PHYTONADIONE- phytonadione tablet
Cipla USA., Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PHYTONADIONE TABLETS safely and effectively. See full prescribing information for PHYTONADIONE TABLETS.

PHYTONADIONE tablets, for oral use
Initial U.S. Approval: 1955

INDICATIONS AND USAGE

Phytonadione 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 ScieGen Pharmaceuticals, Inc. at 1-855-724-3436 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

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

Revised: 11/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Phytonadione 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 absorpsion or synthesis of vitamin K, e.g., obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancrease, 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 phytonadione are not immediate; improvement of international normalized ratio (INR) may take 1 to 8 hours. Interim use of whole blood or component therapy may also be necessary if bleeding is severe.

Phytonadione will not counteract the anticoagulant action of heparin.

When phytonadione 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.

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 mg 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 phytonadione are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory. Failure to respond to phytonadione 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 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.

The recommended dose is 2.5 mg to 25 mg or more (sometimes up to 50 mg). Evaluate INR after 6 to 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, pale yellow colored, round, scored tablets, debossed with '**SG 333**' on one side and score line on other side.

4 CONTRAINDICATIONS

Phytonadione 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

Phytonadione may induce temporary resistance to prothrombin-depressing anticoagulants, especially when larger doses of phytonadione 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).

Phytonadione does not affect the anticoagulant action of heparin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

RiskSummary

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 to 4% and 15 to 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_1 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_1 orally, fetal plasma and liver concentrations increased following administration, supporting placental transfer.

8.2 Lactation

RiskSummary

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

8.4 Pediatric Use

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

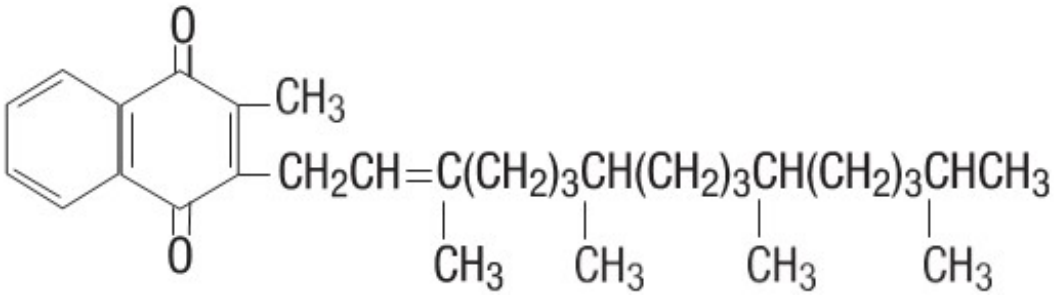
8.5 Geriatric Use

Clinical studies of phytonadione 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 $C_{31}H_{46}O_2$ and its structural formula is:



Phytonadione tablets, USP for oral administration contain 5 mg of phytonadione, USP and are pale yellow colored, round tablets, scored on one side. Inactive ingredients are acacia, anhydrous dibasic calcium phosphate, lactose monohydrate, magnesium stearate, pregelatinized starch, silicon dioxide and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Phytonadione 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 phytonadione. Phytonadione 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

Phytonadione tablets, USP 5 mg, are pale yellow colored, round, scored tablets, debossed with '**SG 333**' on one side and score line on other side. They are supplied as follows:

Bottles of 30 tablets: NDC 69097-999-02

Bottles of 100 tablets: NDC 69097-999-07

Storage

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

17 PATIENT COUNSELING INFORMATION

Vitamin K_1 is fairly rapidly degraded by light; therefore, advise patients to always protect phytonadione from light. Store phytonadione in closed original carton until contents have been used *[see How Supplied/Storage and Handling (16)].*

Manufactured for:
Cipla USA, Inc.
10 Independence Boulevard,
Suite 300, Warren, NJ 07059

