rats. While no teratogenic effects have been detected with ramipril in studies performed in mice, rats, rabbits, and cynomolgus monkeys, fetal risk is increased in humans.

If used in humans during the 2nd and 3rd trimesters increased rates of fetal death, neonatal hypotension, skull hypoplasia, anuria, renal failure, oligohydramnios leading to fetal limb contractures, craniofacial deformation, and hypoplastic lung development were noted. In humans, ramipril has a "black box" warning regarding its use in pregnancy that states "When used in pregnancy during the second and third trimesters, angiotensin-converting enzyme (ACE) inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ramipril should be discontinued as soon as possible." For humans, the FDA categorizes ramipril as category ***D*** for use during the 2nd and 3rd trimesters of 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)* and as category ***C*** for use during the first trimester of 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 ramipril (or ramiprilat) enters milk. Both the veterinary label (UK) and human label recommended not using the drug during nursing.

Overdosage/Acute Toxicity

In dogs, ramipril appears quite safe; dosages as high as 1 gram/kg induced only mild GI distress. Lethal doses in rats and mice were noted at 10–11 g/kg. No information was located on overdoses in cats. In overdose situations, the primary concern is hypotension; supportive treatment with volume expansion with normal saline is recommended to correct blood pressure. Because of the drug's long duration of action, prolonged monitoring and treatment may be required.

Drug Interactions

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

- **ASPIRIN**: Aspirin may potentially negate the decrease in systemic vascular resistance induced by ACE inhibitors. However, in one study in dogs using low-dose aspirin, hemodynamic effects of enalaprilat (active metabolite of enalapril, a related drug) were not affected.
- **ANTIDIABETIC AGENTS** (**insulin, oral agents**): Possible increased risk for hypoglycemia; enhanced monitoring recommended
- **DIURETICS** (*e.g.,* **furosemide, hydrochlorothiazide**): Potential for increased hypotensive effects
- **DIURETICS, POTASSIUM SPARING** (*e.g.,* **spironolactone, triamterene**): Increased hyperkalemic effects, enhanced monitoring of serum potassium
- **NSAIDS**: Potential for increased risk of renal dysfunction or hyperkalemia
- **POTASSIUM SUPPLEMENTS**: Increased risk for hyperkalemia

Laboratory Considerations

- ACE inhibitors may cause a reversible decrease in localization and excretion of **iodohippurate sodium I^{123}/I^{134}**, or **Technetium Tc^{99} pententate** renal imaging in the affected kidney in patients with renal artery stenosis, which could lead to confusion in test interpretation

Doses

DOGS:

a) For treatment of heart failure: Initially, 0.125 mg/kg PO once daily; depending on the severity of pulmonary congestion, dose may be increased to 0.25 mg/kg PO once daily (Label information; *Vasotop*®—Intervet UK)

CATS:

a) For treatment of arterial hypertension: 0.125 mg/kg PO once daily (Graff and Herve 2003)

Monitoring

- Clinical signs of CHF
- Serum electrolytes, creatinine, BUN, urine protein
- CBC with differential, periodic
- Blood pressure (if treating hypertension or clinical signs associated with hypotension arise)

Client Information

- For this drug to be maximally effective it must be given once daily at about the same time each day
- Do not abruptly stop or reduce therapy without veterinarian's approval
- Contact veterinarian if vomiting or diarrhea persist, are severe, or if animal's condition deteriorates

Chemistry/Synonyms

Ramipril occurs as a white to almost white, crystalline powder that is sparingly soluble in water and freely soluble in methyl alcohol.

Ramipril may also be known as Hoe-498, ramiprilis, or ramiprilium. There are many international trade names, including: *Altace*®, *Cardase*®, *Delix*®, *Ramase*®, *Triatec*®, and *Tritace*®.

Storage/Stability

Capsules should be stored at room temperature (15–30°C) protected from light in tight containers.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

None in the USA; in the UK and in other European countries: Ramipril Tablets: 0.625 mg, 1.25 mg, 2.5 mg, & 5 mg; *Vasotop*® (Intervet); (Rx). Approved for use in dogs.

