Adverse Effects
Adverse effects resulting from aminopentamide therapy may include dry mouth, dry eyes, blurred vision, and urinary hesitancy. Urinary retention is a symptom of too high a dose and the drug should be withdrawn until resolved.

Overdosage/Acute Toxicity
No specific information was located regarding acute overdosage clinical signs or treatment for this agent. The following discussion is from the Atropine monograph that could be used as a guideline for treating overdoses:

If a recent oral ingestion, emptying of gut contents and administration of activated charcoal and saline cathartics may be warranted. Treat clinical signs supportively and symptomatically. Do not use phenothiazines as they may contribute to the anticholinergic effects. Fluid therapy and standard treatments for shock may be instituted.

The use of physostigmine is controversial and should probably be reserved for cases where the patient exhibits either extreme agitation and is at risk for injuring themselves or others, or for cases where supraventricular tachycardias and sinus tachycardias are severe or life threatening. The usual dose for physostigmine (human) is: 2 mg IV slowly (for average sized adult), if no response, may repeat every 20 minutes until reversal of toxic antimuscarinic effects or cholinergic effects takes place. The human pediatric dose is 0.02 mg/kg slow IV (repeat q10 minutes as above) and may be a reasonable choice for treatment of small animals. Physostigmine adverse effects (bronchoconstriction, bradycardia, seizures) may be treated with small doses of IV atropine.

Drug Interactions
No specific interactions were noted for this product. The following drug interactions have either been reported or are theoretical in humans or animals receiving atropine, a similar drug and may be of significance in veterinary patients:

- **ANTIHISTAMINES, PROCAINAMIDE, QUINIDINE, MEPERIDINE, BENZODIAZEPINES, PHENOTHIAZINES:** May enhance the activity of atropine and its derivatives
- **PRIMIDONE, DISOPYRAMIDE, NITRATES:** May potentiate the adverse effects of atropine and its derivatives
- **CORTICOSTEROIDS** (**long-term use**): May increase intraocular pressure
- **NITROFURANTOIN, THIAZIDE DIURETICS, SYMPATHOMIMETICS:** Atropine and its derivatives may enhance actions
- **METOCLOPRAMIDE:** Atropine and its derivatives may antagonize metoclopramide actions

Doses
- **DOGS:**
  a) May be administered every 8–12 hours via IM, SC or oral routes. If the desired effect is not attained, the dosage may be gradually increased up to 5 times those listed below: Animals weighing: 10 lbs or less: 0.1 mg; 11–20 lbs: 0.2 mg; 21–50 lbs: 0.3 mg; 51–100 lbs: 0.4 mg; over 100 lbs: 0.5 mg (Package Insert; *Centrine*®—Fort Dodge)
  b) To decrease tenesmus in malabsorption/maldigestion syndromes: 0.1–0.4 mg SC, or IM twice daily–three times daily (Chiapella 1988)
  c) As an antiemetic: 0.1–0.4 mg SC, or IM two to three times daily (Johnson 1984)
- **CATS:**
  a) As in "a" above in dogs
  b) As an antiemetic: 0.1–0.4 mg SC, or IM two to three times daily (Johnson 1984)
  c) As second-line adjunctive therapy for refractory IBD: 0.1–0.4 mg/kg SC two to three times daily (Washabau 2000)

Monitoring
- Clinical efficacy
- Adverse effects (see above)

Client Information
- Contact veterinarian if animal has difficulty urinating or if animal is bothered by dry eyes or mouth

Chemistry/Synonyms
An antispasmodic, anticholinergic agent, aminopentamide hydrogen sulfate has a chemical name of 4-(dimethylamino)-2,2-diphenylvaleramide.

Aminopentamide hydrogen sulfate may also be known as dimevamid or *Centrine*®.

Storage/Stability
Store aminopentamide tablets and injection at controlled room temperature (15–30°C; 59–86°F).

