Pfizer Animal Health
Technical Bulletin

7-, 10-, 14-Day PTI August 2006

Efficacy of DRAXXIN®, followed by 7-, 10-, or 14-day post-treatment intervals, against naturally occurring bovine respiratory disease

Pfizer Animal Health, New York, NY

Key Points

- DRAXXIN® (tulathromycin) Injectable Solution administered as a single subcutaneous (SC) injection was safe and effective for the treatment of bovine respiratory disease (BRD) in high-risk feeder calves.
- Through 56 days there was no significant difference in treatment success, BRD mortality, or average daily gain (ADG) with a 7-, 10- or 14-day minimum post-treatment interval.
- Post-treatment intervals did not significantly affect treatment success, providing management flexibility based on managerial, labor and market factors.

Introduction

DRAXXIN is a highly effective, single-dose antimicrobial medication indicated for treatment of BRD, and control of respiratory disease in cattle at high risk of developing BRD caused by *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.* When administered according to the label dose of 2.5 mg tulathromycin/kg body weight (BW; 1.14 mL/100 lb), tulathromycin is rapidly absorbed, distributes widely, and provides concentrations in bovine lung for an extended period.[1] Clinical efficacy of DRAXXIN for treatment of BRD, as well as for control of respiratory disease in cattle at high risk of developing BRD, has been well documented in multiple studies.[2,3,4]

Based on results of studies with EXCEDE® *(ceftiofur crystalline free acid)* Sterile Suspension, Pfizer Animal Health introduced the concept of prolonged post-treatment intervals.[5,6,7] Data showed that a single administration of EXCEDE provided effective concentrations of medication against the targeted pathogens of BRD for at least 7 days.[5] That information was the impetus for an additional study,[6] which

revealed that a post-treatment interval of 3-, 5- or 7-days resulted in clinical success without increasing the incidence of BRD-associated mortality or chronic cases. Traditional management practices of repeated administration of medication or changing medication were challenged by the prospect that the animal could be allowed to respond and begin to recover while an effective medication was provided by a single injection.

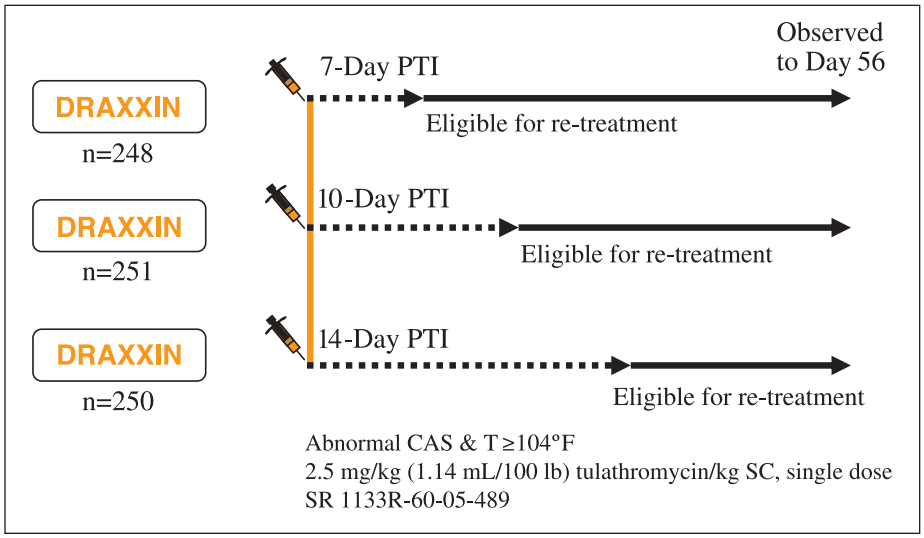
Although the active ingredients in EXCEDE and in DRAXXIN are chemically distinct, the targeted pathogens and approved use of the two products are similar. Previous studies with DRAXXIN were designed so that animals that met re-treatment criteria were eligible to be re-treated 3 days after they received DRAXXIN.[2,3,4] It was of interest, therefore, to know if restricting eligibility for re-treatment would be reflected in clinical efficacy. This technical bulletin presents the results of a study designed to compare the effects of 3 post-treatment intervals (7, 10 or 14 days) on the incidence of BRD in high-risk feeder calves following initial treatment with DRAXXIN.

