Doses

- **DOGS:**
  a) To temporarily reverse the CNS effects of ivermectin toxicosis in support of the diagnosis: 1 mg (total dose) IV (Mealey 2006)
  b) To temporarily reverse the CNS effects of ivermectin toxicosis in support of the diagnosis: 1 mg (total dose)/12 hours IV. May reverse ivermectin-induced coma for 30–90 minutes. In comatose patients, it does not appear to induce seizures, but seizure-like activity can be observed in patients with only minor ataxia and confusion. (Estrada 2002)
  c) Provocative test for narcolepsy/cataplexy if feeding test (*10 pieces of highly tasty food that the dog loves to eat in a row 12–24 inches apart; affected dogs will usually take 2 minutes or longer to eat the food and will have several attacks*) is not successful: Physostigmine at 0.025 mg/kg IV, wait 9–15 minutes and observe response to stimulus (food test or similar). If clinical signs do not appear, may try a higher dose of 0.05 mg/kg as above. Subsequent testing can be done at doses of 0.075 mg/kg and 1 mg/kg as above. Increased severity of signs that may persist for 15–45 minutes in response to stimulus is indicative of cataplexy/narcolepsy. (Shell 2003b)
- **HORSES:** (**Note:** RCI Class 3 drug)
  a) Provocative test in diagnosing cataplexy or narcolepsy: 0.05–0.1 mg/kg slow IV will precipitate a cataplectic attack within 3–10 minutes after administration in affected horses. Untoward effects may include colic or cholinergic stimulation. (Andrews and Matthews 2004).
  b) Provocative test in diagnosing cataplexy or narcolepsy: 0.06–0.08 mg/kg IV. Lack of positive response does not rule out diagnosis of narcolepsy. Diarrhea can occur and caution is advised as horse can cause colic. (Mayhew 2005b)
- **CATTLE:**
  a) For reversal of tall larkspur (*Delphinium barbeya*) poisoning: 0.04–0.08 mg/kg IV rapidly; serial injections may be necessary. (Pfister, Panter et al. 1994)

Monitoring

- Direct patient supervision required for monitoring adverse effects
- Heart rate, blood pressure; monitor heart rhythm if heart rate is abnormal

Client Information

- This medication must be administered in a setting where direct veterinary supervision is available

Chemistry/Synonyms

Physostigmine salicylate is made from an extract of *Physostigma venenosum* (Calabar Bean) seeds. It occurs as white, shining, odorless, crystals or crystalline powder. Upon exposure to heat, light, air, or exposure to traces of metals for a long period, it develops a red tint. One gram is soluble in 75 mL of water and 16 mL of alcohol. The injection has a pH of 3.5–5.

Physostigmine salicylate may also be known as eserine salicylate, physostigmine monosalicylate and *Anticholium*®.

Storage/Stability/Compatibility

The injection (ampules) should be stored below 40°C and preferably between 15–30°C. Protect from light and freezing. Physostigmine is labeled for human use to be administered IV undiluted. It may be given via a Y-site or stopcock port on IV set, but it should not be added to IV solutions. IM dosing (although not approved) is not uncommon in humans.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Physostigmine Salicylate Injection: 1mg/mL in 2 mL ampules, also contains benzyl alcohol 2% and 0.1% sodium metabisulfite; *Antilirium*® (Forest), generic; (Rx)

PHYTONADIONE
VITAMIN K_1

(fye-toe-na-*dye*-ohne) Vitamin K1, Mephyton®

ANTIDOTE, FAT SOLUBLE VITAMIN

Prescriber Highlights

- **Used for the treatment of anticoagulant rodenticide toxicity, dicumarol toxicity associated with sweet clover ingestion in ruminants, sulfaquinoxaline toxicity, & in bleeding disorders associated with faulty formation of vitamin K-dependent coagulation factors**
- **Contraindications: Hypersensitivity; does not correct hypoprothrombinemia due to hepatocellular damage.**
- **Adverse Effects: Anaphylactoid reactions after IV administration, IM use may result in acute bleeding from the site of injection during the early stages of treatment. SC injections or oral dosages may be slowly or poorly absorbed in hypovolemic animals.**
- **May require 6–12 hours for effect**
- **Small gauge needles are recommended for use when injecting SC or IM**

Uses/Indications

The principal uses of exogenously administered phytonadione is in the treatment of anticoagulant rodenticide toxicity. It is also used for treating dicumarol toxicity associated with sweet clover ingestion in ruminants, sulfaquinoxaline toxicity, and in bleeding disorders associated with faulty formation of vitamin K-dependent coagulation factors.

