



## Baytril® 100 (enrofloxacin) Injectable Solution Technical Report

### Safety of Baytril 100 in Swine

Three studies were conducted to demonstrate the safety of Baytril 100 in swine: an acute toxicity study, a margin of safety study and an injection site tolerance study.<sup>1</sup>

#### Key Findings

- No clinical signs of toxicity were observed.
- No differences were noted in hematological and clinical chemistry values.
- No histological lesions were observed.

#### Acute Toxicity Study

##### Study Design

Three crossbred pigs weighing 42–52 pounds were injected with a subcutaneous dose of 50 mg/kg body weight of Baytril 100 for five consecutive days. One cohort pig served as a control and received a similar subcutaneous dose volume of sterile saline for five consecutive days.

Pretreatment blood samples were obtained on study days –6 and –4. On day 0, the pigs were weighed, examined and assigned to groups, and treatment was initiated. Clinical observations were conducted daily. Three days following the final treatment, the pigs were blood sampled, weighed, euthanized and necropsied.

##### Results

No clinical signs of toxicity were observed on any study day. One treated animal was observed with diarrhea on day 1, which resolved by day 2. Swelling at the injection site was noted in the treated pigs but disappeared 24 hours following the final treatment. No differences were noted in hematological and clinical chemistry values between the treated and control animals. No histological lesions were observed at necropsy in any of the tissues, including articular cartilages.

##### Conclusion

The administration of Baytril 100 at 50 mg/kg body weight (6.67X labeled dose) subcutaneously once daily for five consecutive days (5X labeled duration) did not result in drug-induced clinical signs, gross pathological abnormalities or histopathological lesions.



## Key Findings

- A dose-related increase in the incidence of depression, lameness and stiffness occurred in the pig receiving treatments.
- Evaluation of articular cartilage revealed an incidence of lesions in all groups.
- Histological differences between the control and treated groups were not significant.

## Margin of Safety Study

### Study Design

Thirty-two crossbred pigs weighing 94–155 pounds were assigned to four study groups of four barrows and four gilts per group. Three of the treatment groups received either 5, 15 or 25 mg/kg body weight per day of Baytril® 100 (enrofloxacin) (0.76, 2X and 3.34X labeled dose) via subcutaneous injection for 15 consecutive days (15X labeled duration; injection sites were neck, shoulder and rib regions). One treatment group served as the control and received saline injections at a dose volume equal to 25 mg per kg body weight per day via subcutaneous injection for 15 consecutive days. When needed, doses were divided between sites to administer no more than 5 mL per site.

Pretreatment blood samples were obtained on study day –4. On day –1, the pigs were weighed, examined and assigned to groups. Treatment was initiated on day 0. Clinical observations were conducted daily. Blood samples were collected on days 5 and 17. Body weights were recorded on days 6 and 17, and feed intake was recorded throughout the study. Two pigs from each group were necropsied on days 18, 20, 31 and 32.

### Results

In the second week of continuous treatment, a dose-related increase in the incidence and severity of depression, lameness and stiffness occurred in the pigs receiving the 2X and 3.34X treatments. A clinically significant (1 lb/day) decrease in body weight gain was recorded in the pigs in the 3.34X group

compared to the controls and was attributed to the stiffness seen in this group. Clinical signs improved after treatment ended and most lame animals were clinically normal at necropsy (one animal in the 2X group and two animals in the 3.34X were lame at necropsy). The proportion of animals clinically lame during the trial is presented in Table 1.

Evaluation of articular cartilage revealed an incidence of lesions in all groups, including the controls. The lesion consisted of abnormal clustering of chondrocytes called chondrones. This lesion has been described with osteochondrosis and associated with fluoroquinolone treatment in other species.

There was no correlation between the gross and histological cartilage abnormalities and either dose level or clinical lameness. Histological differences between the control and treated groups were not significant. The proportion of animals with articular cartilage abnormalities is presented in Table 1.

