■ **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.

In humans with heart failure, pimobendan is rapidly absorbed with peak levels occurring in less than one hour after dosing. The volume of distribution was about 3.2 L/kg; clearance about 25 mL/min/kg. Terminal half-life is slightly less than 3 hours.

Contraindications/Precautions/Warnings

Pimobendan is contraindicated in animals hypersensitive to it, with hypertrophic cardiomyopathy, aortic stenosis, or any other condition where an augmentation of cardiac output is inappropriate for functional or anatomic reasons. It should be used with caution in patients with uncontrolled cardiac arrhythmias.

The label states the drug has not been evaluated in dogs younger than 6 months of age, dogs with congenital heart defects, diabetes mellitus or other serious metabolic diseases, dogs used for breeding, or pregnant or lactating bitches.

Adverse Effects

Because clinical experience with this drug is still limited, the adverse effect profile is still being developed. In a US field trial (56 day), the adverse effect incidence (at least one occurrence reported per dog) was: poor appetite (38%), lethargy (33%), diarrhea (30%), dyspnea (29%), azotemia (14%), weakness and ataxia (13%), pleural effusion (10%), syncope (9%), cough (7%), sudden death (6%), ascites (6%), and heart murmur (3%).

In a study comparing cardiac adverse effects of pimobendan with benazepril (Chetboul, Lefebvre et al. 2007), dogs with mitral valve regurgitation had increases in systolic function but also developed worsening mitral valve disease and specific mitral valve lesions (acute hemorrhages, endocardial papilloform hyperplasia on the dorsal surfaces of the leaflets, and infiltration of *chordae tendinae* by glycosaminoglycans) not seen in the benazepril group. The authors recommend that patients with mitral valve disease that are treated chronically with pimobendan be regularly and cautiously examined for any worsening mitral valvular lesions and regurgitation.

There is some evidence that pimobendan may increase the development of arrhythmias. Atrial fibrillation or increased ventricular ectopic beats have been reported in dogs on pimobendan, but because cardiomyopathy can cause arrhythmias, a causative effect has not been fully established. A trial of pimobendan in humans with heart failure demonstrated an increased mortality rate while on the drug, but this result has not been duplicated in canine studies.

Reproductive/Nursing Safety

The label states the drug has not been evaluated in dogs used for breeding, or pregnant or lactating bitches. When pimobendan was given in high dosages (300 mg/kg) to pregnant laboratory animals, increased resorptions occurred. Rabbits given 100 mg/kg showed no adverse fetal effects.

No information on the safety of pimobendan during nursing was located.

Overdosage/Acute Toxicity

No specific information was located. In case of an animal overdose, contact an animal poison control center.

Drug Interactions

In field trials, the drug is labeled as being used safely with furosemide, digoxin, enalapril, atenolol, nitroglycerin, hydralazine, diltiazem, antiparasitic products (including heartworm preventative), antibiotics, famotidine, theophylline, levothyroxin, diphenhydramine, hydrocodone, metoclopramide and butorphanol.

The U.K. label states that "pimobendan-induced increase in contractility of the heart are attenuated in the presence of the calcium antagonist **verapamil** and the beta-antagonist **propranolol**." It is assumed that other drugs in these categories (*e.g.*, diltiazem, atenolol) may also have effect.

Milrinone, a human drug that also inhibits phosphodiesterase, has been used with a variety of other drugs (*e.g.*, cardiac glycosides, lidocaine, hydralazine, prazosin, quinidine, nitroglycerin, furosemide, warfarin, spironolactone, heparin, potassium) without apparent problems, but because pimobendan also increases calcium sensitivity, comparing the two drugs may not be fully informative.

Laboratory Considerations

No laboratory interactions or special considerations were located.

Doses

- **DOGS:**
  a) For management of the signs of mild, moderate or severe congestive heart failure due to AV valve insufficiency or dilated cardiomyopathy: 0.5 mg/kg total daily dose. Divide daily dose into two portions that are not necessarily equal (using whole and half tablets) and administer approximately 12 hours apart. (Label directions; *Vetmedin*®—B-I)
  b) For treatment of congestive heart failure secondary to myxomatous mitral valve disease (MMVD): 0.4–0.6 mg/kg PO divided twice daily (Lombard 2004)
  c) For treatment of heart failure secondary to dilated cardiomyopathy or chronic mitral valve insufficiency: 0.25 mg/kg PO twice daily (O'Grady, Minors et al. 2004)
  d) 0.2–0.6 mg/kg PO divided q12h (U.K. Label directions; *Vetmedin*®—BI; 2003)

Monitoring

- Cardiovascular parameters used to monitor heart function, including ECG (rate/rhythm), blood pressure, echo studies, clinical signs, etc.

Client Information

- Give medication approximately one hour before feeding.
- Clients should understand that there is limited clinical experience with this drug, that there may be risks (arrhythmias) associated with its use, and that pimobendan is a treatment, and not a cure for heart failure.
- Compliance with the veterinarian's instructions is essential.
- Keep out of reach of children.

Chemistry/Synonyms

A benzimidazole-derivative phosphodiesterase inhibitor, pimobendan occurs as a white or slightly yellowish, hygroscopic powder. It is practically insoluble in water and slightly soluble in acetone or methyl alcohol. Pimobendans's chemical name is: 4,5-Dihydro-6-[2-(p-methyoxyphenyl)-5-benzimidazolyl]-5-methyl-3(2H) pyridazinone. It has a molecular weight of 334.4.

Pimobendan may also be known as: UDCG-115, *Acardi*®, and *Vetmedin*®.