Materials and Methods

Crossbred heifer feeder calves, which originated from auction sales in Missouri, Arkansas, Kentucky and Tennessee, were assembled at a research facility. The calves were 4 to 10 months of age and had a mean BW of 473 lb (324 to 640 lb). Calves meeting enrollment criteria and exhibiting clinical signs of BRD were treated with DRAXXIN (2.5 mg/kg, 1.14 mL/100 lb) and assigned to 1 of 3 groups having a minimum post-treatment interval of 7, 10 or 14 days, respectively (Figure 1). Enrollment criteria included: no concurrent disease that could interfere with diagnosis or treatment of BRD; no antimicrobial treatment since arrival; a clinical attitude score (CAS) of 1, 2, or 3 *plus* a rectal temperature of ≥104°F. According to the CAS system, 0=normal, bright, alert, responsive; 1=mild depression, signs of weakness usually not present; 2=moderate depression, some signs of weakness, may be reluctant to stand; 3=severe depression, difficulty standing, head lowered or extended; or 4=moribund. Calves that did not meet the rectal temperature requirement were returned to the arrival pen and could be enrolled later if they met inclusion criteria. Full enrollment of 759 calves was achieved in 15 days. Following initial DRAXXIN treatment, cattle were housed outdoors in dirt-floor pens by treatment group, where they remained until slaughter.

During the first 56 days of study, animals were observed daily. An animal was considered a treatment failure if it had completed its minimum re-treatment interval and 1) scored a CAS of 1 or 2 with a rectal temperature ≥104°F, *or* 2) scored a CAS of 3 or 4 regardless of rectal temperature. Animals that failed to respond to DRAXXIN treatment received first re-treatment with A180® *(danofloxacin mesylate)* [6.0 mg danofloxacin/kg initially and a second treatment 48 hours later], followed by a 3-day post-treatment interval. Second re-treatment was with LIQUAMYCIN® LA-200® *(oxytetracycline injection)* [9.0 mg oxytetracycline/lb] and third re-treatment was with Nuflor® [40.0 mg florfenicol/kg], both followed by a 3-day post-treatment interval. Animals eligible for a fourth re-treatment were declared chronics.

Figure 1. Experimental Design



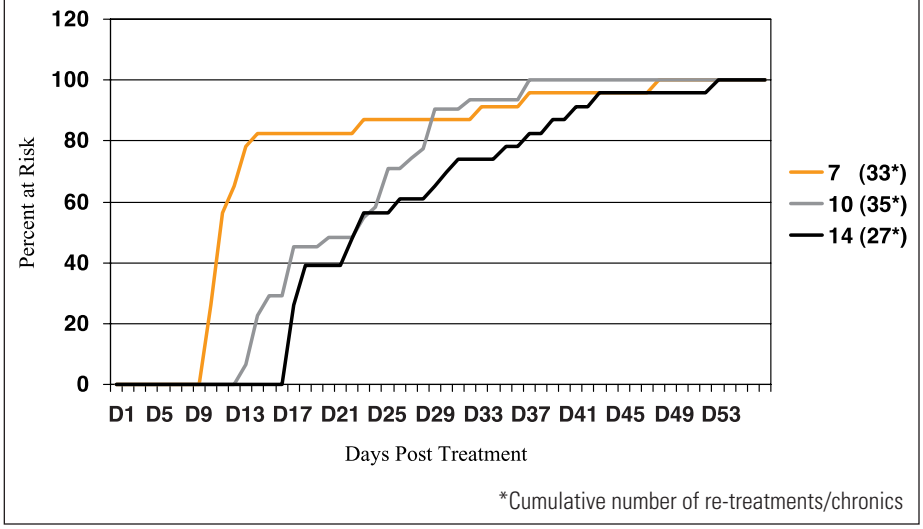
Results

The DRAXXIN first-treatment success (defined as the percentage of animals that did not qualify for BRD re-treatment, were not BRD mortalities, and were not removed for non-BRD reasons) was not significantly different ($P>0.19$) among cattle with a 7-day minimum post-treatment interval (85.9%), 10-day minimum post-treatment interval (85.3%), or 14-day minimum post-treatment interval (88.8%; Table 1). Cumulative distribution of first re-treatments are shown in Figure 2. Figure 3 shows re-treatment by each day eligible. Time

Table 1. Summary of Results Through Day 56			
	DRAXXIN 7-Day	**DRAXXIN 10-Day**	**DRAXXIN 14-Day**
Animals Enrolled	253	253	253
Removals (Non-BRD or Protocol Deviation*)	5	2	3
Treatment Success % (no.)	85.9 (213/248)	85.3 (214/251)	88.8 (222/250)
BRD Mortality % (no.)	0.8 (2/248)	0.8 (2/251)	0.4 (1/250)
First Non-Response	23	31	23
Second Non-Response	7	4	3
Third Non-Response	2	0	0
BRD Chronics % (no.)	0.4 (1/248)	0 (0/251)	0.4 (1/250)
LSM Average Daily Gain, Deads Out lb/day [SD] (range)	2.70 [0.70] (-0.18 - 4.14)	2.72 [0.67] (0.64 - 4.46)	2.55 [0.74] (-0.79 - 4.14)

*7-Day = 5 removals (2 CNS, 1 musculoskeletal, 1 traumatic reticuloperitonitis, 1 protocol deviation)
10-Day = 2 removals (1 protocol deviation, 1 abdominal disease not related to BRD)
14-Day = 3 removals (1 CNS, 2 musculoskeletal)

Figure 2. Cumulative First Re-treatments



*Cumulative number of re-treatments/chronics

to 50% re-treatments for the 7-, 10- and 14-day groups corresponded to Days 9, 21, and 24 of the study for each group, respectively.