### Conclusion

Baytril 100 had an adverse effect on joints and cartilage when administered at doses of 2X and 3.34X the labeled dose for 15X the labeled duration. An adequate margin of safety was demonstrated for Baytril 100 Injectable Solution when administered once by subcutaneous injection at 7.5 mg/kg body weight.

**Table 1** — Incidence of clinical lameness and articular cartilage lesions in pigs treated with Baytril 100 Injectable Solution for 15 consecutive days.

Baytril 100 dose (mg/kg BW)	Portion of clinically lame pigs	Portion of pigs with cartilage abnormalities
0	2/8	2/8
5 (0.67X)	1/8	1/8
15 (2X)	4/8	5/8
25 (3.34X)	8/8	3/8

## Key Findings

- Baytril 100 injection site reactivity was minimal.
- No swelling was noticed at any site.
- Microscopically, there was no evidence of abscess formation.

## Injection Site Tolerance Study

### Study Design

Fifteen crossbred pigs weighing 42–51 pounds were ranked by weight and randomly assigned to five necropsy groups of three pigs each. All animals were injected subcutaneously with 5 mg/kg of Baytril 100 on the right side of the neck for five continuous days. Treated pigs served as their own controls via saline injections in the opposite side of the neck.

Each injection site was observed, palpated and scored for swelling prior to treatment on day 0 and on days 1, 2, 3, 4, 7, 14, 24, 44 and 64. Three pigs were necropsied on days 7, 14, 24, 44 and 64.

### Results

Baytril 100 injection site reactivity was minimal (17 of 75 sites) with all swelling scores described as slight or mild. No swelling was noted at any site after day 14. All saline sites were clinically normal.

Visible lesions described as subcutaneous discoloration and pale areas with cystic or red stippled appearance or firmness were observed in pigs necropsied between days 7 and 24. Microscopically, there was no evidence of abscess formation. By day 24, lesions samples only exhibited evidence of healing and slight scar formation.

### Conclusion

Subcutaneous injection of Baytril 100 may result in discoloration or firmness of the subcutaneous tissue and superficial musculature that persists beyond five days. This may result in trim loss of edible tissue at slaughter.

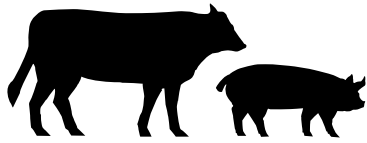
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Swine intended for human consumption must not be slaughtered within 5 days of receiving a single injection dose.



# Baytril® 100

## (enrofloxacin)



### 100 mg/mL Antimicrobial Injectable Solution

For Subcutaneous Use in Beef Cattle, Non-Lactating Dairy Cattle and Swine Only  
Not For Use In Female Dairy Cattle 20 Months of Age or Older  
Or In Calves To Be Processed For Veal

#### CAUTION:

Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.  
Federal (U.S.A.) law prohibits the extra-label use of this drug in food-producing animals.

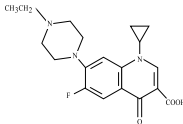
#### PRODUCT DESCRIPTION:

Baytril® 100 is a sterile, ready-to-use injectable antimicrobial solution that contains enrofloxacin, a broad-spectrum fluoroquinolone antimicrobial agent.

Each mL of Baytril® 100 contains 100 mg of enrofloxacin. Excipients are L-arginine base 200 mg, n-butyl alcohol 30 mg, benzyl alcohol (as a preservative) 20 mg and water for injection q.s.

#### CHEMICAL NOMENCLATURE AND STRUCTURE:

1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.



#### INDICATIONS:

**Cattle:** Baytril® 100 is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* (previously *Haemophilus somnus*) in beef and non-lactating dairy cattle.

**Swine:** Baytril® 100 is indicated for the treatment and control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis* and *Streptococcus suis*.

#### DOSAGE AND ADMINISTRATION:

Baytril® 100 provides flexible dosages and durations of therapy.

Baytril® 100 may be administered as a single dose for one day (cattle and swine) or for multiple days (cattle) of therapy. Selection of the appropriate dose and duration of therapy should be based on an assessment of the severity of disease, pathogen susceptibility and clinical response.

