Data Sheet

Konakion® MM
Konakion® MM paediatric

Phytomenadione, 10 mg/1 mL and 2 mg/0.2 mL mixed micelle solution

Procoagulant factor

Composition

Active ingredient

Phytomenadione (synthetic vitamin K_1).

Each Konakion MM amber glass ampoule contains 10 mg phytomenadione in 1mL of clear bile acid/lecithin mixed-micelle (MM) solution (filling volume 1.15 mL) for oral or intravenous (IV) administration.

Each Konakion MM paediatric amber glass ampoule contains 2 mg of phytomenadione in 0.2 mL of clear bile acid/lecithin mixed-micelle (MM) solution (filling volume 0.3 mL) for oral or parenteral administration.

Excipients

Glycocholic acid, sodium hydroxide, lecithin, hydrochloric acid, water for injections.

Appearance

Clear to slightly opalescent liquid, practically free from particles.

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. It does not, however, neutralise the activity of heparin; protamine is the antagonist of heparin.

Vitamin K_1 is ineffective in hereditary hypoprothrombinemia or hypoprothrombinemia induced by severe hepatic failure.

Lack of vitamin K_1 leads to an increased tendency to haemorrhagic disease in the newborn. Vitamin K_1 administration, which promotes synthesis of the above-mentioned coagulation factors by the liver, can reverse an abnormal coagulation status and bleeding due to vitamin K_1 deficiency.

Pharmacokinetics

In the Konakion MM and Konakion MM paediatric ampoules, vitamin K_1 is solubilised by means of a physiological colloid system of bile acid-lecithin micelles, a transport medium also found in the body.

Absorption

A pharmacokinetic study indicated that the MM solution of vitamin K_1 administered orally is rapidly and effectively absorbed from the small intestine. Absorption is limited in the absence of bile.

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 IV administration and 4–6 hours after oral doses.

Distribution

Vitamin K_1 accumulates predominantly in the liver and is stored in the body only for short periods of time.

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 IV 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 placental barrier from mother to child and is poorly distributed into breast milk.

Metabolism

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

Elimination

The elimination half-life of vitamin K_1 in plasma of neonatal is about 70 hours.

Following metabolic degradation, vitamin K_1 is excreted in the bile and urine as glucuronide and sulphate conjugates. The terminal half-life in adults is 14 ± 6 hours after IV administration and 10 ± 6 hours after oral administration. Less than 10% of a dose is excreted unchanged in the urine.

Pharmacokinetic of oral vs. iv mixed micellar vitamin K prophylaxis in special populations

Infants with cholestatic liver disease

A randomized study with 44 cholestatic infants of up to 26 weeks of age compared the pharmacokinetics of 2 mg oral versus 1 mg intravenous mixed micellar vitamin K prophylaxis.

The main outcome measures were serum concentrations of vitamin K_1 and undercarboxylated prothrombin (PIVKA-II) before and for up to 4 days after a single dose of mixed micellar vitamin K_1 1 mg intravenously or 2 mg orally. A comparison was also made between vitamin K_1 levels 24 hours

after oral vitamin K_1 administration in the above infants with those of 14 healthy newborns given the same dose.

Median serum vitamin K_1 concentrations were similar in the oral and intravenous groups at baseline (0.92 v 1.15 ng/ml) rising to approximately 100 times higher concentrations six hours after intravenous K_1 compared to oral administration (139 ng/ml vs. 1.4 ng/ml). Moreover in the oral group the low median value and wide range of serum K_1 compared unfavorably with the much higher levels observed in healthy infants given the same oral dose.

The study suggested an impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 17% achieved an incremental rise in serum vitamin K_1 > 10 ng/ml.

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 Dosage and Administration).

Indications

Haemorrhage or risk of haemorrhage as a result of severe 'hypoprothrombinemia' (i.e. deficiency of clotting factors II, VII, IX and X) of various aetiologies, including overdosage of courmarin-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, sulphonamides or salicylates).

Prophylaxis and treatment of haemorrhagic disease in the newborn.

Dosage and Administration

Dosage

Adults

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) 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 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

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 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

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

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

Infants under 1 year of age

For this patient group Konakion MM paediatric 2 mg/0.2 mL ampoules should be used.

