during Y-site injection with bleomycin sulfate, cisplatin, cyclophosphamide, droperidol, fluorouracil, leucovorin calcium, methotrexate sodium, metoclopramide HCl, mitomycin, vinblastine sulfate and vincristine sulfate.

Doxorubicin HCl **compatibility information conflicts** or is dependent on diluent or concentration factors with the following drugs or solutions: vinblastine sulfate (in syringes and as an IV additive). Compatibility is dependent upon factors such as pH, concentration, temperature and diluent used; consult specialized references or a hospital pharmacist for more specific information

Doxorubicin HCl is reportedly physically **incompatible** with the following solutions or drugs: aminophylline, cephalothin sodium, dexamethasone sodium phosphate, diazepam, fluorouracil (as an IV additive only), furosemide, heparin sodium, and hydrocortisone sodium succinate.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Doxorubicin HCl (Conventional) Lyophilized Powder for Injection, (conventional): 10 mg, 20 mg, 50 mg, and 150 mg vials; *Adriamycin RDF*® (Pharmacia & Upjohn); generic (Bedford); (Rx). Reconstitute with appropriate amount of 0.9% sodium chloride for final concentration of 2 mg/mL.

Doxorubicin HCl (Conventional) Injection (aqueous): 2 mg/mL in 5 mL, 10 mL, 25 mL, and 100 mL; *Adriamycin PFS*® (Pharmacia & Upjohn), generic (Bedford); (Rx)

Doxorubicin, Liposomal Injection: 20 mg in 10 mL & 50 mg in 30 mL single-use vials; *Doxil*® (Ortho Biotech); (Rx)

DOXYCYCLINE CALCIUM
DOXYCYCLINE HYCLATE
DOXYCYCLINE MONOHYDRATE

(dox-i-sye-kleen) Vibramycin®

TETRACYCLINE ANTIBIOTIC

Prescriber Highlights

- Oral & parenteral tetracycline antibiotic
- Contraindications: Hypersensitivity
- Bone & teeth abnormalities are less likely to be caused then with other tetracyclines, but use with caution in pregnant & young animals
- May be used in patients with renal insufficiency
- Not for IV injection in horses; do not give IM or SC to any species
- Most common adverse effects are GI
- Drug Interactions

Uses/Indications

Although there are no veterinary-approved doxycycline products available, its favorable pharmacokinetic parameters (longer half-life, higher CNS penetration) when compared to either tetracycline HCl or oxytetracycline HCl make it a reasonable choice to use in small animals when a tetracycline is indicated, particularly when a tetracycline is indicated in an azotemic patient.

In avian species, some clinicians feel that doxycycline is the drug of choice in the oral treatment of psittacosis, particularly when treating only a few birds.

Pharmacology/Actions

Tetracyclines generally act as bacteriostatic antibiotics and inhibit protein synthesis by reversibly binding to 30S ribosomal subunits of susceptible organisms, thereby preventing binding to those ribosomes of aminoacyl transfer-RNA. Tetracyclines also are believed to reversibly bind to 50S ribosomes and, additionally, alter cytoplasmic membrane permeability in susceptible organisms. In high concentrations, tetracyclines can also inhibit protein synthesis by mammalian cells.

As a class, the tetracyclines have activity against most mycoplasma, spirochetes (including the Lyme disease organism), Chlamydia and Rickettsia. Against gram-positive bacteria, the tetracyclines have activity against some strains of staphylococcus and streptococci, but resistance by these organisms is increasing. Gram-positive bacteria that are usually covered by tetracyclines include: *Actinomyces* spp., *Bacillus anthracis, Clostridium perfringens* and *tetani*, *Listeria monocytogenes* and Nocardia. Among gram-negative bacteria that tetracyclines usually have *in vitro* and *in vivo* activity against, include *Bordetella* spp., Brucella, Bartonella, *Haemophilus* spp., *Pasturella multocida*, Shigella, and *Yersinia pestis*. Many or most strains of *E. coli*, Klebsiella, Bacteroides, Enterobacter, Proteus and *Pseudomonas aeruginosa* are resistant to the tetracyclines.

Doxycycline generally has very similar activity as other tetracyclines against susceptible organisms, but some strains of bacteria may be more susceptible to doxycycline or minocycline and additional *in vitro* testing may be required.