#### Cattle:

**Single-Dose Therapy:** Administer once, a subcutaneous dose of 7.5 - 12.5 mg/kg of body weight (3.4 - 5.7 mL/100 lb).

**Multiple-Day Therapy:** Administer daily, a subcutaneous dose of 2.5 - 5.0 mg/kg of body weight (1.1 - 2.3 mL/100 lb). Treatment should be repeated at 24-hour intervals for three days. Additional treatments may be given on Days 4 and 5 to animals that have shown clinical improvement but not total recovery.

Administered dose volume should not exceed 20 mL per injection site.

Table 1 – Baytril® 100 Dose and Treatment Schedule for Cattle\*

WEIGHT (lb)	Single-Dose Therapy	Multiple-Day Therapy
	7.5 - 12.5 mg/kg Dose Volume (mL)	2.5 - 5.0 mg/kg Dose Volume (mL)
100	3.5 - 5.5	1.5 - 2.0
200	7.0 - 11.0	2.5 - 4.5
300	10.5 - 17.0	3.5 - 6.5
400	14.0 - 22.5	4.5 - 9.0
500	17.0 - 28.5	5.5 - 11.5
600	20.5 - 34.0	7.0 - 13.5
700	24.0 - 39.5	8.0 - 16.0
800	27.5 - 45.5	9.0 - 18.0
900	31.0 - 51.0	10.0 - 20.5
1000	34.0 - 57.0	11.0 - 23.0
1100	37.5 - 62.5	12.5 - 25.0

\*Dose volumes have been rounded to the nearest 0.5 mL within the dose range.

#### Swine:

Administer once, behind the ear, a subcutaneous dose of 7.5 mg/kg of body weight (3.4 mL/100 lb).

Administered dose volume should not exceed 5 mL per injection site.

Table 2 – Baytril® 100 Dose and Treatment Schedule for Swine

WEIGHT (lb)	Dose Volume
	(mL)
50	1.7
100	3.4
150	5.1
200	6.8
250	8.5

#### RESIDUE WARNINGS:

**Cattle:** Animals intended for human consumption must not be slaughtered within 28 days from the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of enrofloxacin in this class of cattle may cause milk residues. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

**Swine:** Animals intended for human consumption must not be slaughtered within 5 days of receiving a single-injection dose.

#### HUMAN WARNINGS:

**For use in animals only. Keep out of the reach of children.** Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. For customer service or to obtain product information, including a Material Safety Data Sheet, call 1-800-633-3796. For medical emergencies or to report adverse reactions, call 1-800-422-9874.

#### PRECAUTIONS:

The effects of enrofloxacin on cattle or swine reproductive performance, pregnancy and lactation have not been adequately determined.

The long-term effects on articular joint cartilage have not been determined in pigs above market weight.

Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

Baytril® 100 contains different excipients than other Baytril® products. The safety and efficacy of this formulation in species other than cattle and swine have not been determined.

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 shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. See Animal Safety section for additional information.

#### ADVERSE REACTIONS:

No adverse reactions were observed during clinical trials.

#### MICROBIOLOGY:

Enrofloxacin is bactericidal and exerts its antibacterial effect by inhibiting bacterial DNA gyrase (a type II topoisomerase) thereby preventing DNA supercoiling and replication which leads to cell death.<sup>1</sup> Enrofloxacin is active against Gram-negative and Gram-positive bacteria.

#### EFFECTIVENESS:

**Cattle:** A total of 845 calves with naturally-occurring BRD were treated with Baytril® 100 in eight field trials located in five cattle-feeding states. Response to treatment was compared to non-treated controls. Single-dose and multiple-day therapy regimens were evaluated. BRD and mortality were significantly reduced in enrofloxacin-treated calves. No adverse reactions were reported in treated animals.

