PHYTONADIONE- phytonadione injection, emulsion
GLENMARK PHARMACEUTICALS INC

Phytonadione Injectable Emulsion, USP
Aqueous Dispersion of Phytonadione
Ampul
Rx only
Protect from light.
Keep ampuls in tray until time of use.

WARNING — INTRAVENOUS AND INTRAMUSCULAR 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. Severe reactions, including fatalities, have also been reported following INTRAMUSCULAR administration.

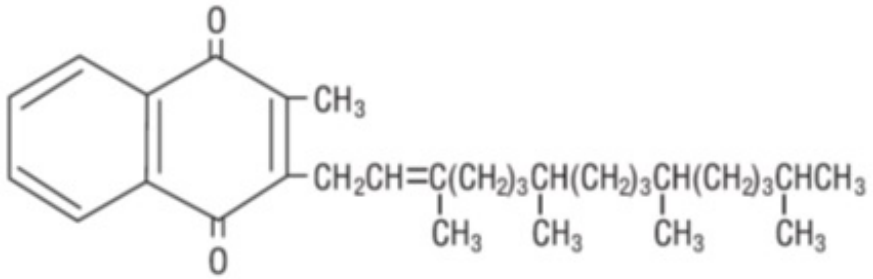
Typically these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first time.

Therefore the INTRAVENOUS and INTRAMUSCULAR routes should be restricted to those situations where the subcutaneous route is not feasible and the serious risk involved is considered justified.

DESCRIPTION

Phytonadione is a vitamin, which is a clear, yellow to amber, viscous, odorless or nearly odorless liquid. It is practically insoluble in water, sparingly soluble in ethanol and miscible with fatty oils. It has a molecular weight of 450.70.

Phytonadione is 2-Methyl-3',7',11',15'-tetramethyl-hexadec-2'-en-1-yl-naphthalene-1,4 dione. Its empirical formula is $C_{31}H_{46}O_2$ and its structural formula is:



Phytonadione Injectable Emulsion, USP is a yellow, sterile, nonpyrogenic aqueous dispersion available for injection by the intravenous, intramuscular and subcutaneous routes. Each milliliter contains phytonadione, USP 10 mg, polyoxyl 35 castor oil 70 mg, dextrose monohydrate 37.5 mg in water for injection; benzyl alcohol 9 mg added as preservative. May contain hydrochloric acid for pH adjustment. pH is 6.3 (5.0 to 7.0). Phytonadione is oxygen sensitive.

CLINICAL PHARMACOLOGY

Phytonadione Injectable Emulsion aqueous dispersion of Phytonadione 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 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-carboxy-glutamic acid residues convert the precursors 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 dispersion, 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 Injectable Emulsion 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 Injectable Emulsion 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.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

WARNINGS

Benzyl alcohol as a preservative in Bacteriostatic Sodium Chloride Injection has been associated with toxicity in newborns. Data are unavailable on the toxicity of other preservatives in this age group. There is no evidence to suggest that the small amount of benzyl alcohol contained in Phytonadione Injectable Emulsion, when used as recommended, is associated with toxicity.

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 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 Phytonadione 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.

Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired.

Premature neonates are particularly at risk because their kidneys are immature, and they required large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

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 Injectable Emulsion.

Pregnancy

Animal reproduction studies have not been conducted with phytonadione injectable emulsion. It is also not known whether phytonadione injectable emulsion can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phytonadione injectable emulsion 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 injectable emulsion is administered to a nursing woman.

Pediatric Use

Hemolysis, jaundice, and hyperbilirubinemia in neonates, particularly those that are premature, may be related to the dose of phytonadione injectable emulsion. Therefore, the recommended dose should not be exceeded (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Deaths have occurred after intravenous and intramuscular administration. (See Box Warning.)

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 Injectable Emulsion in the mouse is 41.5 and 52

mL/kg for the 0.2% and 1% concentrations, respectively.

