- **BISPHOSPHONATES** (**alendronate,** etc.): May increase risk for GI ulceration
- **CORTICOSTEROIDS:** Concomitant administration with NSAIDs may significantly increase the risks for GI adverse effects
- **CYCLOSPORINE:** May increase risk for nephrotoxicity
- **FLUCONAZOLE:** May increase NSAID levels
- **FLUOXETINE:** Hallucinations reported in some human patients taking with ketorolac
- **FUROSEMIDE:** Ketorolac may reduce the saluretic and diuretic effects of furosemide
- **METHOTREXATE:** Serious toxicity has occurred when NSAIDs have been used concomitantly with methotrexate; use together with extreme caution
- **MUSCLE RELAXANTS, NONDEPOLARIZING:** Ketorolac may potentiate effects
- **PROBENECID:** May cause a significant increase in serum levels and half-life of ketorolac

Doses

- **DOGS:**
  a) As an analgesic: 0.5 mg/kg IV three times daily or 0.3 mg/kg PO twice daily. Repeated doses have considerable potential for causing GI or renal toxicity. Treated dogs should receive misoprostol. (Dowling 2000)
  b) As an analgesic: 0.3–0.5 mg/kg IV, IM q8–12h for one or two doses (Scherk 2003a)
- **CATS:**
  a) As an analgesic: 0.25 mg/kg IM q8–12h for one or two doses (Scherk 2003a)
- **GOATS:**
  a) As an analgesic: 0.3–0.7 mg/kg IV, IM, SC, PO three times daily (Resources 2000)
- **RABBITS/RODENTS/SMALL MAMMALS:**
  a) As an analgesic: Mice: 0.7–10 mg/kg PO once daily. Rats: 3–5 mg/kg PO once to twice a day; 1 mg/kg IM once to twice a day (Huerkamp 2000)

Monitoring

- Analgesic/antiinflammatory efficacy
- GI: appetite, feces (occult blood, diarrhea)

Client Information

- Notify veterinarian if signs of GI distress (anorexia, vomiting, diarrhea, black feces, or blood in stool) occur, or if the animal becomes depressed.

Chemistry/Synonyms

A carboxylic acid derivative nonsteroidal antiinflammatory agent, ketorolac tromethamine occurs as an off-white crystalline powder with a pKa of 3.54 (in water). More than 500 mg are soluble in one mL of water at room temperature. The commercially available injection is a clear, slightly yellow solution with a pH of 6.9–7.9. Sodium chloride is added to make the solution isotonic.

Ketorolac tromethamine may also be known as RS-37619-00-31-3; many trade names are available.

Storage/Stability/Compatibility

Both the tablets and injection should be stored at room temperature and protected from light. Protect the tablets from excessive humidity. It is recommended not to mix the injection with other drugs in the same syringe. The injection is stable for at least 48 hours in commonly used IV solutions.

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:

Ketorolac Tromethamine Tablets: 10 mg; generic; (Rx)

Ketorolac Tromethamine Injection: 15 mg/mL & 30 mg/mL in 1 mL, 2 mL vials, & 10 mL multiple-dose vials; generic; (Rx)

A topical ophthalmic preparation is also available; see the ophthalmology section in the appendix for further information.

L-Asparaginase — see Asparaginase
L-Thyroxine — see Levothyroxine Sodium
Lactated Ringer's — see the appendix section on intravenous fluids

LACTULOSE

(*lak*-tyoo-lose) Cephulac®

DISACCHARIDE LAXATIVE/AMMONIA REDUCER

Prescriber Highlights

- Disaccharide laxative & reducer of blood ammonia levels
- Adverse Effects: Flatulence, gastric distention, cramping, etc.; diarrhea & dehydration are signs of overdosage
- Cats dislike the taste of lactulose & administration may be difficult
- May alter insulin requirements in diabetics

Uses/Indications

The primary use of lactulose in veterinary medicine is to reduce ammonia blood levels in the prevention and treatment of hepatic encephalopathy (portal-systemic encephalopathy; PSE) in small animals and pet birds. It is also used as a laxative in small animals.

Pharmacology/Actions

Lactulose is a disaccharide (galactose/fructose) that is not hydrolyzable by mammalian and, probably, avian gut enzymes. Upon reaching the colon, lactulose is metabolized by the resident bacteria resulting in the formation of low molecular weight acids (lactic, formic, acetic) and CO_2. These acids have a dual effect; they increase osmotic pressure drawing water into the bowel causing a laxative effect and also acidify colonic contents. The acidification causes ammonia NH_3 (ammonia) to migrate from the blood into the colon where it is trapped as $[NH_4]^+$ (ammonium ion) and expelled with the feces.

Pharmacokinetics

In humans, less than 3% of an oral dose of lactulose in absorbed (in the small intestine). The absorbed drug is not metabolized and excreted unchanged in the urine within 24 hours.

Contraindications/Precautions/Warnings

Lactulose syrup contains some free lactose and galactose, and may alter the insulin requirements in diabetic patients. In patients with preexisting fluid and electrolyte imbalances, lactulose may exacerbate these conditions if it causes diarrhea; use cautiously.