There was no difference ($P > 0.31$) in BRD mortality (DRAXXIN 7-day=0.8%; DRAXXIN 10-day=0.8%; DRAXXIN 14-day=0.4%) or in combined incidence of BRD mortality and BRD chronic cases (DRAXXIN 7-day=1.2%; DRAXXIN 10-day=0.8%; DRAXXIN 14-day=0.8%) among treatment groups. There was no significant difference ($P > 0.09$) in ADG among cattle in any of the treatment groups (DRAXXIN 7-day=2.70 lb/day; DRAXXIN 10-day=2.72 lb/day; DRAXXIN 14-day=2.55 lb/day).

Through 56 days there was no significant difference in treatment success, BRD mortality or ADG in feeder calves with a 7-, 10- or 14-day minimum post-treatment interval following a single DRAXXIN injection for the treatment of BRD.

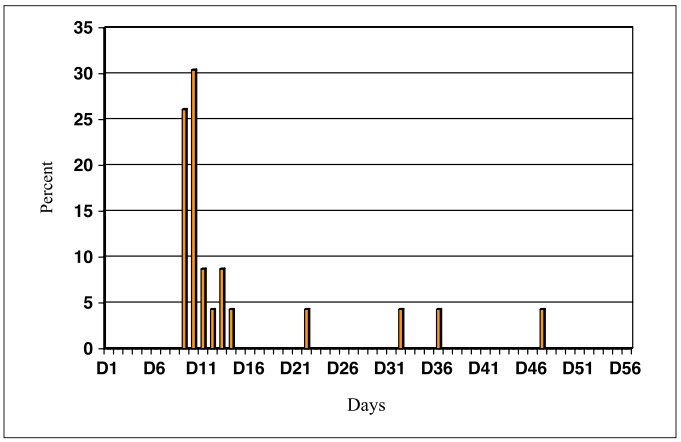
Discussion

Pfizer Animal Health introduced the concept of a prolonged re-treatment or post-treatment interval (PTI)—a period of time after treatment when no further treatments for BRD are administered—after obtaining results of studies using EXCEDE. Clinical studies were designed to test the hypothesis that administering additional treatments based on clinical signs alone, while adequate concentrations of active drug and metabolites are still present, does not increase treatment success. Two studies demonstrated this hypothesis to be true for EXCEDE.[5,6] Both studies found significantly higher 28-day single-treatment success using EXCEDE with a 7-day PTI than with 3- or 5-day PTIs. In addition, EXCEDE with a 7-day PTI significantly increased 56-day treatment success by 14 percentage points over Baytril® (enrofloxacin) 100 Antimicrobial Injectable Solution with a 3-day PTI.[7] This improvement was achieved without increasing mortality or negatively affecting ADG. Traditional management practices of repeated administration of medication or changing medication were challenged by the prospect that the animal could be allowed to respond and begin recovery following a single injection of effective medication.

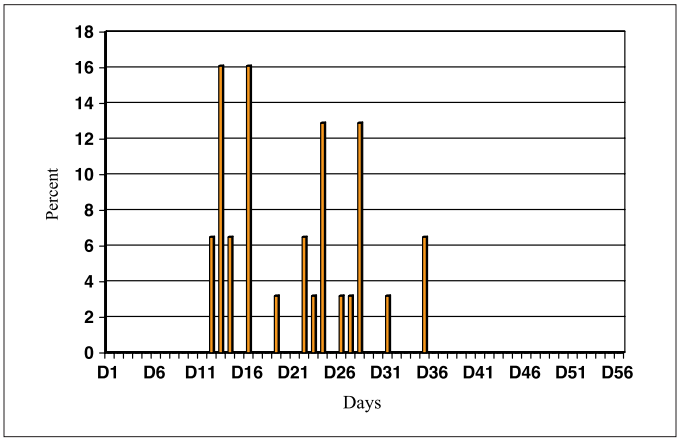
Although the active ingredients in EXCEDE and DRAXXIN are chemically distinct, the targeted pathogens and approved use and management applications of the two products are similar. In previous studies of DRAXXIN, animals meeting re-treatment criteria could be treated 3 days after receiving DRAXXIN. The objective of the current study was to evaluate post-treatment intervals after a single dose of DRAXXIN so that results could be used to help veterinarians and producers make management decisions for their individual needs. Results of this study revealed no significant difference in measured responses among the 3 treatment groups. However, it is important to note that the lack of numerical differences among treatment groups with respect to ADG could be due to a lack of statistical resolution.

