However, such practice has been controversial, particularly as regards the route. Some consider that oral dosage is less invasive and more acceptable to parents. However, there has also been concern about the adequacy of absorption of oral phytomenadione. In addition, there was some evidence to suggest that a single intramuscular dose was more effective than a single oral dose in preventing late VKDB, and that repeated oral doses might be required, which may be less convenient and carry the risk of poor compliance. More recently, a possible increased risk of childhood cancer in neonates treated with intramuscular, but not oral, phytomenadione has been reported.

Although the association remains controversial, it led to recommendations for the preferential use of oral vitamin K in neonates at low-risk of VKDB in some countries, including the UK8 and Germany, 9 whereas other countries, including the USA, still preferred the intramuscular route for all neonates.

There is still no agreement on the most effective route or dosage regimen, and study of this has been complicated by issues concerning the available formulations. A colloidal, micelle formulation (licensed for oral use in some countries) was introduced to replace the original preparation which contained polyoxyl castor oil, propylene glycol, and phenol (unlicensed for oral use but often given in this way).

Although replacing the original formulation has eased concerns about the safety of its excipents, it is not known if the new formulation provides sustained protection when given intramuscularly. Oral absorption of the new formulation has also prompted discussion. 12 A report13 of the failure of prophylaxis in 3 breast-fed babies (2 of whom had unidentified cholestatic liver disease) who received 2 oral doses of the micellar formulation, as recommended in Switzerland, emphasises the importance of the third, and possibly, other, follow-up doses. Plasma vitamin K concentrations in breast-fed infants receiving 3 oral doses of this formulation were at least equal to concentrations in those receiving a single intramuscular dose. 14 A study in Germany, however, found the micellar oral formulation to be no more efficacious than older vitamin K preparations, 15 and a pharmacokinetic study found its absorption to be unreliable in infants with conjugated hyperbilirubinaemia; 16 the authors suggest that even 3 oral doses may not provide sufficient protection against VKDB in infants with latent cholestasis.

Advice issued in 1998 from the UK Department of Health17 advocates that all newborn infants should receive vitamin K prophylaxis, both oral and intramuscular routes should be available, and that parents should be involved in the dedsion on which route is used. In healthy neonates of 36 weeks' gestation or over, licensed product information in the UK recommends a dose of 1 mg phytomenadione as a single intramuscular injection soon after birth. Alternatively, 2 mg may be given orally soon after birth, followed by a second dose of 2 mg at 4 to 7 days; a third oral dose of 2 mg should be given to exclusively breast-fed babies one month after birth. In preterm neonates of less than 36 weeks' gestation, an intramuscular or intravenous dose of 400 micrograms/kg (maximum I mg) may be given soon after birth. The BNFC states that the intramuscular route should be used in those infants considered to be at particular risk for VKDB, and also suggests that infants with cholestaticdisease should be given either intramuscular or intravenous phytomenadione as oral absorption is likely to be impaired. Additionally, subsequent oral doses are suggested for neonates given an initial intravenous dose, in order to provide comparable prolonged protection to the intramuscular route.

Other regimens have been investigated or are in use elsewhere. One hospital in the USA has satisfactorily used, for many years, a single 2-mg dose given via nasogastric tube to neonates after birth, 18 although the American Academy of Pediatrics still advocates use of the intramuscular route. In Denmark, a 2 -mg oral or intramuscular dose at birth followed by a weekly oral dose of 1 mg during the first 3 months of life has effectively prevented any late VKDB in healthy breast-fed babies. 19 In the Netherlands a lower dose regimen of 1 mg orally or intramuscularly at birth, followed by 25 micrograms daily or 1 mg weekly by mouth from 1 week to 3 months of age has been found satisfactory. 20 However, a retrospective comparison of dose regimens used in Denmark and the Netherlands revealed that the lower doses used in the Netherlands did not provide protection against VKDB in breast-fed infants with unrecognised cholestasis due to biliary atresia. In France, for formula-fed neonates at no risk of haemorrhage, 2 mg is given orally at birth, followed by a second dose between day 2 and 7; infants who are breast-fed are given weekly oral doses of 2 mg untilemphasis has been on prevention.