**Swine:** A total of 590 pigs were treated with Baytril® 100 or saline in two separate natural infection SRD field trials. For the treatment of SRD, the success rate of enrofloxacin-treated pigs that were defined as "sick and febrile" (increased respiratory rate, labored or dyspneic breathing, depressed attitude and a rectal temperature  $\geq 104.0^{\circ}\text{F}$ ) was statistically significantly greater than the success rate of saline-treated "sick and febrile" pigs. For the control of SRD, mean rectal temperature, mortality (one trial) and morbidity were statistically significantly lower for enrofloxacin-treated pigs in pens containing a percentage of "sick and febrile" pigs compared to saline-treated pigs.

#### TOXICOLOGY:

The oral LD50 for laboratory rats was greater than 5000 mg/kg of body weight. Ninety-day feeding studies in dogs and rats revealed no observable adverse effects at treatment rates of 3 and 40 mg/kg respectively. Chronic studies in rats and mice revealed no observable adverse effects at 5.3 and 323 mg/kg respectively. There was no evidence of carcinogenic effect in laboratory animal models. A two-generation rat reproduction study revealed no effect with 10 mg/kg treatments. No teratogenic effects were observed in rabbits at doses of 25 mg/kg or in rats at 50 mg/kg.

#### ANIMAL SAFETY:

**Cattle:** Safety studies were conducted in feeder calves using single doses of 5, 15 and 25 mg/kg for 15 consecutive days and 50 mg/kg for 5 consecutive days. No clinical signs of toxicity were observed when a dose of 5 mg/kg was administered for 15 days. Clinical signs of depression, incoordination and muscle fasciculation were observed in calves when doses of 15 or 25 mg/kg were administered for 10 to 15 days. Clinical signs of depression, inappetence and incoordination were observed when a dose of 50 mg/kg was administered for 3 days. No drug-related abnormalities in clinical pathology parameters were identified. No articular cartilage lesions were observed after examination of stifle joints from animals administered 25 mg/kg for 15 days.

A safety study was conducted in 23-day-old calves using doses of 5, 15 and 25 mg/kg for 15 consecutive days. No clinical signs of toxicity or changes in clinical pathology parameters were observed. No articular cartilage lesions were observed in the stifle joints at any dose level at 2 days and 9 days following 15 days of drug administration.

An injection site study conducted in feeder calves demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue and underlying muscle. No painful responses to administration were observed.

**Swine:** A safety study was conducted in 32 pigs weighing approximately 57 kg (125 lb) using single doses of 5, 15, or 25 mg/kg daily for 15 consecutive days. Incidental lameness of short duration was observed in all groups, including the saline-treated controls. Musculoskeletal stiffness was observed following the 15 and 25 mg/kg treatments with clinical signs appearing during the second week of treatment. Clinical signs of lameness improved after treatment ceased and most animals were clinically normal at necropsy.

A second study was conducted in two pigs weighing approximately 23 kg (50 lb), treated with 50 mg/kg for 5 consecutive days. There were no clinical signs of toxicity or pathological changes.

An injection site study conducted in pigs demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue. No painful responses to administration were observed.

**STORAGE CONDITIONS:** Protect from direct sunlight. Do not refrigerate, freeze or store at or above 40°C (104°F). Precipitation may occur due to cold temperature. To redissolve, warm and then shake the vial.

#### HOW SUPPLIED:

Baytril® 100:

Code: 08711170-023699	100 mg/mL	100 mL Bottle
Code: 08711278-032199	100 mg/mL	250 mL Bottle

#### REFERENCES:

1. Hooper, D.C., Wolfson, J.S., *Quinolone Antimicrobial Agents*, 2<sup>nd</sup> ed, 59 - 75, 1993.

U.S. Patent No. 5,756,506

For customer service or to obtain product information, including a Material Safety Data Sheet, call 1-800-633-3796.

For medical emergencies or to report adverse reactions, call 1-800-422-9874.

Baytril® 100  
BR051608

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NADA 141-068, Approved by FDA



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Shawnee Mission, Kansas 66201 U.S.A.

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