Figure 3. Frequency Distribution of Re-treatments for Each Experimental Group

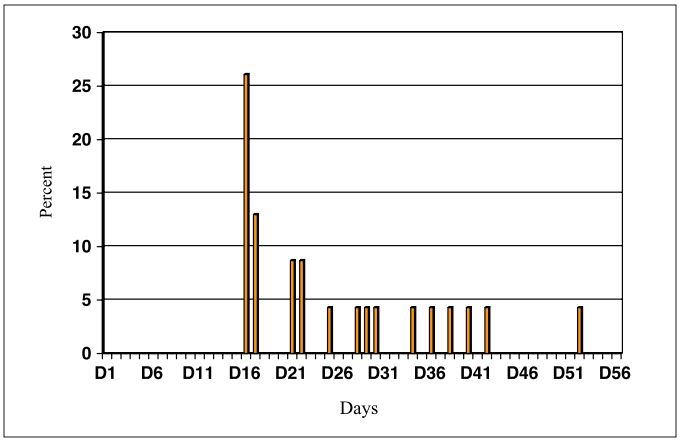
a. In the 7-day group, 50% of re-treatments occurred by Day 9.



b. In the 10-day group, 50% of re-treatments occurred by Day 21.



c. In the 14-day group, 50% of re-treatments occurred by Day 24.



While results of this study with respect to treatment success are clear, all cattle and management systems may not be similar to those in this study. The post-treatment intervals selected for this study were intended to stretch management practices further than has been done previously. With any sick animal, re-assessment of the diagnosis and monitoring of response to treatment are very important to selecting an optimal post-treatment interval, as well as to subsequent adjustments to treatment according to the needs of the patient.

Post-treatment patterns are valuable parameters to monitor on individual operations to help determine what the optimum post-treatment interval should be for any single-injection or extended-duration anti-infective. Optimum post-treatment intervals may vary with management philosophy, weight and class of cattle, and other environmental considerations. Therefore, it is important to evaluate post-treatment patterns (illustrated in Figure 3) on individual operations to determine the appropriate time for re-treatment following DRAXXIN initial therapy. This study was not designed to analyze statistically these post-treatment trends, but monitoring these trends would be valuable to help producers and veterinarians capitalize on the flexibility that the superior efficacy of DRAXXIN affords in terms of time management, labor, hospital management and cattle flow.

Conclusions

There was no significant difference in this 56-day study in treatment success, BRD mortality or ADG in feeder calves with a 7-, 10- or 14-day minimum post-treatment interval following a single DRAXXIN injection for the treatment of BRD.

Do not use DRAXXIN in female dairy cattle 20 months of age or older. Effects on reproductive performance, pregnancy and lactation have not been determined. Do not use in calves to be processed for veal. Do not use in chickens or turkeys. Do not use in animals known to be hypersensitive to the product.

As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug. Though safe in cattle when properly given, inadvertent intra-arterial injection in the ear is possible and is fatal. EXCEDE has a pre-slaughter withdrawal time of 13 days.

Do not use A180 in cattle intended for dairy production or to be processed for veal.

References

1 Nowakowski MA, Inskeep P, Risk J, Skogerboe TL, Benchaoui HA, Meinert TR. Sherington J, Sunderland SJ. Pharmacokinetics and lung tissue concentrations of tulathromycin, a new triamilide antibiotic, in cattle. *Vet Ther* 2004;5:60-74.

2 Nutsch RG, Skogerboe TL, Rooney KA, Weigel DJ, Gajewski K, Lechtenberg KF. Comparative efficacy of tulathromycin, tilmicosin and florfenicol in the treatment of bovine respiratory disease in stocker cattle. *Vet Ther* 2005;6(2):167-179.

3 Skogerboe TL, Rooney KA, Nutsch RG, Weigel DJ, Gajewski K, Kilgore WR. Comparative efficacy of tulathromycin versus florfenicol and tilmicosin against undifferentiated bovine respiratory disease in feedlot cattle. *Vet Ther* 2005;6(2):180-196.

4 Rooney KA, Nutsch RG, Skogerboe TL, Weigel DJ, Kimberly K, Kilgore WR. Efficacy of tulathromycin compared with tilmicosin and florfenicol for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease. *Vet Ther* 2005:6(2):154-166.

5 Hibbard B, Bryson WL, Follis SL, et al. Duration of therapy with EXCEDE® or Micotil® in a bovine respiratory disease challenge model. New York, NY: Pfizer Animal Health; 2004. EXD04019.

6 Hibbard B, Robb EJ, Meyer JA, Bryson L, Lucas MJ, Dame KJ. Outcomes of 3-, 5-, or 7-day post-treatment intervals after a single administration of EXCEDE®. New York, NY: Pfizer Animal Health; 2004. EXD04023.

7 Meyer JA, Moseley WM, Lucas MJ, et al. Efficacy of EXCEDE® followed by 3- or 7-day post-treatment intervals vs. Baytril® followed by a 3-day post-treatment interval in treatment of bovine respiratory disease. New York, NY: Pfizer Animal Health; 2004. EXD04024.

Prepared from Study Report 1133R-60-05-489.