HUMAN-LABELED PRODUCTS:

Ramipril Capsules: 1.25 mg, 2.5 mg, 5 mg, & 10 mg; *Altace*® (Monarch); (Rx)

RANITIDINE HCL

(rah-*nit*-a-deen) Zantac®

H_2 RECEPTOR ANTAGONIST; PROKINETIC

Prescriber Highlights

- **H_2 receptor antagonist similar to cimetidine, but fewer drug interactions; used to reduce acid output in stomach; also has prokinetic activity**
- **Contraindications: Hypersensitivity. Caution: Geriatric patients, hepatic or renal insufficiency**
- **Adverse Effects: Rare. IV boluses may cause vomiting. Potentially: Mental confusion, agranulocytosis, & transient cardiac arrhythmias (too rapid IV injection). Pain at the injection site after IM administration.**

Uses/Indications

In veterinary medicine, ranitidine has been used for the treatment and/or prophylaxis of gastric, abomasal, and duodenal ulcers, uremic gastritis, stress-related or drug-induced erosive gastritis, esophagitis, duodenal gastric reflux and esophageal reflux. It has also been employed to treat hypersecretory conditions associated with gastrinomas and systemic mastocytosis. Because of its effects on gastric motility, ranitidine may be useful in increasing gastric emptying, particularly when delayed gastric emptying is associated with gastric ulcer disease. Ranitidine may also be useful to stimulate colonic activity in cats via its prokinetic effects.

Pharmacology/Actions

At the H_2 receptors of the parietal cells, ranitidine competitively inhibits histamine, thereby reducing gastric acid output both during basal conditions and when stimulated by food, amino acids, pentagastrin, histamine, or insulin. Ranitidine is between 3–13 times more potent (on a molar basis) as cimetidine.

While ranitidine may cause gastric emptying times to be delayed, it more likely will stimulate GI motility by inhibiting acetylcholinesterase (thereby increasing acetylcholine at muscarinic receptors). Lower esophageal sphincter pressures may be increased by ranitidine. By decreasing the amount of gastric juice produced, ranitidine decreases the amount of pepsin secreted.

Ranitidine, unlike cimetidine, does not appear to have any appreciable effect on serum prolactin levels, although it may inhibit the release of vasopressin.

Pharmacokinetics

In dogs, the oral bioavailability is approximately 81%, serum half-life is 2.2 hours and volume of distribution 2.6 L/kg.

In horses, oral ranitidine has a bioavailability of about 27% in adults and 38% in foals. Peak levels after oral dosing occur in about 100 minutes in adults and 60 minutes in foals. Apparent volume of distribution is approximately 1.1 L/kg and 1.5 L/kg in adults and foals, respectively. Clearance in adults is approximately 10 mL/min/kg and 13.3 mL/min/kg in foals.

In humans, ranitidine is absorbed rapidly after oral administration, but undergoes extensive first-pass metabolism with a net systemic bioavailability of approximately 50%. Peak levels occur at about 2–3 hours after oral dosing. Food does not appreciably alter the extent of absorption or the peak serum levels attained.

Ranitidine is distributed widely throughout the body and is only 10–19% bound to plasma proteins. Ranitidine is distributed into human milk at levels 25–100% of those found in plasma.

Ranitidine is both excreted in the urine by the kidneys (via glomerular filtration and tubular secretion) and metabolized in the liver to inactive metabolites; accumulation of the drug can occur in patients with renal insufficiency. The serum half-life of ranitidine in humans averages 2–3 hours. The duration of action at usual doses is from 8–12 hours.

Contraindications/Precautions/Warnings

Ranitidine is contraindicated in patients who are hypersensitive to it. It should be used cautiously and possibly at reduced dosage in patients with diminished renal function. Ranitidine has caused increased serum ALT levels in humans receiving high, IV doses for longer than 5 days. The manufacturer recommends that with high dose, chronic therapy, serum ALT values be considered for monitoring.