DOSAGE AND ADMINISTRATION

Whenever possible, Phytonadione Injectable Emulsion, USP should be given by the subcutaneous route (See Box Warning). 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 injectable emulsion, USP 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* (See WARNINGS). *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 ampul.

Prophylaxis of Hemorrhagic Disease of the Newborn

The American Academy of Pediatrics recommends that Phytonadione be given to the newborn. A single intramuscular dose of phytonadione injectable emulsion, USP 0.5 to 1 mg within one hour of birth is recommended.

Treatment of Hemorrhagic Disease of the Newborn

Empiric administration of Phytonadione 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 Phytonadione is usually diagnostic of hemorrhagic disease of the newborn, and failure to respond indicates another diagnosis or coagulation disorder.

Phytonadione injectable emulsion, USP 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 injectable emulsion, USP 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.

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

Newborns	Dosage
Hemorrhagic Disease of the Newborn Prophylaxis	0.5 to 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 anticoagulants)
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)

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

HOW SUPPLIED

Phytonadione Injectable Emulsion, USP is supplied as follows:

Unit of Sale	Concentration
NDC 68462-758-25 25 ampuls (Bundle of 5 clamcells, each	10 mg/mL

clamcell containing 5 single-dose ampuls)	

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Protect from light. Keep ampuls in tray until time of use.

Manufactured by:
Gland Pharma Limited,
Hyderabad-502 307, India.

Distributed by:

Glenmark Pharmaceuticals Inc., USA

Mahwah, NJ 07430

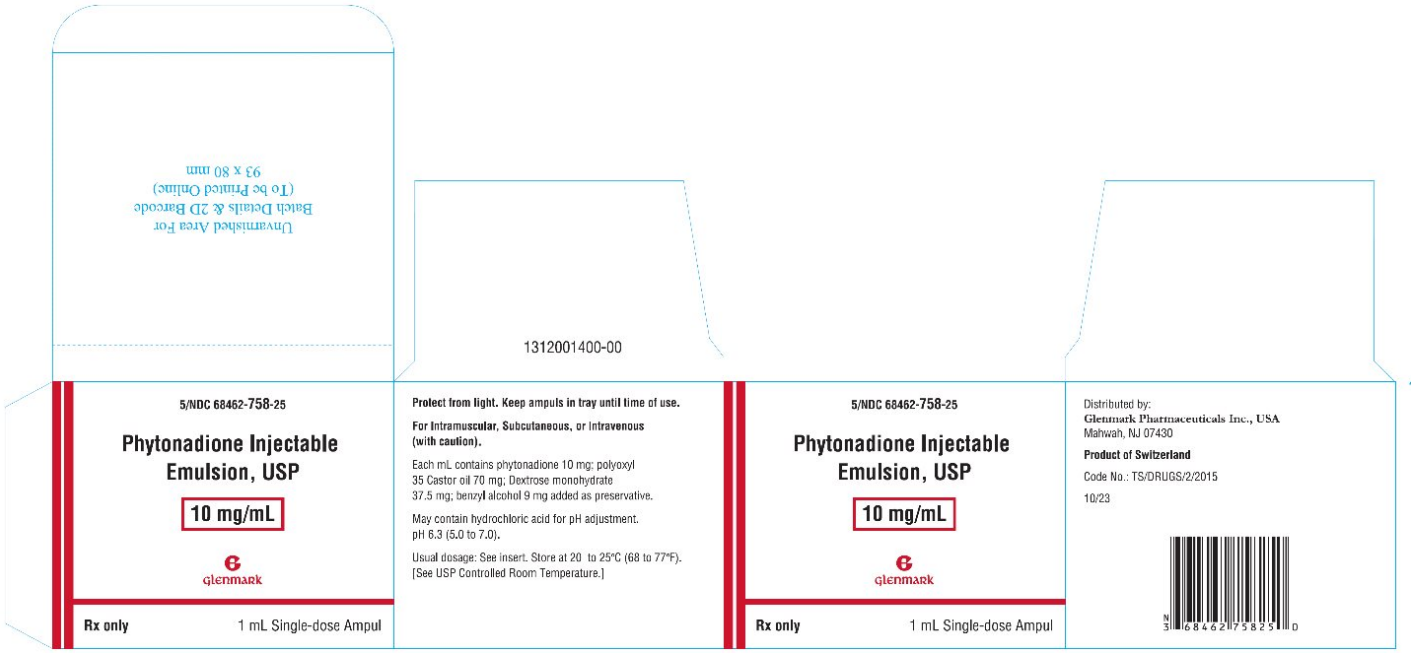
Revised: August 2024

Revised: 08/2024

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Outer carton Label

NDC 68462-758-25 25 x 1 mL Single-Dose Ampuls
Phytonadione Injectable
Emulsion, USP
10 mg/mL
For Intramuscular, Subcutaneous
or Intravenous (with caution)
Rx only



Package/Label Display Panel

Tray Label

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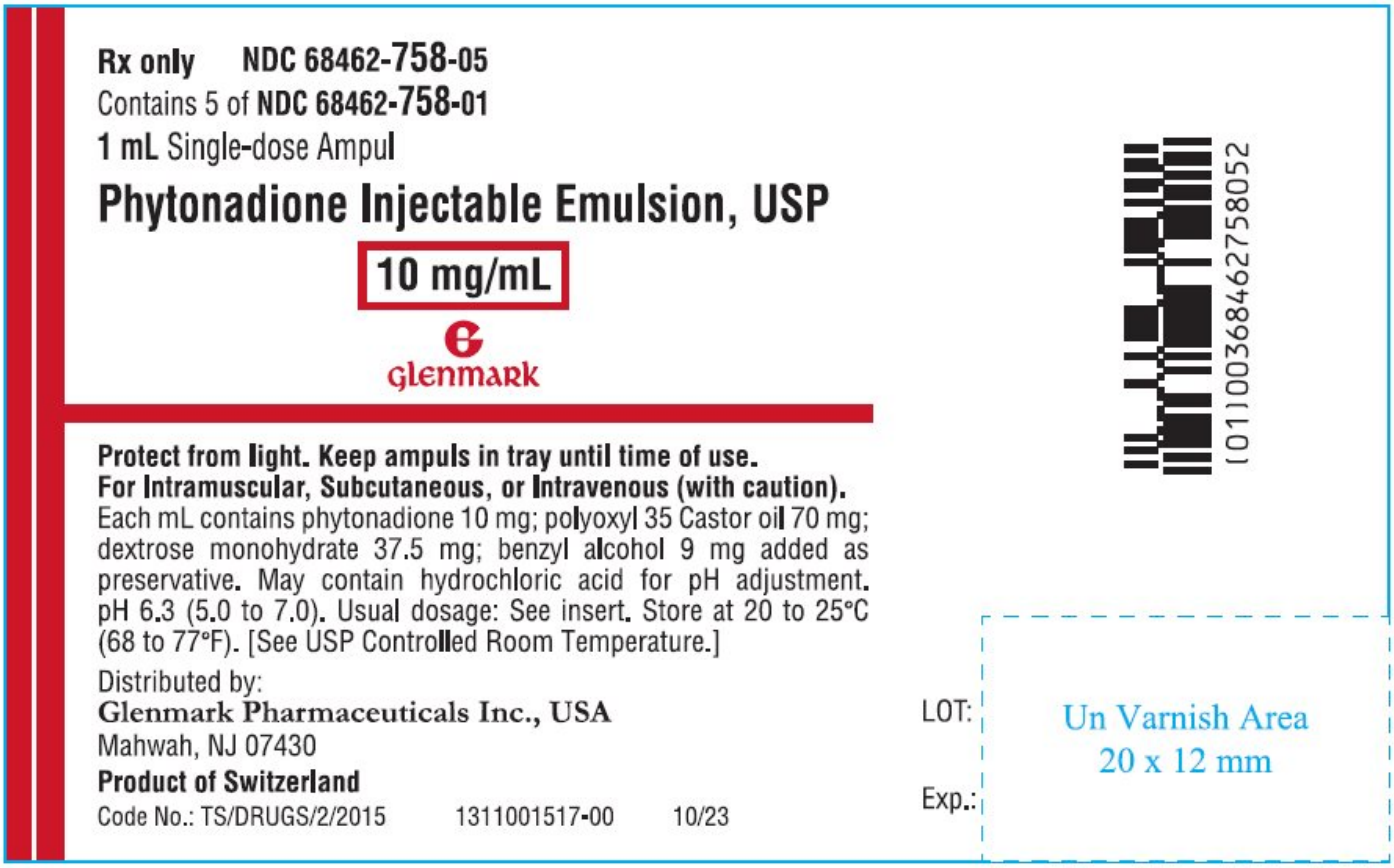
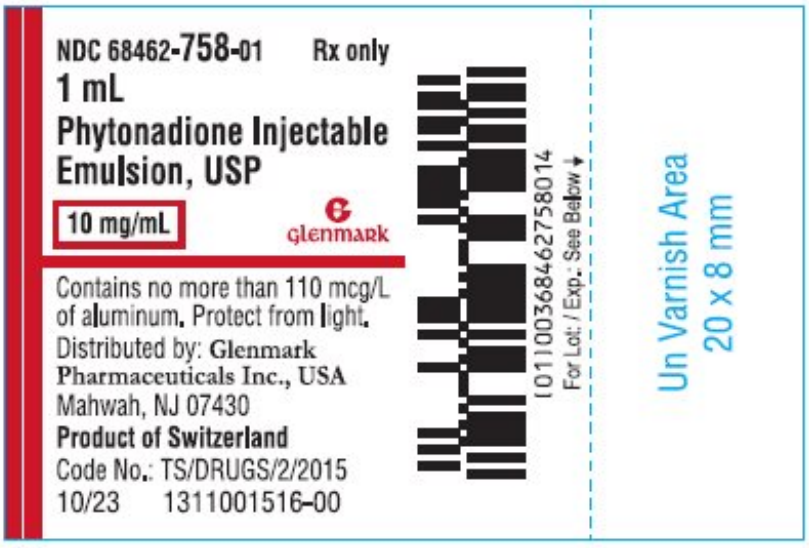
Rx only NDC 68462-758-05
Contains 5 of NDC 68462-758-01
5 x 1 mL Single-Dose Ampuls
Phytonadione Injectable
Emulsion, USP
10 mg/mL



Ampul Label

NDC 68462-758-01 Rx only
1 mL
Phytonadione Injectable
Emulsion, USP
10 mg/mL



PHYTONADIONE

phytonadione injection, emulsion

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68462-758
Route of Administration	INTRAMUSCULAR, INTRAVENOUS, SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PHYTONADIONE (UNII: A034SE7857) (PHYTONADIONE - UNII:A034SE7857)	PHYTONADIONE	10 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
POLYOXYL 35 CASTOR OIL (UNII: 6D4M1DAL6O)	
DEXTROSE MONOHYDRATE (UNII: LX22YL083G)	
BENZYL ALCOHOL (UNII: LKG8494WBH)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68462-758-25	5 in 1 CARTON	12/10/2024	
1	NDC:68462-758-05	5 in 1 TRAY		
1		1 mL in 1 AMPULE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA217386	12/10/2024	

Labeler - GLENMARK PHARMACEUTICALS INC (130597813)

Establishment

Name	Address	ID/FEI	Business Operations
GLAND PHARMA LIMITED		858971074	ANALYSIS(68462-758) , LABEL(68462-758) , MANUFACTURE(68462-758)

Revised: 12/2024 GLENMARK PHARMACEUTICALS INC