Pharmacokinetics

Doxycycline is well absorbed after oral administration. Bioavailability is 90–100% in humans. No bioavailability data was located for veterinary species, but it is thought that the drug is also readily absorbed in monogastric animals. Unlike tetracycline HCl or oxytetracycline, doxycycline absorption may only be reduced by 20% by either food or dairy products in the gut. This is not considered to be clinically important.

Tetracyclines, as a class, are widely distributed to the heart, kidney, lungs, muscle, pleural fluid, bronchial secretions, sputum, bile, saliva, synovial fluid, ascitic fluid, and aqueous and vitreous humor. Doxycycline is more lipid-soluble and penetrates body tissues and fluids better than tetracycline HCl or oxytetracycline, including to the CSF, prostate, and eye. While CSF levels are generally insufficient to treat most bacterial infections, doxycycline has been shown to be efficacious in the treatment of the CNS effects associated with Lyme disease in humans. The volume of distribution at steady-state in dogs is approximately 1.5 L/kg. Doxycycline is bound to plasma proteins in varying amounts dependent upon species. The drug is approximately 25–93% bound to plasma proteins in humans, 75–86% in dogs, and about 93% in cattle and pigs. Cats have higher binding to plasma proteins than dogs.

Doxycycline's elimination from the body is relatively unique. The drug is primarily excreted into the feces via non-biliary routes in an inactive form. It is thought that the drug is partially inactivated in the intestine by chelate formation and then excreted into the intestinal lumen. In dogs, about 75% of a given dose is handled in this manner. Renal excretion of doxycycline can only account for about 25% of a dose in dogs, and biliary excretion less than 5%. The serum half-life of doxycycline in dogs is approximately 10–12 hours and a clearance of about 1.7 mL/kg/min. In calves, the drug has similar pharmacokinetic values. Doxycycline does not accumulate in patients with renal dysfunction.

Contraindications/Precautions/Warnings

Doxycycline is contraindicated in patients hypersensitive to the drug. Because tetracyclines can retard fetal skeletal development and discolor deciduous teeth, they should only be used in the last half of pregnancy when the benefits outweigh the fetal risks. Doxycycline is considered to be less likely to cause these abnormalities than other more water-soluble tetracyclines (*e.g.*, tetracycline, oxytetracycline). Unlike either oxytetracycline or tetracycline, doxycycline can be used in patients with renal insufficiency.

Until further studies documenting the safety of intravenous doxycycline in horses are done, the parenteral route of administering this drug in horses should be considered contraindicated.

Adverse Effects

The most commonly reported side effects of oral doxycycline therapy in dogs and cats are nausea and vomiting. To alleviate these effects, the drug can be given with food without clinically significant reductions in drug absorption.

Oral doxycycline has been implicated in causing esophageal strictures in cats. If using oral tablets, be sure that "pilling" is followed by at least 6 mL of water. Do not dry pill.

Tetracycline therapy (especially long-term) may result in overgrowth (superinfections) of non-susceptible bacteria or fungi.

In humans, doxycycline (or other tetracyclines) has also been associated with photosensitivity reactions and, rarely, hepatotoxicity or blood dyscrasias.

Intravenous injection of even relatively low doses of doxycycline has been associated with cardiac arrhythmias, collapse, and death in horses.

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***D*** for use during pregnancy (*There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***D*** (*Contraindicated. These drugs have been shown to cause congenital malformations or embryotoxicity*.)

Tetracyclines are excreted in milk. Milk:plasma ratios vary between 0.25 and 1.5. Avoid nursing if the dam requires doxycycline.

Overdosage/Acute Toxicity

With the exception of intravenous dosing in horses (see above), doxycycline is apparently quite safe in most mild overdose situations. Oral overdoses would most likely be associated with GI disturbances (vomiting, anorexia, and/or diarrhea). Although doxycycline is less vulnerable to chelation with cations than other tetracyclines, oral administration of divalent or trivalent cation antacids may bind some of the drug and reduce GI distress. Should the patient develop severe emesis or diarrhea, fluids and electrolytes should be monitored and replaced if necessary.

Rapid intravenous injection of doxycycline has induced transient collapse and cardiac arrhythmias in several species, presumably due to chelation with intravascular calcium ions. If overdose quantities are inadvertently administered, these effects may be more pronounced.

