

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MEPHYTON safely and effectively. See full prescribing information for MEPHYTON.

MEPHYTON® (phytonadione tablets), for oral use  
Initial U.S. Approval: 1955

### INDICATIONS AND USAGE

Mephyton is a vitamin K replacement indicated for the treatment of adults with 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:

- Anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives; (1)
- Hypoprothrombinemia secondary to antibacterial therapy; (1)
- 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; (1)
- Other drug-induced hypoprothrombinemia where it is definitively shown that the result is due to interference with vitamin K metabolism, e.g., salicylates. (1)

### DOSAGE AND ADMINISTRATION

- Anticoagulant-Induced Prothrombin Deficiency: 2.5 mg to 10 mg or up to 25 mg (2.2)

- Hypoprothrombinemia Due to Other Causes: 2.5 mg to 25 mg or more (2.2)
- Must be given with bile salts when endogenous supply of bile to gastrointestinal track is deficient. (2.1)

### DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg (3)

### CONTRAINDICATIONS

Hypersensitivity to any component of this medication. (4)

### ADVERSE REACTIONS

Most common adverse reactions are transient “flushing sensations”, “peculiar” sensations of taste and instances of dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dyspnea, and cyanosis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

Anticoagulants: May induce temporary resistance to prothrombin-depressing anticoagulants. (7)

See 17 for PATIENT COUNSELING INFORMATION.

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\* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Mephyton is indicated for the treatment of adults with 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.

- anticoagulant-induced hypoprothrombinemia caused by coumarin or indanedione derivatives;
- hypoprothrombinemia secondary 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.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing Considerations

Avoid the oral route when the clinical disorder would prevent proper absorption. Bile salts must be given with the tablets when the endogenous supply of bile to the gastrointestinal tract is deficient. The coagulant effects of Mephyton are not immediate; improvement of international normalized ratio (INR) may take 1-8 hours. Interim use of whole blood or component therapy may also be necessary if bleeding is severe.

Mephyton will not counteract the anticoagulant action of heparin.

When Mephyton 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. Mephyton is not a clotting agent, but overzealous therapy with vitamin K<sub>1</sub> 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.

### 2.2 Recommended Dosage

#### *Anticoagulant-Induced Prothrombin Deficiency in Adults*

The recommended dose to correct excessively prolonged prothrombin times caused by oral anticoagulant therapy is, 2.5 to 10 mg or up to 25 mg initially. In some instances 50 mg may be required. Frequency and amount of subsequent doses should be determined by prothrombin time response or clinical condition. If, in 12 to 48 hours after oral administration, the prothrombin time has not been shortened satisfactorily, repeat the dose.

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

#### *Hypoprothrombinemia Due to Other Causes in Adults*

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

The recommended dose is 2.5 to 25 mg or more (sometimes up to 50 mg). Evaluate INR after 6-8 hours, and repeat dose if INR remains prolonged. Modify subsequent dosage (amount and frequency) based upon the INR or clinical condition.

## 3 DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, clean, pale yellow, semi-glossy, round, flat, beveled edge, scored and debossed with "VRX" above "405" on one side and debossed with "MEPHYTON" on the other side.

## 4 CONTRAINDICATIONS

Mephyton is contraindicated in patients with a history of a hypersensitivity reaction to phytonadione or inactive ingredients [see Description (11)].

## 6 ADVERSE REACTIONS

The following adverse reactions associated with the use of parenteral phytonadione were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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 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 primarily with doses above those recommended.

## 7 DRUG INTERACTIONS

### Anticoagulants

Mephyton may induce temporary resistance to prothrombin-depressing anticoagulants, especially when larger doses of Mephyton are used. Should this occur, higher doses of anticoagulant therapy may be needed when resuming anticoagulant therapy, or a change in therapy to a different class of anticoagulant may be necessary (i.e., heparin sodium).

Mephyton does not affect the anticoagulant action of heparin.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Published studies with the use of phytonadione during pregnancy have not reported a clear association with phytonadione and adverse developmental outcomes [see Data]. There are maternal and fetal risks associated with vitamin K deficiency during pregnancy [see Clinical Considerations]. Animal reproduction studies have not been conducted with phytonadione.

The estimated background risk for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Clinical Considerations

##### *Disease-associated maternal and/or embryo/fetal risk*

Pregnant women with vitamin K deficiency hypoprothrombinemia may be at increased risk for bleeding diatheses during pregnancy and hemorrhagic events at delivery. Subclinical vitamin K deficiency during pregnancy has been implicated in rare cases of fetal intracranial hemorrhage.

