c) For adjunctive treatment of Nocardiosis, Actinomycosis: 5–25 mg/kg PO, IV q12h (Lemarie 2003a)

d) For Brucillosis in animals that are housed singly and neutered: Minocycline at 25 mg/kg PO once daily for 14 days with dihydrostreptomycin (**Note:** not currently available in the USA) at 5 mg/kg IM twice daily for 7 days. (Root Kustritz 2007)

■ **CATS:**

a) For hemotropic mycoplasmosis: 6–11 mg/kg PO q12h for 21 days. (Greene, Hartmannn et al. 2006)

b) For adjunctive treatment atypical mycobacterial dermal infections: 5–12.5 mg/kg PO, IV q12h (Hnilica 2003a)

c) For adjunctive treatment of Nocardiosis, Actinomycosis: 5–25 mg/kg PO, IV q12h (Lemarie 2003a)

Monitoring

■ Clinical efficacy

■ Adverse effects

Client Information

■ Oral minocycline products may be administered without regard to feeding. Milk or other dairy products do not significantly alter the amount of minocycline absorbed.

■ Give as prescribed for as long as veterinarian recommends even if animal appears well.

Chemistry/Synonyms

A semisynthetic tetracycline, minocycline HCl occurs as a yellow, crystalline powder. It is soluble in water and slightly soluble in alcohol.

Minocycline may also be known as: minocyclini hydrochloridum, *Asolmicina®*, *Cyclimycin®*, *Cyclomin®*, *Dermirex®*, *Meibi®*, *Minogal®*, and *Minox®*; many other trade names are available.

Storage/Stability/Compatibility

Store the oral preparations at room temperature in tight containers. Do not freeze the oral suspension. The injectable should be stored at room temperature and protected from light. After reconstituting with sterile water for injection, solutions with a concentration of 20 mg/mL are stable for 24 hours at room temperature.

While minocycline is **compatible** with the usual intravenous fluids (including Ringer's and lactated Ringer's) do not add any other calcium containing fluid as precipitation could result.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Minocycline HCl Tablets: 50 mg, 75 mg, 100 mg; Extended-Release: 45 mg, 90 mg & 135 mg; Minocycline HCl (Par); *Dynacin®* (Medicis); *Myrac®* (Glades); *Solodyn®* (Medicis); (Rx)

Minocycline HCl Capsules: 50 mg, 75 mg, 100 mg; *Minocin®* (Lederle); *Dynacin®* (Medicis); generic; (Rx)

Minocycline HCl Oral Suspension: 50 mg/5 mL in 60 mL; *Minocin®* (Lederle); (Rx)

Minocycline HCl Powder for Injection cryodessicated: 100 mg per vial; *Minocin®* (Triax); (Rx)

Minocycline HCl Microspheres, Sustained-Release: 1 mg; *Arestin®* (Cord Logistics); (Rx)

MIRTAZAPINE

(mir-*taz*-ah-peen) Remeron®

TETRACYCLIC ANTIDEPRESSANT; 5-HT3 ANTAGONIST

Prescriber Highlights

- Used in veterinary medicine primarily as an appetite stimulant & antiemetic in dogs & cats
- Can be used in conjunction with other antiemetics
- Primary side effect is sedation
- Use lowest effective dose to reduce sedative properties
- Do not exceed 30 mg per day when used for appetite stimulation

Monograph by Dinah Jordan, PharmD, DICVP

Uses/Indications

Currently, the only FDA approved indication for mirtazapine is depression in humans. Reported veterinary uses include treatment of chemotherapy-induced nausea and vomiting (CINV); anorexia associated with renal failure (azotemia), congestive heart failure, gastro-intestinal disorders, liver disease, or neoplasia. Other uses suggested include stress induced diseases; insomnia; post-pyometra symptoms; and post-operative inappetance. Studies have shown that mirtazapine also alleviated sleep apnea in rats and humans.

There are case reports published in human literature of mirtazapine use as treatment for non-mechanical vomiting after gastric bypass, CINV, obsessive-compulsive disorder, nocioception and chronic pain, migraine headache prophylaxis, anti-psychotic induced akathisia, idiopathic nausea and vomiting, serotonin syndrome induced nausea, anorexia, irritable bowel syndrome, resistant hyperemesis gravidarum, and for the treatment of negative symptoms of schizophrenia. Studies in rats have also shown that mirtazapine significantly improves memory.

