

Summary:

The toxicology and safety of Baytril has been extensively studied in various laboratory animals, as well as in the target species dog and cat, where it has been proven to be safe and well tolerated. No adverse effects on blood composition or kidney function were observed, nor was it teratogenic or mutagenic.

In eukaryotes, Baytril like other modern quinolones, has a broad margin of safety because compared to prokaryotes, their enzyme analogue to DNA gyrase is 100-1000 times less susceptible to "topoisomerase inhibitors".

Common to all quinolones is that they may produce cartilage lesions in weight-bearing joints of growing dogs. Safety studies have shown that puppies between 1 and 4 weeks of age tolerated treatment with Baytril for up to 10 days at maximum doses of 25 mg/kg b.w. without showing adverse effects. In young dogs above 6 weeks of age, however, cartilage was affected depending on the dose and duration of Baytril administration. By contrast, young cats dosed with Baytril at maximum doses of 25 mg/kg b.w. for up to 30 days did not develop cartilage lesions. Thus, as a matter of precaution, all growing dogs were excluded from treatment. However, no evidence exists that Baytril treatment of pregnant or nursing dogs would have a negative influence on the cartilage development of the offspring.

Toxicity of fluoroquinolones on mammalian cells in general is low due to the fact that the enzyme analogue to bacterial DNA gyrase in eukaryotes is 100 to 1000 times less susceptible to "gyrase inhibitors" (1). This is also the reason for the large therapeutic margin of the fluoroquinolones.

For quinolones in general, side effects on different organ systems (CNS, gastrointestinal tract or locomotory system) have been reported. Enrofloxacin has undergone considerable toxicological and safety testing in laboratory species such as mice, rats and guinea pigs, as well as in the target species dog and cat (2).

- Central Nervous System

For Baytril, no noteworthy effects on the CNS of mice and rats have been observed; there is also no indication of central nervous system effects in dogs and cats. The recommendation not to treat dogs with CNS disorders, e.g., epilepsy, is a matter of precaution, which applies to all fluoroquinolones (2).

In human patients undergoing quinolone therapy, however, CNS effects of mild symptoms such as dizziness, headache and insomnia have been reported. It was suggested that these drugs competitively inhibit receptor binding of gamma-aminobutyric acid (GABA), an inhibitory transmitter of the CNS (3). Structural similarity of substituents of some quinolones at the C7-position with the binding region of the GABA molecule may be the reason for this phenomenon (4).

- Gastrointestinal Tract

As with all antiinfectives, gastrointestinal disturbances such as nausea, vomiting or diarrhea may occasionally occur. In experimental studies on dogs, vomiting was induced only in doses far exceeding the therapeutic recommendations (> 1000 mg/kg b.w. PO) (2). As Baytril has only minimal effects on anaerobic organisms, which represent a considerable part of the normal bowel flora, the incidence of intestinal side effects may be less frequent compared to antiinfectives of other families (3).

- Cartilage Lesions

Quinolones have been demonstrated to cause cartilage erosion in the joints of growing dogs. Histologically, vesicles in the articular cartilage are formed, which can progressively rupture and produce cartilaginous erosion. This observation is due to an early phase burst in oxidative metabolism and to disturbances in the electrolyte (Mg ++) household of immature chondrocytes. Experimental and clinical findings suggest that bearing of weight by joints may be important in the pathogenesis of these lesions (4).

To clarify whether Baytril can safely be used at therapeutic doses in growing dogs, a number of studies in animals of different breeds and ages have been conducted (2).

It appears that very young dogs between 1 and 4 weeks of age tolerate treatment with Baytril from 5 to 25 mg/kg b.w. for up to 10 days without developing cartilage lesions.

In animals older than 6 weeks, lesions occurred to a certain extent, depending on dosage and duration of treatment. As it is not possible to exactly determine the age up until which the drug is to be considered safe in puppies, all dogs under 12 months (18 months in giant breeds) were excluded from treatment as a matter of precaution (2). There is, however, no evidence that treatment of pregnant or nursing dogs would have any negative influence on the joint cartilage development of the offspring (2).

In contrast to dogs, cartilage lesions could not be demonstrated in growing cats from two to 10 months of age when treated with Baytril doses of up to 25 mg/kg b.w. for up to 30 days. It can be concluded that cartilage tolerance towards enrofloxacin is higher in cats than in dogs (2).

