamin K<sub>1</sub> 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 K₁-2,3-epoxide. Some of this metabolite is reconverted into 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 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 K₁ 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 K₁ can be repeated as needed.

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

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>INR</th>
<th>Oral vitamin K₁</th>
<th>Intravenous vitamin K₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>5-9</td>
<td>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)</td>
<td>0.5 to 1.0 mg 0.5 to 1.0 mg</td>
</tr>
<tr>
<td></td>
<td>&gt;9</td>
<td>2.5 to 5.0 mg (up to 10.0 mg)</td>
<td>1.0 mg</td>
</tr>
</tbody>
</table>
Konakion MM Ampoules 10 mg / 1 ml

MoH approved Prescribing Information

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>INR</th>
<th>Oral vitamin K₁</th>
<th>Intravenous vitamin K₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acenocoumarol</td>
<td>5-8</td>
<td>1.0 to 2.0 mg</td>
<td>1.0 to 2.0 mg</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>3.0 to 5.0 mg</td>
<td>1.0 to 2.0 mg</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>5-9</td>
<td>2.0 to 5.0 mg</td>
<td>2.0 to 5.0 mg</td>
</tr>
<tr>
<td></td>
<td>&gt;9</td>
<td>2.0 to 5.0 mg</td>
<td>2.0 to 5.0 mg</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>Not recommended</td>
<td>Individually adapted doses</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Condition</th>
<th>Intravenous vitamin K₁</th>
<th>Concomitant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Major bleeding</td>
<td>5.0 to 10.0 mg</td>
<td>FFP or PCC</td>
</tr>
<tr>
<td></td>
<td>Life-threatening bleeding</td>
<td>10.0 mg</td>
<td>FFP, PCC, or recombinant factor VIIa</td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>Major bleeding</td>
<td>5.0 mg</td>
<td>FFP, PCC, or prothrombin concentrates and factor VII</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>Major bleeding with INR &lt;5.0</td>
<td>5.0 mg</td>
<td>PCC</td>
</tr>
<tr>
<td></td>
<td>Major bleeding with INR &gt;5.0</td>
<td>10.0 mg</td>
<td>PCC</td>
</tr>
</tbody>
</table>

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 K₁ 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 K₁ 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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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 (\(\geq 1/10\)), common (\(\geq 1/100, <1/10\)), uncommon (\(\geq 1/1,000, <1/100\)), rare (\(\geq 1/10,000, <1/1,000\)) 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.

**Interactions**

Vitamin K\textsubscript{1} antagonizes the effect of coumarin-type anticoagulants. Coadministration of anticonvulsants can impair the action of vitamin K\textsubscript{1}.

**Over dosage**

There is no known clinical syndrome attributable to hypervitaminosis of vitamin K\textsubscript{1}. Reintroduction of anticoagulation may be affected.

**Special remarks**

**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 25°C. 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

**License Number:** 062-28-21477-00

**Manufacturer:** F. Hoffmann-La Roche Ltd., Basel, Switzerland

**License Holder:** Roche Pharmaceuticals (Israel) Ltd., P.O. Box 6391 Hod Hasharon 4524079

*Medicine: keep out of reach of children*