Storage/Stability
Chlorambucil tablets should be stored in light-resistant, well-closed containers under refrigeration (2–8°C; 36–46°F). Tablets can be stored at a maximum of 30°C (86°F) up to one week. An expiration date of one year after manufacture is assigned to the commercially available tablets.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Chlorambucil Tablets: 2 mg; *Leukeran*® (GlaxoSmithKline); (Rx)

CHLORAMPHENICOL
CHLORAMPHENICOL SODIUM SUCCINATE

(klor-am-*fen*-i-kole) Chloromycetin®, Duricol®, Viceton®

BROAD-SPECTRUM ANTIBACTERIAL

Prescriber Highlights
- Broad spectrum antibiotic
- Contraindications: Food animals (banned)
- Extreme caution/avoid use: Preexisting hematologic disorders, pregnancy, neonates, hepatic failure, renal failure (cats); IV use in patients with cardiac failure; use long-term (>14 days) in cats with caution
- May need to reduce dose in patients with hepatic or renal insufficiency
- Adverse Effects: GI; potentially myelosuppressive, especially with high dose, long-term treatment
- Potentially toxic to humans; have dosage-giver avoid direct contact with medication

Uses/Indications
Chloramphenicol is used for a variety of infections in small animals and horses, particularly those caused by anaerobic bacteria. The FDA has prohibited the use of chloramphenicol in animals used for food production because of the human public health implications.

Pharmacology/Actions
Chloramphenicol usually acts as a bacteriostatic antibiotic, but at higher concentrations or against some very susceptible organisms it can be bactericidal. Chloramphenicol acts by binding to the 50S ribosomal subunit of susceptible bacteria, thereby preventing bacterial protein synthesis. Erythromycin, clindamycin, lincomycin, tylosin, etc., also bind to the same site, but unlike these drugs, chloramphenicol appears to also have an affinity for mitochondrial ribosomes of rapidly proliferating mammalian cells (*e.g.*, bone marrow) that may result in reversible bone marrow suppression.

Chloramphenicol has a wide spectrum of activity against many gram-positive and gram-negative organisms. Gram-positive aerobic organisms that are generally susceptible to chloramphenicol include many streptococci and staphylococci. It is also effective against some gram-negative aerobes including Neissiera, Brucella, Salmonella, Shigella, and Haemophilus. Many anaerobic bacteria are sensitive to chloramphenicol including Clostridium, Bacteroides (including *B. fragilis*), Fusobacterium, and Veillonella. Chloramphenicol also has activity against Nocardia, Chlamydia, Mycoplasma, and Rickettsia.

Pharmacokinetics
Chloramphenicol is rapidly absorbed after oral administration with peak serum levels occurring approximately 30 minutes after dosing. The palmitate oral suspension produces significantly lower peak serum levels when administered to fasted cats. The sodium succinate salt is rapidly and well absorbed after IM or SC administration in animals and, contrary to some recommendations, need not be administered only intravenously. The palmitate and sodium succinate is hydrolyzed in the GI tract and liver to the base.

Chloramphenicol is widely distributed throughout the body. Highest levels are found in the liver and kidney, but the drug attains therapeutic levels in most tissues and fluids, including the aqueous and vitreous humor, and synovial fluid. CSF concentrations may be up to 50% of those in the serum when meninges are uninflamed and higher when meninges are inflamed. A 4–6 hour lag time before CSF peak levels occur may be seen. Chloramphenicol concentrations in the prostate are approximately 50% of those in the serum. Because only a small amount of the drug is excreted unchanged into the urine in dogs, chloramphenicol may not be the best choice for lower urinary tract infections in that species. The volume of distribution of chloramphenicol has been reported as 1.8 L/kg in the dog, 2.4 L/kg in the cat, and 1.41 L/kg in horses. Chloramphenicol is about 30–60% bound to plasma proteins, enters milk and crosses the placenta.