Adverse Effects

Signs of flatulence, gastric distention, cramping, etc. are not uncommon early in therapy, but generally abate with time. Diarrhea and dehydration are signs of overdosage; dosage should be reduced.

Cats dislike the taste of lactulose and administration may be difficult.

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 lactulose is excreted in milk, but it would be unexpected.

Overdosage/Acute Toxicity

Excessive doses may cause flatulence, diarrhea, cramping, and dehydration. Replace fluids and electrolytes if necessary.

Drug Interactions

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

- **ANTACIDS, ORAL:** Antacids (non-adsorbable) may reduce the colonic acidification effects (efficacy) of lactulose
- **LAXATIVES, OTHER:** Do not use lactulose with other laxatives as the loose stools that are formed can be falsely attributed to the lactulose with resultant inadequate therapy for hepatic encephalopathy
- **NEOMYCIN:** Theoretically, orally administered antibiotics (*e.g.*, neomycin) could eliminate the bacteria responsible for metabolizing lactulose, thereby reducing its efficacy. However, some data suggests that synergy may occur when lactulose is used with an oral antibiotic (*e.g.*, neomycin) for the treatment of hepatic encephalopathy; enhanced monitoring of lactulose efficacy is probably warranted in cases where an oral antibiotic is added to the therapy

Doses

- **DOGS:**

  For hepatic encephalopathy:
  a) 15–30 mL PO four times a day; adjust the dosage to produce 2–3 soft stools per day (Cornelius and Bjorling 1988)
  b) Give 5 mL per 2.5 lbs. of body weight divided three times a day, may increase as necessary to achieve 2–3 soft stools per day. If patient is in hepatic encephalopathy crisis, may give 20–60 mL via stomach tube every 4–6 hours or may give as an intermittent enema (diluted with water) to total 200–300 mL (300–450 grams). (Tams 2000)
  c) 5–15 mL PO three times daily; adjust dose to induce 2–3 soft stools per day; reduce dosage if diarrhea develops. In certain cases, neomycin with lactulose may be superior to either drug alone. (Hardy 1985)
  d) 1–10 mL PO three times daily; adjust dose to give 3–4 soft stools per day; reduce dose if diarrhea develops. May also give via enema in treating severe hepatic encephalopathy. (Twedt 2005a)

  For constipation:
  a) 1 mL per 4.5 kg of body weight PO q8h initially, then adjust as needed (Kirk 1986)

- **CATS:**

  For hepatic encephalopathy:
  a) 0.25–1 mL PO; individualize dosage until semi-formed stools are produced (Center, Hornbuckle, and Scavelli 1986)

  For constipation:
  a) 1 mL per 4.5 kg of body weight PO q8h initially, then adjust as needed (Kirk 1986)
  b) 0.5 mL/kg q8–12h PO (Sherding 1989); (Washabau and Holt 2000)

- **BIRDS:**

  For hepatic encephalopathy; to stimulate appetite, improve intestinal flora:
  a) Cockatiel: 0.03 mL PO two to three times a day; Amazon: 0.1 mL PO two to three times a day. Reduce dosage if diarrhea develops. May be used for weeks. (Clubb 1986)

- **REPTILES:**

  As a laxative:
  a) Green Iguana: 0.3 mL/kg PO q12h (Wilson 2002a)

Monitoring

- Clinical efficacy (2–3 soft stools per day) when used for PSE
- In long-term use (months) or in patients with preexisting fluid/electrolyte problems, serum electrolytes should be monitored.

Client Information

- Contact veterinarian if diarrhea develops.
- When lactulose is used for hepatic encephalopathy, contact veterinarian if signs worsen or less than 2–3 soft stools are produced per day.

Chemistry/Synonyms

A synthetic derivative of lactose, lactulose is a disaccharide containing one molecule of galactose and one molecule of fructose. It occurs as a white powder that is very slightly soluble in alcohol and very soluble in water. The commercially available solutions are viscous, sweet liquids with an adjusted pH of 3–7.

Lactulose may also be known as lactulosum; many trade names are available.

Storage/Stability

Lactulose syrup should be stored in tight containers, preferably at room temperature; avoid freezing. If exposed to heat or light, darkening or cloudiness of the solution may occur, but apparently this does not affect drug potency.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Lactulose Solution: 10 g lactulose per 15 mL (<1.6 g galactose, <1.2 g lactose and < or = to 1.2 g of other sugars) in 30 mL, 237 mL, 240 mL, 473 mL, 480 mL, 946 mL, 960 mL, 1893 mL, 1920 mL and 3785 mL, 1.89 L and 1.9 L, and UD 30 mL; *Cephulac*® (Hoechst-Marion Roussel); *Cholac*® (Alra); *Constulose*® and *Enulose*® (Alpharma); generic; (Rx)

Lactulose Crystals for Reconstitution: Lactulose (<0.3 g galactose and lactose/10 g) in 10 g and 20 g; *Kristalose*® (Bertek); (Rx)

LEFLUNOMIDE

(le-*floo*-noh-myde) Arava

IMMUNOMODULATING AGENT

Prescriber Highlights

- Immunomodulating drug that may be useful in dogs for treating a variety of immune-mediated conditions such as IMHA, systemic & cutaneous reactive histiocytosis, granulomatous meningoencephalitis, etc.; can be used as part of transplant rejection protocols in dogs. Has been used with methotrexate to treat rheumatoid arthritis in cats.
- Appears well-tolerated in dogs, but number treated is low
- Teratogenic (Category X)
- Active metabolite can persist in body for years
- Treatment can be very expensive

Uses/Indications

Leflunomide is an immunomodulating drug that may be useful in dogs for treating a variety of immune-related conditions such as IMHA, systemic and cutaneous reactive histiocytosis, granulomatous meningoencephalitis, etc; it can be used as part of transplant rejection protocols in dogs.

