MEPHYTON® (Phytonadione) tablets containing 5 mg of phytonadione are yellow, compressed tablets, scored on one side. Inactive ingredients are acacia, calcium phosphate, colloidal silicon dioxide, lactose, magnesium stearate, starch, and talc.

CLINICAL PHARMACOLOGY
MEPHYTON tablets possess the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of 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 residues convert the precursors into active coagulation factors that are subsequently secreted by liver cells into the blood.

Metabolism of Vitamin K: Metabolism of phytonadione to vitamin K1 occurs in the liver to a molecular weight of 450.70. Vitamin K1 is a clear, yellow to amber, viscous, and nearly odorless liquid. It is insoluble in water, soluble in chloroform and slightly soluble in ethanol. It has a molecular weight of 386.

Vitamin K1 is fairly rapidly degraded by light; therefore, always protect MEPHYTON from light. Store MEPHYTON in closed original carton until contents have been used. (See also HOW SUPPLIED, Storage.)

Intravenous Administration: MEPHYTON is rapidly absorbed after intravenous administration. Bile salts must be given with the tablets when the endogenous supply response obtained.

ADVERSE REACTIONS
Severe hypersensitivity reactions, including anaphylactoid reactions and deaths have been reported following parenteral administration. The majority of these reported events occurred following intravenous administration. Transient “flushing sensations” and “peculiar” sensations of taste have been observed with parenteral phytonadione, as well as rare instances of dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dyspnea, and cyanosis. Hyperbilirubinemia has been observed in the newborn following administration of parenteral phytonadione. This has occurred rarely and primarily with doses above those recommended.

OVERDOSE
The intravenous and oral LD50’s in the mouse are approximately 1.17 g/kg and greater than 24.8 g/kg, respectively.

DOSAGE AND ADMINISTRATION

MEPHYTON Summary of Dosage Guidelines

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initial Dose</th>
</tr>
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<tbody>
<tr>
<td>Anticoagulant-Induced Prothrombin Deficiency</td>
<td>2.5 mg-10 mg or up to 25 mg (rarely up to 50 mg)</td>
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Anticoagulant-Induced Prothrombin Deficiency in Adults
To correct excessively prolonged prothrombin times 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 12 to 48 hours after oral administration, the prothrombin time has not been shortened satisfactorily, the dose should be repeated.

CONTRAINdications
Hypersensitivity to any component of this medication.

WARNINGS
An immediate coagulant effect should not be expected after administration of phytonadione. Phytonadione will not counteract the anticoagulant action of heparin.

When vitamin K1 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 K1 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.

Anticoagulant-Induced Prothrombin Deficiency

METHYPHYTON® (Phytonadione) Tablets

Repeats 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 a congenital coagulation defect or that the condition being treated is unresponsive to vitamin K.

Precautions
General
Vitamin K1 is fairly rapidly degraded by light; therefore, always protect MEPHYTON from light. Store MEPHYTON in original closed 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 reintroducing anticoagulant therapy to 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 or impairment of fertility have not been performed with MEPHYTON. MEPHYTON at concentrations up to 2000 mcg/ml with or without metabolic activation, was negative in the Ames microbial mutagen test.

Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with MEPHYTON. It is also not known whether MEPHYTON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. MEPHYTON should be given to a pregnant woman only if clearly needed. Pediatric Use
Safety and effectiveness in pediatric patients have not been established with MEPHYTON. Hemolytic anemia, jaundice, and hyperbilirubinemia in newborns, particularly in premature infants, have been reported with vitamin K.

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 MEPHYTON is administered to a nursing woman.

Geriatric Use
Clinical studies of MEPHYTON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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