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS:

Aminopentamide Hydrogen Sulfate Tablets: 0.2 mg; *Centrine*® (Fort Dodge); (Rx). Approved for use in dogs and cats only.

Aminopentamide Hydrogen Sulfate Injection: 0.5 mg/mL in 10 mL vials; *Centrine*® (Fort Dodge); (Rx). Approved for use in dogs and cats only.

HUMAN-LABELED PRODUCTS: None

AMINOPHYLLINE
THEOPHYLLINE

(am-in-***off***-i-lin); (thee-***off***-i-lin)

PHOSPHODIESTERASE INHIBITOR
BRONCHODILATOR

Prescriber Highlights
- Bronchodilator drug with diuretic activity; used for bronchospasm & cardiogenic pulmonary edema
- Narrow therapeutic index in humans, but dogs appear to be less susceptible to toxic effects at higher plasma levels
- Therapeutic drug monitoring recommended
- Many drug interactions

Uses/Indications
The theophyllines are used primarily for their bronchodilatory effects, often in patients with myocardial failure and/or pulmonary edema. While they are still routinely used, the methylxanthines must be used cautiously due to their adverse effects and toxicity.

Pharmacology/Actions
The theophyllines competitively inhibit phosphodiesterase thereby increasing amounts of cyclic AMP which then increase the release of endogenous epinephrine. The elevated levels of cAMP may also

inhibit the release of histamine and slow reacting substance of anaphylaxis (SRS-A). The myocardial and neuromuscular transmission effects that the theophyllines possess may be a result of translocating intracellular ionized calcium.

The theophyllines directly relax smooth muscles in the bronchi and pulmonary vasculature, induce diuresis, increase gastric acid secretion and inhibit uterine contractions. They have weak chronotropic and inotropic action, stimulate the CNS and can cause respiratory stimulation (centrally-mediated).

Pharmacokinetics

The pharmacokinetics of theophylline have been studied in several domestic species. After oral administration, the rate of absorption of the theophyllines is limited primarily by the dissolution of the dosage form in the gut. In studies in cats, dogs, and horses, bioavailabilities after oral administration are nearly 100% when non-sustained release products are used. One study in dogs that compared various sustained-release products (Koritz, Neff-Davis, and Munsiff 1986), found bioavailabilities ranging from approximately 30–76% depending on the product used.

Theophylline is distributed throughout the extracellular fluids and body tissues. It crosses the placenta and is distributed into milk (70% of serum levels). In dogs, at therapeutic serum levels only about 7–14% is bound to plasma proteins. The volume of distribution of theophylline for dogs has been reported to be 0.82 L/kg. The volume of distribution in cats is reported to be 0.46 L/kg, and in horses, 0.85–1.02 L/kg. Because of the low volumes of distribution and theophylline's low lipid solubility, obese patients should be dosed on a lean body weight basis.

Theophylline is metabolized primarily in the liver (in humans) to 3-methylxanthine which has weak bronchodilitory activity. Renal clearance contributes only about 10% to the overall plasma clearance of theophylline. The reported elimination half-lives (mean values) in various species are: dogs ≈ 5.7 hours; cats ≈ 7.8 hours, pigs ≈ 11 hours; and horses ≈ 11.9 to 17 hours. In humans, there are very wide interpatient variations in serum half-lives and resultant serum levels. It could be expected that similar variability exists in veterinary patients, particularly those with concurrent illnesses.

Contraindications/Precautions/Warnings

The theophyllines are contraindicated in patients who are hypersensitive to any of the xanthines, including theobromine or caffeine. Patients who are hypersensitive to ethylenediamine should not take aminophylline.

The theophyllines should be administered with caution in patients with severe cardiac disease, seizure disorders, gastric ulcers, hyperthyroidism, renal or hepatic disease, severe hypoxia, or severe hypertension. Because it may cause or worsen preexisting arrhythmias, patients with cardiac arrhythmias should receive theophylline only with caution and enhanced monitoring. Neonatal and geriatric patients may have decreased clearances of theophylline and be more sensitive to its toxic effects. Patients with CHF may have prolonged serum half-lives of theophylline.

