ENROFLOXACIN

(en-roe-***flox***-a-sin) Baytril®

FLUOROQUINOLONE ANTIBIOTIC

Prescriber Highlights

- Veterinary oral & injectable fluoroquinolone antibiotic effective against a variety of pathogens; not effective against anaerobes
- In dogs, oral bioavailability is better than ciprofloxacin
- Contraindications: Hypersensitivity; relatively contraindicated for young, growing animals due to cartilage abnormalities
- FDA prohibits extra-label use in food animals
- Caution: Hepatic or renal insufficiency, dehydration
- Higher doses (>5 mg/kg/day) not recommended in cats; may cause blindness
- Adverse Effects: GI distress, CNS stimulation, crystalluria, or hypersensitivity; IV administration can potentially be very risky in small animals
- Administer PO (to dogs/cats) preferably on an empty stomach (unless vomiting occurs)
- Drug interactions
- Should not be used in humans (CNS effects)

Uses/Indications

Enrofloxacin is approved for use in dogs and cats (oral only) for the management of diseases associated with bacteria susceptible to enrofloxacin. Because of the dosage restriction (5 mg/kg) for cats, enrofloxacin is generally used in this species only for the most susceptible bacterial infections. It is also been approved for use in cattle (not dairy cattle or veal calves).

Pharmacology/Actions

Enrofloxacin is a bactericidal agent. The bactericidal activity of enrofloxacin is concentration dependent, with susceptible bacteria cell death occurring within 20–30 minutes of exposure. Enrofloxacin has demonstrated a significant post-antibiotic effect for both gram-negative and -positive bacteria and is active in both stationary and growth phases of bacterial replication.

Its mechanism of action 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 these infections. These drugs have weak activity against most anaerobes and are ineffective in treating anaerobic infections.

Bacterial resistance development is an ongoing concern, as many isolates of *Pseudomonas aeruginosa* are now resistant to enrofloxacin. Resistance occurs by mutation, particularly with *Pseudomonas aeruginosa, Klebsiella pneumonia,* Acinetobacter and enterococci, but plasmid-mediated resistance is not thought to occur.

Pharmacokinetics

Enrofloxacin is well absorbed after oral administration in most species. In dogs, enrofloxacin's bioavailability (approximately 80%) is about twice that of ciprofloxacin after oral dosing. 50% of Cmax is reportedly attained within 15 minutes of dosing and peak levels (Cmax) occur within one hour of dosing. The presence of food in the stomach may delay the rate, but not the extent of absorption. In sheep, enrofloxacin administered orally is about 65–75% bioavailable.

Enrofloxacin is distributed throughout the body. Volume of distribution in dogs is approximately 3–4 L/kg. Only about 27% is bound to canine plasma proteins. Highest concentrations are found in the bile, kidney, liver, lungs, and reproductive system (including prostatic fluid and tissue). Enrofloxacin reportedly concentrates in macrophages. Therapeutic levels are also attained in bone, synovial fluid, skin, muscle, aqueous humor and pleural fluid. Low concentrations are found in the CSF; levels may only reach 6–10% of those found in the serum. In cattle, the volume of distribution is about 1.5 L/kg and in sheep, 0.4 L/kg.

Enrofloxacin is eliminated via both renal and non-renal mechanisms. Approximately 15–50% of the drug is eliminated unchanged into the urine, by both tubular secretion and glomerular filtration. Enrofloxacin is metabolized to various metabolites, most of which are less active than the parent compounds. Approximately 10–40% of circulating enrofloxacin is metabolized to ciprofloxacin in most species including humans, dogs, cats, adult horses, cattle, turtles, and snakes. Foals, pigs, and some lizards apparently do not convert much enrofloxacin, if any, to ciprofloxacin. These metabolites are eliminated both in 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 that may not require dosage adjustment. The approximate elimination half-lives in various species are: dogs 4–5 hours; cats 6 hours; sheep 1.5–4.5 hours; horses 5–6 hours, turtles 18 hours; and alligators 55 hours.

Contraindications/Precautions/Warnings

Enrofloxacin is labeled as contraindicated in small and medium breed dogs from 2 to 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 before treatment since they may be in the rapid-growth phase past 8 months of age. Quinolones are contraindicated in patients hypersensitive to them.

