dicate evidence of fetal risk. The risk of use in pregnant women clearly outweighs any possible benefit.)

It is not known whether leuprolide is excreted in milk; use with caution.

Overdosage/Acute Toxicity

Because of its expense and method of dosing, it is unlikely an acute overdose would occur. Studies in lab animals at dosages of up to 5 gm/kg IM produced no untoward effects.

Drug Interactions

No documented adverse drug interactions with leuprolide were located.

Laboratory Considerations

- Diagnostic tests measuring **pituitary gonadotrophic** and **gonadal functions** may be misleading during, and for several months after discontinuing therapy

Doses

- **FERRETS:**

For treatment of adrenal associated endocrinopathy:

a) Using the depot form: 100 mcg IM once a month (Wagner, Bailey et al. 2001)

b) Using the 4 month depot form: 2 mg IM for a 3 lb ferret; may last 5–6 months. Not as effective with carcinomas. (Weiss 2002a)

c) Using the 30 day depot form: If ferret weighs less than 1 kg: 100 mcg IM q30 days. If weighs >1 kg: 200 mcg IM q30 days. Generally, the drug is diluted from its original concentration to negate the muscle necrosis problem that has been reported. The diluted form appears to remain active after being stored in the freezer for a year. (Murray 2002) (**Note:** The manufacturer states that the depot form is not to be frozen and no studies are known that support the stability of the depot activity when frozen and thawed—Plumb)

d) Using the one month depot form: 100–250 mcg/kg IM every 4 weeks until signs resolve, then every 4–8 weeks as needed, lifelong. Larger ferrets may require the higher dosage range. (Johnson 2006b)

- **BIRDS:**

To inhibit egg laying in pet birds:

a) For inappropriate egg laying (to reduce or prevent ovulation) in Cockatiels using Lupron Depot: 0.375 mg per Cockatiel IM once monthly (Tully 2000)

b) 100 mcg/kg per day. Multiply dose by number of days for effect and give once monthly. Example: 100 mcg/kg for 28 days = 2800 mcg/kg dose (Olsen and Orosz 2000)

Monitoring

- Clinical effects (Birds: decreased egg-laying; Ferrets: decreases in vulvar swelling, pruritus, undesirable sexual behaviors, aggression, and increased hair regrowth

Client Information

- Relatively experimental in birds or ferrets. Long-term safety is not known.
- Can be extremely expensive to treat.

Chemistry/Synonyms

A synthetic nonapeptide analog of GnRH (gonadotropin releasing hormone, gonadorelin, luteinizing hormone-releasing hormone), leuprolide acetate occurs as a white to off-white powder. In water more than 250 mg are soluble in one mL.

Leuprolide may also be known as: leuproprelin, leuprorelinum, abbott-43818, leuprolide acetate, TAP-144, *Carcinil®*, *Daronda®*, *Eligard®*, *Elityran®*, *Enanton®*, *Enantone®*, *Enantone-Gyn®*, *Ginecrin®*, *Lectrum®*, *Leuplin®*, *Lucrin®*, *Lupride®*, *Lupron®*, *Procren®*, *Procrin®*, *Prostap®*, *Reliser®*, *Trenantone®*, *Uno-Enantone®*, and *Viadur®*.

Storage/Stability/Compatibility

The injection should be stored below room temperature (<78°F); do not freeze and protect from light (store in carton until use). The depot form may be stored at room temperature. After reconstituting the suspension is stable for 24 hours, but as it contains no preservative it is recommended for immediate use.