Adverse Effects

The theophyllines can produce CNS stimulation and gastrointestinal irritation after administration by any route. Most adverse effects are related to the serum level of the drug and may be symptomatic of toxic blood levels; dogs appear to tolerate levels that may be very toxic to humans. Some mild CNS excitement and GI disturbances are not uncommon when starting therapy and generally resolve with chronic administration in conjunction with monitoring and dosage adjustments.

Dogs and cats can exhibit clinical signs of nausea and vomiting, insomnia, increased gastric acid secretion, diarrhea, polyphagia, polydipsia, and polyuria. Side effects in horses are generally dose related and may include: nervousness, excitability (auditory, tactile, and visual), tremors, diaphoresis, tachycardia, and ataxia. Seizures or cardiac dysrhythmias may occur in severe intoxications.

Reproductive/Nursing Safety

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.*)

Overdosage/Acute Toxicity

Clinical signs of toxicity (see above) are usually associated with levels greater than 20 mcg/mL in humans and become more severe as the serum level exceeds that value. Tachycardias, arrhythmias, and CNS effects (seizures, hyperthermia) are considered the most life-threatening aspects of toxicity. Dogs appear to tolerate serum levels higher than 20 mcg/mL.

Treatment of theophylline toxicity is supportive. After an oral ingestion, the gut should be emptied, charcoal and a cathartic administered using the standardized methods and cautions associated with these practices. Patients suffering from seizures should have an adequate airway maintained and treated with IV diazepam. The patient should be constantly monitored for cardiac arrhythmias and tachycardia. Fluid and electrolytes should be monitored and corrected as necessary. Hyperthermia may be treated with phenothiazines and tachycardia treated with propranolol if either condition is considered life threatening.

Drug Interactions

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

The following drugs can **decrease** theophylline levels:

- **BARBITURATES** (**phenobarbital**)
- **CARBAMAZEPINE** (may increase or decrease levels)
- **CHARCOAL**
- **HYDANTOINS** (**phenytoin**)
- **ISONIAZID** (may increase or decrease levels)
- **KETOCONAZOLE**
- **LOOP DIURETICS** (**furosemide**); (may increase or decrease levels)
- **RIFAMPIN**
- **SYMPATHOMIMETICS** (**beta-agonists**)

The following drugs can ***increase*** theophylline levels:

- **ALLOPURINOL**
- **BETA-BLOCKERS** (**non-selective such as propranolol**)
- **CALCIUM CHANNEL BLOCKERS** (*e.g.*, **diltiazem, verapamil**)
- **CIMETIDINE**
- **CORTICOSTEROIDS**
- **FLUOROQUINOLONES** (**enrofloxacin, ciprofloxacin**): If adding either, consider reducing the dose of theophylline by 30%. Monitor for toxicity/efficacy. Marbofloxacin reduces clearance of theophylline in dogs, but not with clinical significance. In animals with renal impairment, marbofloxacin may interfere with theophylline metabolism in a clinically relevant manner.
- **MACROLIDES** (*e.g.*, **erythromycin; clindamycin, lincomycin**)
- **THIABENDAZOLE**
- **THYROID HORMONES** (in hypothyroid patients)
- **THEOPHYLLINE** may decrease the effects of following drugs:
- **BENZODIAZEPINES**

- **LITHIUM**
- **PANCURONIUM**
- **PROPOFOL**
- **EPHEDRINE, ISOPROTERENOL**: Toxic synergism (arrhythmias) can occur if theophylline is used concurrently with sympathomimetics (especially ephedrine) or possibly isoproterenol
- **HALOTHANE**: Theophylline with halothane may cause increased incidence of cardiac dysrhythmias
- **KETAMINE**: Theophylline with ketamine can cause an increased incidence of seizures

Laboratory Considerations

- Theophylline can cause falsely elevated values of serum **uric acid** if measured by the Bittner or colorimetric methods. Values are not affected if using the uricase method.
- Theophylline serum levels can be falsely elevated by **furosemide, phenylbutazone, probenecid, theobromine, caffeine, sulfathiazole, chocolate, or acetaminophen** if using a spectrophotometric method of assay.

