Registration & Regulatory Affairs (R & R)

Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC) TEMPLATE

1.3 Product Information

1.3.1 SPC, Labeling and Package Leaflet

SPC-Summary of Product Characteristics

Name of the proprietary product: PHYTOMENADIONE INJECTION BP 10mg/ml

Name of the nonproprietary International Product: PHYTOMENADIONE INJECTION BP 10mg/ml

Route of Administration: Injection

2. Qualitative and Quantitative composition:

Each ml contains:

Phaytomenadione BP 10 MG

Water for Injection BP Q.S.

3. PHARMACEUTICAL FORM

Injection, A clear Yellowish Solution

4.1. Therapeutic indications

Phytomeadione is indicated in the treatment of haemorrhage or threatened haemorrhage associated with a low blood level of prothrombin or factor VII.

The main indication is:

As an antidote to anticoagulant drugs of the coumarin type.

4.2. Posology and method of administration

Posology

Phytomeadione ampoules are for i.v. injection or oral use. The ampoule solution should not be diluted or mixed with other parenteral medicines, but may be injected, where appropriate, into the lower part of the infusion set (via Y-site or 3-way tap), during continuous infusion of sodium chloride 0.9% or 5% dextrose.

The dosage recommendations detailed in the tables below are provided for therapeutic guidance only.

The dose selection for a specific patient should be based not only on the INR value, but various

other risk factors and clinical determinants such as patient characteristics, comorbid conditions and concomitant medications should also be appropriately considered. Hence the actual dose selection should be at the discretion of the treating physician.

Adults: As an antidote to anticoagulant drugs

Severe or life-threatening haemorrhage, e.g. during anticoagulant therapy: The coumarin anticoagulant should be withdrawn and an intravenous injection of Phytomenadione given slowly in a dose of 5-10 mg together with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). The dose of vitamin K1 can be repeated as needed.

The prothrombin level should be estimated three hours later and, if the response has been inadequate, the dose should be repeated. Not more than 40mg of Phytomenadione should be given intravenously in 24 hours.

ELDERLY

Elderly patients tend to be more sensitive to reversal of anticoagulation with Phytomeadione; dosage in this group should be at the lower end of the ranges recommended. Elderly patients with asymptomatic high International Normalized Ratio (INR) with or without mild haemorrhage

For an INR of 5.0 – 9.0, small doses of 0.5 to 1.0 mg i.v. or oral Vitamin K1 have been shown to effectively reduce the INR to <5.0 within 24 hours.

CHILDREN

There are few data regarding the use of Phytomeadione in children over 1 year.

There have been no dose ranging studies in children with haemorrhage. The optimal dose should therefore be decided by the treating physician according to the indication, clinical situation and weight of the patient. However based on clinical experience, the following recommendations are suggested:

Children with major and life threatening bleeding

A dose of 5mg vitamin K1 i.v. is suggested (together with FPP or PCC if appropriate)

INFANTS AND NEONATES

Phytomenadione Ampoules must not be given to infants less than one year old, since no data are yet available on this patient group. For infants under one year of age, Phytomenadione Paediatric should be used (see separate prescribing information).

4.3. Contraindications

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

Phytomenadione ampoules should not be administered intramuscularly because the I.M. route exhibits depot characteristics and continued release of vitamin K1 would lead to difficulties with the re-institution of anticoagulation therapy. Furthermore, I.M. injections given to anticoagulated subjects cause a risk of haematoma formation.