The manufacturer states that the depot form is not to be frozen and no studies are known that support the stability of the depot activity when frozen and thawed.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Leuprolide Acetate Injection: 5 mg/mL in 2.8 mL multi-dose vials; *Lupron®* & *Lupron® for Pediatric Use* (TAP Pharm); generic; (Rx)

Leuprolide Acetate Injection: 22.5 mg in single-use kits with a 2-syringe mixing system and needle; 30 mg & 45 mg in single-use kit with 2-syringe mixing system and syringe containing *Atrigel*; *Eligard®* (Sanofi-Synthelabo); (Rx)

Leuprolide Powder for Injection: lyophilized 7.5 mg in single-use kits with a 2-syringe mixing system and needle; *Eligard®* (Sanofi-Synthelabo); (Rx)

Leuprolide Acetate Microspheres for Injection, lyophilized and preservative free with mannitol: 3.75 mg, 7.5 mg, 11.25 mg, 15 mg single dose kits and pre-filled dual-chamber syringes; *Lupron® Depot* and *Lupron® Depot-Ped* (TAP Pharm); (Rx)

Leuprolide Acetate Microspheres for Injection, lyophilized and preservative free with mannitol: 11.25 mg and 22.5 mg (3 month), 30 mg (4 month) in single pre-filled dual-chamber syringes; *Lupron® Depot-3* or *-4 Month,* (TAP Pharm); (Rx)

Leuprolide Acetate Implants: 72 mg in single-dose kit; *Viadur®* (ALZA Corporation); (Rx)

LEVAMISOLE

(leh-*vam*-i-sole) Levasole®, Tramisol®

ANTIPARASITIC, IMMUNE STIMULANT

Prescriber Highlights

- **Antinematodal parasiticide that also may be useful as an immune stimulant**
- **Contraindications: Milk-producing animals (not approved)**
- **Very cautiously, if at all: Severely debilitated, or significant renal or hepatic impairment; in cattle that are stressed due to vaccination, dehorning, or castration**
- **Not usually used in horses; infrequently used in small animals today as an antiparasitic agent**
- **Numerous adverse effects**

Uses/Indications

Depending on the product licensed, levamisole is indicated for the treatment of many nematodes in cattle, sheep and goats, swine, poultry. In sheep and cattle, levamisole has relatively good activity against abomasal nematodes, small intestinal nematodes (not particularly good against *Strongyloides* spp.), large intestinal nematodes (not *Trichuris* spp.), and lungworms. Adult forms of species that are usually covered by levamisole, include: *Haemonchus* spp., *Trichostrongylus* spp., *Osteragia* spp., *Cooperia* spp., *Nematodirus* spp., *Bunostomum* spp., *Oesophagostomum* spp., *Chabertia* spp., and *Dictyocaulus vivapurus*. Levamisole is less effective against the immature forms of these parasites, and is generally ineffective in cattle (but not sheep) against arrested larval forms. Resistance of parasites to levamisole is a growing concern.

In swine, levamisole is indicated for the treatment of *Ascaris suum*, *Oesophagostomum* spp., Strongyloides, Stephanurus, and Metastrongylus.

Levamisole has been used in dogs as a microfilaricide to treat *Dirofilaria immitis* infection in the past, but is rarely used today. It has also garnered some interest as an immunostimulant in the adjunctive therapy of various neoplasms.

Because of its narrow margin for safety and limited efficacy against many equine parasites, levamisole is not generally used in horses as an antiparasitic agent. It has been tried as an immune stimulant, however.

Pharmacology/Actions

Levamisole stimulates the parasympathetic and sympathetic ganglia in susceptible worms. At higher levels, levamisole interferes with nematode carbohydrate metabolism by blocking fumarate reduction and succinate oxidation. The net effect is a paralyzing effect on the worm that is then expelled alive. Levamisole's effects are considered to be nicotine-like in action.

Levamisole's mechanism of action for its immunostimulating effects are not well understood. It is believed it restores cell-mediated immune function in peripheral T-lymphocytes and stimulates phagocytosis by monocytes. Its immune stimulating effects appear to be more pronounced in animals that are immune-compromised.

Pharmacokinetics

Levamisole is absorbed from the gut after oral dosing and through the skin after dermal application, although bioavailabilities are variable. It is reportedly distributed throughout the body. Levamisole is primarily metabolized with less than 6% excreted unchanged in the urine. Plasma elimination half-lives have been determined for several veterinary species: Cattle, 4–6 hours; Dogs, 1.8–4 hours; and Swine, 3.5–6.8 hours. Metabolites are excreted in both the urine (primarily) and feces.

