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

1 NAME OF THE MEDICINE

Phytomenadione (Vitamin K_1)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Konakion® MM Paediatric 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 2 mg/0.2 mL in a mixed micelles (MM) solution (the micelles are composed of glycocholic acid and lecithin in an aqueous solution). The formulation is available in two volumes, phytomenadione 10 mg/1 mL (adult) and 2 mg/0.2 mL (paediatric).

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

3 PHARMACEUTICAL FORM

Injection, solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Prophylaxis and treatment of vitamin K deficiency bleeding (VKDB).

4.2 DOSE AND METHOD OF ADMINISTRATION

Konakion MM Paediatric may be given by intramuscular, oral or intravenous routes. Care should be taken to ensure the correct dose is given for the chosen route of administration.

Prophylaxis

All healthy neonates

1 mg (0.1 mL) IM at birth is recommended.

Alternatively, 2 mg (0.2 mL) orally at birth, at the time of newborn screening (3-5 days of age) and at 4 weeks.

For predominately formula fed neonates the last oral dose may be omitted.

Neonates with special risk factors

1 mg IM at birth is recommended in neonates with special risk factors. If the neonate has special risk factors and weighs less than 1.5 kg, then 0.5 mg (0.05 mL) is recommended (see Section 4.4 Special warnings and precautions for use).

The size and frequency of further doses should be based on clinical grounds and coagulation status.

Clotting and PIVKA-II (Proteins Induced in Vitamin K Absence) tests are not to be relied upon as indications of deficiency as the relationship between biochemical evidence of deficiency and late VKDB is not clear.

Special Risk Factors

Early and/or classical VKDB

Risk factors include: prematurity, birth asphyxia, delay in establishment of oral feeding, maternal use of anticoagulants, antiepileptics or tuberculostatics and antibiotic treatment.

Late VKDB

Risk factors include liver dysfunction including obstructive jaundice, malabsorption and prolonged use of antibiotics.

Therapy

Initially, 1 mg by intravenous injection, with further doses as required, based on the clinical grounds and coagulation status. In certain circumstances, treatment with Konakion MM Paediatric may need to be accompanied by more direct forms of effective haemorrhage control, such as transfusion of whole blood or coagulation factors, to compensate for severe blood loss and the delayed response to vitamin K_1.

VKDB should be suspected with any minor bleed in infants less than 6 months of age, even if coagulation tests are within normal limits. Clotting and PIVKA-II tests are not to be relied upon as indications of deficiency as the relationship between biochemical evidence of deficiency and late VKDB is not clear.

Administration

Parenteral use

Konakion MM Paediatric should not be diluted or mixed with other parenteral medications.

Oral use

(with the dispenser included in the package)

- after breaking the ampoule, place the dispenser vertically into the ampoule;

- withdraw the solution from the ampoule into the dispenser until the solution reaches the marking on the dispenser (= 2 mg vitamin K_1);

- administer the contents of the dispenser directly into the infant’s mouth.

- repeated doses are advised if the infant spits out or vomits an oral dose or alternatively diarrhoea occurs within 24 hours of administration.

4.3 CONTRAINDICATIONS

Konakion MM Paediatric is contraindicated in patients with known hypersensitivity to any of the ingredients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Anticoagulant Therapy

Konakion MM Paediatric 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.

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 the elderly

Please refer to the Konakion MM 10 mg/1 mL Product Information for recommendations for this group.

Paediatric use

Parenteral administration is associated with a possible risk of kernicterus in premature infants weighing less than 2.5 kg.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Vitamin K_1 antagonises the effects of coumarin and indanedione-type anticoagulants (e.g. warfarin, phenindione).

Co-administration of anticonvulsants can impair the action of vitamin K_1.

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

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

Not applicable, please refer to the Konakion MM 10 mg/1 mL Product Information.

Use in lactation

Vitamin K_1 is poorly excreted into breast milk. Konakion 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)

In rare cases anaphylactoid reactions have been reported after parenteral use of Konakion MM Paediatric. Should an anaphylactoid reaction occur, the usual measures must be taken (e.g. administration of adrenaline and supportive measures as required).

Very rarely, injection site reaction, venous irritation or phlebitis has been reported in association with parenteral administration of Konakion MM solution to adults. This reaction is unlikely in neonates due to the small injection volume (0.2 mL). Rarely, injection site reactions may occur which may be severe, including inflammation, atrophy and necrosis.

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.

The following adverse events have been reported concerning overdose with use of KONAKION in neonates and infants: jaundice, hyperbilirubinaemia, increased glutamine-oxaloacetic transferase and gamma-glutamyl transferase, abdominal pain, constipation, soft stools, malaise, agitation and cutaneous eruption. The causality of those cannot be established. The majority of these adverse events were considered non-serious and resolved without any treatment.

Treatment of suspected overdose should be aimed at alleviating symptoms and 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 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.

Lack of vitamin K_1 leads to an increased tendency of vitamin K deficiency bleeding (VKDB). Administration of vitamin K_1 promotes synthesis of above-mentioned coagulation factors, can reverse an abnormal coagulation status or bleeding due to vitamin K_1 deficiency and thereby reduces the risk of early, classic or late VKDB.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Orally ingested phytomenadione is absorbed primarily in the middle portions of the small intestine. Optimum absorption is possible only in the presence of bile and pancreatic juice. The absolute bioavailability following intramuscular (IM) administration is approximately 80%. The 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.

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 to adults the plasma level after 1 hour is approximately 500 ng/mL and approximately 50 ng/mL at 12 hours. Vitamin K_1 is stored in the body for only short periods of time, 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 an active metabolite vitamin K_1-2,3-epoxide. Some of this metabolite is reconverted into vitamin K_1. Metabolism of vitamin K_1 after birth through epoxidation may occur more rapidly in premature infants.

Excretion

The elimination half-life in plasma is 1.5-3 hours. After metabolic degradation, vitamin K_1 is excreted in the bile and urine as the glucuronide and sulphate conjugates. 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 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 MM ampoule solution should be clear. Following incorrect storage, the solution may become turbid or phase-separation may occur. In this case the ampoule must not be used.

6.5 NATURE AND CONTENTS OF CONTAINER

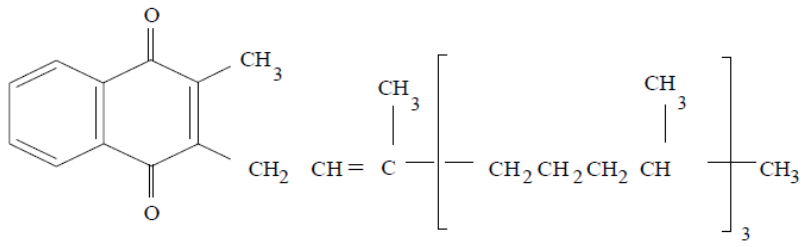
Konakion MM Paediatric ampoules 2 mg/0.2 mL (filling volume 0.3 mL): pack of five amber glass ampoules and 5 dispensers (graduated oral plastic syringes).

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

Pharmaco (Australia) Ltd
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Zenith Towers
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Chatswood, NSW 2067
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9 DATE OF FIRST APPROVAL

7 February 2000

10 DATE OF REVISION

21 January 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor address update