Leflunomide has been used with methotrexate to treat rheumatoid arthritis in cats.

Pharmacology/Actions

Leflunomide inhibits autoimmune T-cell proliferation and autoantibody production by B cells. Leflunomide acts almost exclusively via its active metabolite A77 1726 (M1). This metabolite reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase thereby preventing the formation of ribonucleotide uridine monophosphate (rUMP). This causes decreased DNA and RNA synthesis, inhibition of cell proliferation, and G1 cell cycle arrest.

Pharmacokinetics

Information on the pharmacokinetics of leflunomide in dogs and cats was not located. In humans, leflunomide is rapidly converted to A77 1726 (active metabolite; M1) in the GI mucosa and liver. Peak levels of A77 1726 occur between 6–12 hours after an oral dose. The presence of food in the gut does not appear to affect oral bioavailability. A77 1726 Is highly bound to albumin >99%). A77 1726 is further degraded in the liver as glucuronides and an oxalinic acid compound which are excreted in the urine and bile. Half life is about 15 days, but the drug (A77 1726) can be detectable in patients up to 2 years after it is discontinued.

Contraindications/Precautions/Warnings

Leflunomide is contraindicated during pregnancy and in patients hypersensitive to it. It should be used with extreme caution in patients with immunodeficiency.

Adverse Effects

Leflunomide appears to be well tolerated by dogs. Adverse effects reported include vomiting, lymphopenia, and anemia.

In humans, gastrointestinal effects (diarrhea, nausea), alopecia and rash are most commonly reported. Serious adverse effects that have been reported include hematologic toxicity, dermatologic effects (TEN, Stevens-Johnson, etc.), and hepatotoxicity.

Reproductive/Nursing Safety

Leflunomide should not be used during pregnancy. A variety of teratogenic effects in laboratory animals have been detailed at doses used clinically. In humans, the FDA categorizes this drug as category ***X*** for use during pregnancy (*Studies in animals or humans demonstrate fetal abnormalities or adverse reaction; reports indicate evidence of fetal risk. The risk of use in pregnant women clearly outweighs any possible benefit.*)

It is not known whether leflunomide is excreted in milk; it is suggested to use milk replacer if the dam is receiving the drug.

Overdosage/Acute Toxicity

Acute toxicologic studies in mice and rats have demonstrated that the minimally toxic dose is 200 mg/kg and 100 mg/kg, respectively. Cholestyramine or activated charcoal are recommended to accelerate elimination. Contact an animal poison control center for more information.

Drug Interactions

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

- **CHARCOAL, ACTIVATED:** Can increase elimination and decrease A77 1726 drug concentrations; may be used when more rapid elimination is desirable
- **CHOLESTYRAMINE:** Can increase elimination and decrease A77 1726 drug concentrations; may be used when more rapid elimination is desirable
- **HEPATOTOXIC AGENTS, OTHER:** Increased risk for toxicity
- **METHOTREXATE:** Increased adverse effects and ALT possible
- **PHENYTOIN:** Leflunomide can increase phenytoin levels
- **RIFAMPIN:** Can increase A77 1726 peak levels
- **VACCINES, LIVE VIRUS:** Live virus vaccines should be used with caution, if at all, during leflunomide therapy
- **WARFARIN:** Leflunomide may increase INR

Doses

- **DOGS:**
  a) As an immunosuppressive as part of a protocol (with cyclosporine) following organ transplant: Leflunomide 4–6 mg/kg PO q24h and then to maintain trough plasma levels of 20 mcg/mL. (Sykes 2007)
  b) As an adjunctive immunosuppressive for immune-mediated hemolytic anemia: 4 mg/kg PO q24h. (Chabanne 2006)
  c) For treatment of systemic and cutaneous reactive histiocytosis: 2–4 mg/kg PO once daily to attain trough levels of 20 mcg/mL. (Foil 2003a)
- **CATS:**
  a) For rheumatoid arthritis: Initially, leflunomide at 10 mg (total dose) PO once daily and methotrexate at 2.5 mg (total dose) PO three times on one day per week. When significant improvement occurs, reduce doses of leflunomide to 10 mg PO twice weekly and methotrexate to 2.5 mg PO once weekly. (Bennett 2005)

Monitoring

- Adverse effects (CBC, liver enzymes)
- Trough levels (20 mcg/mL is target)

Client Information

- Relatively experimental when used in veterinary patients; contact veterinarian if any unusual effects are noted
- Treatment can be very expensive