Sterile Injectable Solution Antimicrobial

180 mg of danofloxacin as the mesylate salt/mL

For subcutaneous use in beef cattle.

Not for use in cattle intended for dairy production or in calves to be processed for veal.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits the extra-label use of this drug in food-producing animals.

DESCRIPTION: ADVOCIN is a sterile injectable solution containing danofloxacin mesylate, a synthetic fluoroquinolone antimicrobial agent. Danofloxacin mesylate is the proprietary designation for (1S)-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-4-oxo-3-quinoline carboxylic acid monomethanesulfonate. The empirical formula is C₁₉H₂₀FN₃O₃ • CH₃SO₃H and the molecular weight is 453.49.

Figure 1. The chemical structure of danofloxacin mesylate.

To report adverse reactions or to obtain a copy of the Material Safety Data Sheet (MSDS), call 1-888-963-8471.

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 remain for 24-48 hours after the injection site.

Quinoline-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.

Quinoline-class drugs have been shown to produce erations of weight-bearing joints and other signs of arthropathy in immature, rapidly growing animals of various species. Refer to Animal Safety for information specific to danofloxacin.

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 showed lameness on Day 6. In the same field trial location one of 38 calves treated with 8 mg/kg once became lame 2 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 10,000 liters and the drug is excreted primarily in the urine. The drug is also distributed to the concentrating mechanism of the kidney. Danofloxacin is administered to cattle by subcutaneous injection at doses between 1.25 to 10 mg/kg. No statistically significant gender difference was observed in peak plasma concentration, systemic exposure following a single subcutaneous administration of danofloxacin to heifers and steers at a dose of 6 mg/kg body weight (Table 1).

(b) Microbiology: Danofloxacin exerts its activity by inhibiting the bacterial DNA gyrase enzyme, thereby blocking DNA replication. 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 (Schaetzl/Alexander, Accumed International), and are shown in Table 2.

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/kg danofloxacin/kg body weight. * Mean ± CV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Steers (n=6)</th>
<th>Heifers (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-inf}</td>
<td>9.4 ± 10%</td>
<td>9.8 ± 8%</td>
</tr>
<tr>
<td>Cmax</td>
<td>52 ± 8%</td>
<td>57 ± 10%</td>
</tr>
<tr>
<td>Vss</td>
<td>12,616 ± 12%</td>
<td>12,517 ± 12%</td>
</tr>
<tr>
<td>Cl</td>
<td>3.2 ± 12%</td>
<td>1.7 ± 31%</td>
</tr>
<tr>
<td>Vdss</td>
<td>4.8 ± 18%</td>
<td>2.7 ± 26%</td>
</tr>
</tbody>
</table>

* Administered dose volume would not exceed 15 mL per injection site.

Clinical field studies indicate that ADVOCIN (danofloxacin injection) Sterile Injectable Solution is effective for the control of respiratory disease in beef cattle at high risk of developing BRD. Cattle at high risk of developing BRD typically experience weight loss or one or more of the following risk factors:

- Commingling from multiple sale barns/sources
- Extended transport times and shrink
- Exposure to cold or wet weather conditions or wide temperature swings
- Stressful arrival processing procedures (such as castration, dehorning, or branding)
- Recent weaning or poor vaccination history

RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 4 days from the last treatment. Do not use in cattle intended for dairy production. A withholding period has not been established for this product in preruminating calves.

Do not use in calves to be processed for veal.

HUMAN WARNINGS: For use in animals only. Keep out of reach of children.

Avoid contact with eyes. In case of contact, immediatly 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.

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 feedlot age cattle. These studies were conducted under commercial conditions at 4 locations in North America. Bacterial pathogens isolated in the clinical field trial are provided in the Microbiology section.

The effectiveness of ADVOCIN for the control of BRD in cattle at high risk of developing BRD associated with Mannheimia haemolytica and Pasteurella multocida was demonstrated in a multi-site study conducted in North America. The study enrolled a total of 1,480 commercial, crossbred-beef, Holstein and Holstein-cross steer calves at high risk of developing BRD associated with M. haemolytica and P. multocida. At enrollment, calves were randomly administered a one-time subcutaneous injection of either ADVOCIN at a dosage rate of 8 mg/kg body weight or an equivalent volume of sterile saline. Cattle were observed daily for clinical signs of BRD and were evaluated for clinical success on Day 10 post-treatment.

The treatment success rate of ADVOCIN-treated calves (86.0%) was statistically significantly (p<0.0069) greater than that of saline-treated calves (78.3%) based on back-transformed least squares means. No adverse events associated with ADVOCIN administration were reported in the study.

ANIMAL SAFETY: Safety studies were conducted in feeder calves using single doses of 10, 20, or 30 mg/kg for 4 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 5 days, nor at doses of 18 and 24 mg/kg when administered for 3 days. Articular cartilage lesions, consistent with fluorquinolone chondroplasty, were observed after examination of joints from animals as follows: one of 5 animals administered 30 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 6 animals administered 60 mg/kg for 3 days. Clinical signs of insensitivity, transient lameness (2S), ataxia (2A), tremors (2T), rystagmus (1R), esophagitis (1B), and recumbency (2B) 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, but at the injection site. No clinical signs of toxicity were administered to calves that had received 18 mg/kg. One calf in the 8 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 dose. 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.

OXALOGENOLOGY: Ninety-day oral toxicity studies in dogs and rats established a no observable effect level (NOEL) of 2.5 mg/kg bw/day and 2.4 mg/kg bw/day, respectively. Higher doses in 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 100 mg/kg bw/day (1 g/kg bw/day in rats) or in rabbits at the highest dose tested of 15 mg/kg bw/day. A three-generation rat reproductive toxicity study established a NOEL of 6.25 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 glass, sterile, multi-dose vials. NADA #141-207. Approved by FDA.

Zoetis Distributed by:

Zoetis Inc.
Kalamazoo, MI 49007

Use Only as Directed

CONTACT INFORMATION: To report suspected adverse effects and/or obtain a copy of the MSDS or for technical assistance, call Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact the FDA-VETS or online at http://www.aphis.usda.gov/veterinary/SafetyHealth/animal-drugs.html.

Revised: May 2014

Made in France

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