# AUSTRALIAN PRODUCT INFORMATION – KONAKION® MM (PHYTOMENADIONE (VITAMIN $K_1$)) SOLUTION

## 1 NAME OF THE MEDICINE

Phytomenadione (Vitamin $K_1$)

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KONAKION MM contains as the active ingredient phytomenadione (Vitamin $K_1$) which is 2-methyl-3-phytyl-1,4-naphthaquinone. Phytomenadione is a clear, yellow, very viscous, odourless or nearly odourless oil with a molecular weight of 450.7. It is insoluble in water, soluble 1 in 70 in alcohol, more soluble in dehydrated alcohol; soluble in benzene, chloroform, ether and vegetable oils. It is stable in air but decomposes on exposure to light.

The ampoule contains the active ingredient phytomenadione 10 mg/1 mL in a mixed micelles (MM) solution (the micelles are composed of glycocholic acid and lecithin in an aqueous solution).

For the full list of excipients, see Section 6.1 List of excipients.

## 3 PHARMACEUTICAL FORM

Solution.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Haemorrhage or threatened haemorrhage as a result of severe "hypoprothrombinaemia" (i.e. deficiency of coagulation factors II, VII, IX and X) due, for instance, to overdosage of anticoagulants of the dicoumarol type, or to other forms of hypovitaminosis K (e.g. obstructive jaundice, liver and intestinal disorders, or prolonged administration of antibiotics, sulfonamides or salicylates).

### 4.2 DOSE AND METHOD OF ADMINISTRATION

KONAKION MM ampoules are for IV injection or oral use.

For important information about the expiry, refer to Section 6.3 Shelf life.

Slow IV injection must be reserved for potentially fatal haemorrhage due to overdosage of anticoagulants of the coumarin and indandione series. There is currently no data to advise on the appropriate vitamin $K_1$ dosage in the event of an indandione overdose.

Excessive doses of KONAKION MM impede the resumption of anticoagulant therapy without offering any advantages.

If there is a recurrence of thrombosis while KONAKION MM is being used, IV administration of heparin is recommended as a first measure.

KONAKION MM should not be diluted or mixed with other injectables except, where appropriate, into the lower part of the infusion set during continuous infusion of sodium chloride 0.9% or dextrose 5%.

**Standard Dosage**

*Severe or life-threatening haemorrhage, e.g. during anticoagulant therapy*: The coumarin anticoagulant should be withdrawn and an IV injection of KONAKION MM given slowly (in at least 30 seconds) in a dose of 5-10 mg together with fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC). Vitamin $K_1$ is essential for sustaining the reversal achieved by FFP or PCC. The prothrombin level should be estimated 3 hours later and, if the response has been inadequate, the dose of vitamin $K_1$ can be repeated as needed.

*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 and PCC |
| | **Life-threatening bleeding** | 10.0 mg | *FFP and PCC |

FFP, fresh frozen plasma
PCC, prothrombin complex concentrate
*FFP should be added to PCC as a source of factor VII when used for warfarin reversal.

Close monitoring of all patients with frequent review of INR (International Normalised Ratio) is recommended.

Oral administration of vitamin $K_1$ is not recommended for patients with major or life-threatening bleeding.

*Dose recommendations for vitamin $K_1$ therapy in patients with asymptomatic high International Normalised Ratio (INR) with or without mild haemorrhage*:

Warfarin should be withdrawn prior to administration of vitamin $K_1$.

| Anticoagulant | INR | Oral vitamin $K_1$ * | Intravenous vitamin $K_1$ |
|---|---|---|---|
| Warfarin | 5-9 | 1.0 to 2.5 mg for initial reversal<br>(add. 1.0 to 2.0 mg if INR remains high after 24 h) | 0.5 to 1.0 mg |
| | >9 | 2.5 to 5.0 mg | 1.0 mg |

* Oral vitamin $K_1$ dosing instructions refer to oral dosing of ampoules only.

KONAKION MM may be administered orally with a syringe. Administration with a syringe can be performed as follows: withdraw the required amount from the ampoule using a syringe with a needle attached. Remove the needle from the syringe and administer the contents of the syringe directly into the patient's mouth. Wash down with fluid.

For small doses one or more ampoules of KONAKION MM Paediatric (2 mg/0.2 mL; same solution) can be used.