Pharmacology/Actions

The antidepressant activity of mirtazapine appears to be mediated by antagonism at central pre-synaptic alpha2-receptors, which normally act as a negative feedback mechanism that inhibits further norepinephrine (NE) release. By blocking these receptors, mirtazapine overcomes the negative feedback loop and results in a net increase in NE. This mechanism may also contribute to the appetite stimulating effects of the medication since NE acts at other a-receptors to increase appetite. Additionally, mirtazapine antagonizes several serotonin (5HT) receptor subtypes. The drug is a potent inhibitor of the $5HT_2$ and $5HT_3$ receptors and of histamine (H_1) receptors. Antagonism at the $5HT_3$ receptors accounts for the anti-nausea and antiemetic effects of the drug, and its action at H_1-receptors produces prominent sedative effects. It is a moderate peripheral alpha$_1$ adrenergic antagonist, a property that may explain the occasional orthostatic hypotension associated with its use; it is a moderate antagonist of muscarinic receptors, which may explain the relatively low incidence of anticholinergic effects.

Pharmacokinetics

Complete pharmacokinetic information has not been published for dogs and cats to date. Following oral administration in humans, mirtazapine is rapidly and completely absorbed. Studies in rats showed a linear relationship between the effects of mirtazap-

ine and measured plasma and brain concentrations. Peak plasma concentrations are reached within about 2 hours after an oral dose in humans. Food has minimal effects on both the rate and extent of absorption and does not require adjustments in the dose. Oral bioavailability of mirtazapine is about 20% for rats and dogs, and about 50% for humans.

Mirtazapine is metabolized via multiple pathways and varies by species. In all species tested (humans and laboratory animals), the drug was metabolized via the following mechanisms: 8-hydroxlaton followed by conjugation, N-oxidation, and demethylation followed by conjugation. Humans and guinea pigs also produce metabolites via N+-glucuronidation, whereas mice were the only species found to utilize demethylation followed by CO2 addition and conjugation, and 13-hydroxylation followed by conjugation as methods of mirtazapine breakdown. These processes are conducted primarily by CYP2D6, CYP1A2, and CYP3A4, yet mirtazapine exerts minimal inhibition on any of these cytochromes. Several metabolic pathways of mirtazapine involve conjugation with glucuronide (glucuronidation). Since cats have a limited capacity for glucuronidation, mirtazapine is cleared less rapidly from the system and, therefore, an extended dosing interval is required.

It is estimated that the active metabolite of mirtazapine contributes only 3–6% of the total pharmacodynamic profile of the drug since it is approximately 10-fold less active than mirtazapine and affects the AUC minimally. Therefore, only the levels of the parent compound are considered clinically relevant.

The extent of binding of drugs to plasma proteins sometimes differs considerably among animal species. Plasma protein binding (PPB) for mirtazapine appears to be approximately 70–72% for mice, rats, and dogs, whereas for humans and rabbits it is approximately 85%. Despite the interspecies differences in PPB, no displacement interactions or dosage adjustments for mirtazapine are expected due to its large therapeutic window and nonspecific and relative low affinity for plasma proteins.

Human literature documents that elimination occurs via the urine (75%) and the feces (15%), renal impairment may reduce elimination by 30–50% compared to normal subjects, and hepatic impairment may reduce clearance by up to 30%. Human studies show the elimination half-life of mirtazapine to be long and range from 20–40 hours across age and gender subgroups, so dosage increases should take place no sooner than every 7–14 days. Females (both human and animal) of all ages exhibit significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs. 26 hours for males in humans).

Contraindications/Precautions/Warnings

Mirtazapine is contraindicated in patients with hypersensitivity to mirtazapine or who have taken monoamine oxidase inhibitors (*e.g.*, selegiline) in the past 14 days.

Mirtazapine has been associated with orthostatic hypotension in humans and should, therefore, be used with caution in patients with known cardiac disease or cerebrovascular disease that could be exacerbated by hypotension. Patients with renal impairment, renal failure, or hepatic disease should be monitored while on mirtazapine therapy.