Drug Interactions

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

- **ANTACIDS, ORAL**: When orally administered, tetracyclines can chelate divalent or trivalent cations that can decrease the absorption of the tetracycline or the other drug if it contains these cations. Oral antacids, saline cathartics, or other GI products containing aluminum, calcium, magnesium, zinc, or bismuth cations are most commonly associated with this interaction. Doxycycline has a relatively low affinity for calcium ions, but it is recommended that all oral tetracyclines be given at least 1–2 hours before or after the cation-containing product.
- **BISMUTH SUBSALICYLATE, KAOLIN, PECTIN**: May reduce absorption
- **IRON, ORAL**: Oral iron products are associated with decreased tetracycline absorption, and administration of iron salts should preferably be given 3 hours before or 2 hours after the tetracycline dose.
- **PENICILLINS**: Bacteriostatic drugs, like the tetracyclines, may interfere with bactericidal activity of the penicillins, cephalosporins, and aminoglycosides. There is a fair amount of controversy regarding the actual clinical significance of this interaction, however.
- **PHENOBARBITAL**: May decrease doxycycline half-life and reduce levels
- **WARFARIN**: Tetracyclines may depress plasma prothrombin activity and patients on anticoagulant (*e.g.*, warfarin) therapy may need dosage adjustment.

Laboratory Considerations

- Tetracyclines (not minocycline) may cause falsely elevated values of **urine catecholamines** when using fluorometric methods of determination.
- Tetracyclines reportedly can cause false-positive **urine glucose** results if using the cupric sulfate method of determination (Benedict's reagent, *Clinitest*®), but this may be the result of ascorbic acid that is found in some parenteral formulations of tetracyclines. Tetracyclines have also reportedly caused false-negative results in determining urine glucose when using the glucose oxidase method (*Clinistix*®, *Test-Tape*®).

Doses

- **DOGS:**

  For susceptible infections:

  a) General use for infection: 3–5 mg/kg PO q12h for 7–14 days;

  For soft tissue, urinary tract: 4.4–11 mg/kg PO or IV q12h for 7–14 days;

  For acute *E. canis* infection: 5 mg/kg PO q12h or 10 mg/kg PO q24h for 14–16 days;

  For chronic *E. canis* infection: 10 mg/kg PO q24h for 30–42 days. (Greene, Hartmannn et al. 2006)

  b) For canine ehrlichiosis (anaplasmosis): 5–10 mg/kg PO q12h for 7–10 days (Greig 2000)

  c) For Lyme disease: 10 mg/kg PO q24h for 21–28 days (Appel and Jacobson 1995)

  d) For salmon poisoning disease: 10 mg/kg IV twice a day for at least 7 days (Rikihisa and Zimmerman 1995)

  e) For the renal carrier state of leptospirosis: 5–10 mg/kg PO twice daily for an additional 14 days after penicillin G therapy (25,000–40,000 U/kg IV or IM q12–24h for 14 days) (Ross and Rentko 2000)

  f) For *Toxoplasma gondii*: 5–10 mg/kg PO q12h for 4 weeks (Lappin 2000)

  g) For Rocky Mountain Spotted-Fever (*Rickettsia rickettsii*): 5 mg/kg PO q12h (Breitschwerdt 2000)

  For its antiarthritic effect:

  a) 3–4 mg/kg PO once daily for 7–10 days. (Greene, Hartmannn et al. 2006)

■ **CATS:**

Do not dry pill cats with oral doxycycline; follow with at least 6 mL of water or use a compounded slurry ("triple fish" or similar) to administer.

For susceptible infections:

a) 5 mg/kg PO or IV q12h; administer with food if GI upset occurs; avoid in young animals; avoid or reduce dose in animals with severe liver disease (Vaden and Papich 1995)

b) For clinical hemoplasmosis or bartonellosis: 10 mg/kg PO q12–24h (Lappin 2006a)

c) For feline ehrlichiosis: 5 mg/kg twice daily (Kordick, Lappin et al. 1995)

d) For *Toxoplasma gondii*: 5–10 mg/kg PO q12h for 4 weeks (Lappin 2000)

e) For Hemotropic mycoplasmosis: 5–10 mg/kg PO once daily for 14 days; round dose to nearest whole tablet or capsule;

For Bartonellosis: 50 mg (total dose) PO q12h for 14–28 days;

For systemic infections, bacteremia: 5–11 mg/kg PO or IV q12h as long as necessary;

