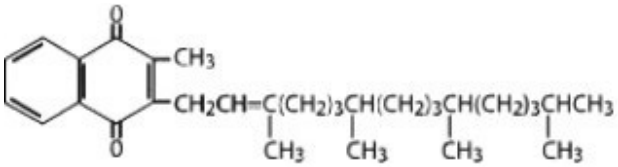
PHYTONADIONE- phytonadione tablet
Cadila Healthcare Limited

Phytonadione Tablets, USP

DESCRIPTION

Phytonadione is a vitamin which is a clear, yellow to amber, very viscous odorless or practically odorless liquid. It is soluble in dehydrated alcohol, in benzene, in chloroform, in ether and slightly soluble in alcohol. It has a molecular weight of 450.70.

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



Each uncoated phytonadione tablet, USP for oral administration contains 5 mg of phytonadione, USP and contains following inactive ingredients: croscarmellose sodium, colloidal silicon dioxide, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

Phytonadione tablets, USP 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 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.

Oral phytonadione is adequately absorbed from the gastrointestinal tract only if bile salts are present. 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 bio synthesis of vitamin K-dependent clotting factors.

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

INDICATIONS AND USAGE

Phytonadione tablets, USP are 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 tablets, USP are indicated in:

- anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives;

- hypoprothrombinemia secondary to antibacterial therapy;
- hypoprothrombinemia secondary to administration of salicylates;
- hypoprothrombinemia secondary to obstructive jaundice or biliary fistulas but only if bile salts are administered concurrently, since otherwise the oral vitamin K will not be absorbed.

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

PRECAUTIONS

General

Vitamin K_1 is fairly rapidly degraded by light; therefore, always protect phytonadione tablets, USP from light. Store phytonadione tablets, USP 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 or impairment of fertility have not been performed with phytonadione tablets, USP.

Phytonadione tablets, USP at concentrations up to 2000 mcg/plate 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 phytonadione tablets, USP. It is also not known whether phytonadione tablets, USP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phytonadione tablets, USP should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established with phytonadione tablets, USP. Hemolysis, 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 phytonadione tablets, USPis administered to a nursing woman.

Geriatric Use

Clinical studies of phytonadione tablets, USP 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.

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.

OVERDOSAGE

The intravenous and oral LD_{50}s in the mouse are approximately 1.17 g/kg and greater than 24.18 g/kg, respectively.

DOSAGE AND ADMINISTRATION

Phytonadione Tablets, USP Summary of Dosage Guidelines(See circular text for details)

Adults	**Initial Dosage**
Anticoagulant-Induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)	2.5 mg to 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 to 25 mg or more (rarely up to 50 mg)

Anticoagulant-Induced Pro thrombin 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 pro thrombin 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.

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

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.

The oral route should be avoided when the clinical disorder would prevent pro per absorption. Bile salts must be given with the tablets when the endogenous supply of bile to the gastrointestinal tract is deficient.

HOW SUPPLIED

Phytonadione Tablets USP, 5 mg are light yellow to yellow colored, round shaped, uncoated tablets engraved with "10 14" on one side and break line on other side and are supplied as follows:

NDC 70771-1318-1 in bottle of 100 tablets

NDC 70771-1318-4 in carton of 100 tablets (10 x 10 unit-dose)

Storage

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please address medical inquiries to, MedicalAffairs@zydususa.com Tel.: 1-877-993-8779 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured by:

Cadila Healthcare Limited

Matoda, Ahmedabad, India.

