BATTLE OF THE BRD ANTIMICROBIALS

ADVOCIN™ (danofloxacin mesylate) vs. BAYTRIL® 100 (enrofloxacin)

WITHDRAWAL TIME: 4 DAYS vs. 28 DAYS

INTRODUCING ADVOCIN™, THE SINGLE DOSE, COST-EFFECTIVE ALTERNATIVE TO BAYTRIL® FOR THE TREATMENT OF BOVINE RESPIRATORY DISEASE (BRD).

NOW IN THE COMPETITION FOR SPEED AND COST-EFFECTIVENESS, ADVOCIN™ PACKS A KNOCKOUT PUNCH.
ADVOCIN™ ACHIEVES A HIGH CONCENTRATION AT THE SITE OF INFECTION

ADVOCIN™ and Baytril® are fluoroquinolones; the efficacy of this class of antimicrobials depends on a high concentration at the site of infection.¹

**Important Safety Information:** Federal law prohibits the extra-label use of all fluoroquinolones including ADVOCIN in food-producing animals. Not for use in cattle intended for dairy production or in calves to be processed for veal. ADVOCIN has a pre-slaughter withdrawal time of four days.

---

**In Vivo Study Results**

A two-dose danofloxacin regimen at 6 mg/kg given twice over a 48-hour period also was included in these studies. The overall pooled results show that there is no significant difference in cure rates between danofloxacin at the one dose at 8 mg/kg or two-dose regimen at 6 mg/kg given twice over 48 hours, and both are significantly different compared with the negative control group.

**Field Studies in Cattle Demonstrate that ADVOCIN is Effective Against BRD²**

**Lung concentrations of active drugs at maximum dose**

*Pharmacokinetic/pharmacodynamic studies are not necessarily representative of clinical results.

**Day 10 BRD cures rates²**

<table>
<thead>
<tr>
<th></th>
<th>Idaho</th>
<th>Nebraska</th>
<th>California</th>
<th>Texas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PERCENT CURE</strong></td>
<td>40</td>
<td>10</td>
<td>35</td>
<td>75</td>
<td>28.3</td>
</tr>
<tr>
<td><strong>Negative control</strong></td>
<td>90</td>
<td>67.5</td>
<td>90</td>
<td>85</td>
<td>83.1</td>
</tr>
<tr>
<td><strong>ADVOCIN 2 mL/100 lb. single dose</strong></td>
<td>90</td>
<td>67.5</td>
<td>90</td>
<td>85</td>
<td>83.1</td>
</tr>
</tbody>
</table>

²Pharmacokinetic/pharmacodynamic studies are not necessarily representative of clinical results.

*Pharmacokinetic/pharmacodynamic studies are not necessarily representative of clinical results.

²Pharmacokinetic/pharmacodynamic studies are not necessarily representative of clinical results.

---

**Important Safety Information:** Federal law prohibits the extra-label use of all fluoroquinolones including ADVOCIN in food-producing animals. Not for use in cattle intended for dairy production or in calves to be processed for veal. ADVOCIN has a pre-slaughter withdrawal time of four days.
STUDIES SHOW THAT CATTLE TREATED WITH ADVOCIN GAINED WEIGHT FASTER DUE TO DISEASE RECOVERY

Effect of ADVOCIN on weight gain in cattle with BRD

<table>
<thead>
<tr>
<th>Least Square Means Weight Gain (lbs.)</th>
<th>Idaho</th>
<th>Nebraska</th>
<th>California</th>
<th>Texas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative control</td>
<td>34.8</td>
<td>21.8</td>
<td>15.4</td>
<td>19.1</td>
</tr>
<tr>
<td>ADVOCIN 2 mL/100 lb. single dose</td>
<td>9.9</td>
<td>7.2</td>
<td>15.4</td>
<td>26.8</td>
</tr>
</tbody>
</table>

COMPARED WITH BAYTRIL, ADVOCIN REQUIRES A LOWER DOSE VOLUME

<table>
<thead>
<tr>
<th></th>
<th>Dose to treat a 500-lb. animal</th>
<th>Number of injections</th>
<th>ADVOCIN 4 days</th>
<th>Baytril 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVOCIN™</td>
<td>10 mL</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baytril</td>
<td>17 mL to 28.5 mL</td>
<td>1-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A 4-DAY WITHDRAWAL TIME MEANS FLEXIBILITY TO TREAT ANIMALS DURING THE ENTIRE FEEDING PERIOD

With a 2 mL/100 lb. dose and a competitive price, ADVOCIN can help you manage BRD while increasing your profit margins.