Doses

Note: Theophyllines have a low therapeutic index; determine dosage carefully. Because of aminophylline/theophylline's pharmacokinetic characteristics, it should be dosed on a lean body weight basis in obese patients. Dosage conversions between aminophylline and theophylline can be easily performed using the information found in the Chemistry section below. Aminophylline causes intense local pain when administered IM and is rarely used or recommended via this route.

- **DOGS:**
  a) Using *Theochron*® Extended-Release Tablets *or Theo-Cap*® Extended-Release Capsules: Give 10 mg/kg PO every 12 hours initially, if no adverse effects are observed and the desired clinical effect is not achieved, give 15 mg/kg PO q12h while monitoring for adverse effects. (Bach, KuKanich et al. 2004)
  b) For adjunctive medical therapy for mild clinical signs associated with tracheal collapse (<50% collapse): aminophylline: 11 mg/kg PO, IM or IV three times daily. (Fossom 2005)
  c) For adjunctive therapy of severe, acute pulmonary edema and bronchoconstriction: Aminophylline 4–8 mg/kg IV or IM, or 6–10 mg/kg PO every 8 hours. Long-term use is not recommended. (Ware 2003)
  d) For cough: Aminophylline: 10 mg/kg PO, IV three times daily (Anderson-Westberg 2005)
  e) As a bronchodilator tor collapsing trachea: 11 mg/kg PO or IV q6–12h (Ettinger and Kantrowitz 2005)
- **CATS:**
  a) Using *Theo-Dur*®: 20 mg/kg PO once daily in the PM; using *Slo-Bid*®: 25 mg/kg PO once daily in the PM (Johnson 2000) [**Note:** The products *Theo-Dur*® and *Slo-Bid*® mentioned in this reference are no longer available in the USA. Although hard data is not presently available to support their use in cats, a reasonable alternative would be to cautiously use the dog dose and products mentioned above in the reference by Bach et al—Plumb]
  b) Using aminophylline tablets: 6.6. mg/kg PO twice daily; using sustained release tablets (*Theo-Dur*®): 25–50 mg (total dose) per cat PO in the evening (Noone 1999)
  c) For adjunctive medical therapy for mild clinical signs associated with tracheal collapse (<50% collapse): aminophylline: 5 mg/kg PO, two times daily. (Fossom 2005)
  d) For adjunctive therapy for bronchoconstriction associated with fulminant CHF: Aminophylline 4–8 mg/kg SC, IM, IV q8–12h. (Ware 2003)
  e) For cough: Aminophylline: 5 mg/kg PO twice daily (Anderson-Westberg 2005)
- **FERRETS:**
  a) 4.25 mg/kg PO 2–3 times a day (Williams 2000)
- **HORSES:** (**Note:** ARCI UCGFS Class 3 Drug)

  NOTE: Intravenous aminophylline should be diluted in at least 100 mL of D_5W or normal saline and administered slowly (not >25 mg/min).

  For adjunctive treatment of pulmonary edema:
  a) Aminophylline 2–7 mg/kg IV q6–12h; Theophylline 5–15 mg/kg PO q12h (Mogg 1999)
  b) 11 mg/kg PO or IV q8–12h. To "load" may either double the initial dose or give both the oral and IV dose at the same time. IV infusion should be in approximately 1 liter of IV fluids and given over 20–60 minutes. Recommend monitoring serum levels. (Foreman 1999)

  For adjunctive treatment for heaves (RAO):
  a) Aminophylline: 5–10 mg/kg PO or IV twice daily. (Lavoie 2003)
  b) Aminophylline: 4–6 mg/kg PO three times a day. (Ainsworth and Hackett 2004)

Monitoring

- Therapeutic efficacy and clinical signs of toxicity
- Serum levels at steady state. The therapeutic serum levels of theophylline in humans are generally described to be between 10–20 micrograms/mL. In small animals, one recommendation for monitoring serum levels is to measure trough concentration; level should be at least above 8–10 mcg/mL (**Note:** Some recommend not exceeding 15 micrograms/mL in horses).