Pharmacology/Actions

Vitamin K_1 is necessary for the synthesis of blood coagulation factors II, VII, IX, and X in the liver. It is believed that Vitamin K_1 is involved in the carboxylation of the inactive precursors of these factors to form active compounds.

Pharmacokinetics

Phytonadione is absorbed from the GI tract in monogastric animals via the intestinal lymphatics, but only in the presence of bile salts. Oral absorption of phytonadione may be significantly enhanced by administration with fatty foods. The relative bioavailability of the drug is increased 4–5 times in dogs given canned dog food with the dose. After oral administration, increases in clotting factors may not occur until 6–12 hours later.

In humans, oral administration may be more rapidly absorbed than with SC administration.

Phytonadione may concentrate in the liver for a short period of time, but is not appreciably stored in the liver or other tissues.

Only small amounts are distributed across the placenta in pregnant animals. Exogenously administered phytonadione enters milk. The elimination of Vitamin K_1 is not well understood.

Contraindications/Precautions/Warnings

Many veterinary clinicians state that the intravenous use of phytonadione is contraindicated because of increased risk of anaphylaxis development, and while intravenous phytonadione is used in human medicine and several intravenous dosage regimens are outlined below in the Dosage section, the FDA-CVM has warned to avoid administering the drug IV. However, in human medicine, intravenous phytonadione is recommended (with caution) for severe bleeding associated with very high INR. Phytonadione is contraindicated in patients hypersensitive to it or any component of its formulation.

Vitamin K does not correct hypoprothrombinemia due to hepatocellular damage.

Adverse Effects

Anaphylactoid reactions have been reported following IV administration of Vitamin K_1; use with extreme caution (See Contraindications above). Intramuscular administration may result in acute bleeding from the site of injection during the early stages of treatment. Small gauge needles are recommended for use when injecting SC or IM. Subcutaneous injections or oral dosages may be slowly or poorly absorbed in animals that are hypovolemic.

Because 6–12 hours may be required for new clotting factors to be synthesized after phytonadione administration, emergency needs for clotting factors must be provided by giving blood products.

Reproductive/Nursing Safety

Phytonadione crosses the placenta only in small amounts, but its safety has not been documented in pregnant animals. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Vitamin K is excreted in maternal milk, but is unlikely to have negative effects in nursing offspring.

Overdosage/Acute Toxicity

Phytonadione is relatively non-toxic, and it would be unlikely that toxic clinical signs would result after a single overdosage. However, refer to the Adverse Effects section for more information.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving phytonadione and may be of significance in veterinary patients:

- **ANTIBIOTICS, ORAL**: Although chronic antibiotic therapy should have no significant effect on the absorption of phytonadione, these drugs may decrease the numbers of vitamin K producing bacteria in the gut
- **MINERAL OIL**: Concomitant administration of oral mineral oil may reduce the absorption of oral vitamin K.
- **WARFARIN**: As would be expected, phytonadione antagonizes the anticoagulant effects of coumarin (and indanedione agents. There are many drugs that may prolong or enhance the effects of anticoagulants and antagonize some of the therapeutic effects of phytonadione, including: **phenylbutazone, aspirin, chloramphenicol, sulfonamides diazoxide, allopurinol, cimetidine, metronidazole, anabolic steroids, erythromycin, ketoconazole, propranolol,** and **thyroid** drugs.

Doses

- **DOGS & CATS:**

  For adjunctive therapy of acute liver failure:

  a) 1–5 mg/kg PO or SC q24h (Rosanski 2002)

  For anticoagulant rodenticide toxicity:

  a) For known warfarin, fumarin, pindone, or valone ingestions: 1 mg/kg PO once daily for 4–6 days.

  For known bromadiolone or brodifacoum ingestions: 2.5 mg/kg PO once daily usually for 2–3 weeks (bromadiolone duration unknown).

  For known diphacinone or chlorphacinone ingestions: 2.5–5 mg/kg PO for 3–4 weeks.