**Special dosage instructions**
*Use in the elderly*: See section 4.4 Special warnings and precautions for use - Use in the elderly. Small doses of 0.5 to 1.0 mg IV or oral vitamin $K_1$ have been 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 30 mcg/kg or one tenth of the full IV adult dose of vitamin $K_1$ has been reported to be effective in reversing asymptomatic high (> 8) INR in clinically well children. KONAKION MM must not be injected intramuscularly to children on oral anticoagulant.

*Infants under one year of age*: For this patient group, KONAKION MM Paediatric should be used.

## 4.3 CONTRAINDICATIONS

KONAKION MM is contraindicated in patients with known hypersensitivity to any of its constituents.

KONAKION MM should not be used for patients with pronounced allergic diathesis.

KONAKION MM ampoules should not be administered intramuscularly as this route of administration exhibits depot characteristics which may cause difficulties in the re-institution of anticoagulant therapy. Furthermore, IM administration of medications to anticoagulated patients cause a risk of haematoma formation.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

KONAKION MM should be considered as adjunctive therapy to blood transfusions for severe haemorrhage due to anticoagulant therapy; it is not effective when heparin-like compounds have been used for anticoagulant therapy; minimal doses should be used to offset refractoriness to coumarin-like anticoagulants if long term anticoagulant therapy is intended.

### Thromboembolism

Vitamin K inhibits the therapeutic effect of coumarin anticoagulants and hence creates a risk of thrombosis. In patients in whom KONAKION MM is being used to reverse the effect of coumarin anticoagulation, careful consideration must be given to the fact that restoring the blood's clotting ability restores the risk of thrombosis, possibly even to an increased extent.

### Mutagenesis

Neither phytomenadione nor phytomenadione in the mixed micellar formulation showed evidence of mutagenic activity in *Salmonella typhimurium*. No evidence of chromosomal aberration in human lymphocytes was demonstrated *in vitro* for phytomenadione, but no tests of potential for DNA damage have been conducted.

### Use in hepatic impairment

Careful monitoring of the INR (International Normalized Ratio) is necessary after administration of KONAKION MM in patients with severely impaired liver function. In severe liver disease, KONAKION MM should be discontinued if no significant effect is noted within 1-2 days after the initial dose.

### Use in the 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 range (see Section 4.2 Dose and method of administration – Special dosage instructions).

### Paediatric use

No data available.

### Effects on laboratory tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

KONAKION MM should not be mixed with infusion solutions (see Section 4.2 Dose and method of administration).

Vitamin $K_1$ antagonises the effects of coumarin-type anticoagulants. Coumarins inhibit epoxide reductase in the vitamin K cycle and hence the cofactor function of vitamin K in the carboxylation reaction. Aspirin and other salicylates also attenuate the effect of vitamin K by inhibiting the carboxylase reductase system.

Cephalosporins with the N-methylthiotetrazole group inhibit vitamin K epoxide reductase and hence the effect of vitamin K.

Co-administration of anticonvulsants can impair the action of vitamin $K_1$. Anticonvulsants such as phenobarbital and phenytoin, as well as the anti-tuberculosis drugs isoniazid and rifampicin, may cause vitamin K deficiency bleeding on the first day of life in newborns whose mothers have taken these drugs during pregnancy. The exact mechanism is still unclear.

Vitamin K inhibits the therapeutic effect of coumarin anticoagulants and hence creates a risk of thrombosis (see Section 4.4 Special warnings and precautions for use).

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**

There have been no studies investigating the effect of phytomenadione on reproductive fertility.

**Use in pregnancy**

Vitamin $K_1$ does not readily cross the placental barrier. There are no specific studies regarding the safety of KONAKION MM in pregnancy and no reproductive studies have been performed in animals. KONAKION MM is contraindicated in pregnant women.

**Use in lactation.**

Vitamin $K_1$ is poorly excreted into breast milk. KONAKION MM is not recommended for nursing mothers as prophylaxis of haemorrhagic disease in the newborn.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 ADVERSE EFFECTS (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 IV administration of KONAKION MM. Should an anaphylactoid reaction occur, the usual measures must be taken (e.g. administration of adrenaline and supportive measures as required).

*General disorders and administration site conditions*
Very rare: Venous irritation or phlebitis in association with IV administration of KONAKION MM. Facial flushing and sweating and unusual taste have been reported.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

There is no known clinical syndrome attributable to hypervitaminosis of vitamin $K_1$. Reintroduction of anticoagulation may be affected.