UNPARALLELED SALES AND TECHNICAL SUPPORT

- Zoetis has the most experienced sales Field Force and Cattle Technical Services team in the industry.
- A Zoetis veterinarian is just a phone call away to help answer any technical questions.

To learn how new fast-acting ADVOCIN can help increase your profit margins, talk to your veterinarian or Zoetis representative.

---

2 Data on file, Study Report Nos. 1133C-60-96-249, 1133C-60-96-250, 1133C-60-97-258, 1133C-60-97-261, Zoetis Inc.
3 Freedom of Information summary for NADA 141-207 (danofloxacin mesylate).
4 Freedom of Information summary for Baytril (enrofloxacin).

All trademarks are the property of Zoetis Inc., its affiliates and/or its licensors. All other trademarks are the property of their respective owners. ©2013 Zoetis Inc. All rights reserved. ADV13003
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 exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. To report adverse reactions or to obtain a copy of the Material Safety Data Sheet (MSDS), call 1-800-366-5288.

PRECAUTIONS: The effects of danofloxacin on bovine reproductive performance, pregnancy, and lactation have not been determined. Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter. 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 the gingiva in immature, rapidly growing animals of various species. Refer to Animal Safety section for additional cautions.

ADVERSE REACTIONS: A hypersensitivity reaction was noted in 2 healthy calves treated with ADVOCIN in a laboratory study. In one location of a multi-site field trial, one out of the 41 calves treated with 6 mg/kg 48 hours shaved lameness on Day 6 only. In the same field trial location one of 38 calves treated with 8 mg/kg once became lame 4 days after treatment and remained lame on the last day of the study (Day 10). Another calf in the same treatment group developed lameness on the last day of the study.

CLINICAL PHARMACOLOGY:
(a) Pharmacokinetics: Danofloxacin distributes extensively throughout the body, as evidenced by a steady state volume of distribution (Vss) in cattle exceeding 1 L/kg. Danofloxacin last concentrations in the lung homogenates markedly exceed those observed in plasma, further suggesting extensive distribution to the site of infection. Danofloxacin is rapidly eliminated from the body (apparent terminal elimination T1/2 ranging from 3-6 hours), and negligible accumulation was observed when animals were dosed twice, 48 hours apart. Danofloxacin is rapidly absorbed and is highly bioavailable when administered as a subcutaneous injection in the neck. Linear pharmacokinetics has been demonstrated when danofloxacin is administered to cattle by subcutaneous injection at doses between 2.5 and 10 mg/kg. No statistically significant gender difference was observed in peak or total systemic exposure following a single subcutaneous administration of danofloxacin to heifers and steers at a dose of 6 mg/kg body weight (Table 1).

Table 1. Danofloxacin pharmacokinetic values in male and female cattle (n=6/group) after a single subcutaneous injection into the lateral neck region at a dose of 6 mg danofloxacin/kg body weight

<table>
<thead>
<tr>
<th>Steers</th>
<th>Heifers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± CV</td>
<td>Mean ± CV</td>
</tr>
<tr>
<td>AUC0-24 μg x hr/mL</td>
<td>9.4 ± 1.25</td>
</tr>
<tr>
<td>t1/2</td>
<td>10.5 ± 6.2</td>
</tr>
<tr>
<td>CL/L/hr</td>
<td>32 ± 1.2</td>
</tr>
<tr>
<td>V/D kg</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td>F%</td>
<td>92 ± 5</td>
</tr>
</tbody>
</table>

(b) Microbiology: Danofloxacin exerts its activity by inhibiting the bacterial DNA gyrase enzyme, thereby blocking DNA replication. Inhibition of DNA gyrase is lethal to bacteria and danofloxacin has been shown to be rapidly bactericidal. Danofloxacin is active against gram-negative and gram-positive bacteria.

The Minimum Inhibitory Concentrations (MIC) of danofloxacin for pathogens isolated in natural infections from various clinical studies in North America, 1996–1997, were determined using the standardized microdilution technique (Sensititre/Alamar, Accumed International), and are shown in Table 2.