Client Information

- Give dosage as prescribed by veterinarian to maximize the drug's benefit

Chemistry/Synonyms

Xanthine derivatives, aminophylline and theophylline are considered to be respiratory smooth muscle relaxants but, they also have other pharmacologic actions. Aminophylline differs from theophylline only by the addition of ethylenediamine to its structure and may have different amounts of molecules of water of hydration. 100 mg of aminophylline (hydrous) contains approximately 79 mg of theophylline (anhydrous);100 mg of aminophylline (anhydrous) contains approximately 86 mg theophylline (anhydrous). Conversely, 100 mg of theophylline (anhydrous) is equivalent to 116 mg of aminophylline (anhydrous) and 127 mg aminophylline (hydrous).

Aminophylline occurs as bitter-tasting, white or slightly yellow granules or powder with a slight ammoniacal odor and a pK_a of 5. Aminophylline is soluble in water and insoluble in alcohol.

Theophylline occurs as bitter-tasting, odorless, white, crystalline powder with a melting point between 270–274°C. It is sparingly soluble in alcohol and only slightly soluble in water at a pH of 7, but solubility increases with increasing pH.

Aminophylline may also be known as: aminofilina, aminophyllinum, euphyllinum, metaphyllin, theophyllaminum, theophylline and ethylenediamine, theophylline ethylenediamine compound, or theophyllinum ethylenediaminum; many trade names are available.

Theophylline may also be known as: anhydrous theophylline, teofillina, or theophyllinum; many trade names are available.

Storage/Stability/Compatibility

Unless otherwise specified by the manufacturer, store aminophylline and theophylline oral products in tight, light-resistant containers at room temperature. Do not crush or split sustained-release oral products unless label states it is permissible.

Aminophylline for injection should be stored in single-use containers in which carbon dioxide has been removed. It should also be stored at temperatures below 30°C and protected from freezing and light. Upon exposure to air (carbon dioxide), aminophylline will absorb carbon dioxide, lose ethylenediamine and liberate free theophylline that can precipitate out of solution. Do not inject aminophylline solutions that contain either a precipitate or visible crystals.

Aminophylline for injection is reportedly **compatible** when mixed with all commonly used IV solutions, but may be **incompatible** with 10% fructose or invert sugar solutions.

Aminophylline is reportedly **compatible** when mixed with the following drugs: amobarbital sodium, bretylium tosylate, calcium gluconate, chloramphenicol sodium succinate, dexamethasone sodium phosphate, dopamine HCl, erythromycin lactobionate, heparin sodium, hydrocortisone sodium succinate, lidocaine HCl, mephentermine sulfate, methicillin sodium, methyldopate HCl, metronidazole with sodium bicarbonate, pentobarbital sodium, phenobarbital sodium, potassium chloride, secobarbital sodium, sodium bicarbonate, sodium iodide, terbutaline sulfate, thiopental sodium, and verapamil HCl.

Aminophylline is reportedly **incompatible** (or data conflicts) with the following drugs: amikacin sulfate, ascorbic acid injection, bleomycin sulfate, cephalothin sodium, cephapirin sodium, clindamycin phosphate, codeine phosphate, corticotropin, dimenhydrinate, dobutamine HCl, doxorubicin HCl, epinephrine HCl, erythromycin gluceptate, hydralazine HCl, hydroxyzine HCl, insulin (regular), isoproterenol HCl, levorphanol bitartrate, meperidine HCl, methadone HCl, methylprednisolone sodium succinate, morphine sulfate, naficillin sodium, norepinephrine bitartrate, oxytetracycline, penicillin G potassium, pentazocine lactate, procaine HCl, prochlorperazine edisylate or mesylate, promazine HCl, promethazine HCl, sulfisoxazole diolamine, tetracycline HCl, vancomycin HCl, and vitamin B complex with C. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used and it is suggested to consult specialized references for more specific information.