Treatment of suspected overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

### Mechanism of action

As a component of an enzyme system, Vitamin $K_1$ promotes the formation in the liver of coagulation factors II (prothrombin), VII, IX and X and of the coagulation inhibitors protein C and protein S, within the body. Anticoagulants of the coumarin and indandione series cause a reversible displacement of Vitamin $K_1$ from this enzyme system, thereby inhibiting the synthesis of these factors. Since this is a competitive displacement, KONAKION MM is a specific antagonist for warfarin and similar anticoagulants. It is not capable, however, of terminating the action of heparin; for this purpose a salt of protamine should be used.

Vitamin $K_1$ administration, which promotes synthesis of the abovementioned coagulation factors by the liver, can reverse an abnormal coagulation status or bleeding due to Vitamin $K_1$ deficiency. Vitamin $K_1$ is ineffective in hereditary hypoprothrombinaemia or hypoprothrombinaemia induced by severe hepatic failure.

### Clinical trials

No data available.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

A pharmacokinetic study indicated that the MM solution of vitamin $K_1$ administered orally is rapidly and effectively absorbed. Orally ingested phytomenadione is absorbed primarily in the middle portions of the small intestine. Systemic availability after oral administration is about 50%, with a wide range of interindividual variability. Onset of action occurs approximately 1-3 hours after intravenous (IV) administration and 4-6 hours after oral doses.

Impaired gastrointestinal absorption may occur in conditions such as malabsorption syndromes, short bowel syndrome, biliary atresia and pancreatic insufficiency. The oral dosage for this patient group should therefore be at the higher end of the recommended range (see Section 4.2 Dose and method of administration).

### Distribution

The primary distribution compartment corresponds to the plasma volume. In blood plasma, 90% of vitamin $K_1$ is bound to lipo-proteins (VLDL portion). Vitamin $K_1$ plasma concentration is normally between 0.4 and 1.2 ng/mL. After IV administration of 10 mg KONAKION MM the plasma level after 1 hour is approximately 500 ng/mL and approximately 50 ng/mL at 12 hours.

### Metabolism

Vitamin $K_1$ is rapidly converted into more polar metabolites, including an active metabolite vitamin $K_1$-2,3-epoxide. Some of this metabolite is reconverted into vitamin $K_1$.

### Excretion

After metabolic degradation, vitamin $K_1$ is excreted in the bile and urine as the glucuronide and sulphate conjugates. In one pharmacokinetic study of patients on phenprocoumon (another coumarin), which used a sensitive assay, the terminal half-life in adults was 14 ± 6 hours after IV administration of KONAKION MM. Less than 10% of the medicine is excreted unchanged in the urine.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

No data available.

### Carcinogenicity

No studies on the potential carcinogenic activity of phytomenadione have been conducted.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Glycocholic acid
Lecithin
Sodium hydroxide
Hydrochloric acid
Water for injection

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

During the shelf-life of KONAKION MM it is known that impurities will develop. Although there has been no definite evidence of a safety problem due to these impurities, there are also no adequate safety and toxicity data in relation to the impurities. In order to minimise the amount of impurities, prescribers are encouraged to use the product early in the shelf-life wherever possible.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC. Protect from light.

At the time of use, the ampoule solution should be clear. Following incorrect storage, the solution may become turbid or present a phase separation. In this case the ampoule must not

be used. KONAKION MM ampoules should be used early in the shelf-life wherever possible (see Section 6.3 Shelf life).

### 6.5 NATURE AND CONTENTS OF CONTAINER

KONAKION MM is available in ampoules.

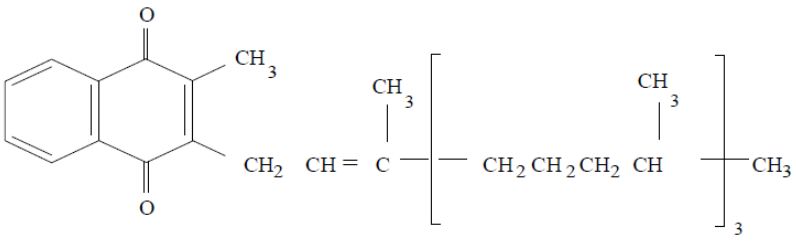
MM Ampoules 10 mg/1 mL, IV, 5s.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

### 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical structure**



**CAS number**

CAS-84-80-0

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

## 8 SPONSOR

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## 9 DATE OF FIRST APPROVAL

8 October 1997

## 10 DATE OF REVISION

21 January 2025

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| **8** | Sponsor address update |