

## **Phytomenadione Injection BP 1mg/0.5ml.**

### **1. Name of the medicinal product**

Phytomenadione Injection BP 1mg/0.5ml  
Taj Pharma.

### **2. Qualitative and quantitative composition**

a) Phytomenadione Injection BP 1mg/0.5ml

Each ml contains:

Phytomenadione	2mg
Polyethylated fattyacid	70mg
Dextrose	37.5mg
Benzyl alcohol	9mg
HCL for pH adjustment.	

### **3. Pharmaceutical form**

The ampoule solution is clear to slightly opalescent, pale yellow in colour and contains the active constituent in a mixed micelles vehicle of glycocholic acid and lecithin.

### **4. Clinical particulars**

#### **4.1 Therapeutic indications**

Konakion MM Paediatric is indicated for the prophylaxis and treatment of vitamin K deficiency bleeding (VKDB) in neonates and infants.

Konakion MM Paediatric can be used, following specialist advice from a haematologist, as an antidote to anticoagulant drugs of the coumarin type in infants and children. For use as an antidote to anticoagulant drugs of the coumarin type in adolescents and adults, refer to Konakion MM Ampoules 10mg/ml.

#### **4.2 Posology and method of administration**

***Prophylaxis of vitamin K deficiency bleeding (VKDB)***

*Healthy neonates of 36 weeks gestation and older:*

Either:

- 1 mg administered by intramuscular injection at birth or soon after birth

or

- 2 mg orally at birth or soon after birth. The oral dose should be followed by a further dose of 2 mg at 4-7 days of age. A further 2 mg oral dose should be given at 1 month after birth. In exclusively formula fed infants the third oral dose can be omitted

*Preterm neonates of less than 36 weeks gestation weighing 2.5 kg or greater, and term neonates at special risk (e.g. prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics):* 1 mg IM or IV at birth or soon after birth. The amount and frequency of further doses should be based on coagulation status.

*Preterm neonates of less than 36 weeks gestation weighing less than 2.5 kg:* 0.4 mg/kg (equivalent to 0.04 ml/kg) IM or IV at birth or soon after birth. This parenteral dose should not be exceeded. The amount and frequency of further doses should be based on coagulation status.

There is evidence that oral prophylaxis is insufficient in patients with underlying cholestatic liver disease and malabsorption (see section 5.1).

**CAUTION:** care is required when calculating and measuring the dose in relation to the baby's weight (10 times dosing errors are common).

**Dosing information for preterm babies at birth for the prophylaxis of Vitamin K deficiency bleeding**

Weight of	Dose of	Injection
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the baby	vitamin K at birth	volume
1 kg	0.4 mg	0.04 ml
1.5 kg	0.6 mg	0.06 ml
2 kg	0.8 mg	0.08 ml
2.5 kg	1 mg	0.1 ml
Over 2.5 kg	1 mg	0.1 ml

Further oral doses in breast-fed infants have been advised, but safety or efficacy data for these additional doses is limited (see section 5.1).

***Therapy of early and/or late vitamin K deficiency bleeding (VKDB)***

Initially 1mg IV and further doses as required, depending on clinical picture and coagulation status. Konakion therapy may need to be accompanied by a more immediate effective treatment, such as transfusion of blood or blood clotting factors to compensate for severe blood loss and delayed response to vitamin K<sub>1</sub>.

***Antidote therapy to anticoagulant drugs of the coumarin type***

There have been no dose ranging studies performed to recommend a specific dose of Konakion MM Paediatric used as an antidote to anticoagulant drugs of the coumarin type in infants and children. Suggested doses are detailed below. Konakion MM Paediatric must be administered by intravenous injection in these patients. It is advisable that a haematologist is consulted about appropriate investigation and treatment in any infant or child in whom Konakion MM Paediatric is being considered.

For patients on warfarin therapy, therapeutic intervention must consider the reason for the patient being on warfarin and whether or not anticoagulant therapy has to be continued (e.g. in a patient with mechanical heart valve

or repeated thrombo-embolic complications) as vitamin K administration is likely to interfere with anticoagulation with warfarin for 2 - 3 weeks. For patients continuing to receive warfarin, the suggested dose for the partial reversal of anticoagulation is 30 micrograms/kg administered by IV injection. Konakion MM Paediatric is only suitable for the administration of doses of 30 micrograms/kg in children weighing over 13 kg.

