INJECTION

AquaMEPHYTON®

(PHYTONADIONE)

Aqueous Colloidal Solution of Vitamin K_1

WARNING - INTRAVENOUS AND INTRAMUSCULAR USE

Severe reactions, including fatalities, have occurred during and immediately after INTRAVENOUS injection of AquaMEPHYTON* (Phytonadione), even when precautions have been taken to dilute the AquaMEPHYTON and to avoid rapid infusion. Severe reactions including fatalities, have also been reported following INTRAMUSCULAR administration. Typically, these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving AquaMEPHYTON for the first time. Therefore, the INTRAVENOUS and INTRAMUSCULAR routes should be restricted to those situations where the subcutaneous route is not feasible and the serious risk involved is considered justified.

DESCRIPTION

Phytonadione is a vitamin, which is a clear, 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.

Phytonadione is 2-methyl-3-phytyl-1, 4-naphthoquinone. Its empirical formula is $C_{31}H_{46}O_2$ and its structural formula is:

AquaMEPHYTON injection is a yellow, sterile, aqueous colloidal solution of vitamin K_1, with a pH of 5.0 to 7.0, available for injection by the intravenous, intramuscular, and subcutaneous routes.

Each milliliter contains:

Phytonadione	2 mg or 10 mg
Inactive ingredients:	
Polyoxyethylated fatty acid derivative	70 mg
Dextrose	37.5 mg
Water for Injection, q.s.	1 mL
Added as preservative:	
Benzyl alcohol	9 mg

CLINICAL PHARMACOLOGY

AquaMEPHYTON aqueous colloidal solution of vitamin K_1 for parenteral injection, possesses the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). The prothrombin test is sensitive to the levels of three of these four

factors — II, VII, and X. Vitamin K is an essential cofactor for a microsomal enzyme that catalyzes the post-translational carboxylation of multiple, specific, peptide-bound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The resulting gamma-carboxyglutamic acid residues convert the precursors into active coagulation factors that are subsequently secreted by liver cells into the blood.

Phytonadione is readily absorbed following intramuscular administration. After absorption, phytonadione is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues. Little is known about the metabolic fate of vitamin K. Almost no free unmetabolized vitamin K appears in bile or urine.

In normal animals and humans, phytonadione is virtually devoid of pharmacodynamic activity. However, in animals and humans deficient in vitamin K, the pharmacological action of vitamin K is related to its normal physiological function, that is, to promote the hepatic biosynthesis of vitamin K dependent clotting factors.

The action of the aqueous colloidal solution, when administered intravenously, is generally detectable within an hour or two and hemorrhage is usually controlled within 3 to 6 hours. A normal prothrombin level may often be obtained in 12 to 14 hours.

In the prophylaxis and treatment of hemorrhagic disease of the newborn, phytonadione has demonstrated a greater margin of safety than that of the water-soluble vitamin K analogues.

INDICATIONS AND USAGE

AquaMEPHYTON is indicated in the following coagulation disorders which are due to faulty formation of factors II, VII, IX and X when caused by vitamin K deficiency or interference with vitamin K activity.

AquaMEPHYTON injection is indicated in:

- — anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives;
- — prophylaxis and therapy of hemorrhagic disease of the newborn;
- — hypoprothrombinemia due to antibacterial therapy;
- — hypoprothrombinemia secondary to factors limiting absorption or synthesis of vitamin K, e.g., obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancreas, and regional enteritis;
- — other drug-induced hypoprothrombinemia where it is definitely shown that the result is due to interference with vitamin K metabolism, e.g., salicylates.

CONTRAINDICATION

Hypersensitivity to any component of this medication.

WARNINGS

Use benzyl alcohol-free formulations in neonates and infants, if available. Serious and fatal

adverse reactions including “gasping syndrome” can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including AquaMEPHYTON. The “gasping syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

When prescribing AquaMEPHYTON in infants, consider the combined daily metabolic load of benzyl alcohol from all sources including AquaMEPHYTON (contains 9 mg of benzyl alcohol per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.

An immediate coagulant effect should not be expected after administration of phytonadione. It takes a minimum of 1 to 2 hours for measurable improvement in the prothrombin time. Whole blood or component therapy may also be necessary if bleeding is severe.

Phytonadione will not counteract the anticoagulant action of heparin.

When vitamin K_1 is used to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy still being indicated, the patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy. Phytonadione is not a clotting agent, but overzealous therapy with vitamin K_1 may restore conditions which originally permitted thromboembolic phenomena. Dosage should be kept as low as possible, and prothrombin time should be checked regularly as clinical conditions indicate.

Repeated large doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate that the condition being treated is inherently unresponsive to vitamin K.

PRECAUTIONS

General

Vitamin K_1 is fairly rapidly degraded by light; therefore, always protect AquaMEPHYTON from light. Store AquaMEPHYTON in closed original carton until contents have been used. (See also HOW SUPPLIED**,** *Storage.)*

Drug Interactions

Temporary resistance to prothrombin-depressing anticoagulants may result, especially when larger doses of phytonadione are used. If relatively large doses have been employed, it may be necessary when reinstituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant, or to use one which acts on a different principle, such as heparin sodium.

Laboratory Tests

Prothrombin time should be checked regularly as clinical conditions indicate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of carcinogenicity, mutagenesis or impairment of fertility have not been conducted with AquaMEPHYTON.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with AquaMEPHYTON. It is also not known whether AquaMEPHYTON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. AquaMEPHYTON 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 AquaMEPHYTON is administered to a nursing woman.