Adverse Effects

Adverse effects appear to be very rare in animals at the dosages generally used. Potential adverse effects (documented in humans) that might be seen include mental confusion and headache. Rarely, agranulocytosis may develop and, if given rapidly IV, transient cardiac arrhythmias may be seen. Pain at the injection site may be noted after IM administration. IV boluses have been associated with vomiting in small 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.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as class: ***B*** (*Safe for use if used cautiously. Studies in laboratory animals may have uncovered some risk, but these drugs appear to be safe in dogs and cats or these drugs are safe if they are not administered when the animal is near term.*)

Ranitidine is excreted in human breast milk with milk:plasma ratios of approximately 5:1 to 12:1. The drug is not recommended to be used in nursing humans; use with caution in nursing veterinary patients.

Overdosage/Acute Toxicity

Clinical experience with ranitidine overdosage is limited. In laboratory animals, very high dosages (225 mg/kg/day) have been associated with muscular tremors, vomiting and rapid respirations. Single doses of 1 gram/kg in rodents did not cause death.

Treatment of overdoses in animals should be handled using standard protocols for oral ingestions of drugs; clinical signs may be treated symptomatically and supportively if necessary. Hemodialysis and peritoneal dialysis have been noted to remove ranitidine from the body.

Drug Interactions

Unlike cimetidine, ranitidine appears to have much less effect on the hepatic metabolism of drugs and is unlikely to cause clinically relevant drug interactions via this mechanism. The following drug interactions have either been reported or are theoretical in humans or animals receiving ranitidine and may be of significance in veterinary patients:

- **ACETAMINOPHEN**: Ranitidine (dose-dependent) may inhibit acetaminophen metabolism
- **ANTACIDS** (high doses): May decrease the absorption of ranitidine; give at separate times (2 hours apart) if used concurrently
- **KETOCONAZOLE, ITRACONAZOLE**: Absorption may be reduced secondary to increased gastric pH
- **METOPROLOL**: Ranitidine may increase metoprolol half-life, and peak levels
- **NIFEDIPINE**: Ranitidine may increase nifedipine AUC by 30%
- **PROPANTHELINE**: Delays the absorption but increases the peak serum level of ranitidine; relative bioavailability of ranitidine may be increased by 23% when propantheline is administered concomitantly with ranitidine
- **VITAMIN B-12**: Long-term ranitidine use may reduce oral absorption of B-12

Laboratory Considerations

- Ranitidine may cause a false-positive **urine protein** reading when using *Multistix*®. The sulfosalicylic acid reagent is recommended for determining urine protein when the patient is concomitantly receiving ranitidine.

Doses

■ **DOGS:**

For esophagitis:
a) 1–2 mg/kg PO twice daily (Watrous 1988)

For chronic gastritis:
a) 0.5 mg/kg PO twice daily (Hall and Twedt 1988)

For ulcer disease:
a) 0.5–2 mg/kg PO, IV or IM q8–12h (Haskins 2000)
b) 2 mg/kg PO, IV q8h (Matz 1995)
c) 1–2 mg/kg PO, IV, SC q12h (also used for esophagitis) (Sellon 2007b)
d) 2 mg/kg PO, IV q12h (Waddell 2007a)

For gastrinoma:
a) 1–2 mg/kg PO, SC, IV q8–12h (Zerbe and Washabau 2000)
b) 0.5 mg/kg PO, IV or SC twice daily (Kay, Kruth, and Twedt 1988)

To treat hypergastrinemia secondary to chronic renal failure:
a) 1–2 mg/kg PO twice daily (Morgan 1988)

To treat hyperhistaminemia secondary to mast cell tumors:
a) 2 mg/kg q12h (Fox 1995)

As a prokinetic agent to stimulate gastric contractions:
a) 1–2 mg/kg PO q12h (Hall and Washabau 2000)

■ **CATS:**

For ulcer disease/esophagitis::
a) 2.5 mg/kg IV q12h or 3.5 mg/kg PO q12h (Matz 1995), (Johnson 1996)
b) 1–2 mg/kg PO, IV, SC q12h (Sellon 2007b)
c) 2 mg/kg PO, IV q12h (Waddell 2007a)