Other Safety Issues**3/6**

Studies on safety pharmacology using standard test designs were conducted in laboratory animals. Oral enrofloxacin doses of up to 100 mg/kg b.w., 20 times the recommended dosage, showed no significant adverse effects on blood composition, blood coagulation on diuresis. In the bronchoactivity test, no evidence of any effect on the smooth muscles of the respiratory system was found.

It could also be shown that Baytril does not elicit any antiallergic or pseudoallergic reactions. In the rabbit local irritation test and guinea pig skin sensitization test, enrofloxacin as the active substance was not a skin irritant and only slightly irritating to the eye (2). A Baytril 0.5% eyedrop formulation, however, did not produce any irritation after application to the rabbit eye.

- Acute Toxicity

The LD₅₀ values were determined in different species. All acute effects appear at doses far exceeding the therapeutic range (5). Dogs vomit after oral application of doses above 1000 mg/kg b.w., which is 200 times the recommended dosage, such that an LD₅₀ could not be determined (2).

- Subchronic toxicity

In subchronic feeding studies with enrofloxacin as the active substance, carried out over 13 weeks, the no-effect level (NOEL), which is the dose that can be administered with food over prolonged periods without adverse effects, was determined (2).

For rats, mice and adult dogs, general NOELs of 165, 550, and 52 mg/kg b.w., respectively, were found. This means that at the recommended doses adult dogs can be treated safely and for longer time without unwanted effects (2).

- Embryotoxicity and Teratogenicity

Trials in rats daily treated with enrofloxacin (0, 50, 210, and 875 mg/kg b.w.) from the 6th to the 15th day of gestation produced no evidence of teratogenic effects from enrofloxacin, including the highest dosage group. Maternal toxic effects after 210 and 875 mg/kg, however, resulted in slightly reduced fetal weights and delayed ossification. In the highest dosage group, which received 175 times the dosage recommended for dogs and cats, smaller litter sizes were observed. A dosage of 50 mg enrofloxacin per kg body weight was tolerated without any adverse effect to mothers and offspring (5).

- Mutagenicity

The point mutagenic effect of enrofloxacin was studied in the Salmonella Microsome Test (Ames-Test) and in ovarian cells of the Chinese hamster (CHO-HGPRT forward mutation assay). The Unscheduled DNA Synthesis Test was performed to check for damage to the DNA. These test systems produced no evidence of any mutagenic effect (5).

General Toxicology of Enrofloxacin (2) Studies in Laboratory Animals			
Species	Dose Rate (mg/kg b.w.)	Parameter	Result
Mouse/Rat	0/10/30/100 p.o.	CNS, general	No muscle relaxing, analgesic, anticonvulsive, kataleptic effects; no influence on central coordination, reflex response, neuromuscular transmission
Guinea pig	in vitro - 10 µg/ml	Isolated trachea	No change in tonus, no effect on histamine or leucotriene D ₄ induced spasm
Rat	0/10/30/100 p.o.	Blood biochemistry	No effect on coagulation, thrombocyte aggregation, fibrinolysis; no change in blood glucose or triglycerides in fed rats, in fasting rats elevation at 100 mg/kg
Rabbit	0/8.3/25/83 i.v.	Cardiovascular system	Slight decrease in heart rate and respiratory frequency at 83 mg/kg
Rat	0/10/30/100 p.o.	Urine excretion Sodium Potassium	No effect at 10 and 30 mg/kg, at 100 mg/kg increase in potassium excretion
Rat	0/10/30/100 p.o.	Gastrointestinal effects	No influence on carbon passage, no gastric lesion, no change in gastric acid secretion
Guinea pig	in vitro - 10 µg/ml	Isolated ileum	No contraction or relaxation; inhibits contraction induced by histamine, acetylcholine or carbachol
Rat	in vitro	Peritoneal mast cells	No pseudoallergic or antiallergic effects

Acute Toxicity of Enrofloxacin (2)			
Species	Sex	Route of administration	Approx. LD ₅₀ (mg/kg b.w.)
Rat	m, f	p.o.	> 5000
Mouse	m f	p.o. p.o.	> 5000 4336
Rabbit	m, f	p.o.	500 - 800
Dog (Beagle)	m, f	p.o.	Vomitus after 1000 and 5000 mg/kg
Mouse	m f	i.V. i.V.	225 220
Rabbit	m, f	Dermal	> 2000
Rat	m, f	Inhalation	3547 mg/m ³
Rabbit-local irritation, skin:		not irritating	
eye:		slightly irritating	
Guinea Pig - skin sensitization:		no allergic reaction	