Pfizer Animal Health

BEEF FRIENDLY

Draxxin®
(tulathromycin)
Injectable Solution

Antibiotic
100 mg of tulathromycin/mL

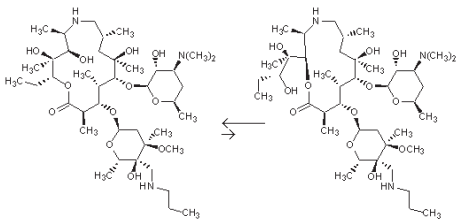
For subcutaneous injection in beef and non-lactating dairy cattle and intramuscular injection in swine only.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
DRAXXIN Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass; triamilide. Each mL of DRAXXIN contains 100 mg of tulathromycin as the free base in a 50% propylene glycol vehicle, monothioglycerol (5 mg/mL), with citric and hydrochloric acids added to adjust pH.

DRAXXIN consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio. Structures of the isomers are shown below.

Figure 1.



The chemical names of the isomers are (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyrano-syl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2S,3S,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribohexopyranosyl]oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylohexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS
Cattle
DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni (Haemophilus somnus), and for the control of respiratory disease in cattle at high risk of developing BRD, associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni (Haemophilus somnus).

Swine
DRAXXIN Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica and Haemophilus parasuis.

DOSAGE AND ADMINISTRATION
Cattle
Inject subcutaneously as a single dose in the neck of cattle at a dosage of 2.5 mg/kg (1.1 mL/100 lb) body weight (BW). Do not inject more than 10 mL per injection site.

Table 1. DRAXXIN Cattle Dosing Guide

Animal Weight (Pounds)	Dose Volume (mL)
100	1.1
200	2.3
300	3.4
400	4.5
500	5.7
600	6.8
700	8.0
800	9.1
900	10.2
1000	11.4

Swine
Inject intramuscularly as a single dose in the neck of swine at a dosage of 2.5 mg/kg (0.25 mL/22 lb) BW. Do not inject more than 2.5 mL per injection site.

Table 2. DRAXXIN Swine Dosing Guide

Animal Weight (Pounds)	Dose Volume (mL)
15	0.2
30	0.3
50	0.6
70	0.8
90	1.0
110	1.3
130	1.5
150	1.7
170	1.9
190	2.2
210	2.4
230	2.6
250	2.8
270	3.1
290	3.3

CONTRAINDICATIONS
The use of DRAXXIN Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS
FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.
NOT FOR USE IN CHICKENS OR TURKEYS.

RESIDUE WARNINGS
Cattle
Cattle intended for human consumption must not be slaughtered within 18 days from the last treatment. Do not use in female dairy cattle 20 months of age or older. 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
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

PRECAUTIONS
Cattle
The effects of DRAXXIN 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.

Swine
The effects of DRAXXIN on porcine reproductive performance, pregnancy and lactation have not been determined. Intramuscular injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

ADVERSE REACTIONS
Cattle
In one field study, two calves treated with DRAXXIN at 2.5 mg/kg BW exhibited transient hypersalivation. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

Swine
In one field study, one out of 40 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

CLINICAL PHARMACOLOGY
At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the extracellular pathogen activity typically associated with the macrolides.[1] Markedly higher tulathromycin concentrations are observed in the lungs as compared to the plasma. The extent to which lung concentrations represent free (active) drug was not examined. Therefore, the clinical relevance of these elevated lung concentrations is undetermined.

Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens.[2] They also tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the MIC of the targeted pathogen. Under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial activity. Macrolides also exhibit a post-antibiotic effect (PAE), the duration of which tends to be both drug and pathogen dependent. In general, by increasing the macrolide concentration and the exposure time, the PAE will increase to some maximal duration. Of the two variables, concentration and exposure time, drug concentration tends to be the most powerful determinant of the duration of PAE.

Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.

Cattle
Following subcutaneous administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, tulathromycin is rapidly and nearly completely absorbed. Peak plasma concentrations generally occur within 15 minutes after dosing and product relative bioavailability exceeds 90%. Total systemic clearance is approximately 170 mL/hr/kg. Tulathromycin distributes extensively into body tissues, as evidenced by volume of distribution values of approximately 11 L/kg in healthy ruminating calves.[3] This extensive volume of distribution is largely responsible for the long elimination half-life of this compound [approximately 2.75 days in the plasma (based on quantifiable terminal plasma drug concentrations) versus 8.75 days for total lung concentrations (based on data from healthy animals)]. Linear pharmacokinetics are observed with subcutaneous doses ranging from 1.27 mg/kg BW to 5.0 mg/kg BW. No pharmacokinetic differences are observed in castrated male versus female calves.

Swine
Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed (T_{max} ~0.25 hour). Subsequently, the drug rapidly distributes into body tissues, achieving a volume of distribution exceeding 15 L/kg. The free drug is rapidly cleared from the systemic circulation ($CL_{systemic}$ =187 mL/hr/kg). However, it has a long terminal elimination half-life (60 to 90 hours) owing to its extensive volume of distribution. Although pulmonary tulathromycin concentrations are substantially higher than concentrations observed in the plasma, the clinical significance of these findings is undetermined. There are no gender differences in swine tulathromycin pharmacokinetics.