Pediatric Use

Hemolysis, jaundice, and hyperbilirubinemia in newborns, particularly in premature infants, may be related to the dose of AquaMEPHYTON. Therefore, the recommended dose should not be exceeded (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Serious adverse reactions including fatal reactions and the “gasping syndrome” occurred in premature neonates and infants in the intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.
When prescribing AquaMEPHYTON in infants consider the combined daily metabolic load of benzyl alcohol from all sources including AquaMEPHYTON (AquaMEPHYTON contains 9 mg of benzyl alcohol) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known *[see Warnings]*.

ADVERSE REACTIONS

Deaths have occurred after intravenous and intramuscular administration. (See Box Warning.)

Transient "flushing sensations" and "peculiar" sensations of taste have been observed, as well as instances of dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dyspnea, and cyanosis.

Pain, swelling, and tenderness at the injection site may occur.

The possibility of allergic sensitivity, including an anaphylactoid reaction, should be kept in mind.

Usually after repeated injection, erythematous, indurated, pruritic plaques have occurred; these have progressed to scleroderma-like lesions that have persisted for long periods. In other cases, these lesions have resembled erythema perstans.

Hyperbilirubinemia has been observed in the newborn following administration of phytonadione. This has occurred primarily with doses above those recommended. (See PRECAUTIONS, *Pediatric Use*.)

To report **SUSPECTED ADVERSE REACTIONS**, contact Teligent Pharma, Inc. at 1-856-697-1441, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

The intravenous LD_{50} of AquaMEPHYTON in the mouse is 41.5 and 52 mL/kg for the 0.2% and 1% concentrations, respectively.

DOSAGE AND ADMINISTRATION

Whenever possible, AquaMEPHYTON should be given by the subcutaneous route (see Box Warning). When intravenous administration is considered unavoidable, the drug should be injected very slowly, not exceeding 1 mg per minute.

Protect from light at all times.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Dilution

AquaMEPHYTON may be diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or 5% Dextrose and Sodium Chloride Injection. Benzyl alcohol as a preservative has been associated with toxicity in newborns. *Therefore, all of the above diluents should be preservative- free* (see WARNINGS). *Other diluents should not be used*. When dilutions are indicated, administration should be started immediately after mixture with the diluent, and unused portions of the dilution should be discarded, as well as unused contents of the ampul.

Prophylaxis of Hemorrhagic Disease of the Newborn

The American Academy of Pediatrics recommends that vitamin K_1 be given to the newborn. A single intramuscular dose of AquaMEPHYTON 0.5 to 1 mg within one hour of birth is recommended.

Treatment of Hemorrhagic Disease of the Newborn

Empiric administration of vitamin K_1 should not replace proper laboratory evaluation of the coagulation mechanism. A prompt response (shortening of the prothrombin time in 2 to 4 hours) following administration of vitamin K_1 is usually diagnostic of hemorrhagic disease of the newborn, and failure to respond indicates another diagnosis or

coagulation disorder.

AquaMEPHYTON 1 mg should be given either subcutaneously or intramuscularly. Higher doses may be necessary if the mother has been receiving oral anticoagulants.

Whole blood or component therapy may be indicated if bleeding is excessive. This therapy, however, does not correct the underlying disorder and AquaMEPHYTON should be given concurrently.

Anticoagulant-Induced Prothrombin Deficiency in Adults
To correct excessively prolonged prothrombin time caused by oral anticoagulant therapy — 2.5 to 10 mg or up to 25 mg initially is recommended. In instances 50 mg may be required. Frequency and amount of subsequent doses should be determined by prothrombin time response or clinical condition (see WARNINGS). If in 6 to 8 hours after parenteral administration the prothrombin time has not been shortened satisfactorily, the dose should be repeated.

AquaMEPHYTON® Summary of Dosage Guidelines
(See circular text for details)

Newborns	**Dosage**
Hemorrhagic Disease of the Newborn Prophylaxis	0.5 to 1 mg Intramuscular within 1 hour of birth
Treatment	1 mg Subcutaneous or Intramuscular (Higher doses may be necessary if the mother has been receiving oral anticoagulants)
Adults	**Initial Dosage**
Anticoagulant-Induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)	2.5 mg to 10 mg or more
Hypoprothrombinemia Due to other causes (Antibiotics; Salicylates or other drugs; Factors limiting absorption or synthesis)	2.5 mg to 25 mg or more

In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

Hypoprothrombinemia Due to Other Causes in Adults
A dosage of 2.5 to 25 mg or more (up to 50 mg) is recommended, the amount and route of administration depending upon the severity of the condition and response obtained.

If possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms (such as salicylates, antibiotics) is suggested as an alternative to administering concurrent AquaMEPHYTON. The severity of the coagulation disorder should determine whether the immediate administration of AquaMEPHYTON is required in addition to discontinuation or reduction of interfering drugs.

HOW SUPPLIED

AquaMEPHYTON is a yellow, sterile, aqueous colloidal solution and is supplied in a package of 25 as follows:

NDC No.	Container	Amount of AquaMEPHYTON® In Container	Volume	Concentration
52565-092-01	1 mL Ampul	1 mg	0.5 mL	2 mg/mL
52565-093-01	1 mL Ampul	10 mg	1 mL	10 mg/mL

Storage

Store container in original carton. Always protect AquaMEPHYTON from light. Store container in closed original carton until contents have been used. (See PRECAUTIONS, *General*)

Manufactured by:

Valdepharm
Val De Reuil 27100
France

Distributed by:

Teligent Pharma, Inc.
Buena, NJ 08310

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