CIPROFLOXACIN

(sip-roe-***flox***-a-sin) Cipro®

FLUOROQUINOLONE ANTIBIOTIC

Prescriber Highlights

- Human-label fluoroquinolone antibiotic
- In dogs, oral bioavailability lower than enrofloxacin
- Available as a true IV product
- Contraindications: Hypersensitivity. Relatively contraindicated for young, growing animals due to cartilage abnormalities
- Caution: Hepatic or renal insufficiency, dehydration
- Adverse Effects: GI distress, CNS stimulation, crystalluria, & hypersensitivity
- Administer PO preferably on an empty stomach
- Drug interactions

Uses/Indications

Because of its similar spectrum of activity, ciprofloxacin could be used as an alternative to enrofloxacin when a larger oral dosage form or intravenous product is desired. But the two compounds cannot be considered equivalent because of pharmacokinetic differences (see below).

Pharmacology/Actions

Ciprofloxacin is a bactericidal and a concentration dependent agent, with susceptible bacteria cell death occurring within 20–30 minutes of exposure. Ciprofloxacin has demonstrated a significant post-antibiotic effect for both gram-negative and gram-positive bacteria and is active in both stationary and growth phases of bacterial replication. Its mechanism of action is not thoroughly understood, but it is believed to act by inhibiting bacterial DNA-gyrase (a type-II topoisomerase), thereby preventing DNA supercoiling and DNA synthesis.

Both enrofloxacin and ciprofloxacin have similar spectrums of activity. These agents have good activity against many gram-negative bacilli and cocci, including most species and strains of P*seudomonas aeruginosa, Klebsiella* spp., *E. coli,* Enterobacter, Campylobacter, Shigella, Salmonella, Aeromonas, Haemophilus, Proteus, Yersinia, Serratia, and Vibrio species. Of the currently commercially available quinolones, ciprofloxacin and enrofloxacin have the lowest MIC values for the majority of these pathogens treated. Other organisms that are generally susceptible include *Brucella* spp. *Chlamydia trachomatis,* Staphylococci (including penicillinase-producing and methicillin-resistant strains), Mycoplasma, and *Mycobacterium* spp. (not the etiologic agent for Johne's disease).

The fluoroquinolones have variable activity against most Streptococci and are not usually recommended for use in treating these infections. These drugs have weak activity against most anaerobes and are ineffective in treating anaerobic infections.

Resistance does occur by mutation, particularly with *Pseudomonas aeruginosa, Klebsiella pneumonia,* Acinetobacter, and enterococci, but plasmid-mediated resistance does not seem to occur.

Pharmacokinetics

Both enrofloxacin and ciprofloxacin are well absorbed after oral administration in most species; in dogs however, enrofloxacin's bioavailability is at least twice that of ciprofloxacin after oral dosing. In humans, the oral bioavailability of ciprofloxacin has been reported to be between 50–85%. Studies of the oral bioavailability in ponies have shown that ciprofloxacin is poorly absorbed (2–12%) while enrofloxacin in foals apparently is well absorbed.

In humans, the volume of distribution in adults for ciprofloxacin is about 2–3.5 L/kg and it is approximately 20–40% bound to serum proteins.

Ciprofloxacin is one of the metabolites of enrofloxacin. Approximately 15–50% of the drugs are eliminated unchanged into the urine by both tubular secretion and glomerular filtration. Enrofloxacin/ciprofloxacin are metabolized to various metabolites that are less active than the parent compounds. Approximately 10–40% of circulating enrofloxacin is metabolized to ciprofloxacin in most species. These metabolites are eliminated in both the urine and feces. Because of the dual (renal and hepatic) means of elimination, patients with severely impaired renal function may have slightly prolonged half-lives and higher serum levels but may not require dosage adjustment.

The pharmacokinetics of ciprofloxacin has been studied in dogs, calves, and pigs. Oral bioavailability is approximately 50% in calves and 40% (only one pig studied) in pigs and it has an elimination half-life of about 2.5 hours in both species. Protein binding was significantly different for each species, with calves having about 70% of the drug bound and pigs only about 23% bound to plasma proteins. Elimination half-life is reported to be about 2.5 hours in dogs.