Because ciprofloxacin has occasionally been reported to cause crystalluria in humans, animals should not be allowed to become dehydrated during therapy with either ciprofloxacin or enrofloxacin. Enrofloxacin may cause 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 of the canine or bovine injectable products in cats or administered to dogs via other non-approved parenteral routes (IV, SC) is controversial and may result in significant adverse effects. Parenteral administration in cats at doses less than 5 mg/kg have reportedly caused ophthalmic toxicity (blindness). Because of the

high pH (approx. 11) of the solution, subcutaneous administration in any species may cause pain and tissue damage. If administered rapidly or undiluted IV to dogs, there is an increased risk for cardiac arrhythmias, hypotension, vomiting, and mast cell degranulation (histamine and other mediator release).

The extra-label use in dogs of the IM 22.7 mg/mL (2.27%) product diluted 1:1 to 1:10 with sodium chloride 0.9% for slow IV administration (over at least 10 minutes; some give over 30–45 minutes) has anecdotally been described. However, the rapid absorption of enrofloxacin after IM administration in dogs (peak levels in about 30 minutes) questions the necessity of using this non-approved route (IV) of administration. Injectable enrofloxacin must not be mixed with, or come into contact with any IV solution containing magnesium (*e.g.*, *Normosol-R*, *Plasmalyte-R, -A*, or *–56*); morbidity and mortality secondary to micro-precipitants lodging in patient lungs have been reported. Dilution and extra-label use in small animals of the large animal product (100 mg/mL; 10%) via any route is discouraged.

Enrofloxacin should not be used by humans; it may cause hallucinations, vivid dreams, and headache.

Adverse Effects

With the exception of potential cartilage abnormalities in young animals (see Contraindications above), the adverse effect profile of enrofloxacin is usually limited to GI distress (vomiting, anorexia). In dogs, rare incidences of elevated hepatic enzymes, ataxia, seizures, depression, lethargy, and nervousness have also been reported. Hypersensitivity reactions or crystalluria could potentially occur.

In cats, rare incidences of ocular toxicity have been reported characterized by mydriasis, retinal degeneration, and blindness. These effects were generally seen at higher dosage ranges (>15 mg/kg) and have necessitated a reduction in dosage recommendations in cats to a maximum of 5 mg/kg/day. Other rare adverse effects seen in cats may include: vomiting, anorexia, elevated hepatic enzymes, diarrhea, ataxia, seizures, depression/lethargy, vocalization, and aggression.

Reproductive/Nursing Safety

The safety of enrofloxacin in pregnant dogs has been investigated. Breeding, pregnant, and lactating dogs receiving up to 15 mg/kg day demonstrated no treatment related effects. However, because of the risks of cartilage abnormalities in young animals, the fluoroquinolones are not generally recommended for use during pregnancy unless the benefits of therapy clearly outweigh the risks. Limited studies in male dogs at various dosages have indicated no effects on male breeding performance.

Safety in breeding, pregnant, or lactating cats has not been established.

Overdosage/Acute Toxicity

It is unlikely an acute overdose in dogs with enrofloxacin would result in clinical signs more serious than either anorexia or vomiting, but the adverse effects noted above could occur. Dogs receiving 10X the labeled dosage rate of enrofloxacin for at least 14 days developed only vomiting and anorexia. Death occurred in some dogs when fed 25 times the labeled rate for 11 days, however.

In cats overdoses can be serious (blindness, seizures).

There were 306 exposures to enrofloxacin reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases 277 were dogs with 31 showing clinical signs and the remaining 43 cases were cats with 4 showing clinical signs. Common findings in dogs recorded in decreasing frequency included vomiting, diarrhea, seizures, ataxia and fasciculation. Findings in cats recorded in decreasing frequency included seizures, vomiting and blindness.