MICROBIOLOGY
Cattle
In vitro activity of tulathromycin has been demonstrated against Mannheimia haemolytica, Pasteurella multocida and Histophilus somni (Haemophilus somnus), the three major pathogens associated with BRD.

All minimum inhibitory concentration (MIC) values were determined using the 9:1 isomer ratio of this compound. The MICs of tulathromycin were determined for isolates obtained from animals enrolled in field studies in the U.S. during 1999.

Table 3. Tulathromycin MIC values from field studies evaluating BRD in the U.S.

Organism	No. Isolates	MIC_{90}† (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica*	642	2.0	0.5 to 64.0
Pasteurella multocida*	221	1.0	0.25 to 64.0
Histophilus somni (Haemophilus somnus)*	36	4.0	1.0 to 4.0
Mycoplasma bovis**	35	1.0	≤0.063 to 2.0

†The minimum inhibitory concentration for 90% of the isolates.
*Clinical isolates supported by clinical data and indications for use.
**The correlation between in vitro susceptibility data and clinical response has not been confirmed.

Swine
In vitro activity of tulathromycin has been demonstrated against Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, and Haemophilus parasuis, commonly isolated pathogens associated with SRD.

All minimum inhibitory concentration (MIC) values were determined using the 9:1 isomer ratio of this compound. The MICs of tulathromycin were determined for isolates obtained from swine enrolled in SRD field studies in the U.S. and Canada during 2000 through 2002.

Table 4. Tulathromycin MIC values from field studies evaluating SRD in the U.S. and Canada.

Organism	No. Isolates	MIC_{90}* (µg/mL)	MIC range (µg/mL)
Actinobacillus pleuropneumoniae	135	32.0	16.0 to 32.0
Haemophilus parasuis	31	2.0	0.25 to >64.0
Pasteurella multocida	55	2.0	0.5 to >64.0
Bordetella bronchiseptica	42	8.0	2.0 to 8.0

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

EFFECTIVENESS
Cattle
In a multi-location field study, 314 calves with naturally occurring BRD were treated with DRAXXIN. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude/activity, normal respiration, and a rectal temperature of ≤104°F on Day 14. The cure rate was significantly higher (P≤0.05) in DRAXXIN-treated calves (78%) compared to saline-treated calves (24%). There were two BRD-related deaths in the DRAXXIN-treated calves compared to nine BRD-related deaths in the saline-treated calves.

In another multi-location field study with 399 calves at high risk of developing BRD, administration of DRAXXIN resulted in a significantly reduced incidence of BRD (11%) compared to saline-treated calves (59%). Effectiveness evaluation was based on scored clinical signs of normal attitude/activity, normal respiration, and a rectal temperature of ≤104°F on Day 14. There were no BRD-related deaths in the DRAXXIN-treated calves compared to two BRD-related deaths in the saline-treated calves.

Swine
In a multi-location field study, 266 pigs with naturally occurring SRD were treated with DRAXXIN. Responses to treatment were compared to saline-treated controls. Success was defined as a pig with a normal attitude, normal respiration, and a rectal temperature of <104°F on Day 7. The treatment success rate was significantly greater (P≤0.05) in DRAXXIN-treated pigs (70.5%) compared to saline-treated pigs (46.1%).

ANIMAL SAFETY
Cattle
Safety studies were conducted in feeder calves receiving a single subcutaneous dose of 25 mg/kg BW, or 3 weekly treatments of 2.5, 7.5 or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site and corresponding histopathologic changes were seen in animals in all dosage groups. These lesions showed signs of resolving over time. No other drug-related lesions were observed macroscopically or microscopically.

An exploratory study was conducted in feeder calves receiving a single subcutaneous dose of 10, 12.5 or 15 mg/kg BW. Macroscopically, no lesions were observed. Microscopically, minimal to mild myocardial degeneration was seen in one of six calves administered 12.5 mg/kg BW once and two of six calves administered 15 mg/kg BW once.

A safety study was conducted in calves 13 to 27 days of age receiving 2.5 mg/kg BW or 7.5 mg/kg BW once subcutaneously. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.

Swine
Safety studies were conducted in pigs receiving a single intramuscular dose of 25 mg/kg BW, or 3 weekly intramuscular doses of 2.5, 7.5 or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including restlessness and excessive vocalization. Tremors occurred briefly in one animal receiving 7.5 mg/kg BW. Discoloration and edema of injection site tissues and corresponding histopathologic changes were seen in animals at all dosages and resolved over time. No other drug-related lesions were observed macroscopically or microscopically.

STORAGE CONDITIONS
Store at or below 25°C (77°F).