For Ehrlichiosis or Anaplasmosis: 5–10 mg/kg PO q12h for 21 days. (Greene, Hartmannn et al. 2006)

■ **HORSES:**

WARNING: Doxycycline intravenously in horses has been associated with fatalities. Until further work is done demonstrating the safety of this drug, it cannot be recommended for parenteral use in this species.

a) For Lyme disease: 10 mg/kg PO once to twice daily for up to 30 days (Divers 1999)

■ **RABBITS/RODENTS/SMALL MAMMALS:**

a) Mice, Rats: For mycoplasmal pneumonia: 5 mg/kg PO twice daily with enrofloxacin (10 mg/kg PO twice daily) (Burke 1999)

b) Chinchillas, Gerbils, Guinea Pigs, Hamsters, Mice, Rats: 2.5–5 mg/kg PO q12h. Do not use in young or pregnant animals. (Adamcak and Otten 2000)

■ **BIRDS:**

For Psittacosis (Chlamydiosis):

a) Routes of treatment include intramuscular injections, oral dosage with a suspension, medicated mash (approximately 1000 mg per kg of feed), and water-soluble approaches.

IM: 75–100 mg/kg IM every 5–7 days for the first 4 weeks and subsequently every 5 days for the duration of a 45 day treatment.

PO: 40–50 mg/kg PO once daily for cockatiels, Senegal parrots, Blue fronted and Orange winged amazons, 25 mg/kg PO once daily for African Grey parrots, Goffin's cockatoos, Blue and gold macaws and Green winged macaws. Empirically: 25–50 mg/kg PO once a day is the recommended starting dosage for unstudied avian species. (Speer 1999)

b) In psittacines: 17.6–26.4 mg/kg PO twice daily using the oral syrup or suspension. For initial therapy in severe cases: 22–44 mg/kg IV once or twice; do not give IM. Long-term therapy (45 days) can be given as 200 mg (from capsules) per pound of food. (Clubb 1986)

c) Using the oral liquid/suspension: 50 mg/kg PO every 24 hours, or divided every 12 hours (use less for macaws). Using the hyclate salt on corn, beans, rice and oatmeal: 1 gram per kg of feed. Using the injectable product (*Vibaravenos*®—may not be available commercially in the USA): 100 mg/kg IM once weekly (75 mg/kg IM once weekly in macaws and lovebirds) (Bauck and Hoefer 1993)

d) Ratites: 2–3.5 mg/kg PO twice daily (Jenson 1998)

■ **REPTILES:**

For susceptible infections:

a) For chelonians: 10 mg/kg PO once daily for 4 weeks. Useful for bacterial respiratory infections in tortoises having suspected Mycoplasma infections.

b) In most species: 10 mg/kg PO once daily for 10–45 days (Gauvin 1993)

Monitoring

■ Clinical efficacy

■ Adverse effects

Client Information

■ Do not "dry pill" as esophageal damage can occur; if using oral tablets or capsules, especially in cats, give medication followed by at least one 6 mL (a little more than a teaspoonful) of liquid. In cats, buttering the lips after administration to induce salivation and reduce esophageal transit time has been suggested.

■ Oral doxycycline products may be administered without regard to feeding, but giving with some food may reduce gastrointestinal effects. Milk or other dairy products do not significantly alter the amount of doxycycline absorbed.

Chemistry/Synonyms

A semi-synthetic tetracycline that is derived from oxytetracycline, doxycycline is available as hyclate, calcium and monohydrate salts. The hyclate salt is used in the injectable dosage form and in oral tablets and capsules. It occurs as a yellow, crystalline powder that is soluble in water and slightly soluble in alcohol. After reconstitution with sterile water, the hyclate injection has a pH of 1.8–3.3. Doxycycline hyclate may also be known as doxycycline hydrochloride.

The monohydrate salt is found in the oral powder for reconstitution. It occurs as a yellow, crystalline powder that is very slightly soluble in water and sparingly soluble in alcohol. The calcium salt is formed *in situ* during manufacturing. It is found in the commercially available oral syrup.

Doxycycline may also be known as: doxycycline monohydrate, doxycyclinum, and GS-3065; many trade names are available.

Storage/Stability/Compatibility

Doxycycline hyclate tablets and capsules should be stored in tight, light resistant containers at temperatures less than 30°C, and preferably at room temperature (15–30°C). After reconstituting with water, the monohydrate oral suspension is stable for 14 days when stored at room temperature.

