CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 083722Orig1s011

Name: Phytonadione Injection USP, l mg/0.5 ml

Sponsor: International Medication Systems, Limited

Approval Date: December 9, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 083722Orig1s011

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APPLICATION NUMBER:

ANDA 083722Orig1s011

APPROVAL LETTER

ANDA 83-722/S-011

DEC 9 1992

International Medication Systems Limited
Attention: Stephen A. Campbell
1886 Santa Anita Avenue
South El Monte, California 91733

Dear Sir:

Reference is made to your supplemental new drug application dated February 28, 1992, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for Phytonadione Injection USP.

Reference is also made to your communication dated August 20, 1992, amending this supplement.

The supplemental application provides for revised final printed package insert labeling reflecting changes throughout the text to be in accord with the labeling of the listed drug AquaMEPHYTON®.

We have completed the review of this supplemental application and it is approved. Our letter of March 1, 1976, detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained in our files.

Sincerely yours,

Yana Ruth Mille for/ 12/9/92

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 83-722/S-011
DUP/Division
HFD-82
HFC-130/JAllen
HFD-600/RF
HFD-638/CShannon/JPhillips/11/25/92
fam 12/7/92/83722S.011
Approval

CShannon 12-7-92

Y. Mille for JP
12/9/92

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 083722Orig1s011

LABELING

6911400G

PHYTONADIONE INJECTION, USP

Aqueous Colloidal Solution of Vitamin K_1

DEC 9 1992

WARNING—INTRAVENOUS USE

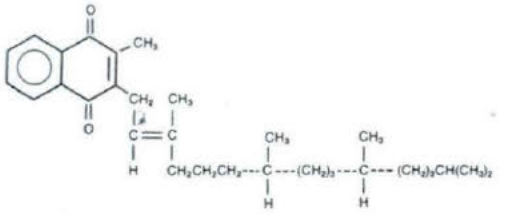
Severe reactions, including fatalities, have occurred during and immediately after INTRAVENOUS injection of phytonadione, even when precautions have been taken to dilute the phytonadione and to avoid rapid infusion. Usually, these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first time. The risks of the INTRAVENOUS route should be restricted to those situations where other routes are not feasible and the serious risk involved is considered justified.

APPROVED

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:



Phytonadione Injection, USP, is a yellow, sterile, aqueous colloidal solution of vitamin K_1, with a pH of 3.5 to 7.0, available for injection by the intravenous, intramuscular, and subcutaneous route.

Each 0.5 mL contains 1 mg phytonadione (Vitamin K_1), 10 mg polysorbate 80, 10.4 mg propylene glycol, 0.17 mg sodium acetate anhydrous, and 0.00002 mL acetic acid glacial. The air above the liquid in the individual containers has been displaced by flushing with nitrogen during the filling operation.

CLINICAL PHARMACOLOGY

Phytonadione 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 posttranslational carboxylation of multiple, specific, peptidebound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The resulting gamma-carboxyglutamic acid residues convert the precusors 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

Phytonadione 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.

Phytonadione 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

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

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 phytonadione.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with phytonadione. It is also not known whether phytonadione can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phytonadione 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 phytonadione 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 phytonadione. Therefore, the recommended dose should not be exceeded (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Deaths have occurred after intravenous administration. (See Box Warning at beginning of insert.)

Transient "flushing sensations" and "peculiar" sensations of taste have been observed, as well as rare 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.

Infrequently, usually after repeated injection, erythematous, indurated, pruritic plaques have occurred; rarely, 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 rarely and primarily with doses above those recommended. (See PRECAUTIONS, *Pediatric Use*.)

OVERDOSAGE

The intravenous LD_{50} of Phytonadione Injection in the mouse is 41.5 and 52 mL/kg for the 0.2% and 1.0% concentrations, respectively.

DOSAGE AND ADMINISTRATION

Whenever possible, phytonadione should be given by the subcutaneous or intramuscular route. 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
Phytonadione 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. 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 vial.

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 phytonadione 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.

Phytonadione 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 phytonadione 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 rare 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.

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 (rarely 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 phytonadione. The severity of the coagulation disorder should determine whether the immediate administration of phytonadione is required in addition to discontinuation or reduction of interfering drugs.

Phytonadione
Summary of Dosage Guidelines
(See insert text for details)

Newborns	Dosage
Hemorrhagic Disease of the Newborn	
Prophylaxis	0.5 - 1 mg IM within 1 hour of birth
Treatment	1 mg SC or IM (Higher doses may be necessary if the mother has been receiving oral anti-coagulants)

Adults	Initial Dosage
Anticoagulant - induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)	2.5 mg - 10 mg or up to 25 mg (rarely 50 mg)
Hypoprothrombinemia due to other causes (Antibiotics; Salicylates or other drugs; Factors limiting absorption or synthesis)	2.5 mg - 25 mg or more (rarely up to 50 mg)

HOW SUPPLIED

In unit use packages containing one single dose vial and a MIN-I-JET® vial injector.

Phytonadione Injection, USP, 1 mg in 0.5 mL

Stock No. 1140 NDC 0548-1140-00 DIN 00243876

Twenty-five unit use packages per carton.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light.

Manufactured under U.S. Patent No. 3,376,866.

CAUTION: Federal law (U.S.A.) prohibits dispensing without prescription.

IMS INTERNATIONAL MEDICATION SYSTEMS, LIMITED
So. El Monte, CA 91733, U.S.A.

Distributed in Canada by:
INTERNATIONAL MEDICATION SYSTEMS OF CANADA LTD., 406 Watline Ave., Mississauga, Ontario L4Z 1X2

Rev. 4-92

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 083722Orig1s011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ANDA 83-722/S-010

MAR 25 1992

International Medication Systems Limited
Attention: Stephen A. Campbell
1886 Santa Anita Avenue
South El Monte, California 91733

Dear Sir:

Reference is made to your supplemental new drug application dated February 28, 1992, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for Phytonadione Injection USP.

The supplemental application provides for revised package insert labeling reflecting changes throughout the text.

We have completed our review of this supplemental application and it is approvable. However, before the supplemental application may be approved, it is necessary that you further revise the package insert labeling.

Since our communication dated August 28, 1991, the innovator's product AquaMEPHYTON® (Merck Sharp and Dohme) package insert labeling has undergone another revision (revised March 1991, approved September 26, 1991). Please revise your package insert labeling as described below, then submit twelve final printed copies as an amendment to this supplement.

A. CLINICAL PHARMACOLOGY, paragraph 1, delete the last sentence and revise to read:

... 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 posttranslational carboxylation of multiple, specific, peptidebound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The resulting gamma-carboxyglutamic acid residues convert the precusors into active coagulation factors that are subsequently secreted by liver cells into the blood.

B. DOSAGE AND ADMINISTRATION

1. Change "1.0 mg" to "1 mg" throughout this section.

2. Directions for Dilution, sentence 2 should be retained:

Benzyl alcohol as a preservative has been associated with toxicity in newborns.

[redacted] (b) (4)

[redacted] (b) (4) we believe the warning statement should remain since one of the INDICATIONS for this product is specifically for newborns and the practitioner should be alert to the possibility of the problem.

3. Summary of Dosage Guidelines Table

i) Do not indent the heading "Newborns".

ii) Reformat Hemorrhagic Disease of the Newborn section of the Table so that the dosages correctly correspond to "Prophylaxis" and "Treatment". Insert spacing to better differentiate these two therapies.

The changes provided for in this supplemental application may not be initiated until you have been notified in writing that the supplemental application is approved.

Sincerely yours,

Ken Johnsson /pz 3-25-92

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc;
HFD-638
HFD-600
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