Contraindications/Precautions/Warnings

Ciprofloxacin, as is enrofloxacin, should be considered contraindicated in small and medium breed dogs from 2–8 months of age. Bubble-like changes in articular cartilage have been noted when the drug was given at 2–5 times recommend doses for 30 days, although clinical signs have only been seen at the 5X dose. To avoid cartilage damage, large and giant breed dogs may need to wait longer than the recommended 8 months since they may be in the rapid-growth phase past 8 months of age. Quinolones are also contraindicated in patients hypersensitive to them.

Because ciprofloxacin has occasionally been reported to cause crystalluria, animals should not be allowed to become dehydrated during therapy with either ciprofloxacin or enrofloxacin. In humans, ciprofloxacin has been associated with CNS stimulation and should be used with caution in patients with seizure disorders. Patients with severe renal or hepatic impairment may require dosage adjustments to prevent drug accumulation.

Use high dose ciprofloxacin in cats with caution. No reports of retinal toxicity (as can be seen with high dose enrofloxacin) secondary to ciprofloxacin in cats were located and retinal toxicity appears to be less likely since it is less lipophilic than enrofloxacin; however caution is advised.

Adverse Effects

With the exception of potential cartilage abnormalities in young animals (see Contraindications above), the adverse effect profile of fluoroquinolones appears to be minimal. GI distress (vomiting, anorexia) is the most frequently, yet uncommon, reported adverse effect. Although not reported thus far in animals, hypersensitivity reactions, crystalluria, and CNS effects (dizziness, stimulation) could potentially occur.

Reproductive/Nursing Safety

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.*)

Ciprofloxacin is distributed into milk, but oral absorption should be negligible. No adverse effects have been reported in nursing human infants of mothers receiving ciprofloxacin.

Overdosage

Little specific information is available. See the enrofloxacin monograph for more information.

Drug Interactions

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

- **ANTACIDS/DAIRY PRODUCTS** containing cations (Mg^{++}, Al^{+++}, Ca^{++}) may bind to ciprofloxacin and prevent its absorption; separate doses of these products by at least 2 hours from ciprofloxacin
- **ANTIBIOTICS, OTHER** (**aminoglycosides, 3rd-generation cephalosporins, penicillins—extended-spectrum**: Synergism may occur, but is not predictable, against some bacteria (particularly *Pseudomonas aeruginosa*) with these compounds. Although enrofloxacin/ciprofloxacin has minimal activity against anaerobes, *in vitro* synergy has been reported when used with **clindamycin** against strains of Peptostreptococcus, Lactobacillus and *Bacteroides fragilis*.
- **CYCLOSPORINE**: Fluoroquinolones may exacerbate the nephrotoxicity, and reduce the metabolism of, cyclosporine (used systemically)
- **GLYBURIDE**: Severe hypoglycemia possible
- **IRON, ZINC** (**oral**): Decreased ciprofloxacin absorption; separate doses by at least two hours
- **METHOTREXATE**: Increased MTX levels possible with resultant toxicity
- **NITROFURANTOIN**: May antagonize the antimicrobial activity of the fluoroquinolones; concomitant use is not recommended
- **PHENYTOIN**: Ciprofloxacin may alter phenytoin levels
- **PROBENECID**: Blocks tubular secretion of ciprofloxacin and may increase its blood level and half-life
- **SUCRALFATE**: May inhibit absorption of ciprofloxacin; separate doses of these drugs by at least 2 hours
- **THEOPHYLLINE**: Ciprofloxacin may increase theophylline blood levels
- **WARFARIN**: Potential for increased warfarin effects

Laboratory Considerations

- In some human patients, the fluoroquinolones have caused increases in **liver enzymes, BUN,** and **creatinine** and decreases in **hematocrit**. The clinical relevance of these mild changes is not known at this time.

Doses

- **DOGS:**

  For susceptible infections:

  a) 5–15 mg/kg PO q12h; Avoid or reduce dosage of these drugs in animals with severe renal failure; avoid in young animals or in pregnant or breeding animals. (Vaden and Papich 1995)

  b) For UTI: 10 mg/kg PO once daily (q24h) for 7–14 days

  For skin, soft tissue infections: 10–15 mg/kg PO once daily (q24h) for 7–14 days

  For bone systemic infections, bacteremia and more resistant pathogens (*e.g.*, Enterobacter): 20 mg/kg PO once daily (q24h) for 7–14 days (Greene, Hartmannn et al. 2006)

  c) For pyoderma: 11 mg/kg PO q12h (Miller 2005b)