The hyclate injection when reconstituted with a suitable diluent (*e.g.*, D5W, Ringer's injection, Sodium Chloride 0.9%, or Plasma-Lyte 56 in D5W) to a concentration of 0.1 to 1 mg/mL may be stored for 72 hours if refrigerated. Frozen reconstituted solutions (10 mg/mL in sterile water) are stable for at least 8 weeks if kept at -20°C, but should not be refrozen once thawed. If solutions are stored at room temperature, different manufacturers give different recommendations regarding stability, ranging from 12–48 hours. Infusions should generally be completed within 12 hours of administration.

Doxycycline hyclate for injection is reportedly physically **compatible** with the following IV infusion solutions and drugs: D5W, Ringer's injection, sodium chloride 0.9%, or Plasma-Lyte 56 in D5W, Plasma-Lyte 148 in D5W, Normosol M in D5W, Normosol R in D5W, invert sugar 10%, acyclovir sodium, hydromorphone HCl, magnesium sulfate, meperidine HCl, morphine sulfate, perphenazine and ranitidine HCl. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used;

consult specialized references or a hospital pharmacist for more specific information.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

None for systemic use.

Doxycycline gel: 8.5% activity once mixed. (2 syringe system); *Doxirobe*® (Pfizer); (Rx). Approved for dogs; oral application for the prevention and treatment of periodontal disease.

HUMAN-LABELED PRODUCTS:

Doxycycline (as the hyclate) Tablets & Capsules: 20 mg, 50 mg, & 100 mg; *Periostat*® (CollaGenex), *Vibramycin*® *& Vibra-Tabs*® (Pfizer); generic; (Rx)

Doxycycline (as the hyclate) Delayed-Release Tablets & Capsules: 75 mg & 100 mg and 40 mg (30 mg immediate release & 10 mg delayed release); *Doryx*® (Warner Chilcott); *Oracea*® (CollaGenex); (Rx)

Doxycycline (as monohydrate) Tablets and Capsules: 50 mg, 75 mg & 100 mg; *Monodox*® (Oclassen); *Adoxa*® (Bioglan); generic; (Rx)

Doxycycline Capsules (coated-pellets) (as hyclate): 75 mg and 100 mg; *Doryx*® (Warner Chilcott); Doxycycline (Eon); (Rx)

Doxycycline (as the monohydrate) Powder for Oral Suspension: 5 mg/mL after reconstitution in 60 mL; *Vibramycin*® (Pfizer); (Rx)

Doxycycline (as the calcium salt) Oral Syrup: 10 mg/mL in 473 mL; *Vibramycin*® (Pfizer); (Rx)

Doxycycline Injection: 42.5 mg (as hyclate, 10%) in 2 syringe mixing system and blunt cannula; *Atridox*® (CollaGenex); (Rx)

Doxycycline (as the hyclate) Lyophilized Powder for Injection: 100 mg and 200 mg in vials; *Doxy*®*-100* and *-200* (AAP); generic; (Rx)

EDETATE CALCIUM DISODIUM
CALCIUM EDTA

(***ed***-a-tayt) Calcium Disodium Versenate®

ANTIDOTE

Prescriber Highlights

- Heavy metal chelator used primarily for lead or zinc toxicity
- Contraindications: Patients with anuria
- Extreme caution: Decreased renal function
- Recommend using SC route when treating small animals; do not give PO
- Adverse Effects: Renal toxicity (renal tubular necrosis); may cause depression & GI clinical signs in dogs

Uses/Indications

CaEDTA is used as a chelating agent in the treatment of lead poisoning. Succimer is more commonly recommended today for treating lead poisoning in dogs and cats.

CaEDTA may used in combination with dimercaprol treatment.

Pharmacology/Actions

The calcium in CaEDTA can be displaced by divalent or trivalent metals to form a stable water soluble complex that can be excreted in the urine. One gram of CaEDTA can theoretically bind 620 mg of lead, but in reality only about 5 mg per gram is actually excreted into the urine in lead poisoned patients. In addition to chelating lead, CaEDTA chelates and eliminates zinc from the body. CaEDTA also binds cadmium, copper, iron, and manganese, but to a much lesser extent than either lead or zinc. CaEDTA is relatively ineffective for use in treating mercury, gold, or arsenic poisoning.