Manufactured by:
ScieGen Pharmaceuticals, Inc.
Hauppauge, NY 11788 USA

Rev: 11/2023

21101736

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 69097-999-02

Phytonadione Tablets USP,

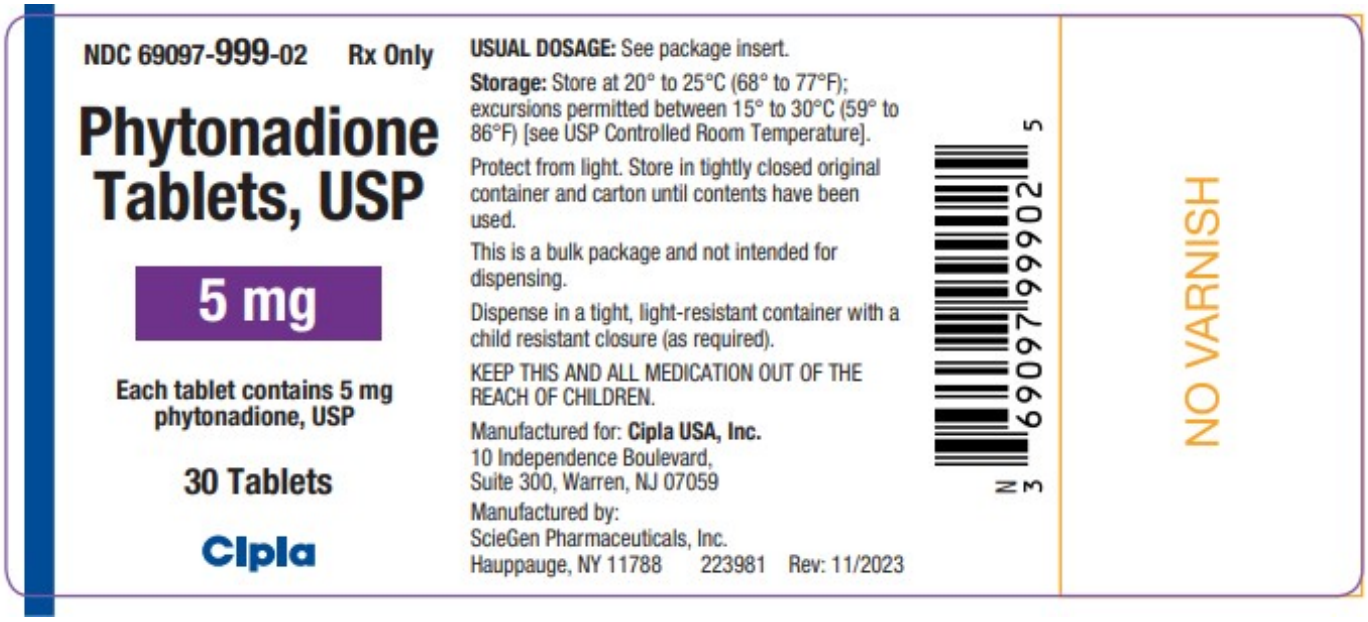
5 mg

Each tablet contains

5 mg phytonadione, USP

30 Tablets Rx only

Cipla.



