Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Konakion MM Ampoules 10 mg/ml Solution for Injection and Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 10 mg vitamin K1 (phytomenadione) per 1 ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection and oral solution.

The solution is clear to slightly opalescent, pale yellow in colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Konakion is indicated in the treatment of haemorrhage or threatened haemorrhage associated with a low blood level of prothrombin or factor VII. The main indication is:

As an antidote to anticoagulant drugs of the coumarin type.

4.2 Posology and method of administration

Konakion MM ampoules are for intravenous injection or oral use. The ampoule solution should not be diluted or mixed with other parenteral medicines, but may be injected, where appropriate, into the lower part of the infusion set (via Y-site or 3-way tap), during continuous infusion of sodium chloride 0.9% or 5% dextrose.

The dosage recommendations detailed in the tables below are provided for therapeutic guidance only.

The dose selection for a specific patient should be based not only on the INR value, but various other risk factors and clinical determinants such as patient characteristics, comorbid conditions and concomitant medications should also be appropriately considered. Hence the actual dose selection should be at the discretion of the treating physician.

Adults: As an antidote to anticoagulant drugs
Severe or life-threatening haemorrhage, e.g. during anticoagulant therapy: The coumarin anticoagulant should be withdrawn and an intravenous injection of Konakion MM given slowly in a dose of 5-10 mg together with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). The dose of vitamin K1can be repeated as needed. The prothrombin level should be estimated three hours later and, if the response has been inadequate, the dose should be repeated. Not more than 40 mg of Konakion MM should be given intravenously in 24 hours.

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 VIIa
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

Less severe haemorrhage:
In patients with less severe haemorrhage or in patients with asymptomatic high International Normalized Ratio (INR) without haemorrhage Konakion MM can be given orally or intravenously.

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

Anticoagulant	INR	**Oral** vitamin K1	**Intravenous** vitamin K1
Warfarin	5.0 - 9.0	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
	> 9.0	2.5 to 5.0 mg (up to 10 mg)	1.0 mg
Acenocoumarol	5.0 - 8.0	1.0 to 2.0 mg	1.0 to 2.0 mg
	> 8.0	3.0 to 5.0 mg	1.0 to 2.0 mg
Phenprocoumon	5.0 - 9.0	2.0 to 5.0 mg	2.0 to 5.0 mg
	> 9.0	2.0 to 5.0 mg	2.0 to 5.0 mg
	> 10.0	not recommended	Individually adapted doses

Vitamin K therapy is considered more effective than simple warfarin withdrawal in reversing elevated INR values. Nevertheless, simple withholding of one or several VKA doses is a possible therapeutic option.

For small doses one or more ampoules of Konakion MM Paediatric (2 mg/0.2 ml: same solution) can be used.

Special dosage instructions

Elderly
Elderly patients tend to be more sensitive to reversal of anticoagulation with Konakion MM; dosage in this group should be at the lower end of the ranges recommended.

Elderly patients with asymptomatic high International Normalized Ratio (INR) with or without mild haemorrhage

For an INR of 5.0 – 9.0, small doses of 0.5 to 1 mg intravenous or oral Vitamin K1 have been shown to effectively reduce the INR to < 5.0 within 24 hours.

Children
There are few data regarding the use of Konakion MM in children over 1 year.
There have been no dose ranging studies in children with haemorrhage. The optimal dose should therefore be decided by the treating physician according to the indication, clinical situation and weight of the patient. However, based on clinical experience, the following recommendations are suggested:

Children with major and life-threatening bleeding

A dose of 5 mg vitamin K1 by intravenous injection is suggested (together with FPP or PCC if appropriate)

Children with asymptomatic high International Normalized Ratio (INR) with or without mild haemorrhage

Intravenous vitamin K1 in doses of 30 micrograms/kg have been reported to be effective in reversing asymptomatic high (> 8.0) INR in clinically well children.

Infants and Neonates
Konakion MM Ampoules must not be given to infants less than one year old, since no data are yet available on this patient group. For infants under one year of age, Konakion MM Paediatric should be used (see separate prescribing information).