The suggested dose of vitamin K for patients requiring a complete reversal of a warfarin overdose is 250-300 micrograms/kg administered by IV injection. It should be noted that the earliest effect seen with vitamin K treatment is at 4 to 6 hours and therefore, in patients with severe haemorrhage, replacement with coagulation factor concentrates may be indicated (discuss with haematologist). Konakion MM Paediatric is only suitable for the administration of doses of 250-300 micrograms/kg in children weighing over 1.6 kg. Prothrombin time should be measured 2 to 6 hours later and if the response has not been adequate, Konakion MM Paediatric administration may be repeated. Frequent monitoring of vitamin K dependent clotting factors is essential in these patients.

***Method of administration***

Konakion MM Paediatric can be administered by intramuscular or intravenous injection or by oral administration depending on the indication.

*Parenteral use:* For the administration of injection volumes of 0.04 ml (0.4 mg) to 0.1 ml (1 mg), 0.5 ml syringes with 0.01 ml graduations are recommended, see section 6.6 *Instructions for use/handling*.

Administration of Konakion MM Paediatric by i.v. infusion is not recommended because Konakion MM Paediatric must not be diluted or mixed with other parenteral medications. However, Konakion MM Paediatric may be administered by injecting the dose into the lower part of an infusion set containing 5% dextrose or 0.9% sodium chloride running at  $\geq 0.7$  ml/minute, see section 6.2 *Incompatibilities*.

*Oral use:* For oral administration, oral dispensers are provided in the pack. After breaking the ampoule open, 0.2 ml of solution should be withdrawn into the oral dispenser until it reaches the mark on the dispenser (0.2 ml = 2 mg vitamin K). Drop the contents of the dispenser directly into the baby's mouth by pressing the plunger.

#### **4.3 Contraindications**

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

#### **4.4 Special warnings and precautions for use**

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.

Parenteral administration to premature babies weighing less than 2.5kg may increase the risk for the development of kernicterus (bilirubin encephalopathy).

Infants with cholestatic disease must receive Konakion MM Paediatric by intramuscular or intravenous injection since oral absorption is impaired in these patients.

Konakion MM Paediatric must be administered by intravenous injection when used as an antidote to anticoagulant drugs of the coumarin type, as intramuscular injections may result in significant bleeding in these patients.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

No significant interactions are known other than antagonism of coumarin anticoagulants.

#### **4.6 Fertility, pregnancy and lactation**

Not applicable

#### **4.7 Effects on ability to drive and use machines**

Not applicable

#### **4.8 Undesirable effects**

There have been reports of anaphylactoid reactions after intravenous injections of Konakion MM. Local irritation may occur at the injection site but is unlikely due to the small injection volume. Rarely, injection site reactions may occur which may be severe, including inflammation, atrophy and necrosis.

#### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

#### **4.9 Overdose**

There is no known clinical syndrome attributable to hypervitaminosis of vitamin K<sub>1</sub>.

The following adverse events have been reported concerning overdose with use of Konakion in neonates and infants: jaundice, hyperbilirubinaemia, increase GOT and GGT, 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.

### **5. Pharmacological properties**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group:  
Antihæmorrhagics (vitamins).

Konaktion MM is a preparation of synthetic phytomenadione (vitamin K<sub>1</sub>). The presence of vitamin K<sub>1</sub> is essential for the formation within the body of prothrombin, factor VII, factor IX and factor X, and of the coagulation inhibitors, protein C and protein S.

Vitamin K<sub>1</sub> does not readily cross the placental barrier from mother to child and is poorly excreted in breast milk.

Lack of vitamin K<sub>1</sub> leads to an increased tendency to hæmorrhagic disease in the newborn. Vitamin K<sub>1</sub> administration, which promotes synthesis of the above-mentioned coagulation factors by the liver, can reverse an abnormal coagulation status due to vitamin K<sub>1</sub> deficiency.

#### *Paediatric population*

A prospective randomised controlled study included 44 infants (1-26 weeks of age) with conjugated hyperbilirubinaemia (idiopathic neonatal hepatitis - 17 patients, biliary atresia - 13, total parenteral nutrition cholestasis - 3, Alagille's syndrome -2, alpha 1 antitrypsin deficiency - 2, inspissated bile syndrome - 2, and 5 miscellaneous diagnoses (fructosaemia, galactosaemia, choledochal cyst, necrotising enterocolitis, cytomegalovirus hepatitis). The pharmacokinetics and efficacy of oral versus intravenous mixed micellar vitamin K prophylaxis in infants with cholestatic liver disease was compared.

