DIN 02480891
FOR VETERINARY USE ONLY

Pr Enrotron 50™

Enrofloxacin injection 50 mg/mL
Antimicrobial

Description: Each mL of injectable solution contains: enrofloxacin 50 mg (active ingredient), n-butyl alcohol 30 mg (preservative), potassium hydroxide and hydrochloric acid q.s. for pH adjustment and water for injection, q.s. (inactive ingredients).
Enrofloxacin is a synthetic chemo-therapeutic agent from the class of the quinolone carboxylic acid derivatives. It has antibacterial activity against a broad spectrum of Gram negative and Gram positive bacteria (see Table 1). Its chemical nomenclature is 1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.
Indications: Enrotron 50 is indicated for the management of diseases in dogs associated with bacteria susceptible to enrofloxacin.
Dosage and administration: The optimum dose of Enrotron 50 (enrofloxacin injection) has been established at 2.5 mg/kg (1.13 mg/lb) of body weight administered twice daily (every 12 hours). Enrotron 50 may be used in dogs twice daily (every 12 hours) by intramuscular injection for up to three days (6 doses). Different injection sites must be used for each treatment. Twelve hours following the last injection, dosing, should continue with enrofloxacin tablets given once daily for 2-3 days beyond cessation of clinical signs. Total treatment time with enrofloxacin should not exceed 30 days. If no improvement is seen within five days, the diagnosis should be re-evaluated and a different course of therapy considered.
Contraindications: Enrofloxacin is contraindicated in dogs known to be hypersensitive to quinolones. Based on the studies discussed under the section on Animal Safety, the use of enrofloxacin is contraindicated in small and medium breeds of dogs during the rapid growth phase (between 2 and 8 months of age). The safe use of enrofloxacin has not been established in large and giant breeds during the rapid growth phase. Large breeds may be in this phase for up to one year of age and the giant breeds for up to 18 months.
Caution: Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures. Quinolone-class drugs have been associated with cartilage erosions in weight-bearing joints and other forms of arthropathy in immature animals of various species.
Drug interactions: Concomitant therapy with other drugs that are metabolized in the liver may reduce the clearance rates of the quinolone and the other drug. No incompatibilities with other drugs are known at this time.
Warnings: To limit the potential development of antimicrobial resistance:
- fluoroquinolone drugs such as Enrotron 50 should not be used indiscriminately.
- Enrotron 50 should not be used in food producing animals.
Keep out of reach of children.
Adverse reactions:
Post Approval Experience: The following adverse experiences, although rare, are based on voluntary post-approval adverse drug experience reporting. The categories of reactions are listed in decreasing order of frequency by body system.
Gastrointestinal: Anorexia, diarrhea, vomiting, elevated liver enzymes
Neurologic: Ataxia, seizures
Behavioral: Depression, lethargy, nervousness
Microbiology: Enrofloxacin, a 4-fluoroquinolone compound, is bactericidal with activity against a broad spectrum of both Gram negative and Gram positive bacteria. Fluoroquinolones elicit their bactericidal properties through interactions with two intercellular enzymes - DNA gyrase (DNA topoisomerase II) and DNA topoisomerase IV - which are essential for bacterial DNA transcription, synthesis and replication. It is believed that fluoroquinolones actively bind with DNA:ENZYME complexes and thereby inhibit the essential processes catalyzed by the enzymes (DNA supercoiling and chromosomal decatenation)[1]. The ultimate outcome of fluoroquinolone intervention is DNA fragmentation and bacterial cell death.[2,3]
Enrofloxacin minimum inhibitory concentrations (MICs) were determined for canine and feline bacterial isolates originating from natural infections of the dermal, gastrointestinal, respiratory and urinary systems. Seven hundred and thirty-eight (738) isolates were collected from 14 different diagnostic laboratories located throughout the United States. Bacterial identity was confirmed by colony morphology, Gram stain and biochemical testing; for mycoplasmas, identity was confirmed by colony morphology and Dienes stain. The *in vitro* susceptibilities of all bacterial and mycoplasma isolates were determined by enrofloxacin microbroth dilution methods and the resultant enrofloxacin MIC50 and MIC90 values are presented in Table 1. *In vitro* susceptibility testing was performed in accordance with guidelines established by the National Committee for Clinical Laboratory Standards (NCCLS; Document M31-P, Volume 14, November 20).

Table 1 - MIC Values for Enrofloxacin Against Canine and Feline Pathogens (Diagnostic laboratory isolates, 1997)

Organism	Isolates	MIC_{50}(µg/ml)	MIC_{90}(µg/ml)
Bordetella spp.	*25*	*0.5*	*0.5*
Enterococcus spp.	*40*	*1*	*2*
Escherichia coli	*138*	*0.03*	*0.06*
Klebsiella pneumoniae	*32*	*0.06*	*0.12*
Mycoplasma spp.	*76*	*0.25*	*0.5*
Pasteurella spp.	*16*	*0.015*	*0.03*
Proteus spp.	*88*	*0.12*	*0.25*
Pseudomonas aeruginosa	*69*	*1*	*8*
Salmonella spp.	*15*	*0.06*	*0.25*
Staphylococcus intermedius	*119*	*0.12*	*0.25*
Staphylococcus spp.	*120*	*0.12*	*0.25*