It has long been known that giving vitamin K to the neonate soon after birth can reduce the incidence of VKDB . Menadiol sodium phosphate was formerly used, but reports in the 1950s of jaundice and kernicterus in infants given this vitamin K analogue caused concern, and led to the preferential use of phytomenadione either intramuscularly or orally. Giving phytomenadione, has been standard practice for neonates considered at high risk of VKDB, suchcessation of exclusive breast feeding. For neonates at high risk of haemorrhage, however. The first dose is given intramuscularly, or even by slow intravenous injection, according to the clinical state of the infant.

Although phytomenadione crosses the placenta slowly and to a limited extent it is nevertheless recommended that pregnant women receiving drugs that are vitamin K antagonists (particularlyantiepileptics) should receive phytomenadione l0 to 20 mg daily from 36 weeks of gestation. This is in addition to the requirement that their neonates, who are at high risk of VKDB, receive intramuscular phytomenadione soon after birth. Maternal phytomenadione has been investigated as a means of improving vitamin K status in breastfeed neonates. In l study, 5 mg daily for 12 weeks was effective for this purpose.

PREGNANCY

Animal reproduction studies have not been conducted with Vitamin K1 Injection. It is also not known whether Vitamin K1 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Vitamin K1 Injection should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Vitamin K1 Injection is administered to a nursing woman

INTERACTIONS

Vitamin K decreases the effects of oral anticoagulants, and is used to counteract excessive effects of these drugs, see Dosage and Administration: Vitamin K may reduce the response to resumed therapy with anticoagulants for a week or more

ADVERSE EFFECTS:

Intravenous doses of phytomenadione have caused severe reactions resembling hypersensitivity or anaphylaxis. Symptoms have included facial flushing, sweating, chest constriction and chest pain, dyspnoea, cyanosis, and cardiovascular collapse; fatalities have been reported.

Anaphylactic reactions have generally been associated with an overly rapid rate of infusion but have also been reported even when the solution was diluted and infused slowly. They are generally thought to be due to polyoxylcastor oil which is present as a surfactant in some parenteral formulations; reports of such reactions with formulations that do not contain polyoxyl castor oil are rare Pain, swelling, and phlebitis may occur at the injection site when phytomenadione is given. Localised skin reactions including atrophy or necrosis have been reported after intramuscular or subcutaneous injection of phytomenadione.

Phytomenadione formulations solubilised with lecithin and a bile salt should be given with caution to patients with severely impaired liver function and to premature neonates weighing less than 2.5 kg, since the bile salt may displacebilirubin.

Giving menadione and menadiol sodium phosphate to neonates, especially premature infants, or to the mother during late pregnancy has been associated with the All cross-references refer to entries in Volume Adevelopment in the infant of haemolytic anaemia, hyperbilirubinaemia, and kernicterus, and such use is not recommended. Phytomenadione has a lower risk of haemolysis. Menadione and menadiol sodium phosphate have also been reported to cause haemolysis in patients with G6PD deficiency or vitamin E deficiency.

BREAST FEEDING

Vitamin K is variably distributed into breast milk; a study found phytomenadione concentrations in the first l0 ml of expressed milk ("fore milk") to be lower than those in the last l0 ml ("hind milk") , These changes may be related to the lipid concentration, which is higher in hind milk. Lipid composition also changes over the course of lactation, with pronounced changes in the first week, and the authors proposed that a mechanism exists whereby vitamin K concentration in milk is higher in the first few days of life so as to meet the neonate's nutritional requirements at a time when vitamin K status is precarious.

The American Academy of Pediatricsconsiders that, as no adverse effects have been seen in breast-fed infants whose n1others were receiving phytomenadione, its use is therefore usually compatible with breast feeding.

OVERDOSAGE:

UK licensed product information states that, while there is no known clinical syndrome attributable to hypervitaminosis of phytomenadione, adverse effects have been reported after overdose in neonates and infants. These include jaundice, hyperbilirubinaemia, increases in liver enzyme values, abdominal pain, constipation, soft stools, malaise, agitation, and skin eruptions. Most adverse events were not considered to be serious, and resolved without any treatment.

Storage: -Store Protected from light at a temperature not exceeding 25° C. Do not freeze. Improper Storage may deteriorate the product

Medicine: - Keep out of reach of children.