In most species, chloramphenicol is eliminated primarily by hepatic metabolism via glucuronidative mechanisms. Only about 5–15% of the drug is excreted unchanged in the urine. The cat, having little ability to glucuronidate drugs, excretes 25% or more of a dose as unchanged drug in the urine.

The elimination half-life has been reported as 1.1–5 hours in dogs, <1 hour in foals and ponies, and 4–8 hours in cats. The elimination half-life of chloramphenicol in birds is highly species variable, ranging from 26 minutes in pigeons to nearly 5 hours in bald eagles and peafowl.

The usual serum therapeutic range for chloramphenicol is 5–15 micrograms/mL.

Contraindications/Precautions/Warnings
Chloramphenicol is prohibited by the FDA for use in food animals.

Chloramphenicol is contraindicated in patients hypersensitive to it. Because of the potential for hematopoietic toxicity, the drug should be used with extreme caution, if at all, in patients with preexisting hematologic abnormalities, especially a preexisting nonregenerative anemia. The drug should only be used in patients in hepatic failure when no other effective antibiotics are available. Chloramphenicol should be used with caution in patients with impaired hepatic or renal function as drug accumulation may occur. Those patients may need dosing adjustment, and monitoring of blood levels should be considered.

Chloramphenicol should be used with caution in neonatal animals, particularly in young kittens. In neonates (humans), circulatory collapse (so-called "Gray-baby syndrome") has occurred with chloramphenicol, probably due to toxic levels accumulating secondary to an inability to conjugate the drug or excrete the conjugate effectively.

Adverse Effects

While the toxicity of chloramphenicol in humans has been much discussed, the drug is considered by most to have a low order of toxicity in adult companion animals when appropriately dosed.

The development of aplastic anemia reported in humans, does not appear to be a significant problem for veterinary patients; however, a dose-related bone marrow suppression (reversible) is seen in all species, primarily with long-term therapy. Early signs of bone marrow toxicity can include vacuolation of many of the early cells of the myeloid and erythroid series, lymphocytopenia, and neutropenia.

Other effects that may be noted include anorexia, vomiting, diarrhea, and depression.

It has been said that cats tend to be more sensitive to developing adverse reactions to chloramphenicol than dogs, but this is probably more as a result of the drug's longer half-life in the cat. Cats dosed at 50 mg/kg q12h for 2–3 weeks do develop a high incidence of adverse effects and should be closely monitored when prolonged high-dose therapy is necessary.

Reproductive/Nursing Safety

Chloramphenicol has not been determined to be safe for use during pregnancy. The drug may decrease protein synthesis in the fetus, particularly in the bone marrow. It should only be used when the benefits of therapy clearly outweigh the risks. 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.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***C*** (*These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks.*)

Because chloramphenicol is found in milk in humans at 50% of serum levels, the drug should be given with caution to nursing bitches or queens, particularly within the first week after giving birth.

Overdosage/Acute Toxicity

Because of the potential for serious bone marrow toxicity, large overdoses of chloramphenicol should be handled by emptying the gut using standard protocols. For more information on the toxicity of chloramphenicol, refer to the Adverse Effects section above.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving chloramphenicol and may be of significance in veterinary patients (**Note:** cats may be particularly susceptible to chloramphenicol's effects on the hepatic metabolism of other drugs):

- **ANTI-ANEMIA DRUGS** (**Iron, Vitamin B12, folic acid**): Chloramphenicol may delay hematopoietic response
- **BETA-LACTAM ANTIBIOTICS** (**penicillins, cephalosporins, aminoglycosides**): Potential for antagonism
- **LIDOCAINE**: Chloramphenicol may delay hepatic metabolism
- **MYELOSUPPRESSIVE DRUGS** (*e.g.,* **cyclophosphamide**): Potential for additive bone marrow depression
- **PENTOBARBITAL**: Chloramphenicol has been demonstrated to prolong the duration of pentobarbital anesthesia by 120% in dogs, and 260% in cats
- **PHENOBARBITAL**: Chloramphenicol may inhibit hepatic metabolism and phenobarbital may decrease chloramphenicol concentrations
- **PRIMIDONE**: Anorexia and CNS effects may occur in dogs
- **PROPOFOL**: Chloramphenicol may prolong anesthesia
- **RIFAMPIN**: May decrease serum chloramphenicol levels

Laboratory Considerations

- False-positive **glucosuria** has been reported, but the incidence is unknown.