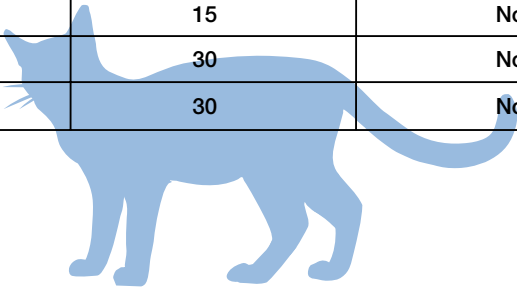
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Subchronic Feeding Studies with Enrofloxacin (2)				
Species	Duration (weeks)	Dose rate		NOEL
		(ppm in feed)	(mg/kg b.w.)	
Rat	13	500/2000 7500	40/165 630	165
Mouse	14	1000/3300 10000 1667	167/550	550
Dog (Beagle)	13	320/800 2000	9/22 52	52

No kidney damage from intrarenal crystallization
 No cataract of optical lens
 Joint lesions: Some rats of highest dose group.
 No observed symptoms in Beagles (12 months age)

Cartilage toxicity in young dogs (2)				
Age (weeks)	Breed	Dose Rate (mg/kg b.w.)	Duration (days)	Findings
6	Mongrel (German Shepherd Mix)	10 / 20	14	No clinical signs, histopath. lesions
5 - 7.5	Mongrel	10	10	No adverse effects
1.5 - 2.5	Various, including large breeds (German Shepherd)	5 / 15 / 25	10 30	No adverse effects, no histopath. lesions
7.5 - 8.5	Beagle	5 / 15 / 25	30	Overextension of carpal joints in highest dose group. Histopath. joint lesions: 5 mg/kg: 1/4 15 mg/kg: 2/4 25 mg/kg: 3/4
10 - 12	Mongrel German Shepherd and Labrador Mix	10	10 / 14	Overextension of carpal joints, exaggerated toe spread after 8-10 d. Histopath. lesion in 1/4 after 10 d 3/4 after 14 d
15	Various, includ. large breeds	5 / 15 / 25	10 30	Lameness; no histopath. lesions up to 15 mg/kg for 30 days
19 - 24	Mongrel includ. large breeds	25	30	Clinical signs after 7 days in 9/14 Regression of clinical signs 30 days after treatment
29 - 34	Mongrel, includ. large breeds	25	30	No adverse effects (no histopath. lesions)
19 - 28	Labrador	5 / 15 / 25	30	No clinical signs at 5 and 15 mg/kg. At 25 mg/kg signs in 3/4 after 3-7 days Histopath. lesions: 5 mg/kg: 2/4 15 mg/kg: 3/4 25 mg/kg: 4/4
12 - 15	Labrador	2.5 / 7.5 / 12.5 15	30 15	No clinical signs at 2.5 mg/kg for 30 days, no histopath. lesions. Histopath. lesions dose related; in 2/3 at 7.5 mg/kg and all animals of the other groups

General Safety of Enrofloxacin in young cats			
Age (weeks)	Dose Rate (mg/kg b.w.)	Duration (days)	Findings
2 - 2.5	5 / 15 / 25	15	No adverse effects
3 - 4	5 / 15 / 25	30	No adverse effects
7 - 10	5 / 15 / 25	30	No adverse effects



Altreuther, 1992. (2)

References:

- (1) Boothe DM: Enrofloxacin revisited. *Veterinary Medicine* 8: 744-753, 1994.
- (2) Altreuther P: Safety and tolerance of enrofloxacin in dogs and cats. *Proceedings 1st Int. Symposium on Baytril: 15-19, 1992.*
- (3) Hooper DC, Wolfson JS: Adverse effects, in Hooper DC, Wolfson JS (eds): *Quinolone Antimicrobial Agents*, ed 2. Washington DC, American Society for Microbiology: 489-512, 1993.
- (4) Brown SA: Fluoroquinolones in animal health. *J Vet Pharmacol Therapy* 19: 1-14, 1996.
- (5) Altreuther P: Data on chemistry and toxicology of Baytril. *Vet Med Rev* 2: 87-89, 1987.