Presentation:- A 1 ml Ampoule pack in tray along with carton & outer pack with 10 inner carton

Manufactured by:
AMERICAN REMEDIES
Care & Cure with Research
American Remedies Healthcare Pvt. Ltd.
(An ISO 9001-2015 Certified Company)
Gala No. 105 to 111, 1st Flr., Bldg. No. E-16/A, Harihar Complex, Bhiwandi, Mumbai - 421302
At. Vill. Surajpur Nahan Road Paonta Sahib, Distt. Sirmour, Himachal Pradesh-173025
E-mail: info@americanremedies.in
ICO: American Remedies LLC, DE, USA

WHO GMP
Scan for Batch Certificate

For the use only of a Registered Medical Practitioner of a Hospital or a Laboratory

℞ Phytomenadione Injection IP 10 mg/ml

AMERICAN KDION 10 Injection VIT-K1

FOR IM/IV USE ONLY

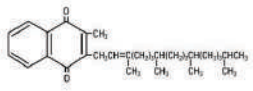
Composition:-

Each ml Contains:-

Phytomenadione	IP	10 mg
Water for Injection	IP	q.s

DESCRIPTION:-

Phytomenadione is a vitamin, which is a clear, Pale-yellow to amber, viscous, odorless or nearly odorless liquid. It is insoluble in water, soluble in chloroform and slightly soluble in ethanol. It has a molecular weight of 450.70. Phytomenadione is 2-methyl-3-(3-7-11-15 tetramethyl-2-hexadecenyl)-naphthoquinone. Its empirical formula is $C_{31}H_{46}O_2$ and its structural formula is:



Phytomenadione

Human Requirements

The minimum daily requirements of vitamin K are not clearly defined but an intake of about 1 microgram/kg daily appears to be adequate. Vitamin K requirements in normal adults can be met from the average diet and from the synthesis of menaquinones (also known as vitamin K2) by bacterial action in the intestine. Vitamin K occurs naturally as Phytomenadione (vitamin K), which is present in many foods, especially leafy green vegetables such as cabbage and spinach, and is also present in avocado, meat, cow's milk, egg-yolk, and some cereals.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement has been set for vitamin K although an intake of 1 microgram/kg daily was considered to be both safe and adequate for adults; a higher intake of 10 micrograms daily (about 2 micrograms/ kg daily) was believed to be justified in infants because of the absence of hepatic menaquinones in early mlife and reliance on dietary vitamin K alone. It was stated that all babies should receive prophylactic vitamin K at birth and for further details concerning neonatal use, see Vitamin K Deficiency Bleeding.

In the USA, adequate intake levels have been determined to be 120 micrograms daily for adult men and 90 micrograms daily for adult women.

PHARMACOLOGY

The fat-soluble vitamin K coupounds phytomenadione and menadione require the presence of bile for their absorption from the gastrointestinal tract; the water-soluble derivatives can be absorbed in the absence of bile. Vitamin K accumulates mainly in the liver but is stored in the body only for short periods of time. Vitamin K does not appear to cross the. placenta readily and it is variably distributed into breast milk<. Phytomenadione is rapidly metabolised to more polar metabolites and is excreted in bile and urine as glucuronide and sulfate conjugates. **Absorption**. Absorption of phytomenadione from the colloidal (micellar) preparation was more irregular and unpredictable after intramuscular than intravenous dosage in healthy adults; 1 when used as an antidote to anticoagulant, this formulation should be given intravenously. In neonates, plasma phytomenadione concentrations were within or above the adult fasting plasma range 24 days after receiving a single dose of the colloidal preparation either orally (3 mg) or intramuscularly (1.5 mg)

DOSAGE AND ADMINISTRATION

Vitamin K is an essential cofactor in the hepatic synthesis of prothrombin (factor II) and other blood clotting factors (factors VII, IX, and X, and proteins C and S) and in the function of proteins such as osteocalcin important for bone development.

Vitamin K deficiency may develop in neonates (see Vitamin K Deficiency Bleeding), but is uncommon in adults, although it may occur in patients with malabsorption syndromes, obstructive jaundice or hepatic disease. Deficiency leads to the development of hypoprothrombinaemia, in which the clotting time of the blood is prolonged and spontaneous bleeding can occur. Coumarin anticoagulants interfere with vitamin K metabolism, and their effects can be antagonised by giving vitamin K. Vitamin K compounds are used in the treatment and prevention of haemorrhage associated with vitamin K deficiency. The dose of vitamin K should be carefully controlled by prothrombin-time estimations.