Abrupt discontinuation of mirtazapine after long-term administration has resulted in withdrawal symptoms such as nausea, headache and malaise in humans. In general, antidepressants may affect blood glucose concentrations because of their indirect effects on the endocrine system; use with caution in patients with diabetes mellitus.

Mirtazapine exhibits very weak anticholinergic activity, consequently, vigilance should be used in patients who might be more susceptible to these effects, such as those with urinary retention, prostatic hypertrophy, acute, untreated closed-angle glaucoma or increased intraocular pressure, or GI obstruction or ileus. Also, effects of mirtazapine may be additive to anticholinergic medications.

Extra care should be taken with active animals as mirtazapine may impair concentration and alertness. Although extremely rare, mirtazapine has been associated with blood dyscrasias in humans and should be used cautiously in patients with pre-existing hematological disease, especially leukopenia, neutropenia, or thrombocytopenia.

Adverse Effects

Mirtazapine appears to be well tolerated in both dogs and cats, but use has been limited and controlled trials are lacking. Besides the desirable side effect of appetite stimulation, other currently reported side effects in animals include drowsiness/sedation, vocalization, hypotension, tachycardia (all dose-dependent).

Reproductive/Nursing Safety

In humans, mirtazapine is FDA pregnancy category ***C*** (*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*). However, reproductive studies in rats, rabbits, and dogs have shown no evidence of teratogenicity. Additional studies in hamsters, rabbits, and rats showed no evidence of fetal genetic mutation or reduction in parental fertility, although there were increases in post-implantation losses and pup deaths, as well as decreased pup birth weight. No fetal harm was reported in any of several case reports of mirtazapine use during pregnancy nor in animal studies.

In animals, mirtazapine is excreted in very small amounts in milk, the implications of which are currently unknown; consequently, it may be prudent to use caution in nursing mothers. Mirtazapine is distributed into human breast milk and safe use in humans during nursing cannot be assured. In one case report mirtazapine concentrations were detected in breast milk, but the examining neuropediatrician detected no adverse effects (including weight gain or sedation) in the infant.

Overdosage/Acute Toxicity

Mirtazapine ingestion of upwards of 10-fold therapeutic dose in humans exhibits minimal toxicity requiring no acute intervention and only 6 hours of observation. Similar effects were seen in patients receiving up to 30 times the recommended dose. Despite these reports, the package insert for mirtazapine recommends that activated charcoal be administered in addition to other standard monitoring activities in an overdose situation.

Drug Interactions

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

- **CLONIDINE:** Mirtazapine may cause increases in blood pressure
- **DIAZEPAM** (and other **benzodiazepines**): Minimal effects on mirtazapine blood levels, but may cause additive impairment of motor skills
- **FLUVOXAMINE:** May cause increased serum concentrations of mirtazapine
- **LINEZOLID:** Increased risk for serotonin syndrome
- **SELEGILINE, AMITRAZ:** Increased risk for serotonin syndrome; MAO inhibitors considered contraindicated with mirtazapine
- **TRAMADOL:** Increased risk for serotonin syndrome

In vitro studies identify mirtazapine as a substrate for several hepatic cytochrome CYP450 isoenzymes including 2D6, 1A2, and 3A4. Mirtazapine is not a potent inhibitor of any of these enzymes; clini-

cally significant pharmacokinetic interactions are not likely with drugs metabolized by CYP enzymes.

Laboratory Considerations
No specific concerns noted.

Doses
Since no safety or efficacy trials have been performed in animals to date, currently recommended doses are based on extrapolations from human medicine and clinical experience in veterinary practice. According to the product package insert and several anecdotal reports, no adjustment is needed in liver disease or kidney dysfunction, although starting at the lower end of the dosage range and titrating up if needed is recommended in such situations.

Note: At doses exceeding 30 mg per day, mirtazapine loses its appetite stimulating properties in humans. Since the ceiling dose for cats and dogs is not currently known, total daily doses ≤30 mg are recommended for appetite stimulation depending upon the weight of the pet.