  Note: Usual dosages and duration—use oral route (with one teaspoon of canned dog food) if animal not vomiting, otherwise SC route preferred over IV. Therapy must be continued for as long as rodenticide is inhibiting vitamin K_1 epoxide recycling. (Felice and Murphy 1995)

  b) For acute cases: Handle animal gently. Avoid IM injections; give fresh, whole blood transfusion 10–20 mL/kg IV (first half rapidly, then at 20 drops/minute). Give oxygen if hypoxic; if dyspneic consider radiographs and thoracentesis for intrathoracic hemorrhage. Then give phytonadione as below.

  For subacute cases: Give phytonadione at 2–3 mg/kg SC q12h for large dogs and 5 mg/kg SC q12h for small dogs and cats. Repeat until coagulation times are normal. Follow with oral phytonadione at 2.5–3 mg/kg PO divided three times daily for 4–6 days if short acting coumarin (*e.g.*, warfarin) or up to 30 days for long-acting agents. (Grauer and Hjelle 1988)

- **RABBITS, RODENTS, SMALL MAMMALS:**

  a) Mice, Rats, Gerbils, Hamsters, Guinea pigs: 1–10 mg/kg IM (Adamcak and Otten 2000)

- **CATTLE:**

  For anticoagulant rodenticide toxicity:

  a) Initially 0.5–2.5 mg/kg IV in D_5W at a rate of 10 mg/minute. Subsequent doses may be given IM or SC. Second generation agents may require 3–4 weeks of treatment. (Bailey 1986b)

  b) 0.5–2.5 mg/kg IM, if IV use is necessary (avoid if possible), dilute in saline or D_5W/saline and give very slowly (not to exceed 5 mg/minute). (Upson 1988)

  c) For acute hypoprothrombinemia with hemorrhage: 0.5–2.5 mg/kg IV, not to exceed 10 mg/minute in mature animals and 5 mg/minute in newborn and very young animals.

  For non-acute hypoprothrombinemia: 0.5–2.5 mg/kg IM or SC (Label directions; *Veda-K1*®—Vedco)

  For sweet clover (dicumarol) toxicity:

  a) Give blood if necessary, then phytonadione 1 mg/kg IV or IM; repeat 2–3 times daily for 2 days. (Osweiler and Ruhr 1986)

- **HORSES:**

  For warfarin (or related compounds) toxicity:

  a) 500 mg SC q4–6h until one-stage prothrombin time (OSPT) returns to normal control values. Whole blood or fresh plasma may also be necessary early in the course of treatment. (Byars 1987)

  b) 0.5–2.5 mg/kg IM, if IV use is necessary (avoid if possible), dilute in saline or D_5W/saline and give very slowly (not to exceed 5 mg/minute). (Upson 1988)

■ **SWINE:**

For warfarin (or related compounds) toxicity:

a) 0.5–2.5 mg/kg IM, if IV use is necessary (avoid if possible), dilute in saline or D_5W/saline and give very slowly (not to exceed 5 mg/minute). (Upson 1988)

■ **SHEEP & GOATS:**

For warfarin (or related compounds) toxicity:

a) 0.5–2.5 mg/kg IM, if IV use is necessary (avoid if possible), dilute in saline or D_5W/saline and give very slowly (not to exceed 5 mg/minute). (Upson 1988)

■ **BIRDS:**

For hemorrhagic disorders:

a) 0.25–0.5 mL/kg IM of the 10 mg/mL injectable product. Commonly used before surgery where hemorrhage is anticipated. (McDonald 1989)

b) 0.2–2.5 mg/kg IM as needed; usually only 1–2 injections are required. May also be used prophylactically when amprolium and sulfas are administered. (Clubb 1986)

Monitoring

■ Clinical efficacy (lack of hemorrhage)

■ One-stage prothrombin time (OSPT); INR

Client Information

■ Because it may take several weeks to eliminate some of the anticoagulant rodenticides from the body, clients must be counseled on the importance of continuing to administer the drug (phytonadione) for as long as instructed or renewed bleeding may occur.

■ Unless otherwise instructed, oral phytonadione should be administered with food, preferably foods high in fat content.

■ During therapy, animals should be kept quiet whether at home or hospitalized.

Chemistry/Synonyms

A naphthoquinone derivative identical to naturally occurring vitamin K_1, phytonadione occurs as a clear, yellow to amber, viscous liquid. It is insoluble in water, slightly soluble in alcohol and soluble in lipids.