Drug Interactions

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

- **ANTACIDS/DAIRY PRODUCTS:** Containing cations (Mg^{++}, Al^{+++}, Ca^{++}) may bind to enrofloxacin and prevent its absorption; separate doses of these products by at least 2 hours
- **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)
- **FLUNIXIN:** Has been shown in dogs to increase the AUC and elimination half-life of enrofloxacin and enrofloxacin increases the AUC and elimination half-life of flunixin; it is unknown if other NSAIDs interact with enrofloxacin in dogs
- **GLYBURIDE:** Severe hypoglycemia possible
- **IRON, ZINC (oral):** Decreased enrofloxacin/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 and their concomitant use is not recommended
- **PHENYTOIN:** Enrofloxacin/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 enrofloxacin; separate doses of these drugs by at least 2 hours
- **THEOPHYLLINE:** Enrofloxacin/ciprofloxacin may increase theophylline blood levels
- **WARFARIN:** Potential for increased warfarin effects

Laboratory Considerations

- Enrofloxacin may cause false-positive **urine glucose** determinations when using cupric sulfate solution (Benedict's Solution, *Clinitest*®). Tests utilizing glucose oxidase (*Tes-Tape*®, *Clinistix*®) are not affected by enrofloxacin
- 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) 5–20 mg/kg per day PO, may be given once daily or divided and given twice daily (q12h). Treatment should continue for at least 2–3 days beyond cessation of clinical signs, to a maximum duration of therapy is 30 days. (Package insert; *Baytril*®—Bayer)

  b) For sepsis: 5–20 mg/kg IV q12h (Hardie 2000)

  c) For skin, urinary infections: 2.5–5 mg/kg PO q12h for 7–14 days;

For deep pyodermas, complicated urinary infections: 5 mg/kg PO once daily (q24h) for 7–14 days (treatment may be required for 10–12 weeks for deep pyoderma, especially in German shepherds);

For lower respiratory tract infections: 5–10 mg/kg PO once daily (q24h) for 7–84 days;

For prostate infections: 5 mg/kg PO twice daily (q12h) for 7–14 days;

For histiocytic ulcerative colitis: 5 mg/kg PO twice daily (q12h) for 21–90 days;

For hemotropic mycoplasmosis: 5 mg/kg PO, IM q12h for 7–14 days;

For systemic orthopedic infections: 5–11 mg/kg PO, IV, IM, SC q12h for 10 days;

For Pseudomonas infections in soft tissues: 11–20 mg/kg PO, IM, SC q12h for 7 days minimum, treat as long as necessary;

For bacteremia, sepsis: 11 mg/kg PO, IV, IM, SC q12h for as long as necessary. (Greene, Hartmannn et al. 2006)

■ **CATS:**

For susceptible infections:

a) 5 mg/kg per day PO, may be given once daily or divided and given twice daily (q12h). Treatment should continue for at least 2–3 days beyond cessation of clinical signs, to a maximum duration of therapy is 30 days. (Package insert; *Baytril*®—Bayer)

■ **HORSES:**

Note: Usage of enrofloxacin in horses remains somewhat controversial. While there has been much discussion regarding the potential for cartilage abnormalities or other arthropathies in horses, objective data are lacking. At present, however, enrofloxacin probably should only be used in adult horses when other antibiotics are inappropriate. If using *Baytril*® injection orally in horses, it can be very irritating to the mouth. This may be alleviated by coating the liquid with molasses or preparing a gel (below) and rinsing the horse's mouth with water after administration.

An oral gel formulated from the bovine injectable product has been described (Epstein, Cohen et al. 2004). 100 mL of the 100 mg/mL bovine injection (*Baytril*®*100*) is used. Stevia (0.35 g) is mixed with approximately 15 mL of liquid enrofloxacin until dissolved. Apple flavoring 0.6 mL is added until dissolved. Sodium carboxymethylcellulose (2 g) is sprinkled over the mixture and stirred until incorporated. Immediately begin gradually adding the remaining enrofloxacin (85 mL) before the mixture solidifies. Approximate concentration is 100 mg/mL. Stable for up to 84 days if kept in the refrigerator and protected from light.

a) 7.5 mg/kg PO or IV once daily for susceptible respiratory infections (Ainsworth and Hackett 2004)

b) Using the compounded gel as described above. 7.5 mg/kg PO once daily. Horses should be fasted for 11–14 hours prior to dosing and for 1–2 hours after dosing, but should have access to water. Rinse horse's mouth with water after dosing to reduce risks for oral ulceration. (Epstein, Cohen et al. 2004)