Prophylaxis

For all healthy neonates

2 mg orally at birth or shortly after birth, followed by a further 2 mg dose four to seven days later.

A single 1 mg (0.1 mL) dose i.m. is recommended in children who are not assured of receiving a second oral dose or, in the case of breast-fed children, who are not assured of receiving a third oral dose.

Exclusively breast-fed babies

In addition to the recommendations for all neonates, 2 mg orally should be given after four to six weeks.

Neonates with special risk factors
(e.g. prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics):

- 1 mg intramuscularly or intravenously at birth or shortly after birth if the oral route is unsuitable.
- Intramuscular and i.v. doses should not exceed 0.4 mg/kg (equivalent to 0.04 mL/kg) in premature infants weighing less than 2.5 kg (see Precautions).
- The size and frequency of further doses should be based on coagulation status.

Therapy
Initially, 1 mg by IV injection, with further doses as required, based on the clinical picture 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.

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 IV or oral vitamin K_1 have been shown to effectively reduce the INR to < 5.0 within 24 hours (see 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 IV adult dose of vitamin K_1 has been reported to be effective in reversing asymptomatic high (> 8) INR in clinically well children.

Administration

Konakion MM 10 mg/1 mL

Konakion MM 10 mg/1 mL ampoules are for IV injection or oral use.

Intravenous Use
The ampoule solution should not be diluted or mixed with other parenteral medications except, 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 2 mg/0.2 mL should be used in neonates and infants under one year of age.

Oral Use
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.

Konakion MM paediatric 2 mg/0.2 mL

Oral use
1. With the dispensers included in the package:
   - after breaking the ampoule, place a dispenser vertically into the ampoule;

- withdraw the solution from the ampoule into the dispenser until the solution reaches the marking of the dispenser (= 2 mg vitamin K_1);
- administer the contents of the dispenser directly into the newborn's mouth

2. If no dispenser is available an alternative method of oral administration is the use of a syringe as follows:
   - the required volume should be withdrawn from the ampoule with a syringe and needle;
   - after removal of the needle the content of the syringe should be administered directly from the syringe into the newborn's mouth.

Parenteral use

Konakion MM paediatric 2 mg/0.2 mL ampoules are for IV or IM injection. Konakion MM paediatric should not be diluted or mixed with other parenteral medications. It may however be injected into the lower part of an infusion set.

Contraindications

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

Konakion MM 10 mg/1 mL ampoules should not be administered intramuscularly (IM) because the IMIM route exhibits depot characteristics and continued release of vitamin K_1 would lead to difficulties with the re-institution of anticoagulation therapy. Furthermore, IM. injections given to anticoagulated subjects cause a risk of haematoma formation.

Precautions

At the time of use, the mixed-micelle ampoule solutions 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.

Parenteral administration may be associated with an increased risk of kernicterus in premature infants weighing less than 2.5 kg.

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 medicine 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 foetus.

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 haemorrhagic 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 haemorrhagic 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 (≥ 1/1000, < 1/100), rare (≥ 1/10,000, < 1/1000) and very rare (< 1/10,000) including isolated reports.

Immune system disorders
Very rare: Anaphylactoid reactions after IV administration of Konakion MM.

General disorders and administration site conditions
Very rare: Venous irritation or phlebitis in association with IV administration of Konakion MM.

Local irritation may occur at the injection site of Konakion MM paediatric, but is unlikely in view of the small injection volume.

Interactions

Vitamin K_1 antagonises 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.

The following adverse events have been reported concerning overdose with use of Konakion in neonates and infants: jaundice, hyperbilirubinaemia, increased glutamine-oxaloacetic acid 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.

Special Remarks

Stability

This medicine should not be used after the expiry date shown on the pack.

Konakion MM and Konakion MM paediatric ampoule solution should be protected from light and should not be stored above 25°C. The solution should not be frozen.

The ampoule solutions must be clear when used. Improper storage can cause turbidity or phase separation. In such cases, ampoules must not be used.

For stability reasons, the unused contents of open ampoules cannot be used and should be discarded.

Medicine Classification

General Sale Medicine

Packs

Konakion MM 10 mg/1 mL	Packs of 5 ampoules
Konakion MM paediatric 2 mg/0.2 mL*	Packs of 5 ampoules

* Pack contains 5 dispensers for oral administration.

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