- **CATS:**

  For susceptible infections:

  a) Ciprofloxacin: 5–15 mg/kg PO q12h

  Avoid or reduce dosage of these drugs in animals with severe renal failure; avoid in young animals or in pregnant or breeding animals. (Vaden and Papich 1995)

- **FERRETS:**

  For susceptible infections:

  a) 5–15 mg/kg PO twice daily (Williams 2000)

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

  a) Rabbits: 5–20 mg/kg PO q12h (Ivey and Morrisey 2000)

  b) Chinchillas, Gerbils, Guinea Pigs, Hamsters, Mice, Rats: 7–20 mg/kg PO q12h (Adamcak and Otten 2000)

- **BIRDS:**

  For susceptible gram-negative infections:

  a) Using ciprofloxacin 500 mg tablets: 20–40 mg/kg PO twice daily. Crushed tablet goes into suspension well, but must be shaken well before administering. (McDonald 1989)

  b) Ciprofloxacin (using crushed tablets): 20 mg/kg PO q12h (Bauck and Hoefer 1993)

  c) Ciprofloxacin (using crushed tablets or suspend) 10–15 mg/kg PO q12h (Hoeffer 1995)

  d) Ratites: 3–6 mg/kg PO twice daily (Jenson 1998)

Monitoring

- Clinical efficacy
- Adverse effects

Chemistry/Synonyms

A fluoroquinolone antibiotic, ciprofloxacin HCl occurs as a faintly yellowish to yellow, crystalline powder. It is slightly soluble in water. Ciprofloxacin is related structurally to the veterinary-approved drug enrofloxacin (enrofloxacin has an additional ethyl group on the piperazinyl ring).

Ciprofloxacin may also be known as ciprofloxacine, ciprofloxacinum, ciprofloxacino, Bay-q-3939, or *Cipro®*.

Storage/Stability/Compatibility

Unless otherwise directed by the manufacturer, ciprofloxacin tablets should be stored in tight containers at temperatures less than 30°C. Protect from strong UV light. The injection should be stored at 5°–25°C and protected from light and freezing.

Ciprofloxacin injection is reportedly **compatible** with the following IV solutions and drugs: Dextrose 5%, D5 and ¼ or ½ NaCl, Ringer's, LRS, normal saline, amikacin sulfate, aztreonam, cimetidine, cyclosporine, dobutamine, dopamine, fluconazole, gentamicin, lidocaine, midazolam, KCl, ranitidine, tobramycin, and vitamin B complex.

Ciprofloxacin injection is reportedly **incompatible** with aminophylline, amphotericin B, azithromycin, ceftazidime, cefuroxime, clindamycin, heparin sodium, sodium bicarbonate, and ticarcillin.

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: None

HUMAN-LABELED PRODUCTS:

Ciprofloxacin Oral Tablets: 100 mg, 250 mg, 500 mg & 750 mg; *Cipro®* (Bayer); generic; (Rx)

Ciprofloxacin Extended-Release Tablets: 500 mg & 1000 mg; *Cipro XR®* (Bayer); generic; (Rx)

Ciprofloxacin Powder for Oral Suspension: 50 mg/mL (5%), 100 mg/mL (10%) when reconstituted; *Cipro®* (Bayer); generic; (Rx)

Ciprofloxacin Injection: 200 mg in 20 mL vials, 100 mL in 5% dextrose flexible containers (0.2%) and 120 mL bulk; 400 mg in 40 mL vials (1%), 200 mL in 5% dextrose flexible containers (0.2%) and 120 mL bulk; *Cipro® I.V.* (Bayer); generic; (Rx)

CISAPRIDE

(*sis*-a-pride)

PROMOTILITY AGENT

Prescriber Highlights

- Oral GI prokinetic agent, used in several species for GI stasis, reflux esophagitis, & constipation/megacolon (cats)
- No longer commercially available, must be obtained from a compounding pharmacy
- Contraindications: Hypersensitivity, GI perforation or obstruction, hemorrhage
- Caution: Pregnancy
- Adverse effects appear to be minimal in veterinary patients
- Drug interactions

Uses/Indications

Proposed uses for cisapride in small animals includes esophageal reflux and treatment of primary gastric stasis disorders. Cisapride has been found to be useful in the treatment of constipation and megacolon in cats.