Table 2. Danofloxacin minimum inhibitory concentration (MIC) values of indicated pathogens isolated from 1996-1997 pivotal BRD treatment field studies in the U.S.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number of Isolates</th>
<th>MIC50 (μg/mL)</th>
<th>MIC90 (μg/mL)</th>
<th>MIC Range (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasteurella multocida</td>
<td>94</td>
<td>≤0.015</td>
<td>0.06</td>
<td>≤0.015 to 0.12</td>
</tr>
<tr>
<td>Mannheimia haemolytica</td>
<td>106</td>
<td>0.06</td>
<td>0.06</td>
<td>≤0.015 to 0.12</td>
</tr>
</tbody>
</table>

* The correlation between in vitro susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 90% and 90% of the most susceptible isolates, respectively.

EFFECTIVENESS: The effectiveness of 8 mg/kg administered once and the 6 mg/kg BW alternate day regimen was confirmed in 4 well-controlled studies of naturally acquired bacterial respiratory infections in cattle. At the highest dose tested, effects were observed under commercial conditions at 4 locations in North America. Bacterial pathogens isolated in the clinical field trial are provided in the Microbiology section.

ANIMAL SAFETY: Safety studies were conducted in feeder calves using single doses of 10, 20, or 30 mg/kg for 6 consecutive days and 18, 24, or 60 mg/kg for 3 consecutive days. No clinical signs of toxicity were observed at doses of 10 and 20 mg/kg when administered for 6 days, nor at doses of 18 mg/kg, 24 mg/kg when administered for 3 days. Articular cartilage lesions, consistent with quinolone chondropathy, were observed after examination of femurs from animals as follows: one of 5 animals administered 18 mg/kg for 3 days; one of 6 animals administered 20 mg/kg for 6 days; 5 of 6 animals administered 30 mg/kg for 6 days; and in all 4 animals administered 60 mg/kg for 3 days. Clinical signs of inappetence, transient lameness (2/8), ataxia (2/8), tremors (2/8), nystagmus (1/8), exophthalmos (1/8), and recumbency (2/8) were observed when a dose of 30 mg/kg was administered for 6 consecutive days. Recumbency and depression were seen in one out of 4 animals administered 60 mg/kg for 3 days. Swelling at the injection site was noted at each dose level.

Safety was also evaluated in 21-day-old calves. In one group, these immature animals were given injections of 8 mg/kg on study days 0, 2, 3, 5, 6, and 8. A second group of animals received injections of 18 mg/kg for a total of 2 injections 48 hours apart. The only treatment-related sign was erythema of the nasolabial fold in 3 of 6 calves that received 18 mg/kg. One calf in the 6 mg/kg group had pre-treatment scleral erythema, and developed nasal erythema after treatment that may or may not have been treatment-related. No changes in clinical pathology parameters were observed. No articular cartilage lesions were observed in the joints at any dosage.

An injection site study conducted in feeder calves demonstrated that the product can induce a transient local reaction in the subcutaneous tissue and underlying tissue.

TOXICOLOGY: Ninety-day oral toxicity studies in dogs and rats established a no observable effect level (NOEL) of 2.5 mg/kg bw/day and 4 mg/kg bw/day, respectively. Higher doses of juvenile dogs produced arthropathy, a typical quinolone-associated side effect. In chronic rodent bioassays, no evidence of carcinogenicity was associated with long-term danofloxacin administration in rats and mice. No teratogenic effects were observed in rodents at doses up to 50 mg/kg bw/day (mice) or 100 mg/kg bw/day (rats) using single doses of 15 mg/kg bodyweight/day. A three-generation rat reproductive toxicology study established a NOEL of 0.25 mg/kg bw/day. Microbial safety analyses indicate that danofloxacin residues present in edible tissues of treated animals under the current use conditions would most likely not cause adverse effects on the human intestinal microflora of the consumer.

STORAGE INFORMATION: Store at or below 30°C (86°F). Protect from light. Protect from freezing. The color is yellow to amber and does not affect potency.

HOW SUPPLIED: ADVOCIN (180 mg danofloxacin/mL) is supplied in 100- and 250-mL amber-glass, sterile, multi-dose vials.

NADA #141-207. Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc, NY, NY 10017

Pfizer Animal Health

Use Only as Directed

CONTACT INFORMATION: To report suspected adverse effects and/or obtain a copy of the MSDS for or technical assistance, call Pfizer Animal Health at 1-800-366-5288.

For a complete listing of adverse reactions for ADVOCIN Sterile Injectable Solution reported to CVM see: http://www.fda.gov/AnimalVeterinary/SafetyHealth

THERE IS A RISK OF USER PHOTOSENSITIZATION WITHIN A FEW HOURS AFTER EXPOSURE TO QUINOLONES. IF EXCESSIVE ACCIDENTAL EXPOSURE OCCURS, AVOID DIRECT SUNLIGHT.