Phytonadione Injectable Emulsion USP

Aqueous Dispersion of Phytonadione Injectable Emulsion Ample

Biclyl

Issued: May 2019

Protect from light. Keep ampules in carton 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 injectate 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/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, odourless or nearly odourless liquid. It is insoluble in water, soluble in chloroform and slightly soluble in ethanol. Its molecular weight is 450.70. Phytonadione is 2-methyl-3-phytyl-1,4-naphthoquinone. Its empirical formula is 

\[
\text{C}_{20}\text{H}_{21}\text{O}_4
\]

and its structural formula is:

![Structural formula of Phytonadione](image)

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 10 mg, polyethylene glycol 350, benzyl alcohol 0.9 mg added as preservative. May contain hydrochloric acid for pH adjustment; pH is 3.0 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 X), and Stuart factor (factor X). The prothrombin factor is sensitive to the levels of three of these four factors—II, VII, and X. The resulting gamma-carbonel-glutamic acid residues convert the precursors into active clotting factors and 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 phytonadione. After intramuscular injection, no free or unmetabolized Vitamin K appears in the 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 Analogs.

**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:

- Anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives,
- prothrombin and therapy of hemorrhagic disease of the newborn,
- hypoprothrombinemia due to anticoagulant therapy,
- hypoprothrombinemia secondary to factors limiting absorption or synthesis of Vitamin K, e.g., obstructive jaundice, bilateral fistula, sprue, ulcers, colitis, celiac disease, intestinal resection, cystic fibrosis, and regional enteritis,
- other/undefined hypoprothrombinemia when there is no evidence that the result is due to interference with phytonadione metabolism, e.g., sallies.

**CONTRAINDICATION**

Hypersensitivity to any component of this medication.

**WARNINGS**

Phytonadione is a vitamin that is a preservative in Parenteral Sodium Chloride Injection. Phytonadione 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 hemorrhage persists.

Phytonadione will not counteract the anticoagulant action of heparin.

When administration is begun to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy may be indicated. However, the patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy. Phytonadione is not a cloting agent, but overzealous therapy with phytonadione injectable emulsion may produce 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.

**WARNINGS**

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 require 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 re instituted anticoagulant therapy to use somewhat larger amounts of calcium and phosphate, depressing anticoagulant, or to use one which acts on a different principle, such as heparin sodium.
Phytonadione Injectable Emulsion, Summary of Dosage Guidelines (See circular for details)

<table>
<thead>
<tr>
<th>Newborns</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic Disease of the Newborn</td>
<td>0.5 to 1mg IM within 1 hour of birth</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>1 mg SC or IM</td>
</tr>
<tr>
<td>Anticoagulant-Induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>Initial Dosage</td>
</tr>
<tr>
<td>Anticoagulant-Induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)</td>
<td>2.5 to 25 mg or more (rarely up to 50 mg)</td>
</tr>
<tr>
<td>Hypoprothrombinemia Due to Other Causes (Antibiotics; Salicylates or other drugs)</td>
<td>2.5 to 25 mg or more (rarely up to 50 mg)</td>
</tr>
</tbody>
</table>

In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

Hypoprothrombinemia Due to Other Causes

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

NON-SUPPLIED

Phytonadione injectable emulsion, USP is supplied as follows:

For Carton:

<table>
<thead>
<tr>
<th>Package Description</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg in 1 mL amp in 25 x 1 mL Ampules</td>
<td>4101-400-01</td>
</tr>
</tbody>
</table>

For Ampoules:

<table>
<thead>
<tr>
<th>Package Description</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg in 1 mL amp</td>
<td>4101-400-01</td>
</tr>
</tbody>
</table>

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

Protect from light. Keep ampules in cartons until time of use.

Rx Only

Distributor: Dr. Reddy’s Laboratories Inc., Princeton, N.J. 08540

Made in India

Issued: 0519

Dr. Reddy’s

To report SUSPECTED ADVERSE REACTIONS, contact Dr. Reddy's Laboratories Inc., at 1-888-375-3794, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.