Storage/Stability

Unless otherwise labeled, pimobendan chewable tablets or capsules should be stored at room temperature below 25°C (77°F) in a dry place.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Pimobendan Chewable Tablets: 1.25 mg, 2.5 mg and 5 mg: *Vetmedin*® (B-I); (Rx). Approved for use in dogs.

HUMAN-LABELED PRODUCTS: None

PIPERACILLIN SODIUM

(***pype***-er-ah-sill-in) **Pipracil®**

EXTENDED SPECTRUM PENICILLIN

Prescriber Highlights

- Extended-action penicillin, with good gram-negative spectrum, including many strains of Pseudomonas
- Limited experience in veterinary medicine, but appears quite safe
- Also available with a beta-lactamase inhibitor (tazobactam); see the next monograph

Uses/Indications

Although veterinary experience is limited with piperacillin or piperacillin/tazobactam, these drugs have expanded coverage against many bacteria and may be suitable for empiric use until culture and susceptibility data are available, or for surgical prophylaxis when gram-negative or mixed aerobic/anaerobic infections are concerns.

Pharmacology/Actions

Piperacillin is a bactericidal, extended action acylaminopenicillin that inhibits septum formation and cell wall synthesis in susceptible bacteria. It has a wide spectrum of activity against many aerobic and anaerobic gram-positive (including many enterococci) and gram-negative bacteria. It has a similar spectrum of activity as the aminopenicillins, but with additional activity against several gram-negative organisms of the family Enterobacteriaceae, including many strains of *Pseudomonas aeruginosa*. Like the aminopenicillins, it is susceptible to inactivation by beta-lactamases. The addition of a beta-lactamase inhibitor (tazobactam) in the product *Zosyn*® (see next monograph), increases piperacillin's spectrum of activity against many beta lactamase producing strains of bacteria.

Pharmacokinetics

Limited information is available for veterinary species. In mares, piperacillin has an elimination half-life of about 7 hours. IM bioavailability is 86% and protein binding about 19%.

In humans, piperacillin is not appreciably absorbed from the gut so it must be administered parenterally. After IM administration peak levels occur in about 30 minutes. The drug exhibits low protein binding and has a volume of distribution of 0.1L/kg. It is widely distributed into many tissues and fluids including lung, gallbladder, intestinal mucosa, uterus, bile, and interstitial fluid. With inflamed meninges, piperacillin levels in the CSF are approximately 30% those in serum. If meninges are normal, CSF concentrations are only about 6% of serum levels. Piperacillin crosses the placenta and is distributed into milk in low concentrations. Piperacillin is metabolized somewhat in the liver to a desethyl metabolite that has only minimal antibacterial activity. Piperacillin is primarily (68%) eliminated unchanged in the urine via active tubular secretion and glomerular filtration; it is also excreted in the bile. Elimination half-life in humans is approximately one hour.

Contraindications/Precautions/Warnings

Piperacillin should not be used in patients with documented hypersensitive reactions to a beta-lactam.

Because of sodium content, high dosages of piperacillin may adversely affect patients with cardiac failure or hypernatremic conditions.

Dosage adjustment may be required in patients with significantly decreased renal function (CrCl <40 mL/min).

Adverse Effects

Piperacillin is generally well tolerated. Hypersensitivity reactions are possible. Local effects (thrombophlebitis, etc.) associated with intravenous injection or pain after IM injection may occur. Alterations in gut flora may lead to antibiotic-associated diarrhea.

In humans, piperacillin has caused coagulation abnormalities on occasion, particularly in patients with renal failure. Very high doses may cause neurotoxicity (seizures); again, these are more likely in patients with diminished renal function. Superinfections with *Clostridium difficile* have been reported rarely.

Reproductive/Nursing Safety

Piperacillin is thought relatively safe to use during pregnancy. No teratogenic effects have been attributed to it in either humans or laboratory animals. In humans, the FDA categorizes piperacillin as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*)

Piperacillin is distributed in milk in low concentrations; it is likely safe to use during nursing.

Overdosage/Acute Toxicity

Single overdoses are unlikely to pose much risk although very large overdoses may cause vomiting, diarrhea, or neurotoxicity. Dogs receiving up to 800 mg/kg/day of piperacillin/tazobactam for 6 months demonstrated no serious toxic effects. Doses at 400 mg/kg/day or greater caused some transient effects to the liver (glycogen granules in the cytoplasm and increases in smooth endoplasmic reticulum in hepatocytes) that were mostly reversed after one month.

Treatment for overdoses, if required, is supportive.

Drug Interactions

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

- **AMINOGLYCOSIDES** (**amikacin, gentamicin, tobramycin**): *In vitro* studies have demonstrated that penicillins can have synergistic or additive activity against certain bacteria when used with aminoglycosides. Beta-lactam antibiotics, however, can inactivate aminoglycosides *in vitro* and *in vivo* in patients in renal failure or when penicillins are used in massive dosages. Amikacin is considered the most resistant aminoglycoside to this inactivation.
- **ANTICOAGULANTS**: Because piperacillin may rarely affect platelets, increased monitoring of coagulation parameters is suggested for patients on heparin or warfarin
- **METHOTREXATE**: Piperacillin may increase MTX serum levels
- **PROBENECID**: Can reduce the renal tubular secretion of piperacillin thereby maintaining higher systemic levels for longer periods; this potential "beneficial" interaction requires further investigation before dosing recommendations can be made for veterinary patients
- **VECURONIUM**: Piperacillin may prolong neuromuscular blockade