- **DOGS:**

As an appetite stimulant and/or antiemetic:

a) 0.6 mg/kg PO q 24 h not to exceed 30 mg per day for appetite stimulation (Jordan 2007)
   Dogs <20 lb. = 3.75 mg PO q24h;
   21–50 lb. = 7.5 mg PO q 24h;
   50–75 lb. = 15 mg PO q24h;
   >75 lb. = 15 mg PO q12h or 30 mg PO q24h (once daily) (Jordan 2007)

- **CATS:**

As an appetite stimulant and/or antiemetic:

a) 3.75 mg PO q72h (every 3 days) (Jordan 2007)
b) 3 mg per cat PO q72h (every 3 days) (Churchill 2006)
c) 3–4 mg per cat PO q72h (every 3 days) (Scherk 2006)

Monitoring
- Clinical efficacy measured by the following parameters: increased appetite, decreased episodes of vomiting, and weight gain
- Adverse Effects

Client Information
- Give only the prescribed dose.
- Report excessive drowsiness or vocalization to your veterinarian.
- If your pet is receiving the orally disintegrating tablets, make sure hands are dry before handling the tablet. Place the tablet under the animal's tongue and hold mouth closed for several seconds to allow it to dissolve (should occur quickly). After the tablet has melted, offer the patient water.
- May be given without regard to food.

Chemistry/Synonyms
A member of the piperazino-azepine group of compounds, mirtazapine is classified as an atypical tetracyclic antidepressant and is not chemically related to other antidepressants. Mirtazapine, with a molecular weight of 265.36, occurs as a white to creamy white crystalline powder that is slightly soluble in water.

Mirtazapine may also be known as 6-azamianserin, Org-3770, mepirzapine and *Remeron*®; many trade names for international products are available.

Storage/Stability
The coated tablets and the orally disintegrating tablets should be stored at 25°C (77°F) with excursions permitted to 15–30°C (59–86°F). Protect from light and moisture. The stability of the orally disintegrating tablets once removed from the tablet blister is unknown and immediate use is recommended.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Mirtazapine Oral Tablets: 7.5 mg 15 mg, 30 mg, 45 mg; *Remeron*® (Organon), generic; (Rx)

Mirtazapine Orally Disintegrating Tablets: 15 mg, 30 mg, 45 mg; *Remeron SolTab*® (Organon), generic; (Rx)

MISOPROSTOL

(mye-soe-***prost***-ole) Cytotec®

PROSTAGLANDIN E_1 ANALOG

Prescriber Highlights
- Prostaglandin E_1 analog for treating or preventing gastric ulcers, especially associated with NSAIDs; may also be useful as an abortifacient, & to treat atopy or cyclosporine-induced nephrotoxicity
- Contraindications: Pregnancy, nursing mothers (diarrhea in the nursing offspring)
- Caution: Sensitivity to prostaglandins or prostaglandin analogs; patients with cerebral or coronary vascular disease
- Adverse Effects: GI distress (diarrhea, abdominal pain, vomiting, & flatulence); Potentially, uterine contractions & vaginal bleeding in female dogs
- Pregnant women should handle with caution

Uses/Indications
Misoprostol may be useful as primary or adjunctive therapy in treating or preventing gastric ulceration, especially when caused or aggravated by non-steroidal antiinflammatory drugs (NSAIDs). Misoprostol is most useful to prevent GI ulceration or GI adverse effects (anorexia, vomiting) associated with NSAID therapy. While it can be used for treating gastric ulcers, other drugs are probably just as effective and less expensive. It does not appear to be very effective in reducing gastric ulceration secondary to high dose corticosteroid therapy

Misoprostol may be efficacious in reducing or reversing cyclosporine-induced nephrotoxicity. More data is needed to confirm this effect.

One study demonstrated that misoprostol can reduce the clinical signs associated with atopy somewhat in dogs.

Misoprostol's effects on uterine contractibility and cervical softening/opening make it effective as an adjunctive treatment in pregnancy termination.

Pharmacology/Actions
Misoprostol has two main pharmacologic effects that make it a potentially useful agent. By a direct action on parietal cells, it inhibits its basal and nocturnal gastric acid secretion as well as gastric acid