Contraindications/Precautions/Warnings

Levamisole is contraindicated in lactating animals (not approved). It should be used cautiously, if at all, in animals that are severely debilitated, or significant renal or hepatic impairment.

Use cautiously or, preferably, delay use in cattle that are stressed due to vaccination, dehorning, or castration.

Levamisole is not indicated for use as a dirofilarial adulticide.

Avoid, if possible, administering levamisole intramuscularly to birds.

Adverse Effects

Adverse effects that may be seen in cattle can include muzzle foaming or hypersalivation, excitement or trembling, lip-licking and head shaking. These effects are generally noted with higher than recommended doses or if levamisole is used concomitantly with organophosphates. Signs generally subside within 2 hours. When injecting into cattle, swelling may occur at the injection site. This will usually abate in 7–14 days, but may be objectionable in animals that are close to slaughter.

In sheep, levamisole may cause a transient excitability in some animals after dosing. In goats, levamisole may cause depression, hyperesthesia, and salivation. Injecting levamisole SC in goats apparently causes a stinging sensation.

In swine, levamisole may cause salivation or muzzle foaming. Swine infected with lungworms may develop coughing or vomiting.

Adverse effects that may be seen in dogs include GI disturbances (usually vomiting, diarrhea), neurotoxicity (panting, shaking, agitation or other behavioral changes), immune-mediated anemia, agranulocytosis, dyspnea, pulmonary edema, immune-mediated skin eruptions (erythroedema, erythema multiforme, toxic epidermal necrolysis), and lethargy.

Adverse effects seen in cats include hypersalivation, excitement, mydriasis, and vomiting.

Reproductive/Nursing Safety

There is little information available regarding the safety of this drug in pregnant animals. Although levamisole is considered relatively safe to use in large animals that are pregnant, use only if the potential benefits 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.*)

Levamisole is excreted in cows' milk; use with caution in nursing dams.

Overdosage/Toxicity

Signs of levamisole toxicity often mimic those of organophosphate toxicity. Signs may include hypersalivation, hyperesthesias and irritability, clonic seizures, CNS depression, dyspnea, defecation, urination, and collapse. These effects are best treated by supportive means as animals generally recover within hours of dosing. Acute levamisole overdosage can result in death due to respiratory failure. Should respiratory failure occur, artificial ventilation with oxygen should be instituted until recovery occurs. Cardiac arrhythmias may also be seen. If the ingestion was oral, emptying the gut and/or administering charcoal with cathartics may be indicated.

Levamisole is considered to be more dangerous when administered parenterally than when given orally or topically. Intravenous administration is particularly hazardous, and is never recommended.

In pet birds (cockatoos, budgerigars, Mynah birds, parrots, etc.), 40 mg/kg has been reported as a toxic dose when administered SC. IM injections may cause more severe toxicity. Depression, ataxia, leg and wing paralysis, mydriasis, regurgitation, and death may be seen after a toxic dose in birds.

Drug Interactions

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

- **ASPIRIN**: Levamisole may increase salicylate levels
- **CHLORAMPHENICOL**: Fatalities have been reported after concomitant levamisole and chloramphenicol administration; avoid using these agents together

- **CHOLINESTERASE-INHIBITING DRUGS** (*e.g.*, **organophosphates, neostigmine**): Could theoretically enhance the toxic effects of levamisole; use together with caution
- **NICOTINE-LIKE COMPOUNDS** (*e.g.*, **pyrantel, morantel, diethylcarbamazine**): Could theoretically enhance the toxic effects of levamisole; use together with caution.
- **WARFARIN**: Increased risk for bleeding