4.4. Special warnings and special precautions for use

- When treating patients with severely impaired liver function, it should be borne in mind that one Phytomenadione
- 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.
- In potentially fatal and severe haemorrhage due to overdosage of coumarin anticoagulants, intravenous injections of Phytomenadione must be administered slowly and not more than 40 mg should be given during a period of 24 hours.
- Phytomenadione therapy should be accompanied by a more immediate effective treatment such as transfusion of whole blood or blood clotting factors.
- When patients with prosthetic heart valves are given transfusions for the treatment of severe or potentially fatal haemorrhages, fresh frozen plasma should be used.
- Care should be taken when selecting the dose of Phytomenadione to ensure that a sub-therapeutic INR is not produced as these can be associated with either thrombosis or subsequent resistance to re-initiation of anticoagulant therapy.
- Smaller doses of 1mg have been found to reduce the INR effectively with less risk of over-correction than larger doses.
- If haemorrhage is severe, a transfusion of fresh whole blood may be necessary whilst awaiting the effect of the vitamin K1.
- Vitamin K1 is not an antidote to heparin.
- Phytomenadione is essentially ‘sodium free’ as it contains less than 1 mmol sodium (2.64mg per 1ml).

4.5. Interactions with other Drug products and other forms of interaction

Vitamin K1 antagonises the effect of coumarin-type anticoagulants. Anti- convulsants, such as phenobarbital and phenytoin, may cause vitamin K deficiency bleeding on the first day of life in

newborns whose mothers have taken these anti- convulsants during pregnancy. The exact mechanism is still unclear.

4.6 Pregnancy and lactation

There is no specific evidence regarding the safety of Phytomenadione in pregnancy but, as with most drugs, the administration during pregnancy should only occur if the benefits outweigh the risks. Phytomenadione is not recommended for pregnant women as prophylaxis of vitamin K deficiency bleeding in the newborn.

4.7. Effects on ability to drive and use machines

NOT APPLICABLE

4.8. Undesirable effects

The too rapid intravenous administration of vitamin K1 has caused reactions, including flushing of the face, sweating, a sense of chest constriction, cyanosis and peripheral vascular collapse. There are only a few unconfirmed reports on the occurrence of possible anaphylactoid reactions after IV injection of Phytomenadione. Very rarely, venous irritation or phlebitis has been reported in association with intravenous administration of Phytomenadione mixed micelle solution.

4.9 OVERDOSE

Hypervitaminosis of vitamin K1 is unknown.

Reintroduction of anti-coagulation may be affected following overdose of this medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Phytomenadione is a synthetic preparation of vitamin K1. The presence of vitamin K1 is essential for the formation within the body of prothrombin, factor VII, factor IX and factor X. Lack of vitamin K leads to an increased tendency to haemorrhage. When an antidote to an anticoagulant is necessary it is essential to use vitamin K1 itself, as vitamin K analogues are much less effective.

5.2 Pharmacokinetic Properties

Absorption

A pharmacokinetic study indicated that the MM solution of vitamin K given orally is rapidly and

effectively absorbed. Oral doses of vitamin K 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 intravenous administration and 4-6 hours after oral doses.

Distribution

The primary distribution compartment corresponds to the plasma volume. In blood plasma, 90% of vitamin K is bound to lipoproteins (VLDL fraction). Normal plasma concentrations of vitamin K range from 0.4 – 1.2 ng/ml). After i.v. administration of 10 mg vitamin K (Konakion MM), the plasma level after 1 hour is about 500 ng/ml and about 50ng/ml at 12 hours. Vitamin K does not readily cross the placenta and is poorly distributed into breast milk.

Metabolism

Vitamin K is rapidly converted into more polar metabolites, including vitamin

Elimination

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

Pharmacokinetics in special clinical conditions

Intestinal absorption of vitamin K 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 section Posology and administration).

5.3. Preclinical safety data

LD (i.v.) of Konakion MM (10mg/ml) in mice: 12.1 - 17.7 ml/kg.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzyl Alcohol

Di Sodium EDTA

Tween 80

Propylene Glycol

Water for Injection

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 Months.

6.4 Special precautions for storage

Do not store above 30ºC.

Store in the original package, in order to protect from moisture

6.5. Nature and contents of container

10 x 1 ml Ampoule pack in a mono carton with Insert

6.6. Instruction for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Not Applicable.

8. MARKETING AUTHORISATION NUMBER

Not Applicable.

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

Not Applicable.

10. DATE OF REVISION OF THE TEXT

Not Applicable.