Doses

- **DOGS:**

  For susceptible infections:

  a) 45–60 mg/kg PO q8h; 45–60 mg/kg IM, SC or IV q6–8h (USPC 1990)

  b) 40–50 mg/kg IV, IM, SC or PO q8h; avoid in young animals or in breeding or pregnant animals; avoid or reduce dosage in animals with severe liver failure. (Vaden and Papich 1995)

  c) For urinary, rickettsial, localized soft tissue infections: 25–50 mg/kg PO q8h for 7 days.

  For systemic infections: 50 mg/kg PO, IV, IM, SC q6–8h for 3–5 days

  For severe bacteremia, sepsis: 50 mg/kg IV, IM or SC q4–6h for 3 days (Greene and Watson 1998)

  d) For Rocky Mountain Spotted Fever: 15–20 mg/kg q8h PO, IM or IV for 14–21 days (Sellon and Breitschwerdt 1995)

  e) For susceptible infectious otitis: 50 mg/kg PO q8h (Rosenkrantz 2006b)

- **CATS:**

  For susceptible infections:

  a) 25–50 mg/kg PO q12h; 12–30 mg/kg IM, SC or IV q12h (USPC 1990)

  b) 50 mg (total dose) IV, IM, SC or PO q8h; avoid in young animals or in breeding or pregnant animals; avoid or reduce dosage in animals with severe liver failure (Vaden and Papich 1995)

  c) For urinary, localized soft tissue infections: 50 mg per cat (total dose) PO q12h for 14 days.

  For systemic infections: 25–50 mg/kg PO, IV, IM, SC q12h for 14 days or less

  For severe bacteremia, sepsis: 50 mg per cat (total dose) PO, IV, IM or SC q6–8h for 5 days or less. (Greene and Watson 1998)

- **RABBITS/RODENTS/SMALL MAMMALS:**

  a) Rabbits: 30–50 mg/kg PO, SC, IM, IV q8–24h (Ivey and Morrisey 2000)

  b) Hedgehogs: 50 mg/kg PO q12h; 30–50 mg/kg SC, IM, IV or IO q12h (Smith 2000)

  c) Chinchillas: 30–50 mg/kg PO, SC, IM q12h (Hayes 2000)

  d) Gerbils, Guinea Pigs, Hamsters, Mice, Rats: 20–50 mg/kg (succinate salt) SC q6–12h (Adamcak and Otten 2000)

  e) Guinea pigs for pneumonia: 30–50 mg/kg PO q12h (Johnson 2006d)

- **FERRETS:**

  For proliferative colitis:

  a) 10–40 mg/kg q8h PO for 2 weeks or 50 mg/kg PO q12h for 10 days (Fox 1995)

  b) 50 mg/kg q12h PO for 14–21 days (Johnson 2006c)

  For susceptible infections:

  a) 50 mg/kg PO twice daily (using palmitate salt—may be unavailable) or 50 mg/kg SC or IM twice daily (succinate salt) (Williams 2000)

■ **HORSES:**

For susceptible infections:

a) 55 mg/kg PO q6h (Foreman 1999)
b) Chloramphenicol sodium succinate: 25 mg/kg IM q8h (Baggot and Prescott 1987)
c) Foals: Chloramphenicol sodium succinate: 50 mg/kg IV q6–8h (use longer dosage interval in premature foals and those less than 2 days old) (Caprile and Short 1987)
d) 45–60 mg/kg PO q8h; 45–60 mg/kg IM, SC or IV q6–8h (USPC 1990)
e) Foals: 20 mg/kg PO or IV q4h (Furr 1999)
f) Foals: Chloramphenicol sodium succinate: 25–50 mg/kg IV q4–8h; chloramphenicol base or palmitate: 40–50 mg/kg PO q6–8h (Brumbaugh 1999)