Doses

- **DOGS:**

As an immune stimulant:

a) For recurrent cutaneous infections: 2.2 mg/kg PO every other day, with appropriate antimicrobial therapy (Rosenkrantz 1989)

b) 0.5–2 mg/kg PO 3 times a week (Kirk 1989)

c) For adjunctive therapy in dogs with chronic pyoderma: 0.5–1.5 mg/kg PO 2–3 times a week (efficacy not established) (Lorenz 1984)

d) For adjunctive therapy in dogs with chronic pyoderma: 2.2 mg/kg PO every other day (may only be efficacious in 10% of cases) (Ihrke 1986)

e) For adjunctive therapy in aspergillosis/penicillinosis: 2–5 mg/kg PO every other day (Prueter 1988)

As an alternative treatment for SLE:

a) 3–7 mg/kg PO every other day for 4 months; alone or in combination with corticosteroids (Marks and Henry 2000)

As a microfilaricide (**Note**: Rarely recommended today):

a) 11 mg/kg PO for 6–12 days. Examine blood on 6th day of treatment; discontinue therapy when microfilaria negative. May cause neurologic signs, vomiting, behavioral changes, or possibly death. If treatment is prolonged (>15 days), there is increased likelihood of toxicity. (Todd, Paul, DiPietro 1985)

b) 11 mg/kg PO for 6–12 days. Examine for microfilaria within 7–10 days and at weekly intervals until eliminated or treatment is halted. Retching and vomiting are common. Avoid giving on an empty stomach or immediately after drinking water. A "conditioning" dose of 5 mg/kg PO once a day may be necessary. Stop therapy if abnormal behavior or ataxia develops. (Knight 1988)

For treatment of *Angiostrongylus vasorum*:

a) 7.5 mg/kg (route not specified) for two consecutive days, followed by 10 mg/kg for 2 days; if the infection is not cleared, the regimen is repeated. (Bowman 2006a)

For the treatment of lungworms:

a) For *Crenosoma vulpis*: 8 mg/kg once (Todd, Paul, and DiPietro 1985)

b) For Capillaria: 7–12 mg/kg once daily PO for 3–7 days

For *Filaroides osleri:* 7–12 mg/kg once daily PO for 20–45 days (Roudebush 1985)

c) 7.5 mg/kg PO twice daily or 25 mg/kg PO every other day for 10 days (Bauer 1988)

d) For *Capillaria aerophilia*: 10 mg/kg PO once daily for 5 days; repeat in 9 days (Reinemeyer 1995)

- **CATS:**

For the treatment of lungworms:

a) 20–40 mg/kg PO every other day for 5–6 treatments (Kirk 1989)

b) For *Aelurostrongylus abstrusus*: 100 mg PO daily every other day for 5 treatments; give atropine (0.5 mg SC, 15 minutes before administering); or 15 mg/kg PO every other day for 3 treatments, then 3 days later: 30 mg/kg PO, then 2 days later: 60 mg/kg.

For *Capillaria aerophilia*: 4.4 mg/kg SC for 2 days, then 8.8 mg/kg once 2 weeks later; or 5 mg/kg PO once daily for 5 days, followed by 9 days of no therapy, repeat two times (Todd, Paul, and DiPietro 1985)

c) 25 mg/kg every other day for 10–14 days (Roudebush 1985)

d) For *Capillaria aerophilia*: 10 mg/kg PO once daily for 5 days; repeat in 9 days (Reinemeyer 1995)

For treatment of *Ollulanus tricuspis*:

a) 5 mg/kg SC (Todd, Paul, and DiPietro 1985)

As a microfilaricide:

a) 10 mg/kg PO for 7 days (Dillon 1986)

As an immune-stimulant:

a) For adjunctive therapy of feline plasma-cell gingivitis/pharyngitis: 25 mg PO every other day for 3 doses (DeNovo, Potter, and Woolfson 1988)

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

a) Rabbits: For nematodes: 12.5–20 mg/kg PO (for gastric nematodes) or SC (for extragastric nematodes) (Ivey and Morrisey 2000)

- **HORSES:**

As an immunostimulant:

a) Dosages have ranged from 2.5 mg/kg injected at 7 day intervals, and 2.2 mg/kg PO every 24 hours for 3 days, then off for 4 days for a period of 4–6 weeks. Anecdotal reports of beneficial effects in the treatment of nasal viral papillomas, COPD, and EPM have been suggested. (Bentz 2006a)