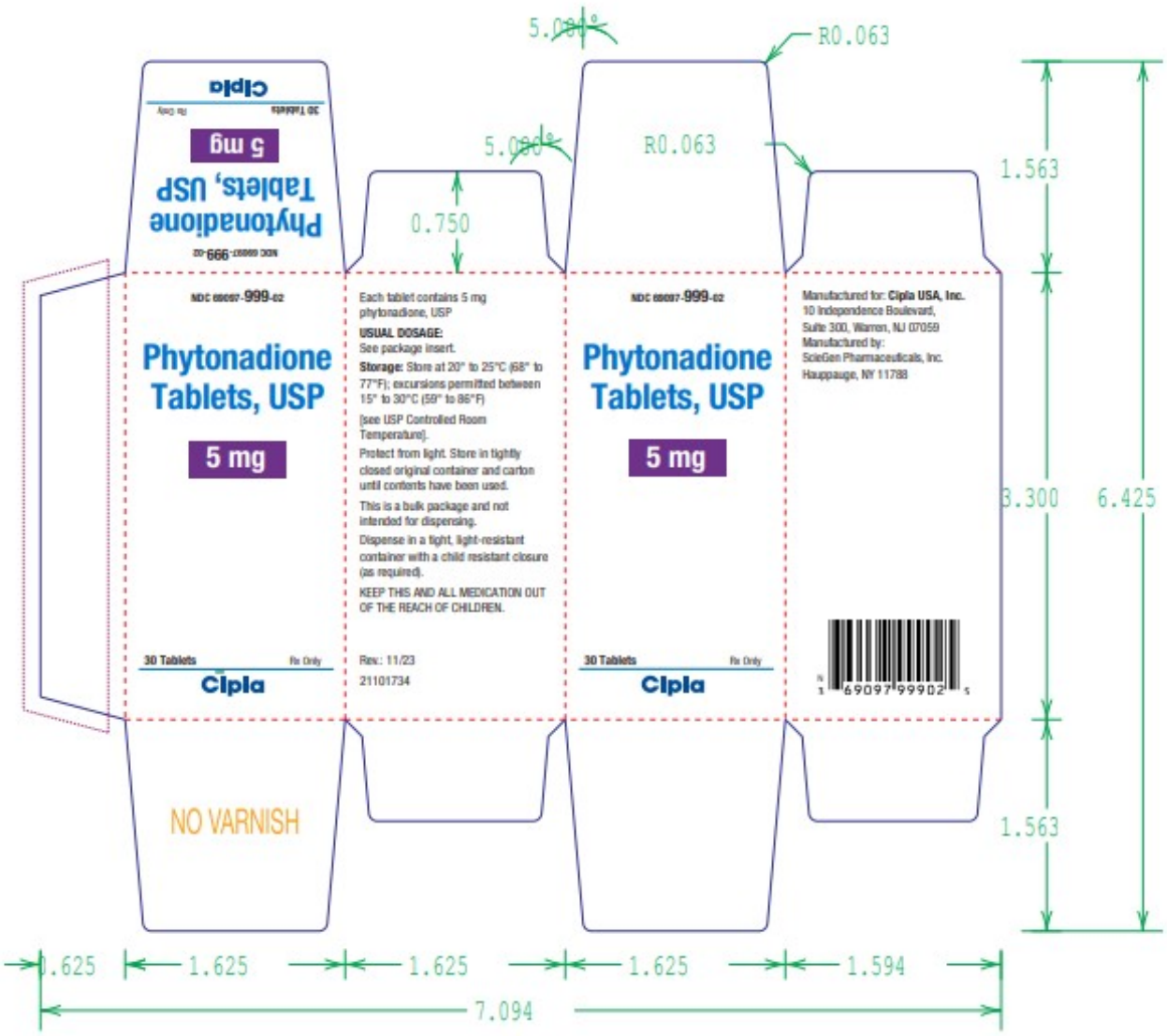
NDC 69097-999-02

Phytonadione Tablets USP,

5 mg

30 Tablets Rx only

Cipla.



NDC 69097-999-07

Phytonadione Tablets USP,

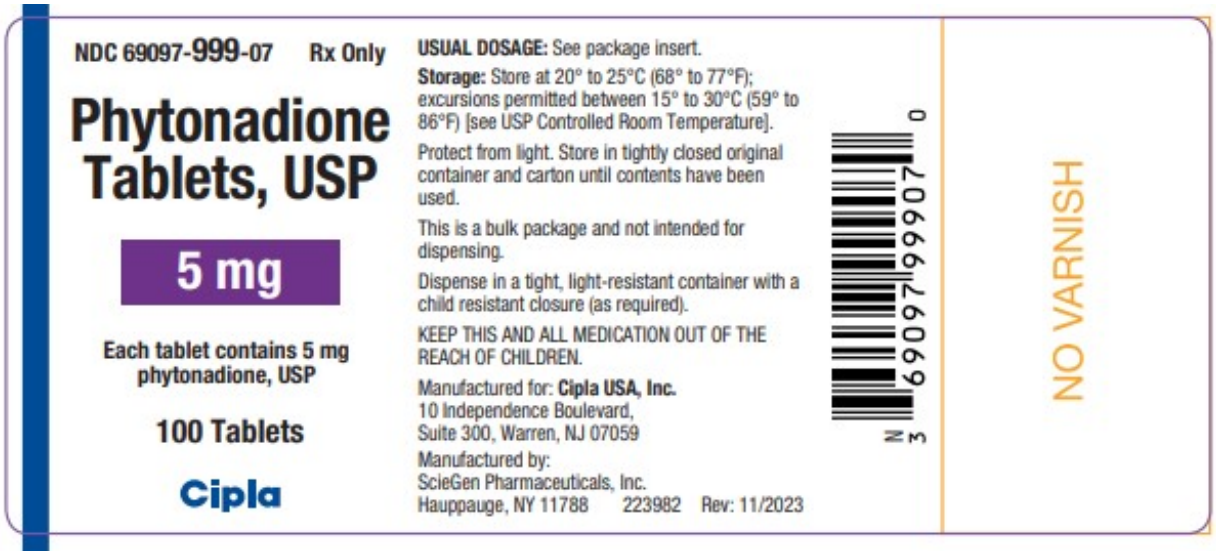
5 mg

Each tablet contains

5 mg phytonadione, USP

100 Tablets Rx only

Cipla.