#### Data

##### *Human Data*

Phytonadione has been measured in cord blood of infants whose mothers were treated with phytonadione during pregnancy in concentrations lower than seen in maternal plasma. Administration of vitamin K<sub>1</sub> to pregnant women shortly before delivery increased both maternal and cord blood concentrations. Published data do not report a clear association with phytonadione and adverse maternal or fetal outcomes when used during pregnancy. However, these studies cannot

definitively establish the absence of any risk because of methodologic limitations including small sample size and lack of blinding.

#### *Animal Data*

In pregnant rats receiving vitamin K<sub>1</sub> orally, fetal plasma and liver concentrations increased following administration, supporting placental transfer.

### **8.2 Lactation**

#### Risk Summary

Phytonadione is present in breastmilk. There are no data on the effects of Mephyton on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the clinical need for Mephyton and any potential adverse effects on the breastfed child from Mephyton or from the underlying maternal condition.

### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established with Mephyton. Hemolysis, jaundice, and hyperbilirubinemia in newborns, particularly in premature infants, have been reported with vitamin K.

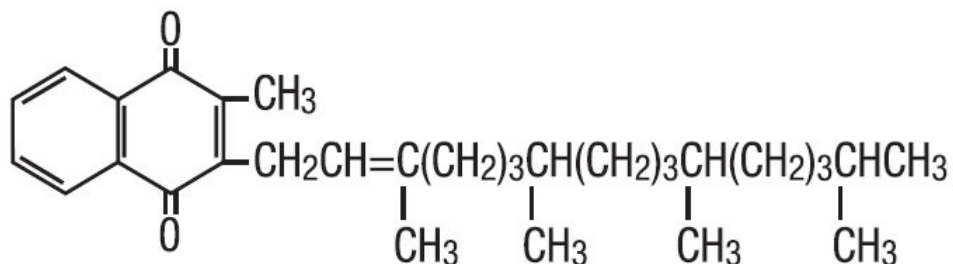
### **8.5 Geriatric Use**

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 cautious, 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.

## **11 DESCRIPTION**

Phytonadione is a vitamin K replacement, which 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 450.7.

Phytonadione is 2-methyl-3-phytyl-1, 4-naphthoquinone. Its empirical formula is C<sub>31</sub>H<sub>46</sub>O<sub>2</sub> and its structural formula is:



Mephyton<sup>®</sup> (phytonadione tablets) for oral administration contain 5 mg of phytonadione and are clean, pale yellow, semi-glossy, round, flat, beveled edge, scored and debossed with “VRX” above “405” on one side and debossed with “MEPHYTON” on the other side. Inactive ingredients are acacia, calcium phosphate, colloidal silicon dioxide, lactose, magnesium stearate, starch, and talc.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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 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, 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.

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.

### 12.2 Pharmacodynamics

Phytonadione tablets generally exert their effect within 6 to 10 hours.

### 12.3 Pharmacokinetics

#### Absorption

Oral phytonadione is adequately absorbed from the gastrointestinal tract only if bile salts are present.

#### Distribution

After absorption, phytonadione is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues.

#### Elimination

Little is known about the metabolic fate of vitamin K. Almost no free unmetabolized vitamin K appears in bile or urine.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of carcinogenicity or impairment of fertility have not been performed with Mephyton. Mephyton at concentrations up to 2,000 mcg/plate, with or without metabolic activation, was negative in the Ames microbial mutagen test.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Mephyton<sup>®</sup> tablets, 5 mg, are clean, pale yellow, semi-glossy, round, flat, beveled edge, scored and debossed with “VRX” above “405” on one side and debossed with “MEPHYTON” on the other side. They are supplied as follows:

NDC 0187-1704-05 bottles of 100.

#### Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Always protect Mephyton from light. Store in tightly closed original container and carton until contents have been used.

## 17 PATIENT COUNSELING INFORMATION

Vitamin K<sub>1</sub> is fairly rapidly degraded by light; therefore, advise patients to always protect Mephyton from light. Store Mephyton in closed original carton until contents have been used [*see How Supplied/Storage and Handling (16)*].

### **Distributed by:**

Bausch Health US, LLC  
Bridgewater, NJ 08807 USA

### **Manufactured by:**

Bausch Health Companies Inc.  
Steinbach, MB R5G 1Z7, Canada

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