HOW SUPPLIED
DRAXXIN Injectable Solution is available in the following package sizes:
100 mL vial
250 mL vial
500 mL vial

[1] Carbon C. Pharmacodynamics of macrolides, azalides, and streptogramins: effect on extracellular pathogens. Clin Infect Dis 1998;27:28-32.
[2] Nightingale CJ. Pharmacokinetics and pharmacodynamics of newer macrolides. Pediatr Infect Dis J 1997;16:438-443.
[3] Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.

U.S. Patents: See US 6,329,345; US 6,420,536; US 6,514,945; US 6,583,274; US 6,777,393

NADA 141-244, Approved by FDA

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To request a material safety data sheet call **1-800-733-5500.**
For additional DRAXXIN product information call:
1-888-DRAXXIN or go to **www.DRAXXIN.com**

TAKE TIME OBSERVE LABEL DIRECTIONS

79-9947-00-0
March 2005

For subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle. For subcutaneous injection in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) in beef and non-lactating dairy cattle.

CAUTION

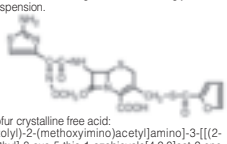
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

EXCEDE Sterile Suspension is a ready-to-use formulation that contains the crystalline free acid of ceftiofur, which is a broad spectrum cephalosporin antibiotic active against Gram-positive and Gram-negative bacteria including ß-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal, in vitro, resulting from inhibition of cell wall synthesis.

Each mL of this ready-to-use sterile suspension contains ceftiofur crystalline free acid equivalent to 200 mg ceftiofur, in a Miglyol® and cottonseed oil based suspension.

Figure 1. Structure of ceftiofur crystalline free acid:



Chemical name of ceftiofur crystalline free acid:
7-[[2-(2-Amino-4-thiazolyl)-2-(methoxyimino)acetyl]amino]-3-[[(2-furanylcarbonyl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene 2-carboxylic acid

INDICATIONS

EXCEDE Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni in beef, non-lactating dairy, and lactating dairy cattle. EXCEDE Sterile Suspension is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with M. haemolytica, P. multocida, and H. somni.

DOSAGE

Treatment

Administer as a single subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) to cattle at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) body weight (1.5 mL sterile suspension per 100 lb body weight).

In beef and non-lactating dairy cattle, EXCEDE Sterile Suspension may also be administered as a single subcutaneous injection in the middle third of the posterior aspect of the ear at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) body weight (1.5 mL sterile suspension per 100 lb body weight).

Most animals will respond to treatment within three to five days. If no improvement is observed, the diagnosis should be reevaluated.

Control

Administer as a subcutaneous injection either in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) to beef and non-lactating dairy cattle at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) body weight (1.5 mL sterile suspension per 100 lb body weight).

Clinical studies indicate that administration of EXCEDE Sterile Suspension is effective for the control of respiratory disease in beef and non-lactating dairy cattle at "high risk" of developing BRD. One or more of the following factors typically characterizes calves on arrival at high risk of developing BRD.

- Cattle are from multiple farm origins,
- cattle have had extended transport times (that may have included few if any rest stops),
- ambient temperature change from origin to arrival of 30° F or more,
- cattle have had continued exposure to extremely wet or cold weather conditions,
- cattle have experienced excessive shrink or excessive arrival processing procedures (such as castration, dehorning).

Table 1. Dosing Schedule for EXCEDE Sterile Suspension

Weight (lb)	Treatment at 3 mg CE/lb (mL)	Weight (lb)	Treatment at 3 mg CE/lb (mL)
100	1.5	1100	16.5
200	3.0	1200	18.0
300	4.5	1300	19.5
400	6.0	1400	21.0
500	7.5	1500	22.5
600	9.0	1600	24.0
700	10.5	1700	25.5
800	12.0	1800	27.0
900	13.5	1900	28.5
1000	15.0	2000	30.0

ADMINISTRATION

ADMINISTRATION FOR THE MIDDLE THIRD OF THE EAR

- **Shake well before using.** Please read the complete package insert before administering EXCEDE Sterile Suspension subcutaneously in the posterior ear of cattle.
- Deposit as a single subcutaneous injection in the middle third of the posterior aspect of the ear, avoiding all blood vessels. See Figures 2 and 3.
- Adjust the needle insertion point to avoid any blood vessels, previous implants, ear tags or ear tag holes. Do not administer intra-arterially.
- Deliver the entire contents of the syringe.
- When administered correctly, a subcutaneous bleb of EXCEDE Sterile Suspension will appear.
- When withdrawing the needle, apply pressure to the needle insertion point, and massage toward the base of the ear.

ADMINISTRATION FOR THE BASE OF THE EAR

- **Shake well before using.** Please read the complete package insert before administering EXCEDE Sterile Suspension subcutaneously at the posterior aspect of the ear where it attaches to the head (base of the ear).
- Hold the syringe and needle behind the ear to be dosed so the needle and syringe point in the direction of an imaginary line that would pass through the head toward the animal's opposite eye. See Figures 4 and 5.
- Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining this angle. See Figure 4.
- Deliver the entire contents of the syringe.
- Do not administer EXCEDE Sterile Suspension in the neck.