As a prokinetic agent to stimulate colonic motility:
a) 1–2 mg/kg PO q8–12h (Washabau and Holt 2000)
b) 1–2 mg/kg PO q12h (Scherk 2003b)

■ **HORSES:** (**Note:** ARCI UCGFS Class 5 Drug)
a) 6.6 mg/kg PO q8h (Andrews and Nadeau 1999)
b) Foals: 6.6 mg/kg IV q4h *or* 0.8–2.2 mg/kg IV four times a day; 5–10 mg/kg PO two to four times a day. (Wilkins 2004b)
c) 1.5–2 mg/kg IV or IM q6–8h; 6.6 mg/kg PO q8h (Sanchez 2004a)

Monitoring

■ Clinical efficacy (dependent on reason for use); monitored by decrease in clinical signs, endoscopic examination, blood in feces, etc.

Client Information

■ To maximize the benefit of this medication, it must be administered as prescribed by the veterinarian; symptoms may reoccur if dosages are missed.

Chemistry/Synonyms

An H_2 receptor antagonist, ranitidine HCl occurs as a white to pale-yellow granular substance with a bitter taste and a sulfur-like odor. The drug has pK_as of 8.2 and 2.7. One gram is approximately soluble in 1.5 mL of water or 6 mL of alcohol. The commercially available injection has a pH of 6.7–7.3.

Ranitidine HCl may also be known as: AH-19065, ranitidini hydrochloridum; many trade names are available.

Storage/Stability

Ranitidine tablets should be stored in tight, light-resistant containers at room temperature. The injectable product should be stored protected from light and at a temperature less than 30°C. A slight darkening of the injectable solution does not affect the potency of the drug.

Ranitidine injection is reportedly stable up to 48 hours when mixed with the commonly used IV solutions (including 5% sodium bicarbonate).

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 5 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Ranitidine HCl Tablets: 75 mg, 150 mg & 300 mg (as base); *Zantac®* (GlaxoSmithKline); (Rx); *Zantac® 75 & -150* (Pfizer Consumer Healthcare); generic; (Rx or OTC)

Ranitidine HCl Effervescent Tablets: 25 mg & 150 mg (as base); *Zantac® EFFERdose* (GlaxoSmithKline); (Rx)

Ranitidine HCl Syrup: 15 mg/mL (as base) in 480 mL; *Zantac®* (GlaxoSmithKline); (Rx)

Ranitidine HCl Injection: 1 mg/mL (premixed) & 25 mg/mL in 50 mL (preservative free) plastic containers, 2 mL single-dose and 6 mL multi-dose vials; *Zantac®* (GlaxoSmithKline); generic (Bedford); (Rx)

RIFAMPIN

(***rif***-am-pin) **Rifadin®, Rimactane®**

ANTIMICROBIAL

Prescriber Highlights

- **Antimicrobial with activity against a variety of microbes (Rhodococcus, mycobacteria, staphylococci); has some antifungal & antiviral activity as well.**
- **Contraindications: Hypersensitivity to it or other rifamycins**
- **Caution: Preexisting hepatic dysfunction (may need to reduce dosage)**
- **Adverse Effects: Uncommon; potentially rashes, GI distress, & increases in liver enzymes.**
- **Should not be used alone as resistance develops rapidly**
- **Preferably, give on an empty stomach**
- **May cause red/orange urine, tears, & sweat (harmless)**
- **Drug Interactions, lab interactions**

Uses/Indications

The principle use of rifampin in veterinary medicine is in the treatment of *Rhodococcus equi* (*Corynebacterium equi*) infections (usually with erythromycin estolate) in young horses. It may also be useful to treat proliferative enteropathy caused by *Lawsonia intracellularis* in foals.

In small animals, the drug is sometimes used in combination with other antifungal agents (amphotericin B and 5-FC) in the treatment of histoplasmosis or aspergillosis with CNS involvement.