■ **BIRDS:**

For susceptible infections:

a) Chloramphenicol sodium succinate: 80 mg/kg IM two to three times daily, 50 mg/kg IV three to four times daily
Chloramphenicol palmitate suspension (30 mg/mL): 0.1 mL/30 grams of body weight three to four times daily. Do not use for initial therapy in life-threatening infections. Must use parenteral form if crop stasis occurs. (Clubb 1986)
b) Chloramphenicol palmitate suspension (30 mg/mL): 75 mg/kg three times a day; absorption is erratic, but well-tolerated and efficacious in baby birds with enteric infections being hand fed. Will settle out if added to drinking water. (McDonald 1989)
c) Succinate: 50 mg/kg IM or IV q8h; Palmitate: 75 mg/kg PO q8h (Hoeffer 1995)
d) Ratites (not to be used for food): 35–50 mg/kg PO, IM, IV or SC 3 times daily for 3 days (Jenson 1998)

■ **REPTILES:**

For susceptible infections:

a) For most species using the sodium succinate salt: 20–50 mg/kg IM or SC for up to 3 weeks. Chloramphenicol is often a good initial choice until sensitivity results are available. (Gauvin 1993)
b) 30–50 mg/kg/day IV, or IM for 7–14 days (Lewbart 2001)

Monitoring

■ Clinical efficacy
■ Adverse effects; chronic therapy should be associated with routine CBC monitoring

Client Information

■ **MUST NOT** be used in any animal to be used for food production
■ There is evidence that humans exposed to chloramphenicol have an increased risk of developing fatal aplastic anemia. Products should be handled with care. Do not inhale powder and wash hands after handling tablets.
■ Crushed tablets or capsule contents are very bitter tasting and animals may not accept the drug if presented in this manner

Chemistry/Synonyms

Originally isolated from *Streptomyces venezuelae*, chloramphenicol is now produced synthetically. It occurs as fine, white to grayish, yellow white, elongated plates or needle-like crystals with a pK_a of 5.5. It is freely soluble in alcohol and about 2.5 mg are soluble in 1 mL of water at 25°C.

Chloramphenicol sodium succinate occurs as a white to light yellow powder. It is freely soluble in both water and alcohol. Commercially available chloramphenicol sodium succinate for injection contains 2.3 mEq of sodium per gram of chloramphenicol. Chloramphenicol may also be known as: chloramphenicolum, chloranfenicol, cloranfenicol, kloramfenikol, or laevomycetinum; many trade names are available.

Storage/Stability/Compatibility

Chloramphenicol capsules and tablets should be stored in tight containers at room temperature (15–30°C). The palmitate oral suspension should be stored in tight containers at room temperature and protected from light or freezing.

The sodium succinate powder for injection should be stored at temperatures less than 40°, preferably between 15–30°C. After reconstituting the sodium succinate injection with sterile water, the solution is stable for 30 days at room temperature and 6 months if frozen. The solution should be discarded if it becomes cloudy.

The following drugs and solutions are reportedly **compatible** with chloramphenicol sodium succinate injection: all commonly used intravenous fluids, amikacin sulfate, aminophylline, ampicillin sodium (in syringe for 1 hr.) ascorbic acid, calcium chloride/gluconate, cephalothin sodium, cephapirin sodium, colistimethate sodium, corticotropin, cyanocobalamin, dimenhydrinate, dopamine HCl, ephedrine sulfate, heparin sodium, hydrocortisone sodium succinate, hydroxyzine HCl, kanamycin sulfate, lidocaine HCl, magnesium sulfate, metaraminol bitartrate, methicillin sodium, methyldopate HCl, methylprednisolone sodium succinate, metronidazole with or without sodium bicarbonate, nafcillin sodium, oxacillin sodium, oxytocin, penicillin G potassium/sodium, pentobarbital sodium, phenylephrine HCl with or without sodium bicarbonate, phytonadione, plasma protein fraction, potassium chloride, promazine HCl, ranitidine HCl, sodium bicarbonate, thiopental sodium, verapamil HCl, and vitamin B-complex with C.