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:

The listing below is a sampling of products and sizes available; consult specialized references for a more complete listing.

Aminophylline Tablets: 100 mg (79 mg theophylline) & 200 mg (158 mg theophylline); generic; (Rx)

Aminophylline Injection: 250 mg (equiv. to 197 mg theophylline) mL in 10 mL & 20 mL vials, amps and syringes; generic; (Rx)

Theophylline Time Released Capsules and Tablets: 100 mg, 125 mg 200 mg, 300 mg, 400 mg, 450 mg, & 600 mg. (**Note:** Different products have different claimed release rates which may or may not correspond to actual times in veterinary patients; Theophylline Extended-Release (Dey); *Theo-24*® (UCB Pharma); *Theophylline SR* (various); *Theochron*® (Forest, various); Theophylline (Able); *Theocron*® (Inwood); *Uniphyl*® (Purdue Frederick); generic; (Rx)

Theophylline Tablets and Capsules: 100 mg, 200 mg, & 300 mg; *Bronkodyl*® (Winthrop); *Elixophyllin*® (Forest); generic; (Rx)

Theophylline Elixir: 80 mg/15 mL (26.7 mg/5 mL) in pt, gal, UD 15 and 30 mL, *Asmalix*® (Century); *Elixophyllin*® (Forest); *Lanophyllin*® (Lannett); generic; (Rx)

Theophylline & Dextrose Injection: 200 mg/container in 50 mL (4 mg/mL) & 100 mL (2 mg/mL); 400 mg/container in 100 mL (4 mg/mL), 250 mL (1.6 mg/mL), 500 mL (0.8 mg/mL) & 1000 mL (0.4 mg/mL); 800 mg/container in 250 mL (3.2 mg/mL), 500 mL (1.6 mg/mL) & 1000 mL (0.8 mg/mL); Theophylline & 5% Dextrose (Abbott & Baxter); (Rx)

AMIODARONE HCL

(a-mee-oh-***da***-rone) Cordarone®, Pacerone®

CLASS III ANTIARRHYTHMIC

Prescriber Highlights

- Antidysrhythmic agent that can be used in dogs for arrhythmias associated with left ventricular dysfunction or to convert atrial fib into sinus rhythm; very limited experience warrants cautious use
- May be useful in horses to convert atrial fib or V tach into sinus rhythm
- Contraindicated in 2nd, 3rd degree heart block, bradyarrhythmias
- In DOGS: GI disturbances (vomiting, anorexia) most likely adverse effect, but neutropenia, thrombocytopenia, bradycardia, hepatotoxicity, positive Coombs' test reported
- In HORSES: Limited use, accurate adverse effect profile to be determined; Hind limb weakness, increased bilirubin reported when used IV to convert atrial fib
- Many drug interactions

Uses/Indications

Because of its potential toxicity and lack of experience with use in canine and equine patients, amiodarone is usually used when other less toxic or commonly used drugs are ineffective. It may be useful in dogs and horses to convert atrial fib into sinus rhythm and in dogs for arrhythmias associated with left ventricular dysfunction. In horses, one horse with Ventricular tachycardia was converted into sinus rhythm using amiodarone.

As the risk of sudden death is high in Doberman pinschers exhibiting rapid, wide-complex ventricular tachycardia or syncope with recurrent VPC's, amiodarone may be useful when other drug therapies are ineffective.

Pharmacology/Actions

Amiodarone's mechanism of action is not fully understood; it apparently is a potassium channel blocker that possesses unique pharmacology from other antiarrhythmic agents. It can be best classi-