Pharmacology/Actions

Cisapride increases lower esophageal peristalsis and sphincter pressure and accelerates gastric emptying. The drug's proposed mechanism of action enhances the release of acetylcholine at the myenteric plexus, but does not induce nicotinic or muscarinic receptor stimulation. Acetylcholinesterase activity is not inhibited. Cisapride blocks dopaminergic receptors to a lesser extent than does metoclopramide and does not increase gastric acid secretion.

Pharmacokinetics

Human data: After oral administration, cisapride is rapidly absorbed with an absolute bioavailability of 35–40%. The drug is highly bound to plasma proteins and apparently extensively distributed throughout the body. Cisapride is extensively metabolized and its elimination half-life is about 8–10 hours.

Contraindications/Precautions/Warnings

Cisapride is contraindicated in patients in whom increased gastrointestinal motility could be harmful (*e.g.*, perforation, obstruction, GI hemorrhage) or those who are hypersensitive to the drug.

Adverse Effects

Cisapride appears to be safe in cats at the dosages recommended. Occasionally vomiting, diarrhea, and abdominal discomfort may be noted. Although considered very rare in veterinary patients, prolonged QT intervals or other cardiac arrhythmias are possibilities.

In humans, the primary adverse effects are gastrointestinal related with diarrhea and abdominal pain most commonly reported, but the drug was removed from the market due to concerns with QT-interval prolongation.

Dosage may need to be decreased in patients with severe hepatic impairment.

Reproductive/Nursing Safety

Cisapride at high dosages (>40 mg/kg/day) caused fertility impairment in female rats. At doses 12 to 100 times the maximum recommended, cisapride caused embryotoxicity and fetotoxicity in rabbits and rats. Its use during pregnancy should occur only when the benefits outweigh the risks. Cisapride is excreted in maternal milk in low levels; use with caution in nursing mothers.

Overdosage/Acute Toxicity

In one reported human overdose of 540 mg, the patient developed GI distress and urinary frequency. LD_{50} doses in various lab animals range from 160–4000 mg/kg. Adverse effects reported for overdoses in dogs include diarrhea, hypotonia, dyspnea, catalepsy, loss of righting reflex, tremors, or seizures. Significant overdoses should be handled using standard gut emptying protocols when appropriate; supportive therapy should be initiated when required.

Drug Interactions

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

- **ANTICHOLINERGIC AGENTS:** Use of anticholinergic agents may diminish the effects of cisapride
- **BENZODIAZEPINES:** Cisapride may enhance the sedative effects of alcohol or benzodiazepines
- **WARFARIN:** Cisapride may enhance anticoagulant effects; additional monitoring and anticoagulant dosage adjustments may be required
- **ORAL DRUGS WITH A NARROW THERAPEUTIC INDEX:** May need serum levels monitored more closely when adding or discontinuing cisapride as cisapride can decrease GI transit times and potentially affect the absorption of other oral drugs

  As cisapride is metabolized via cytochrome P450 (3A4 in humans), the following medications/foods that can inhibit this enzyme may lead to increased cisapride levels with an increased risk for cisapride cardiotoxicity:

- **AMIODARONE**
- **ANTIFUNGALS** (**ketoconazole, itraconazole, fluconazole**)
- **CHLORAMPHENICOL**
- **CIMETIDINE**
- **FLUVOXAMINE**
- **GRAPEFRUIT JUICE/POWDER**
- **MACROLIDE ANTIBIOTICS** (**except azithromycin**) **Note:** In one study in dogs erythromycin did not alter cisapride pharmacokinetics

  The following drugs may increase QT interval and use with cisapride may increase this risk:

- **AMIODARONE**
- **CLARITHROMYCIN**
- **MOXIFLOXACIN**
- **PROCAINAMIDE**
- **QUINIDINE**
- **SOTALOL**
- **TRICYCLIC ANTIDEPRESSANTS** (**amitriptyline, imipramine**)

Doses

- **DOGS:**

  As a promotility agent

  a) 0.5 mg/kg three times daily; decrease dose if abnormal GI signs or abdominal pain result (Hall 1994)

  b) To reduce regurgitation associated with megaesophagus: 0.55 mg/kg PO once to three times daily. Practically: 2.5 mg per dose for dogs weighing between 5–10 lbs.; 5 mg per dose for dogs weighing between 11–40 lbs; and 10 mg per dose for dogs greater than 40 lbs. Administer no closer than 30 minutes before feeding. (Tams 1994)