The following drugs and solutions are reportedly **incompatible** (or compatibility data conflicts) with chloramphenicol sodium succinate injection: chlorpromazine HCl, glycopyrrolate, metoclopramide HCl, oxytetracycline HCl, polymyxin B sulfate, prochlorperazine edislyate/mesylate, promethazine HCl, tetracycline HCl, and vancomycin 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:

Chloramphenicol Oral Tablets and Capsules: 50 mg (*Duricol*® only), 100 mg (*Duricol*® only), 250 mg, 500 mg, & 1 gram (*Viceton*® only); Approved for use in dogs only. *Duricol*® *Chloramphenicol Capsules USP* (VPC), *Viceton*® (Bimeda); (Rx)

An ophthalmic 1% ointment (*Vetrachloracin*®—Pharmaderm) is also available.

HUMAN-LABELED PRODUCTS:

Chloramphenicol Powder for Injection: 1 gram (100 mg/mL as sodium succinate when reconstituted); *Chloromycetin*® *Sodium Succinate* (Parke-Davis); generic; (Rx)

Ophthalmic preparations are also available.

CHLORDIAZEPOXIDE ± CLIDINIUM BR

(klor-dye-az-e-***pox***-ide) ± (kli-***din***-ee-um) Librium®, Librax®

BENZODIAZEPINE ± ANTIMUSCARINIC

Prescriber Highlights

- Benzodiazepine for behavior problems (phobias, etc.) & with an antimuscarinic (clidinium) for irritable bowel syndrome in dogs
- Not commonly used, so little has been published on adverse effects (similar to diazepam +/- atropine)
- Potentially teratogenic

Uses/Indications

Chlordiazepoxide alone may be a useful adjunct to treating certain behaviors where benzodiazepines may be useful including noise phobias in dogs; inter-cat aggression and urine spraying in cats. When combined with clidinium, it may be useful symptomatic therapy for dogs with irritable bowel syndrome.

Pharmacology/Actions

The subcortical levels (primarily limbic, thalamic, and hypothalamic) of the CNS are depressed by chlordiazepoxide and other benzodiazepines thus producing the anxiolytic, sedative, skeletal muscle relaxant and anticonvulsant effects seen. The exact mechanism of action is unknown but postulated mechanisms include: antagonism of serotonin, increased release of and/or facilitation of gamma-aminobutyric acid (GABA) activity, and diminished release or turnover of acetylcholine in the CNS. Benzodiazepine specific receptors have been located in the mammalian brain, kidney, liver, lung, and heart. In all species studied, receptors are lacking in the white matter.

Clidinium bromide is an antimuscarinic with its main action to reduce GI motility and secretion similarly to atropine. Clidinium is a quaternary ammonium compound and, unlike atropine, does not cross appreciably into the CNS or the eye and should not exhibit the same extent of CNS or ocular adverse effects that atropine possesses. For further information, refer to the atropine monograph.

Pharmacokinetics

Chlordiazepoxide is rapidly absorbed following oral administration. It is highly lipid soluble and is widely distributed throughout the body. It readily crosses the blood-brain barrier and is fairly highly bound to plasma proteins. Chlordiazepoxide is metabolized in the liver to several metabolites, including: desmethyldiazepam (nordiazepam), desmethylchlordiazepoxide and oxazepam, all of which are pharmacologically active and can have considerable half lives. These are eventually conjugated with glucuronide and eliminated primarily in the urine. Because of the active metabolites, serum values of chlordiazepoxide are not useful in predicting efficacy.