Administration for oral use
Konakion MM solution can be given orally with a syringe (e.g. 1 ml syringe).
The ampoule solution should not be diluted. Withdraw the required amount from the ampoule using a syringe with attached needle. Remove the needle from the syringe and administer the contents of the syringe directly into the patient's mouth. Wash down with fluid.

4.3 Contraindications

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

Konakion MM ampoules should not be administered intramuscularly because the intramuscular route exhibits depot characteristics and continued release of vitamin K1 would lead to difficulties with the re-institution of anticoagulation therapy. Furthermore, intramuscular 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 Konakion MM Ampoule 10 mg/1ml contains 54.6 mg glycocholic acid. Careful monitoring of the INR is necessary after administration of Konakion MM 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 must be administered slowly and not more than 40 mg should be given during a period of 24 hours.

Konakion MM 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 haemorrhages, fresh frozen plasma should be used.

Care should be taken when selecting the dose of Konakion MM to ensure that a sub-therapeutic INR is not produced as these can be associated with either thrombosis or subsequent resistance to re-initiation of anticoagulant therapy. Smaller doses of 1 mg have been found to reduce the INR effectively with less risk of over-correction than larger doses.

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.

Konakion MM is essentially ‘sodium free’ as it contains less than 1 mmol sodium (2.64 mg per 1 ml).

4.5 Interaction with other medicinal products and other forms of interaction

Vitamin K1 antagonises the effect of coumarin-type anticoagulants. Anti- convulsants, such as phenobarbital and phenytoin, may cause vitamin K deficiency bleeding on the first day of life in newborns whose mothers have taken these anti-convulsants during pregnancy. The exact mechanism is still unclear.

4.6 Fertility, pregnancy and lactation

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

Konakion 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 known.

4.8 Undesirable effects

The too rapid intravenous administration of vitamin K1 has caused reactions, including flushing of the face, sweating, a sense of chest constriction, cyanosis and peripheral vascular collapse.

There are only a few unconfirmed reports on the occurrence of possible anaphylactoid reactions after intravenous injection of Konakion MM. Very rarely, venous irritation or phlebitis has been reported in association with intravenous administration of Konakion MM (mixed micelle) 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. Healthcare professionals are asked to report any suspected adverse reactions (see details below):

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Hypervitaminosis of vitamin K_1 is unknown.

Reintroduction of anti-coagulation may be affected following overdose of this medicinal product.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics, vitamin K, ATC code B02BA01

Konakion MM is a synthetic preparation of vitamin K1. The presence of vitamin K1 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 K1 itself, as vitamin K analogues are much less effective.

5.2 Pharmacokinetic properties

Absorption
A pharmacokinetic study indicated that the MM solution of vitamin K1 given orally is rapidly and effectively absorbed.

Oral doses of vitamin K1 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 K1 is bound to lipoproteins (VLDL fraction). Normal plasma concentrations of vitamin K1 range from 0.4 – 1.2 nanograms/ml. After intravenous administration of 10 mg vitamin K1 (Konakion MM), the plasma level after 1 hour is about 500 nanograms/ml and about 50 nanograms/ml at 12 hours. 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 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 intravenous administration and 10 ± 6 h after oral administration. Less than 10% of a dose is excreted unchanged in the urine.

Pharmacokinetics in special clinical conditions
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 4.2 Posology and administration).

5.3 Preclinical safety data

LD50 (intravenous) of Konakion MM (10 mg/ml) in mice: 12.1 - 17.7 ml/kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycocholic acid
Sodium hydroxide
Lecithin
Hydrochloric acid
Water for injection

6.2 Incompatibilities

Konakion MM ampoule solution should not be diluted. See Section 4.2.

6.3 Shelf life

2 years.
Once opened use immediately.

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Ten 1 ml Type I amber glass ampoules.

6.6 Special precautions for disposal and other handling

Konakion MM ampoule solution should not be diluted.

Do not use if the solution is turbid.

For single use only.

7 MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489
Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 April 1990

Date of last renewal: 5 April 2010

10 DATE OF REVISION OF THE TEXT

October 2023