Phytomenadione is a naturally occurring vitamin K substance. It is the only vitamin K compound used to reverse hypoprothrombinaemia and haemorrhage caused by anticoagulant therapy. It is not effective as a heparin antidote. For over-anticoagulation, the dose depends on the international normalised ratio (INR) and the degree of haemorrhage. Typical doses of phytomenadione are 0.5 to 10 mg by slow intravenous injection or up to 5 mg orally.

Depending on the solubilising agents used, some formulations of phytomenadione are more suitable for intravenous use than others, and dosage details vary. Phytomenadione has also been used in hypoprothrombinaemia due to certain cephalosporins.

Menadiol sodium phosphate is a water-soluble derivative of menadione, a synthetic lipid-soluble vitamin K analogue. It may be used for the prevention of vitamin K deficiency in patients with malabsorption syndromes in whom oral phytomenadione may be inefficiently absorbed. It is given in usual oral doses equivalent to 10 to 40 mg of menadiolphosphate daily.

Administration in children.

Vitamin K deficiency can occur in children with fat malabsorption, particularly in those with cholestasis or severe liver disease. Neonates are relatively deficient in vitamin K and are at risk of bleeding if not supplemented, see Vitamin K Deficiency Bleeding, Vitamin K is also used to reverse over-anticoagulation in children.

Phytomenadione is the only vitamin K compound used to reverse hypoprothrombinaemia and haemorrhage caused by coumarin anticoagulants. For over-anticoagulation in children, specialist advice is recommended; the dose depends on the international normalised ratio (INR), the degree of haemorrhage, and whether continued antic· oagulation is required. The BNFC suggests the following phytomenadione doses in children aged 1 month to 18 years:

- No significant bleeding or if continued anticoagulationrequired: intravenous injection of 15 to 30 micrograms/kg (maximum 1 mg) as a single dose, repeated as necessary
- Significant bleeding or if continued anticoagulation not required: intravenous injection of 250 to 300 micrograms/kg (maximum 10 mg) as a single dose. UK licensed product information allows this dose to be repeated if response is inadequate after 2 to 6 hours

In less severe cases, an oral dose of phytomenadione 5 or 10 mg has been used in children.

The water-soluble derivative, menadiol sodium phosphate, is given as supplementation in vitamin K malabsorption.

The BNFC suggests the following oral doses, expressed as menadiol phosphate, according to age:

- 1to 12 years: 5 to 10 mg daily
- 12 to 18 years: 10 to 20 mg daily

In neonates with biliary atresia and liver disease oral phytomenadione1 mg daily may be given.

For discussion of the use of vitamin K in the management of neonatal intraventricular haemorrhage,

Vitamin K deficiency bleeding

Vitamin K deficiency bleeding (VKDB; haemorrhagic disease of the new-born; HDN) , of which 3 types have been recognised, is associated with a clotting defect due to vitamin K deficiency . 1'2

- In early VKDB bleeding occurs at the time of delivery or during the first 24 hours of life and is typically seen in infants whose mothers have taken drugs that affect vitamin K metabolism such as warfarin, some antiepileptics,rifampicin, or is oniazid.
- Classic VKDB, the most common type, usually occurs at 2 to 5 days of age and breast feeding is an important factor as human breast milk has a much lower content of vitamin K than either cow's milk or infant formulas.
- Late VKDB presents frequently as intracranial haemorrhagein infants over one month of age. The vitamin-K deficiency in these cases can be either idiopathic (usuallyin breast-fed infants who did not receive vitamin K at birth) and/or can be a secondary manifestation of other disorders such as chronic diarrhoea, cystic fibrosis or other malabsorption syndromes, biliary atresia, or α1 -antitrypsin deficiency.

Treatment of VKDB involves use of intravenous phytomenadione, usually 1mg initially with further doses depending on response. More immediate treatment, in the form of blood transfusion or blood clotting factors, may be needed to compensate for severe blood loss and delayed response to vitamin K. VKDB, particularly the late type, carries a high risk of morbidity or death; therefore, theas those who had a complicated delivery, those born prematurely, and those whose mothers were receiving antiepileptic therapy. Since it is not possible to selectively identify all neonates that are at risk for VKDB, the routine use of phytomenadione in all neonates has been advocated.