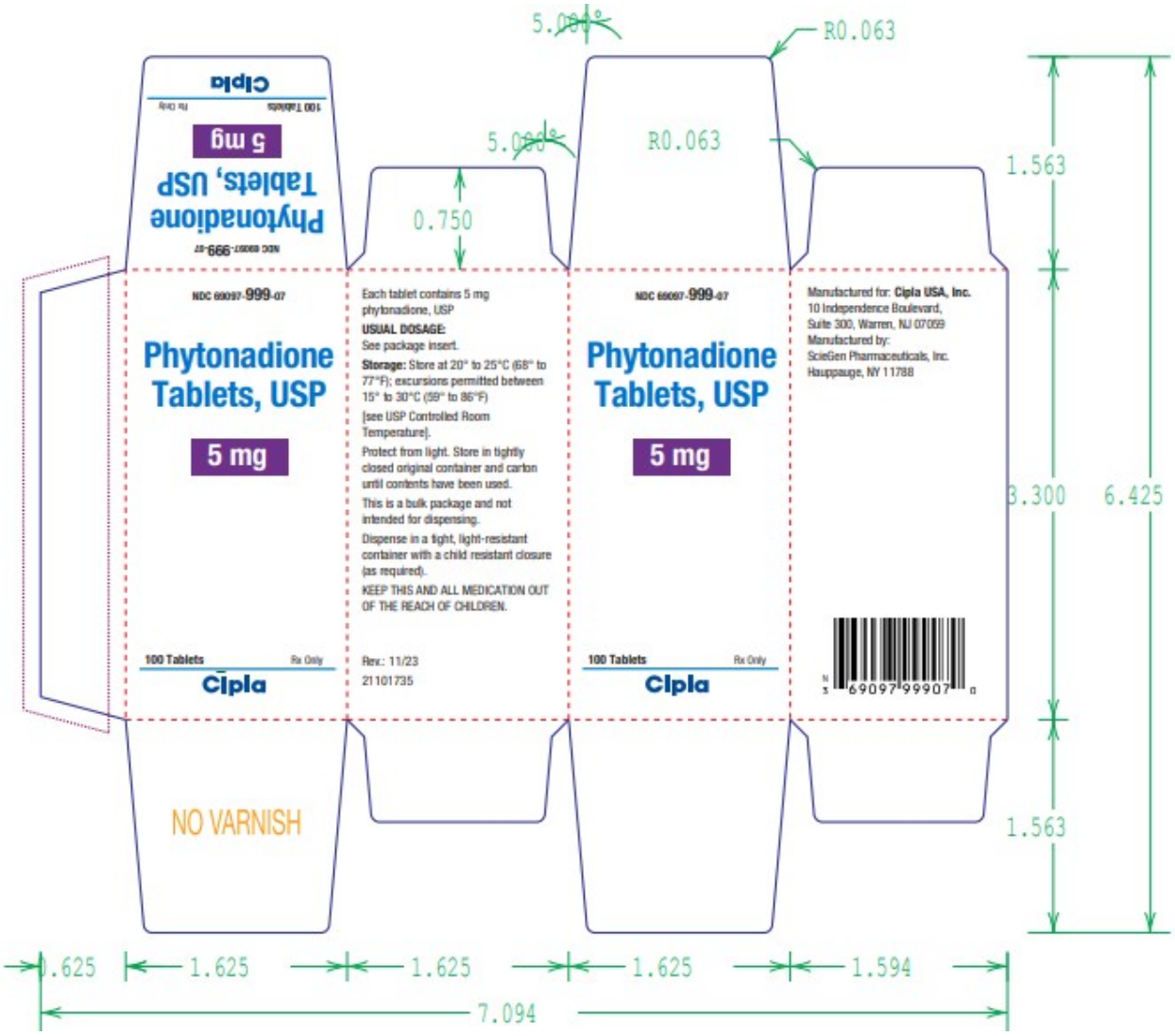
NDC 69097-999-07

Phytonadione Tablets USP,

5 mg

100 Tablets Rx only

Cipla.



PHYTONADIONE

phytonadione tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69097-999
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**
ACACIA (UNII: 5C5403N26O)	
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

STARCH, CORN (UNII: O8232NY3SJ)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics

Color	yellow (pale yellow)	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	SG;333
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69097-999-02	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/01/2023	
2	NDC:69097-999-07	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/01/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA213329	12/01/2023	

Labeler - Cipla USA., Inc. (078719707)

Registrant - ScieGen Pharmaceuticals, Inc (079391286)

Establishment

Name	Address	ID/FEI	Business Operations
ScieGen Pharmaceuticals, Inc		079391286	manufacture(69097-999) , analysis(69097-999) , pack(69097-999) , label(69097-999)

Revised: 11/2023 Cipla USA., Inc.