Phytonadione may also be known as: methylphytylnaphthochinonum, phylloquinone, phytomenadionum, phytomenadione, vitamin K_1, *AmTech®, Glakay®, Aqua-Mephyton®, K1®, K-Caps®, K-Chews®, K-Ject®, KP®, Kanakion®, Kanavit®, Kavit®, Kaytwo®, Kaywan®, Kenadion®, Konakion®, Konakion Novum®, Mephyton®, Pertix-Solo®, Veda-K1, Vikatron®,* Vita-Jec®, or *Vitamon K®*.

Storage/Stability/Compatibility

Phytonadione should be protected from light at all times, as it is quite sensitive to light. If used as an intravenous infusion, the container should be wrapped with an opaque material. Tablets and capsules should be stored in well-closed, light-resistant containers.

Because most veterinary clinicians state that phytonadione is contraindicated for intravenous use; consult specialized references or a hospital pharmacist for more specific information on compatibility of phytonadione with other agents.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Phytonadione Oral Capsules: 25 mg; *K-Caps®* (Butler), *Veda-K1® Capsules* (Vedco), *Veta-K_1®* (Bimeda), *Vitamin K_1* (Phoenix Pharmaceutical, RXV); (Rx) Labeled for use in dogs and cats.

Phytonadione Oral Capsules: 50 mg; *Vitamin K_1 Double Strength®* (Phoenix); (Rx) Labeled for use in dogs.

Phytonadione Oral Tablets, Chewable: 25 mg, 50 mg; *Vitamin K_1 Chewable®* (V.E.T.), *Vitamin K1 Chewablet®* (Pala-Tech), *K-Chews®* (Butler); (Rx). Products may be labeled for use in dogs and cats.

Phytonadione Aqueous Colloidal Solution for Injection: 10 mg/mL in 30 mL and 100 mL vials; *AmTech® Vitamin K_1* (IVX), *K-Ject®* (Butler), *Veda-K_1® Injection* (Vedco), *Vita-Jec®* (RXV), *Vitamin K_1* (Vet Tek, Bimeda, Neogen, Phoenix Pharmaceutical), (Rx) Labeled for use dogs, cats, cattle, calves, horses, swine, sheep, and goats. No withdrawal times listed.

HUMAN-LABELED PRODUCTS:

Phytonadione Tablets: 5 mg; *Mephyton®* (Merck); (Rx)

Phytonadione Injection, Emulsion: 2 mg/mL (aqueous colloidal solution) & 10 mg/mL in 0.5 mL & 1 mL amps; generic (Hospira); (Rx)

PIMOBENDAN

(pi-moe-*ben*-den) Vetmedin®

INODILATOR

Prescriber Highlights

- **Oral drug that may be useful in treatment of congestive heart failure in dogs**
- **Limited clinical experience, particularly in North America; many ongoing studies being performed**
- **May increase risks for arrhythmias**

Uses/Indications

Pimobendan is used to treat dogs with congestive heart failure secondary to dilated cardiomyopathy or chronic mitral valve insufficiency (CMVI).

Pharmacology/Actions

Pimobendan is a so-called inodilator; it has both inotropic and vasodilator effects. Pimobendan usually decreases heart rate (negative chronotrope) in animals with CHF. Its inotropic effects occur via inhibition of phosphodiesterase III (PDE-III) and by increasing intracellular calcium sensitivity in the cardiac contractility apparatus. Cardiac contractility is enhanced without an increase in myocardial oxygen consumption, as pimobendan does not increase intracellular calcium levels. Its vasodilator effects are via vascular PDE-III inhibition and both arterial and venous dilation occur.

Pharmacokinetics

In dogs, following a single oral administration of 0.25 mg/kg pimobendan peak levels of the parent compound and the active metabolite were observed 1–4 hours post-dose (mean: 2 and 3 hours, respectively). Food decreased the bioavailability of an aqueous solution of pimobendan, but the effect of food on the absorption of pimobendan from chewable tablets is unknown. The steady-state volume of distribution of pimobendan is 2.6 L/kg. Protein binding of pimobendan and the active metabolite in dog plasma is >90%. Pimobendan is oxidatively demethylated to a pharmacologically active metabolite which is then conjugated with sulfate or glucuronic acid and excreted mainly via feces. Clearance of pimobendan is approximately 90 mL/min/kg, and the terminal elimination half-lives of pimobendan and the active metabolite are approximately 0.5 hours and 2 hours, respectively. Plasma levels of pimobendan and the active metabolite were below quantifiable levels by 4 and 8 hours respectively after oral administration.