Rev.: 02/19

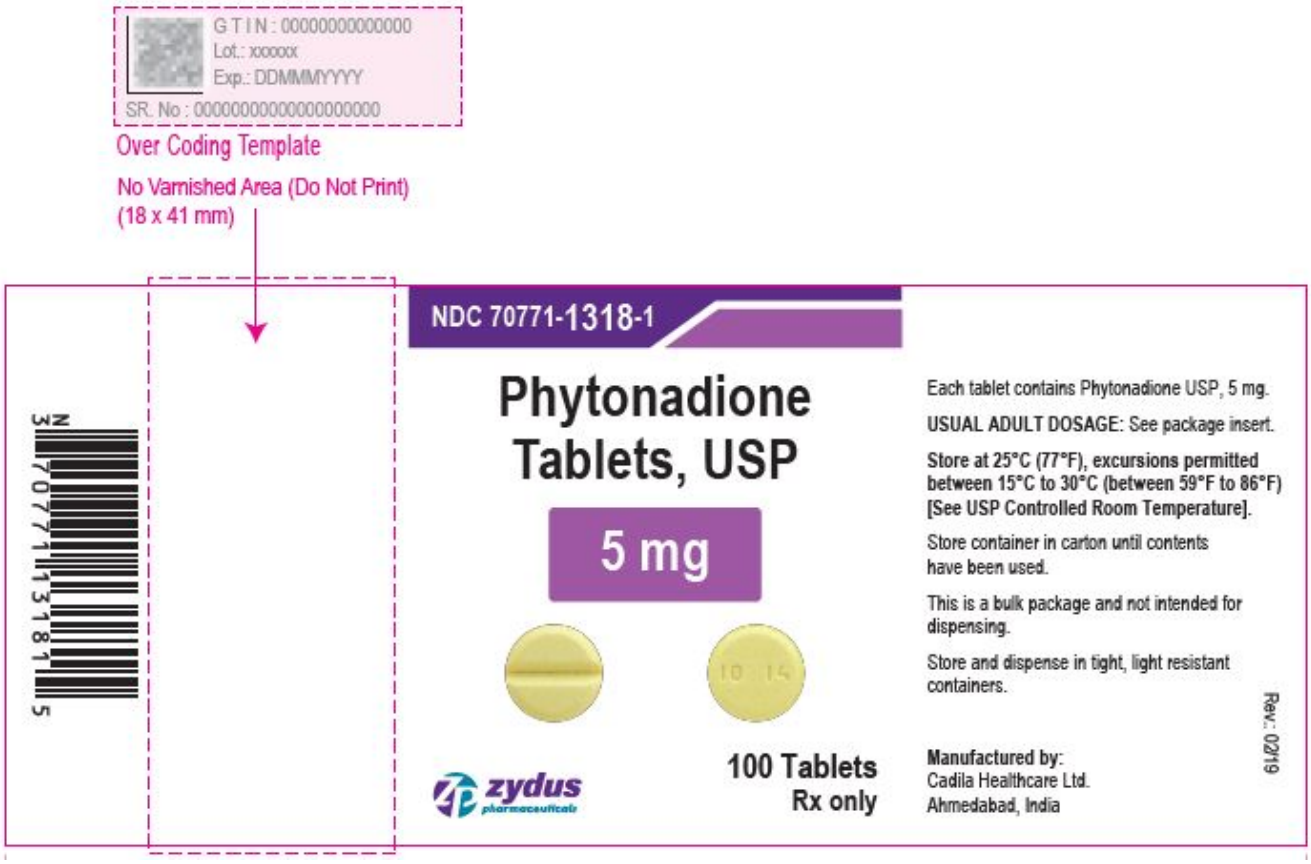
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Phytonadione Tablets USP, 5 mg

100 tablets

NDC 70771-1318-1

Rx only



PHYTONADIONE

phytonadione tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70771-1318
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PHYTONADIONE (UNII: A034SE7857) (PHYTONADIONE - UNII:A034SE7857)	PHYTONADIONE	5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
HYDROXYPROPYL CELLULOSE (110000 WAMW) (UNII: 5Y0974F5PW)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics			
Color	YELLOW (LIGHT YELLOW TO YELLOW)	**Score**	2 pieces
Shape	ROUND (ROUND)	**Size**	7mm

Flavor		**Imprint Code**	1014
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70771-1318-1	1 in 1 CARTON	02/22/2019	
1		100 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:70771-1318-4	10 in 1 CARTON	02/22/2019	
2	NDC:70771-1318-2	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210189	02/22/2019	

Labeler - Cadila Healthcare Limited (918596198)

Registrant - Cadila Healthcare Limited (863362789)

Establishment

Name	Address	ID/FEI	Business Operations
Cadila Healthcare Limited		863362789	ANALYSIS(70771-1318) , MANUFACTURE(70771-1318)

Revised: 2/2019 Cadila Healthcare Limited