

A180™

(danofloxacin mesylate)

Sterile Antimicrobial Injectable Solution

180.0 mg of danofloxacin as the mesylate salt/mL

For subcutaneous use in cattle only

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: A180 is a sterile solution containing danofloxacin mesylate, a synthetic fluoroquinolone antimicrobial agent. Danofloxacin mesylate is the non-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-quinolone carboxylic acid monomethanesulfonate. The empirical formula is $C_{19}H_{20}FN_3O_3 \cdot CH_3SO_3H$ and the molecular weight is 453.49.

Each mL contains 180.0 mg of danofloxacin as the mesylate salt, 200.0 mg 2-pyrrolidone, 50.0 mg polyvinyl pyrrolidone, 20.3 mg heavy magnesium oxide, 2.5 mg phenol, 5.0 mg monothioglycerol, hydrochloric acid or sodium hydroxide as needed to adjust pH, nitrogen headspace and water for injection, q.s.

INDICATIONS: A180 (danofloxacin) injectable solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia (Pasteurella) haemolytica* and *Pasteurella multocida*.

DOSAGE AND ADMINISTRATION: A180 is administered as a subcutaneous dose of 6 mg/kg of body weight (1.5 mL/100 lb). Treatment should be repeated once approximately 48 hours following the first injection. Care should be taken to dose accurately. Administered dose volume should not exceed 15 mL per injection site.

A180 Dosage and Treatment Schedule

**6 mg/kg, given twice,
48 hours apart**

| Cattle Weight (lb) | Dose Volume (mL) |
|-----------------------|------------------|
|-----------------------|------------------|

| | |
|------|------|
| 50 | 0.75 |
| 100 | 1.5 |
| 150 | 2.25 |
| 200 | 3.0 |
| 250 | 3.75 |
| 300 | 4.5 |
| 400 | 6.0 |
| 500 | 7.5 |
| 600 | 9.0 |
| 700 | 10.5 |
| 800 | 12.0 |
| 900 | 13.5 |
| 1000 | 15.0 |

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 withdrawal 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, 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. To report adverse reactions or to obtain a copy of the Material Safety Data Sheet, 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 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 A180 in a laboratory study. In one location of a multi-site field trial, one out of the 41 calves treated with 6 mg/kg q 48 hours showed lameness on Day 6 only. In this 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 (VD_{ss}) exceeding 1 L/kg. Danofloxacin concentrations in the lung homogenates markedly exceed 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 therefore negligible accumulation is expected to occur when animals are dosed with a q48h-dosing regimen.

Danofloxacin is rapidly absorbed and is highly bioavailable when administered as a subcutaneous injection in the neck. No statistically significant gender difference was observed in peak or total systemic exposure following subcutaneous administration. Linear pharmacokinetics has been demonstrated when danofloxacin is administered by subcutaneous injection at doses up to 10 mg/kg. Pharmacokinetic parameter values associated with a 6-mg/kg dose are provided in Table 1.

Table 1. Danofloxacin pharmacokinetic values (6 mg/kg)

| | | Steers | | Heifers | |
|----------------------------------|------------|--------|------------------|---------|-----|
| | | Mean | %CV ^e | Mean | %CV |
| ^a AUC ₀₋₂₄ | µg x hr/mL | 9.4 | 10 | 8.8 | 9 |
| ^b F% | | 92 | 5 | 87 | 3 |
| ^a C _{max} | µg/mL | 1.25 | 16 | 1.27 | 13 |
| ^{a,c} T _{max} | hr | 3.2 | 42 | 1.7 | 31 |
| ^d CL | L/hr | 0.54 | 12 | 0.62 | 9 |
| ^d VD _{ss} | L/kg | 2.7 | 7 | 2.6 | 4 |
| ^a T _{1/2} | hr | 4.8 | 18 | 4.2 | 7 |

^a Pharmacokinetic estimates based upon a 6-mg/ kg subcutaneous injection administered into the lateral neck region. AUC₀₋₂₄ = area under the plasma concentration versus time curve from hr zero to hr 24 postdose. C_{max} = maximum observed concentration. T_{max} = time to C_{max}.

^b F% = extent of drug absorption following subcutaneous administration. Within subject F values were determined as the ratio of AUC_{0-inf} values estimated following a 6-mg/kg dose administered as either a subcutaneous or intravenous injection.

^c T_{max}: statistically significant differences were detected between genders. Given the similarity in C_{max} values, these differences are not expected to have any clinical significance.

^d CL and VD_{ss} were determined from data obtained after intravenous administration of a 6-mg/kg dose.

^e Coefficient of variation %

(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, 1994–1997, were determined using the standardized microdilution technique (SENSITITRE/ALAMAR, Accumed International), and are shown in Table 2.

Table 2. MIC values (µg/mL) of danofloxacin against bacterial isolates from natural infections of cattle

| Species | No. Isolates | Range µg/mL | MIC ₉₀ ** µg/mL |
|---|--------------|-------------|----------------------------|
| <i>Mannheimia (Pasteurella) haemolytica</i> | 363 | ≤0.015–0.12 | 0.06 |
| <i>Pasteurella multocida</i> | 301 | ≤0.015–0.12 | 0.015 |
| <i>Haemophilus somnus</i> * | 32 | ≤0.015–0.06 | 0.06 |

* The clinical significance of these *in-vitro* data has not been demonstrated.

** The minimum inhibitory concentration for 90% of the isolates.

EFFECTIVENESS: The effectiveness of 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.

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 and 24 mg/kg when administered for 3 days. Articular cartilage lesions, consistent with fluoroquinolone chondropathy, were observed after examination of joints 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 (2/6), ataxia (2/6), tremors (2/6), nystagmus (1/6), exophthalmos (1/6), and recumbency (2/6) 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 6 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 nasal pad 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: The approximate oral LD50 for laboratory mice and rats was greater than 2000 mg/kg of body weight. Ninety-day oral gavage studies in dogs and rats established a no observable effect level (NOEL) of 2.4 mg/kg bw/day and 6.25 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 50 mg/kg bw/day (mice) or 100 mg/kg bw/day (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 will 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: A180 (180 mg danofloxacin/mL) is supplied in 100- and 250-mL, amber-glass, sterile, multi-dose vials.

NADA #141-207, Approved by FDA

Use Only as Directed

To report suspected adverse effects, and/or obtain a copy of the MSDS, call 1-800-366-5288.

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