There is some evidence that thiamine supplementation may increase the clinical efficacy of CaEDTA in treating acute lead poisoning in cattle.

Pharmacokinetics

CaEDTA is well absorbed after either IM or SC administration. It is distributed primarily in the extracellular fluid. Unlike dimercaprol, CaEDTA does not penetrate erythrocytes or enter the CNS in appreciable amounts. The drug is rapidly excreted renally, either as unchanged drug or chelated with metals. Changes in urine pH or urine flow do not significantly alter the rate of excretion. Decreased renal function can cause accumulation of the drug and can increase its nephrotoxic potential. In humans with normal renal function, the average elimination half-life of CaEDTA is 20–60 minutes after IV administration, and 1.5 hours after IM administration.

Contraindications/Precautions/Warnings

CaEDTA is contraindicated in patients with anuria. It should be used with extreme caution and with dosage adjustment in patients with diminished renal function.

Most small animal clinicians recommend using the SC route when treating small animals, as IV administration of CaEDTA has been associated with abrupt increases in CSF pressure and death in children with lead-induced cerebral edema.

Lead should be removed from the GI tract before using CaEDTA. Do not administer CaEDTA orally as it may increase the amount of lead absorbed from the GI tract.

Animals with clinical signs of cerebral edema should not be over hydrated.

Adverse Effects

The most serious adverse effect associated with this compound is renal toxicity (renal tubular necrosis), but in dogs, CaEDTA can cause depression, vomiting, and diarrhea. GI clinical signs may be alleviated by zinc supplementation.

Chronic therapy may lead to zinc deficiency; zinc supplementation should be considered in these animals.

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug 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*).

It is not known whether this drug is excreted in milk.

Overdosage/Acute Toxicity

Doses greater than 12 g/kg are lethal in dogs; refer to Adverse Effects for more information.

Drug Interactions

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

- **GLUCOCORTICOIDS**: The renal toxicity of CaEDTA may be enhanced by the concomitant administration of glucocorticoids
- **INSULIN** (**NPH, PZI**): Concurrent administration of CaEDTA with zinc insulin preparations (NPH, PZI) will decrease the sustained action of the insulin preparation

■ **NEPHROTOXIC DRUGS, OTHER**: Use with caution with other nephrotoxic compounds (*e.g.*, **aminoglycosides, amphotericin B**)

Laboratory Considerations

■ CaEDTA may cause increased urine glucose values and/or cause inverted T-waves on ECG

Doses

The manufacturer of the injectable (human) product recommends diluting the injection to a concentration of 2–4 mg/mL with either normal saline or 5% dextrose when used for intravenous use. Because the injection is painful when given IM, it is recommended to add 1 mL of procaine HCl 1% to each mL of injection before administering IM.

■ **DOGS & CATS:**

For lead poisoning:

a) Be sure there is no lead in GI tract before using. Give 100 mg/kg SC divided into 4 daily doses in 5% dextrose for 5 days. May require second course of treatment, particularly if blood lead levels >0.10 ppm. Do not exceed 2 g/day and do not treat for more than 5 consecutive days. (Grauer and Hjelle 1988b)

b) 25 mg/kg SC four times daily for 5 days. Give as 1% solution in D_5W. Provide a 5–7 day rest period between courses of treatment to minimize potential for nephrotoxicity. Succimer is now the treatment of choice for lead in small animals. (Poppenga 2002)

c) Cats: 27.5 mg/kg in 15 mL D_5W SC four times daily for 5 days. Recheck blood lead 2–3 weeks later and repeat therapy (with either CaEDTA or penicillamine) if greater than 0.2 ppm. (Reid and Oehme 1989)

For zinc toxicity:

a) 100 mg/kg divided into four SC doses per day. Dilute in D5W to reduce local irritation at site of injection. Exact dosage is not known nor how long therapy should continue. If possible, monitor serum zinc concentrations and maintain animal's hydration status. (Meurs and Breitschwerdt 1995)

■ **RABBITS/RODENTS/SMALL MAMMALS:**

a) Chinchillas: 30 mg/kg SC q12h (Adamcak and Otten 2000)

■ **HORSES:**

For lead poisoning:

a) Remove animal from source of lead. If severely affected give CaEDTA at 75 mg/kg IV slowly in D_5W or saline daily for 4–5 days (may divide daily dose into 2–3 administrations per day). Stop therapy for 2 days and repeat for another 4–5 days. Give adequate supportive and nutritional therapy. (Oehme 1987d)

