ADVOCIN™
(danofloxacin injection)
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 extralabel use of this drug in food-animals.
DESCRIPTION: ADVOCIN is a sterile injectable solution containing danofloxacin mesylate, a synthetic fluoroquinolone antimicrobial agent. Danofloxacin mesylate is the mesylate 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-quinolone carboxylic acid monomethanesulfonate. The empirical formula is C_{14}H_{11}FNO_4S_2 and the molecular weight is 453.49.

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 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>Male Cattle</th>
<th>Female Cattle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Concentration (µg/mL)</td>
<td>C_{max}</td>
<td>4.0±0.4</td>
<td>3.6±0.5</td>
</tr>
<tr>
<td>Time to Peak Concentration (hr)</td>
<td>t_{max}</td>
<td>4.3±0.4</td>
<td>3.8±0.5</td>
</tr>
<tr>
<td>Area under the plasma concentration versus time curve from time 0 to 24 hr</td>
<td>AUC_{0-24}</td>
<td>25.4±5.0</td>
<td>22.0±4.0</td>
</tr>
<tr>
<td>Clearance (L/hr)</td>
<td>C_L</td>
<td>3.2±0.2</td>
<td>3.1±0.3</td>
</tr>
<tr>
<td>Volume of distribution at steady state (L)</td>
<td>V_{ss}</td>
<td>0.7±0.1</td>
<td>0.6±0.1</td>
</tr>
<tr>
<td>Bioavailability (F%)</td>
<td>F</td>
<td>60±5</td>
<td>65±5</td>
</tr>
<tr>
<td>Half-life (hr)</td>
<td>t_{1/2}</td>
<td>33±7</td>
<td>31±7</td>
</tr>
</tbody>
</table>

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 result in a transient lesion at the site of injection. Quinolone-class drugs should be used with caution in animals with known or suspected central nervous system (CNS) disorders. In such animals, the quinolones have, in rare instances, been associated with CNS stimulation, which may lead to convulsive seizures. Quinolone-class drugs have been shown to produce erasations of cartilage 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 3 calves treated with 6 mg/kg 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 exceeded 1000 L. Danofloxacin concentrations in the liver, kidney, brain, and skeletal muscle markedly exceeded those observed in plasma, further suggesting extensive distribution to the indicated site of infection. Danofloxacin is rapidly eliminated from the body (apparent terminal elimination t_1/2 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 by cattle by subcutaneous injection at doses between 1.25 to 10 mg/kg. No statistically significant gender difference was observed in peak and systemic exposure following a single subcutaneous administration of ADVOCIN 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. Inactivation 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 from naturally acquired bacterial respiratory infections in feedlot age studies of North America, 1996–1997, were determined using the standardized microbroth technique (Knoxe et al, Accused International), and are shown in Table 2.

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

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

**The lowest MIC to encompass 50% 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 feedlot age cattle. These studies were conducted under commercial conditions at 4 locations in North America. Bacterial pathogens isolated in the clinical field trial were 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 1,410 commercial, crossbred-beef, Holstein and Holstein-cross steer calves at high risk of developing BRD associated with M. haemolytica and P. multocida. An enrollment, calves were randomly administered a one-time subcutaneous injection of either ADVOCIN at a dosage rate of 8 mg/kg of 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 (80.8%) was statistically significantly (p<0.0068) 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 19, 25, or 38 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 chondrotoxicity, were observed after examination of joints from animals as follows: one of 5 animals administered 38 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 3 days; and in 4 animals administered 60 mg/kg for 3 days. Clinical signs of inappetence, transient lameness (2X), ataxia (2X), tremors (2X), rystagmus (1X), exophthalmia (1X), and recumbency (2X) were observed when a dose of 30 mg/kg was administered for 6 consecutive days. Recumbency and depression were seen in one of 4 animals administered 60 mg/kg for 3 days. Clinical signs in cattle administered 60 mg/kg were typical of anorexia. 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 adverse effect was erythema of the nasal pad in 3 of 6 calves that 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 pathophysiological 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 7.5 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 rats following doses up to 50 mg/kg bw/day (equivalent to 100 mg/kg bw/day in dogs) or 100 mg/kg bw/day (equivalent to 6.25 mg/kg bw/day in rats) in 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, amber-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 to obtain a copy of the Material Safety Data Sheet (MSDS) or for technical assistance, call Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug reporting for animal drugs, contact the FDA at 1-888-VETS-4YOU or online at http://vets.fda.gov. For reports involving Veterinary/Safety/Health problems, contact 1-800-243-0466.

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