■ **CATTLE:**

a) Enrofloxacin (*Baytril*® *100*) is approved for the treatment of bovine respiratory disease associated with *Pasteurella haemolytica, Pasteurella multocida,* and *Haemophilus sommus*. It is administered by injection and is intended for the treatment of individual animals. The labeled dosage is: 2.5–5 mg/kg SC once daily for 3–5 days or 7.5–12.5 mg/kg SC once. The product is prescription only and is not for use in cattle intended for dairy production or in veal calves. Animals intended for human consumption must not be slaughtered within 28 days from the last treatment. Extralabel use of fluoroquinolones in food animals is prohibited by the FDA.

■ **FERRETS:**

For susceptible infections:

a) 10–20 mg/kg PO, IM, SC twice daily (Williams 2000)

■ **RABBITS/RODENTS/SMALL MAMMALS:**

a) Rabbits: 5 mg/kg PO, SC, IM or IV q12h for 14 days. Drug of choice for Pasteurella. If giving SC, dilute or skin may slough. Do not give injectable product PO because it is very unpalatable (Ivey and Morrisey 2000)

b) Hedgehogs: 5–10 mg/kg PO or SC q12h (Smith 2000)

c) Chinchillas: 5–10 mg/kg PO, IM q12h (Hayes 2000)

d) For mycoplasmal pneumonia in mice and rats: 10 mg/kg PO twice daily with doxycycline (5 mg/kg PO twice daily) (Burke 1999)

e) Chinchillas, Gerbils, Guinea Pigs, Hamsters, Mice, Rats: 5–10 mg/kg PO or IM q12h or 5–20 mg/kg PO or SC q24h. In drinking water: 50–200 mg/liter for 14 days. Do not use in young animals. (Adamcak and Otten 2000)

■ **CAMELIDS:**

For susceptible infections in alpacas:

a) 5 mg/kg SC or 10 mg/kg PO once daily (Gandolf, Papich et al. 2005)

■ **BIRDS:**

For susceptible gram-negative infections:

a) Ratites: 1.5–2.5 mg/kg PO or SC twice daily. Drinking water: 10% solution, 10 mg/kg for 3 days; 5 mg/kg IM (IM injections cause severe muscle necrosis) twice daily for 2 days (Jenson 1998)

b) 15 mg/kg PO, or IM or 250 mg/L of drinking water (Bauck and Hoefer 1993)

A method to make a 10.2 mg/mL oral suspension of enrofloxacin has been described: Make a stock solution of "HMC 0.15%" by mixing 7.5 mL of *Lubrivet*® with 92.5 mL of water. Crush three (3) whole 68 mg tablets with a "pinch" of citric acid. Add crushed mixture to a dispensing vial and 15 mL of "HMC 0.15%." Shake well to dissolve tablet coating; add a sufficient quantity of "HMC 0.15%" to a total of 20 mL and allow to stand at room temperature for 30 minutes to allow tablet coating to completely dissolve. Shake well before use and keep refrigerated. A 14-day expiration date has been assigned. By crushing six (6) tablets, a 20.4 mg/mL suspension may be compounded using the same technique.

■ **REPTILES:**

For susceptible respiratory infections for most species:

a) 5 mg/kg IM every 5 days for 25 days; For chronic respiratory infections in tortoises: 15 mg/kg IM every 72 hours for 5–7 treatments (Gauvin 1993)

Monitoring

- Clinical efficacy
- Adverse effects
- In cats, monitor for mydriasis and/or retinal changes.

Client Information

- Do not crush film-coated tablets, as drug is very bitter tasting
- Animals should have access to water at all times
- Do not exceed dosage recommendations in cats; blindness can occur

Chemistry/Synonyms

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

Enrofloxacin may also be known as: Bay-Vp-2674 or *Baytril®*.

Storage/Stability/Compatibility

Unless otherwise directed by the manufacturer, enrofloxacin tablets should be stored in tight containers at temperatures less than 30°C. Protect from strong UV light. Enrofloxacin has been reported to be soluble and stable in water, but solubility is pH dependent and altering the pH of the commercially available injections can cause precipitation.