■ **FOOD ANIMALS:**

Note: FARAD recommends a 2 day meat and milk withdrawal time after use in food animals. (Haskell, Payne et al. 2005)

For lead poisoning:

a) 110 mg/kg per day in 3–4 divided doses; dilute to 1 gram/mL in D5W; first dose IV, then subcutaneously (Post and Keller 2000)

b) Cattle: 67 mg/kg slow IV twice daily for 2 days; withhold dose for 2 days and then give again for 2 days. Cattle may require 10–14 days to recover and may require several series of treatments. (Bailey 1986b)

c) Cattle: 73.3 mg/kg/day slow IV divided 2–3 times a day for 3–5 days. If additional therapy is required, a 2-day rest period followed by another 5-day treatment regimen is recommended. (Sexton and Buck 1986)

■ **BIRDS:**

For lead poisoning:

a) In psittacines: 35 mg/kg IM twice daily for 5–7 days. After initial therapy, may give orally until all lead fragments are dissolved and/or passed from GI tract. (McDonald 1989)

b) In raptors (falcons): In this study, 25% CaEDTA was given undiluted IM at a dose of 100 mg/kg q12h for 5–25 consecutive days. Falcons were treated if blood lead was >65 mcg/dL for 5 day courses, until blood lead was <20 mcg/dL. No evidence of muscle damage, nephrotoxicity or hepatotoxicity seen. (Samour and Naldo 2004)

Monitoring

■ Blood lead or zinc (serial), and/or urine d-ALA
■ Renal function tests, urinalyses, hydration status
■ Serum phosphorus and calcium values
■ Periodic cardiac rate/rhythm monitoring may be warranted during administration

Client Information

■ Because of the potential toxicity of this agent and the seriousness of most heavy metal intoxications, this drug should be used with close professional supervision only.

Chemistry/Synonyms

A heavy metal chelating agent, edetate calcium disodium (CaEDTA) occurs as an odorless, white, crystalline powder or granules and is a mixture of dihydrate and trihydrate forms. It has a slight saline taste and is slightly hygroscopic. CaEDTA is freely soluble in water and very slightly soluble in alcohol. The commercially available injection (human) has a pH of 6.5–8 and has approximately 5.3 mEq of sodium per gram of CaEDTA.

Edetate calcium disodium may also be known as: sodium calcium edetate, calcium disodium edathamil, calcium disodium edetate, calcium disodium ethylenediaminetetra-acetate, calcium disodium versenate, calcium EDTA, disodium calcium tetracemate, E385, natrii calcii edetas, sodium calciumedetate, *Calcium Disodium Versenate®*, *Calcium Vitis®*, *Calciumedetat-Heyl®*, *Chelante®*, *Chelintox®*, or *Ledclair®*.

Storage/Stability/Compatibility

CaEDTA should be stored at temperatures less than 40°, and preferably at room temperature (15–30°C). The injection can be diluted with either normal saline or 5% dextrose.

Dosage Forms/Regulatory Status

Note: Do not confuse with Edetate Disodium which should *not* be used for lead poisoning as it may cause severe hypocalcemia.

VETERINARY-LABELED PRODUCTS:

None in the USA; may be available from compounding pharmacies.

HUMAN-LABELED PRODUCTS:

Edetate Calcium Disodium Injection: 200 mg/mL in 5 mL amps (1 gram/amp); *Calcium Disodium Versenate®* (3M Pharm.); (Rx)

EDROPHONIUM CHLORIDE

(ed-roe-***foe***-nee-um) Tensilon®, Enlon®

CHOLINERGIC (ANTICHOLINESTERASE) AGENT

Prescriber Highlights

- Short-acting parenteral quanternary ammonium cholinergic used primarily to test for myasthenia gravis
- Secondary indications are to reverse nondepolarizing agents or to treat some SVT's
- Relatively contraindicated: Asthma or mechanical urinary or intestinal tract obstruction
- Caution: Bradycardias or atrioventricular block
- Overdoses can cause cholinergic crisis

Uses/Indications

The primary use for edrophonium is in the diagnosis of myasthenia gravis. It can also be used for the reversal of nondepolarizing agents (*e.g.*, vecuronium, pancuronium, metocurine, atracurium, gallamine or tubocurarine). Because of its short duration of action, its clinical usefulness for this indication is questionable as longer acting drugs such as neostigmine or pyridostigmine may be more useful. Edrophonium, in a controlled intensive care-type setting, may also be useful in the diagnosis and treatment of some supraventricular arrhythmias, particularly when other more traditional treatments are ineffective.