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

after oral K<sub>1</sub> administration with those of 14 healthy newborns given the same dose.

Results: At admission, 18 infants (41%) had elevated levels of serum PIVKA-II and eight (18%) had low K<sub>1</sub> concentrations, indicative of subclinical vitamin K deficiency. Median serum K<sub>1</sub> concentrations were similar in the oral and intravenous groups at baseline (0.92 v 1.15 ng/ml), rising to 139 ng/ml six hours after intravenous K<sub>1</sub> but to only 1.4 ng/ml after oral administration. In the latter group, the low median value (0.95 ng/ml) and wide range (< 0.15–111 ng/ml) of serum K<sub>1</sub> compared unfavourably with the much higher levels (median 77, range 11–263 ng/ml) observed in healthy infants given the same oral dose, and suggested impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 4/24 (17%) achieved an incremental rise in serum K<sub>1</sub> > 10 ng/ml.

The data from a retrospective study indicate that weekly oral prophylaxis was effective in the prevention of VKDB. A total of 507 850 live babies were born during the study period, November 1992 to June 2000. Of these infants, 78% and 22% received oral and intra-muscular prophylaxis, respectively; i.e. about 396000 neonates received oral prophylaxis at birth. Weekly oral prophylaxis was recommended for all infants as long as they were mainly breastfed. Oral vitamin K prophylaxis at birth 2 mg phytomenadione, followed by weekly oral vitamin K prophylaxis; 1 mg was administered by the parents until 3 months of age. No cases of VKDB were revealed, i.e. the incidence was 0–0.9:100000 (95% CI).

#### **5.2 Pharmacokinetic properties**

In the mixed micelle solution, vitamin K<sub>1</sub> is solubilised by means of a physiological

colloidal system consisting of lecithin and a bile acid.

Following oral administration vitamin K<sub>1</sub> is absorbed from the small intestine. The systemic availability following oral dosing is approximately 50%, with a wide range of interindividual variability. Absorption is limited in the absence of bile.

After intramuscular administration vitamin K<sub>1</sub> release into the circulation is prolonged, i.e. the IM route acts as a depot. A single 1mg IM dose results in comparable vitamin K<sub>1</sub> concentrations at 1 month as two 2 mg doses (one given at birth and the other at one week).

Vitamin K<sub>1</sub> accumulates predominantly in the liver, is up to 90% bound to lipoproteins in the plasma and is stored in the body only for short periods of time.

Vitamin K<sub>1</sub> is transformed to more polar metabolites, such as phytomenadione-2,3-epoxide.

The half-life of vitamin K<sub>1</sub> in plasma is approximately 72 hours in neonates and about 1.5 to 3 hours in adults. Vitamin K<sub>1</sub> is excreted in bile and urine as the glucuronide and sulfate conjugates.

### **5.3 Preclinical safety data**

None applicable

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Glycocholic acid, lecithin, sodium hydroxide, hydrochloric acid and water

### **6.2 Incompatibilities**

Incompatibilities have been observed with diluted Konakion MM solution and certain siliconised syringes, therefore, Konakion MM Paediatric must not be diluted before injection.

Do not dilute with sodium chloride containing solutions as precipitation may occur, see section 4.2 Posology and Method of Administration.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

Konakion MM Paediatric Ampoule solution should be stored below 25°C and be protected from light. The solution should not be frozen. Do not use if the solution is turbid.

### **6.5 Nature and contents of container**

Amber glass ampoules containing 2 mg phytomenadione in 0.2 ml. Plastic oral dispensers. Packs of 5.

### **6.6 Special precautions for disposal and other handling**

See section 4.2 *Posology and method of administration*, section 4.4 *Special warnings and precautions for use* and section 6.2 *Incompatibilities* for advice regarding the administration of Konakion MM Paediatric.

Undiluted Konakion MM Paediatric is compatible with 0.5ml Omnican 50 syringes supplied by B.Braun.

## **7.Manufactured in India by:**

**TAJ PHARMACEUTICALS LTD.**

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