- **CATTLE:**

For treatment of susceptible nematodes (also refer to specific label directions for approved products):

a) For removal of mature and immature *Dictyocaulus vivapurus*: 5.5–11 mg/kg PO, either given in feed or as a drench or oral bolus. May also be administered SC at 3.3–8 mg/kg. (Bennett 1986)

b) 7.5 mg/kg PO (Brander, Pugh, and Bywater 1982)

- **LLAMAS:**

For treatment of susceptible nematodes:

a) 5–8 mg/kg IM, or PO (Fowler 1989)

b) 5–8 mg/kg PO or SC for 1 day (Cheney and Allen 1989)

- **SWINE:**

For treatment of susceptible nematodes (also refer to specific label directions for approved products):

a) For removal of mature and immature Metastrongylus: 8 mg/kg PO in feed or water (Bennett 1986)

b) 8 mg/kg PO in feed or water (Howard 1986)

c) 7.5 mg/kg PO (Brander, Pugh, and Bywater 1982)

- **SHEEP & GOATS:**

For treatment of susceptible nematodes (also refer to specific label directions for approved products):

a) For removal of mature and immature *Dictyocaulus vivapurus*: 8 mg/kg PO (Bennett 1986)

b) 7.5 mg/kg PO (Brander, Pugh, and Bywater 1982)

- **BIRDS:**

a) Using 13.65% injectable:

For intestinal nematodes: 5–15 mL/gallon of drinking water for 1–3 days; repeat in 10 days. If birds refuse to drink, withhold water prior to treating.

For gavage in Australian Parakeets (or desert species that refuse to drink water): 15 mg/kg; repeat in 10 days

For parenteral use: 4–8 mg/kg IM or SC; repeat in 10–14 days. May cause vomiting, ataxia, or death. Do not use in debilitated birds.

For immunostimulation: 0.3 mL/gallon of water for several weeks

As a parenteral immunostimulant: 2 mg/kg IM or SC. 3 doses at 14 day intervals (Clubb 1986)

b) As a nebulized immunostimulant: 1 mL (of 13.65% levamisole phosphate) in 15 mL saline (Spink 1986)

c) For Capillaria infections: 15–30 mg/kg orally as a single bolus or through a crop tube; or 2.25 mg/gallon of drinking water for 4–5 days. Repeat treatment in 10–14 days. (Flammer 1986)

d) Poultry: 18–36 mg/kg, PO (Brander, Pugh, and Bywater 1982)

e) Ratites: For *Libyastrongylus douglassi*: Give 30 mg/kg PO or IM at one month of age, then once a month for 7 treatments, then 4 times yearly (Jenson 1998)

Monitoring

- Clinical efficacy
- Adverse effects/toxicity observation

Client Information

- Levamisole is not approved for use in dairy animals of breeding age.
- Follow directions on the product label unless otherwise directed by veterinarian. Animals that are severely parasitized or in conditions with constant helminth exposure should be retreated 2–4 weeks after initial treatment.
- Do not administer injectable products IV.
- Report serious adverse effects to veterinarian.

Chemistry/Synonyms

The levo-isomer of dl-tetramisole, levamisole has a greater safety margin than does the racemic mixture. It is available commercially in two salts, a phosphate and a hydrochloride. Levamisole hydrochloride occurs as a white to pale cream colored, odorless or nearly odorless, crystalline powder. One gram is soluble in 2 mL of water.

Levamisole HCl may also be known as: cloridrato de levamizol, ICI-59623, levamisoli hydrochloridum, NSC-177023, R-12564, RP-20605, l-tetramisole hydrochloride, *Amtech®, Ascaridil®, Decaris®, Ergamisol®, Immunol®, Ketrax®, Levasole®, Meglum®, Prohibit®, Solaskil®, Vermisol®,* and *Vizole®*.