Pharmacology/Actions

Edrophonium is an anticholinesterase agent that is very short acting. It briefly attaches to acetylcholinesterase thereby inhibiting its hydrolytic activity on acetylcholine. As acetylcholine accumulates, the following clinical signs may be noted: miosis, increased skeletal and intestinal muscle tone, bronchoconstriction, ureter constriction, salivation, sweating (in animals with sweat glands), and bradycardia.

Pharmacokinetics

Edrophonium is only effective when given parenterally. After IV administration, it begins to have effects on skeletal muscle within one minute and effects may persist for up to 10 minutes. Myasthenic patients may have effects persisting longer after the first dose. Edrophonium's exact metabolic fate and excretion characteristics have not been well described.

Contraindications/Precautions/Warnings

Edrophonium is considered relatively contraindicated in patients with bronchial asthma, or mechanical urinary or intestinal tract obstruction. It should be used with caution (with adequate monitoring and treatment available) in patients with bradycardias or atrioventricular block. Some human patients are documented to be hypersensitive to the drug and exhibit severe cholinergic reactions.

It is recommended to have IV atropine and an endotracheal tube readily available before using edrophonium.

Adverse Effects

Adverse effects associated with edrophonium are generally dose related and cholinergic in nature. Although usually mild and easily treated with a "tincture of time", severe adverse effects are possible with large overdoses (see below).

Reproductive/Nursing Safety

Edrophonium's safety profile during pregnancy is not established; use only when necessary. While no problems have been documented in nursing humans or animals, its safety has not been established. 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.*)

It is unknown whether edrophonium enters maternal milk.

Overdosage/Acute Toxicity

Overdosage of edrophonium may induce a cholinergic crisis. Clinical signs of cholinergic toxicity can include: GI effects (nausea, vomiting, diarrhea), salivation, sweating (in animals able to do so), respiratory effects (increased bronchial secretions, bronchospasm, pulmonary edema, respiratory paralysis), ophthalmic effects (miosis, blurred vision, lacrimation), cardiovascular effects (bradycardia or tachycardia, cardiospasm, hypotension, cardiac arrest), muscle cramps and weakness.

Treatment of edrophonium overdose consists of both respiratory and cardiac supportive therapy and, atropine, if necessary. Refer to the atropine monograph for more information on its use for cholinergic toxicity.

Drug Interactions

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

- **ATROPINE:** Atropine will antagonize the muscarinic effects of edrophonium and some clinicians routinely use the two together, but concurrent use should be used cautiously as atropine can mask the early clinical signs of cholinergic crisis
- **DEXPANTHENOL:** Theoretically, dexpanthenol may have additive effects when used with edrophonium
- **DIGOXIN:** Edrophonium's cardiac effects may be increased in patients receiving digoxin; excessive slowing of heart rate may occur
- **MUSCLE RELAXANTS:** Edrophonium may prolong the Phase I block of depolarizing muscle relaxants (*e.g.*, **succinylcholine, decamethonium**) and edrophonium antagonizes the actions of non-depolarizing neuromuscular blocking agents (*e.g.*, **pancuronium, tubocurarine, gallamine, vecuronium, atracurium**, etc.)

Doses

- **DOGS:**

For presumptive diagnosis of myasthenia gravis (MG):

a) Exercise animal to the point of collapse, then give edrophonium at 0.1 mg/kg IV. In animals whose exercise intolerance is minimal, it may be hard to evaluate. (Shelton 2002)

b) 1–5 mg (total dose) IV (Kline 2001)

c) 1–10 mg (total dose) IV; presumptive positive test results in transient improvement in clinical weakness; sometimes objective criteria for this test are difficult to establish. (LeCouteur 2005)

d) 0.1–0.2 mg/kg IV; have atropine and endotracheal tube readily available in case of overdose. (Abramson 2005)

e) Pre-treat with atropine (0.02–0.04 mg/kg IM or SC); then give edrophonium at 0.1 mg/kg IV. In affected animals, paresis should resolve within one minute and effects should last for up to 15 minutes. (Korenegay 2006)