The canine-approved product (2.27%) for IM injection should be stored protected from light; do not freeze.

The cattle-approved product (10%) injectable solution should be stored protected from sunlight. It should not be refrigerated, frozen or stored above 40°C (104°F). If exposed to cold temperatures, precipitation may occur; to redissolve, warm and then shake the vial.

Injectable enrofloxacin must not be mixed with, or come into contact with any IV solution containing magnesium (*e.g.*, *Normosol-R*, *Plasmalyte-R, -A,* or *-56*); morbidity and mortality secondary to micro-precipitants lodging in patient lungs have been reported.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Enrofloxacin Tablets (Film-Coated) & Oral Taste Tablets: 22.7 mg, 68 mg, 136 mg; *Baytril®* (Bayer Corp); (Rx). Approved for use in dogs and cats.

Enrofloxacin Injection: 22.7 mg/mL (2.27%) in 20 mL vials; *Baytril®* (Bayer Corp); (Rx). Approved for use in dogs.

Enrofloxacin Injection: 100 mg/mL in 100 mL and 250 mL bottles. Approved for use in cattle only. Not for use in cattle intended for dairy production or in calves to be processed for veal. Any extra-label use in food animals is banned by the FDA. Slaughter Withdrawal = 28 days when used as labeled. A withdrawal period has not been established in pre-ruminating calves. *Baytril 100®* (Bayer); (Rx)

HUMAN-LABELED PRODUCTS: None.

Note: Use of enrofloxacin by humans cannot be recommended due to a high degree of CNS effects.

EPHEDRINE SULFATE

(e-*fed*-rin)

SYMPATHOMIMETIC BRONCHODILATOR/ VASOPRESSOR

Prescriber Highlights

- Sympathomimetic used primarily for oral treatment of urinary incontinence & topically for nasal uses
- Contraindications: Severe CV disease, especially with arrhythmias
- Caution: Patients with glaucoma, prostatic hypertrophy, hyperthyroidism, diabetes mellitus, cardiovascular disorders or hypertension
- Adverse Effects: CNS stimulation, tachycardia, hypertension, or anorexia
- Excreted into milk, may affect neonates

Uses/Indications

Ephedrine is used chiefly for the treatment of urethral sphincter hypotonus and resulting incontinence in dogs and cats. It has also been used in an attempt to treat nasal congestion and/or bronchoconstriction in small animals. It can also be used parenterally as a pressor agent in the treatment of shock or anesthesia-associated hypotension.

Pharmacology/Actions

While the exact mechanism of ephedrine's actions are undetermined, it is believed that it indirectly stimulates both alpha-, $beta_1$-, $beta_2$-adrenergic receptors by causing the release of norepinephrine. Prolonged use or excessive dosing frequency can deplete norepinephrine from its storage sites and tachyphylaxis (decreased response) may ensue. Tachyphylaxis has not been documented in dogs or cats, however, when used for urethral sphincter hypotonus.

Pharmacologic effects of ephedrine include: increased vasoconstriction, heart rate, coronary blood flow, blood pressure, mild CNS stimulation, and decreased bronchoconstriction, nasal congestion and appetite. Ephedrine can also increase urethral sphincter tone and produce closure of the bladder neck; its principle veterinary indications are as a result of these effects.

Pharmacokinetics

Ephedrine is rapidly absorbed after oral or parenteral administration. Although not confirmed, ephedrine is thought to cross both the blood-brain barrier and the placenta. Ephedrine is metabolized in the liver and excreted unchanged in the urine. Urine pH may significantly alter excretion characteristics. In humans: at urine pH of 5, half-life is about 3 hours; at urine pH of 6.3, half-life is about 6 hours.

Contraindications/Precautions/Warnings

Ephedrine is contraindicated in patients with severe cardiovascular disease, particularly with arrhythmias. Ephedrine should be used with caution in patients with glaucoma, prostatic hypertrophy, hyperthyroidism, diabetes mellitus, cardiovascular disorders or hypertension.

When administered IV, administration rate should not exceed 10 mg/minute (in humans); it is suggested to scale the rate for veterinary patients.

Adverse Effects