Storage/Stability/Compatibility

Levamisole hydrochloride products should be stored at room temperature (15–30°C), unless otherwise instructed by the manufacturer; avoid temperatures greater than 40°C. Levamisole phosphate injection should be stored at temperatures at or below 21°C (70°F); refrigeration is recommended and freezing should be avoided.

Levamisole tablets should not be crushed nor suspensions made from them.

Dosage Forms/Regulatory Status/Withdrawal Times

In cattle, sheep, and swine a level of 0.1 ppm has been established for negligible residues in edible tissues.

VETERINARY-LABELED PRODUCTS:

Levamisole Phosphate Injection: 136.5 mg/mL (13.65%) in 500 mL vials. Levamisole Injectable (AgriLabs), *Levasole® Injectable Solution 13.65%* (Schering Plough); Approved for use in cattle. Slaughter withdrawal (at labeled dosages) = 7 days. To prevent residues in milk, do not administer to dairy animals of breeding age.

Levamisole Hydrochloride Water Medication: 18.15 g in 0.71 oz bottle. *Levamisole Soluble Pig Wormer* (AgriLabs, Durvet, Aspen); (OTC); *Levasole® Soluble Pig Wormer* (Schering-Plough), *Amtech® Levamisole HCl Pig Wormer* (IVX); (OTC). Approved for use in swine. Slaughter withdrawal (at labeled dosages) = 72 hours

Levamisole Hydrochloride Antihelmintic Oral: *Levasole® Soluble Drench Powder* 46.8 grams/packet (Schering-Plough); (OTC). Approved for use in cattle (Not in dairy animals of breeding age), and sheep. Slaughter withdrawal (at labeled dosages) = 48 hours (cattle); 72 hours (sheep)

Levamisole Hydrochloride Soluble Drench Powder 46.8 grams/packet; 544.5 g/21.34 oz bottle. *Prohibit®* (AgriLabs) (OTC). Approved for use in cattle and sheep. Slaughter withdrawal (at labeled dosages) cattle = 48 hours, sheep = 72 hours. To prevent residues in milk, do not administer to dairy animals of breeding age.

Levamisole HCl Oral Tablets/Boluses: 184 mg bolus: *Levasole® Sheep Wormer Bolus* (Schering Plough); (OTC). Approved for use in sheep. Slaughter withdrawal (at labeled dosages) = 72 hours.

Levamisole 2.19 gram bolus: *Levasole® Cattle Wormer Boluses* (Schering-Plough); (OTC). Approved for use in beef (not for use in dairy animals of breeding age). Slaughter withdrawal (at labeled dosages) = 48 hours.

HUMAN-LABELED PRODUCTS:

Levamisole HCl Tablets: 50 mg levamisole base; *Ergamisol®* (Janssen); (Rx)

LEVETIRACETAM

(lee-ve-tye-***ra***-se-tam) Keppra®

ANTICONVULSANT

Prescriber Highlights

- **May be useful as a third drug adjunct for refractory canine epilepsy or when either phenobarbital or bromides are not tolerated; may also be useful in cats, but less is known**
- **Limited clinical experience; investigations ongoing regarding efficacy, adverse effects**
- **Appears to be well tolerated in dogs & cats**
- **Not substantially metabolized by liver; does not induce hepatic enzymes**
- **Dosage frequency (three times daily) problematic; cost may be prohibitive**

Uses/Indications

Levetiracetam may be useful as a third antiseizure medication in dogs that are not well controlled with phenobarbital and bromides or when either bromides or phenobarbital are not tolerated. Some evidence suggests that in dogs suffering from phenobarbital liver toxicity, the addition of levetiracetam will allow reduction of their phenobarbital dosage without increasing seizure frequency.

Levetiracetam may also be useful as add-on therapy in cats.

Pharmacology/Actions

The exact mechanism for levetiracetam's antiseizure activity is not well understood. It may selectively prevent hypersynchronization of epileptiform burst-firing and propagation of seizure activity. It does not affect normal neuronal excitability.