Breakpoint: Based on *in-vitro* susceptibility, pharmacokinetics and clinical response, the following breakpoints are recommended for canine isolates. These breakpoints have been approved by the National Committee for Clinical Laboratory Standards (NCCLS) and are published in NCCLS document M-31:

Zone Diameter (mm)	MIC µg/mL	Interpretation
> 23	< 0.5	Susceptible (S)
18 - 22	1 - 2	Flexible Label (F)
< 17	> 4	Resistant (R)

A report of 'Susceptible' indicates that the pathogen is likely to be inhibited by plasma levels generally attained with the lower end of the dose range (2.5 mg/kg BW twice daily or 5.0 mg/kg BW once daily). A report of 'Flexible Label' indicates that the pathogen is likely inhibited by plasma levels attained with adherence to the principles of FDA-approved Professional Flexible Labeling in dogs. With enrofloxacin, conditions due to 'F' bacteria can be treated successfully by administration of an intermediary dose within the lower (>5.0 mg/kg BW once daily) and upper (= 20 mg/kg BW once daily) limits of the approved flexible dose range. Determination of the precise dosage is based upon a careful assessment of the interrelationships amongst host (immunocompetency, stress, site of infection, etc.), pathogen (virulence, MIC, emerging resistance, etc.) and chemotherapeutic (dose-dependent vs time-dependent efficacy, postantibiotic effects, toxicity etc.). A report of 'Resistant' indicates that the pathogen is unlikely to be inhibited by plasma levels attained with administration of the highest approved dose (20 mg/kg BW once daily) and alternative antimicrobial therapy should be selected. Standardized procedures require the use of laboratory quality control organisms for both standardized disk diffusion assays and standardized dilution assays. The 5 µg enrofloxacin disk should give the following zone diameters and enrofloxacin powder should provide the following MIC values for reference strains. The indicated ranges for quality control organisms are NCCLS approved.

QC Strain	Zone Diameter (mm)	MIC µg/mL
E. coli ATCC 25922	32 - 40	0.008 - 0.03
P. aeruginosa ATCC 27853	15 - 19	1 - 4
S. aureus ATCC 25923	27 - 31	–
S. aureus ATCC 25913	–	0.03 - 0.12

Distribution in the Body: Enrofloxacin penetrates into all canine tissues and body fluids. Concentrations of drug equal to or greater than the MIC for many pathogens (See Table 1) are reached in most tissues by two hours after dosing at 2.5 mg/kg and are maintained for 8-12 hours after dosing. Particularly high levels of enrofloxacin are found in urine.
Efficacy confirmation:
Clinical efficacy was established in dermal infections (wounds and abscesses) associated with susceptible strains of *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Staphylococcus intermedius*; respiratory infections (pneumonia, tonsillitis, rhinitis) associated with susceptible strains of *Escherichia coli* and *Staphylococcus aureus*; and urinary cystitis associated with susceptible strains of *Escherichia coli, Proteus mirabilis,* and *Staphylococcus aureus*.
Animal safety:
Adult dogs dosed intramuscularly for three treatments at 12.5 mg/kg followed by 57 oral treatments at 12.5 mg/kg, all at 12 hour intervals, did not exhibit either significant clinical signs or effects upon the clinical chemistry, hematological or histological parameters. Significant improvement of clinical signs is observed following drug withdrawal. Microscopic studies have identified lesions of the articular cartilage following 30 day treatments at either 5, 15 or 25 mg/kg in 15-28 week old growing puppies.
Tests indicated no effect on circulating microfilariae or adult heartworms (*Dirofilaria immitis*) when dogs were treated at a daily dosage rate of 15 mg/kg for 30 days. No effect on cholinesterase values was observed.
No adverse effects were observed on reproductive parameters when male dogs received 10 consecutive daily treatments of 15 mg/kg/day at 3 intervals (90, 45 and 14 days) prior to breeding or when female dogs received 10 consecutive daily treatments of 15 mg/kg/day at 4 intervals; between 30 and 0 days prior to breeding, early pregnancy (between 10th & 30th days), late pregnancy (between 40th & 60th days), and during lactation (the first 28 days).
Storage: Store at 15°C – 30°C. Protect from light. Discard unused product after 28 days of first broaching the vial.
How supplied: Entrotron 50 is available in 50-mL and 100-mL multiple dose vials.
References:
1 Hooper DC and Wolfson JS. Mechanisms of quinolone action and bacterial killing, in Quinolone Antimicrobial Agents. Washington DC, American Society for Microbiology, 2nd ed., 1993, 53-75.
2 Gootz TD and Brighty KE. Fluoroquinolone antibacterials: sar, mechanism of action, resistance and clinical aspects. Medicinal Research Reviews 1996; 16(5): 433-486.
3 Drlica K and Zhoa X. DNA gyrase, topoisomerase IV and the 4 quinolones. Microbiology and Molecular Biology Reviews 1997; 61(3):377-392.

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