Little pharmacokinetic data for clidinium is available. The drug is incompletely absorbed from the gut (small intestine). Effects in humans are seen in about an hour; duration of effect is about 3 hours. As the compound is completely ionized *in vivo*, it does not enter the CNS or the eye and therefore unlike atropine does not have effects on those systems. The drug is metabolized principally in the liver, but is also excreted unchanged in the urine.

Contraindications/Precautions/Warnings

Use benzodiazepines cautiously in patients with hepatic or renal disease and in debilitated or geriatric patients. Chlordiazepoxide should only be administered very cautiously to patients in coma, shock or with significant respiratory depression. It is contraindicated in patients with known hypersensitivity to the drug. Chlordiazepoxide should be used very cautiously, if at all, in aggressive patients as it may disinhibit the anxiety that may help prevent these animals from aggressive behavior. Benzodiazepines may impair the abilities of working animals. If administering the drug IV (rarely warranted), be prepared to administer cardiovascular or respiratory support. Give IV slowly.

Clidinium, like other antimuscarinic agents should not be used in patients with tachycardias secondary to thyrotoxicosis or cardiac insufficiency, myocardial ischemia, unstable cardiac status during acute hemorrhage, GI obstructive disease, paralytic ileus, severe ulcerative colitis, obstructive uropathy, or myasthenia gravis.

Antimuscarinic agents should be used with extreme caution in patients with known or suspected GI infections. Antimuscarinic agents can decrease GI motility and prolong retention of the causative agent(s) or toxin(s) resulting in prolonged effects of the toxin. Antimuscarinic agents must also be used with extreme caution in patients with autonomic neuropathy.

Antimuscarinic agents should be used with caution in patients with hepatic or renal disease, geriatric or pediatric patients, hyperthyroidism, hypertension, CHF, tachyarrhythmias, prostatic hypertrophy, or esophageal reflux. Systemic atropine should be used cautiously in horses as it can decrease gut motility and induce colic in susceptible animals. It may also reduce the arrhythmogenic doses of epinephrine. Use of atropine in cattle may result in inappetence and rumen stasis that may persist for several days.

Adverse Effects

Chlordiazepoxide's adverse effects are similar to other benzodiazepines, especially diazepam (they share several active metabolites). As there is much more information with respect to diazepam in dogs or cats than chlordiazepoxide, the following is extrapolated from diazepam information: Dogs could exhibit a contradictory response (CNS excitement) following administration of chlordiazepoxide. The effects with regard to sedation and tranquilization are extremely variable with each dog. Cats could exhibit changes in behavior (irritability, depression, aberrant demeanor) after receiving chlordiazepoxide. There have been reports of cats developing hepatic failure after receiving oral diazepam for several days. It is unknown if chlordiazepoxide also shares this effect. Clinical signs have been reported to occur 5–11 days after beginning oral therapy. Cats that receive diazepam should have baseline liver function tests. These should be repeated and the drug discontinued if emesis, lethargy, inappetence, or ataxia develops.

Clidinium's adverse effects are basically extensions of the drug's pharmacologic effects and are generally dose related. At usual doses effects tend to be mild in relatively healthy patients. More severe effects tend to occur with high or toxic doses. GI effects can include dry mouth (xerostomia), dysphagia, constipation, vomiting, and thirst. GU effects may include urinary retention or hesitancy. Cardiovascular effects include sinus tachycardia (at higher doses), bradycardia (initially or at very low doses), hypertension, hypotension, arrhythmias (ectopic complexes), and circulatory failure.

Reproductive/Nursing Safety

Benzodiazepines have been implicated in causing congenital abnormalities in humans if administered during the first trimester of pregnancy. Infants born of mothers receiving large doses of benzodiazepines shortly before delivery have been reported to suffer from apnea, impaired metabolic response to cold stress, difficulty in feed-