

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Phytomenadione 2mg in 0.2ml solution for injection

2. Qualitative and quantitative composition

Each 0.2ml solution for injection contains 2mg Phytomenadione.

This medicine contains 4mg propylene glycol in each 0.2ml of Vit K1 Paediatric Solution for Injection

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection

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

4. Clinical particulars

4.1 Therapeutic indications

Phytomenadione 2mg/0.2ml is indicated for the prophylaxis and treatment of vitamin K deficiency bleeding (VKDB) in neonates and infants.

Phytomenadione 2mg/0.2ml can be used, following specialist advice from a haematologist, as an antidote to anticoagulant drugs of the coumarin type in infants and children.

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 the baby	Dose of vitamin K at birth	Injection 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. Phytomenadione 2mg/0.2ml 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 K₁.

Antidote therapy to anticoagulant drugs of the coumarin type

There have been no dose ranging studies performed to recommend a specific dose of this medicine as an antidote to anticoagulant drugs of the coumarin type in infants and children. Suggested doses are detailed below. Phytomenadione 2mg/0.2ml 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 Phytomenadione 2mg/0.2ml 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. Phytomenadione 2mg/0.2ml 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). Phytomenadione 2mg/0.2ml 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, Phytomenadione 2 mg/0.2 ml administration may be repeated. Frequent monitoring of vitamin K dependent clotting factors is essential in these patients.

Method of administration

This medicine 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 0.04ml (0.4mg) to 0.1ml (1mg), 0.5ml syringes with 0.01ml graduations are recommended, see section 6.6 *Instructions for use/handling*.

Administration of Phytomenadione 2mg/0.2ml by IV infusion is not recommended because it must not be diluted or mixed with other parenteral medications. However, it 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 ≥ 0.7 ml/minute, see section 6.2 *Incompatibilities*.

Oral use: For oral administration. After breaking the ampoule open, 0.2ml of solution should be withdrawn using an oral syringe. Drop the contents of the oral syringe 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 Phytomenadione 2mg/0.2ml by intramuscular or intravenous injection since oral absorption is impaired in these patients.

Phytomenadione 2mg/0.2ml 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 this medicine. 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: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org/>

4.9 Overdose

There is no known clinical syndrome attributable to hypervitaminosis of vitamin K₁.

The following adverse events have been reported concerning overdose with use of Phytomenadione 2mg/0.2ml in neonates and infants: jaundice, hyperbilirubinemia, 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: Antihemorrhagics (vitamins),

ATC code B02BA01.

Phytomenadione 2mg/0.2ml is a preparation of synthetic phytomenadione (vitamin K₁). The presence of vitamin K₁ 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 K₁ does not readily cross the placental barrier from mother to child and is poorly excreted in breast milk.

Lack of vitamin K₁ leads to an increased tendency to haemorrhagic disease in the new-born. Vitamin K₁ administration, which promotes synthesis of the above-mentioned coagulation factors by the liver, can reverse an abnormal coagulation status due to vitamin K₁ deficiency.

Paediatric population

A prospective randomised controlled study included 44 infants (1-26 weeks of age) with conjugated hyperbilirubinemia (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 K₁ and undercarboxylated prothrombin (PIVKA-II) before and for up to 4 days after a single dose of mixed micellar K₁ 1mg intravenously or 2mg orally. A comparison was also made between K₁ levels 24 hours after oral K₁ administration with those of 14 healthy new-borns given the same dose.

Results: At admission, 18 infants (41%) had elevated levels of serum PIVKA-II and eight (18%) had low K₁ concentrations, indicative of subclinical vitamin K deficiency. Median serum K₁ 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 K₁ but to only 1.4 ng/ml after oral administration. In the latter group, the low median value (0.95ng/ml) and wide range (< 0.15–111ng/ml) of serum K₁ compared unfavourably with the much higher levels (median 77, range 11–263ng/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 K₁ > 10ng/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 2mg 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 K₁ is solubilised by means of a physiological colloidal system.

Following oral administration vitamin K₁ 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 K₁ release into the circulation is prolonged, i.e. the IM route acts as a depot. A single 1mg IM dose results in comparable vitamin K₁ concentrations at 1 month as two 2mg doses (one given at birth and the other at one week).

Vitamin K₁ 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 K₁ is transformed to more polar metabolites, such as phytomenadione-2,3-epoxide.

The half-life of vitamin K₁ in plasma is approximately 72 hours in neonates and about 1.5 to 3 hours in adults. Vitamin K₁ 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

Macrogol 15 hydroxy stearate

Sodium acetate

Sodium metabisulfite

Glacial acetic acid

Propylene glycol

Water for injections.

6.2 Incompatibilities

Incompatibilities have been observed with diluted Phytomenadione 2mg/0.2ml solution and certain siliconized syringes, therefore, Phytomenadione 2mg/0.2ml 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

24 Months

6.4 Special precautions for storage

Do not store above 30°C. Do not use if the solution is turbid.

Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Amber glass ampoules, glass type I, Ph. Eur.

Pack sizes: 5 x 0.2ml

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 this medicine.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder

Name: Tasa Pharma Ltd
Address: Unit C1-C3, Kay Complex Mombasa Road, Nairobi,
P.O. Box 3959-00506
Country: Kenya

Manufacturing site addresses

Name: Tasa Pharma Ltd
Address: Unit C1-C3, Kay Complex Mombasa Road, Nairobi,
P.O. Box 3959-00506
Country: Kenya

8. Marketing authorization number

H2024/CTD10598/24089

9. Date of first registration

09/02/2024

10. Date of revision of the text

November 2024