CONTRAINDICATIONS

As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing latex gloves.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet (MSDS) please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

Injection of EXCEDE Sterile Suspension into the arteries of the ear is likely to result in sudden death to the animal.

RESIDUE WARNINGS

- **Following label use as a single treatment, a 13-day pre-slaughter withdrawal period is required.**
- **Following label use as a single treatment, no milk discard period is required for this product.**
- **Use of dosages in excess of 6.6 mg CE/kg or administration by unapproved routes (subcutaneous injection in the neck or intramuscular injection) may cause violative 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.**

PRECAUTIONS

Following subcutaneous injection in the middle third of the posterior aspect of the ear, thickening and swelling (characterized by aseptic cellular infiltrate) of the ear may occur. As with other parenteral injections, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

Following injections at the posterior aspect of the ear where it attaches to the head (base of the ear), areas of discoloration and signs of inflammation may persist at least 13 days post administration resulting in trim loss of edible tissue at slaughter. Injection of volumes greater than 20 mL, in the middle third of the ear, may result in open draining lesions in a small percentage of cattle.

The effects of ceftiofur on bovine reproductive performance, pregnancy, and lactation have not been determined.

ADVERSE EFFECTS

Administration of EXCEDE Sterile Suspension into the ear arteries is likely to result in sudden death in cattle. During the conduct of clinical studies, there was a low incidence of acute death (nine out of approximately 6000 animals). Three of these deaths were confirmed to be the result of inadvertent intra-arterial injection. No other adverse systemic effects were noted for either the antibiotic or formulation during any of the clinical and target animal safety studies.

CLINICAL PHARMACOLOGY

Cattle: Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder), ceftiofur hydrochloride (EXCENEL® RTU Sterile Suspension), or ceftiofur crystalline free acid (EXCEDE Sterile Suspension) is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Subcutaneous administration of ceftiofur crystalline free acid, either in the middle third of the posterior aspect of the ear (middle third of the ear, MOE) of beef and non-lactating dairy cattle, or in the posterior aspect of the ear where it attaches to the head (base of the ear, BOE) of beef, non-lactating dairy, and lactating dairy cattle, provides therapeutic concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma above the MIC_{90} for the bovine respiratory disease (BRD) label pathogens, Pasteurella multocida, Mannheimia haemolytica and Histophilus somni, for generally not less than 150 hours after a single administration (See Figure 6).

The pharmacokinetic parameters for the two subcutaneous locations of injection (MOE and BOE) are found in Table 2. Statistical analyses of the data from these two subcutaneous injection sites (MOE and BOE) demonstrate that they are therapeutically equivalent.

Figure 6. Average plasma concentrations of ceftiofur and desfuroylceftiofur-related metabolites after administration of EXCEDE Sterile Suspension at 6.6 mg ceftiofur equivalents (CE)/kg via subcutaneous injection into one of two different locations of the ear, middle third of the ear (MOE Cattle) and base of the ear (BOE Cattle) in beef cattle as well into the base of the ear (BOE Lactating) in lactating dairy cattle.

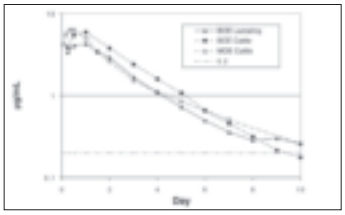


Table 2. Pharmacokinetic parameters measured after a single SC administration of 3 mg CE/lb body weight (BW) of EXCEDE Sterile Suspension in either the middle third of the ear or the base of the ear.

Pharmacokinetic Parameter	Beef - Middle Third of the Ear Mean Value ± Standard Deviation	Beef - Base of the Ear Mean Value ± Standard Deviation	Dairy Cow - Base of the Ear Mean Value ± Standard Deviation
C_{max} (µg/mL)	6.90 ± 2.68	6.39 ± 1.79	4.44 ± 1.65
t_{max} (h)	12.0 ± 6.2	19.8 ± 5.81	19.00 ± 8.02
$AUC_{0\text{-}LOQ}$ (µg•h/mL)	376 ± 66.1	412 ± 67.3	313 ± 85.5
$t_{>0.2,\ model}$ (h)	183 ± 40.8	NE	NE
$t_{>0.2,\ nca}$ (h)	246 ± 48.5	218 ± 45.5	205 ± 35.7
$t_{1/2}$ (h)	62.3 ± 13.5	40.7 ± 11.2	43.92 ± 9.84

C_{max} (µg/mL) = maximum plasma concentration (in µg CE/mL).
t_{max} (h) = the time after injection when C_{max} occurs (in hours).
$AUC_{0\text{-}LOQ}$ (µg•h/mL) = the area under the plasma concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg CE/mL).
$t_{>0.2,\ model}$ (h) = the time plasma concentrations remain above 0.2 µg CE/mL (in hours), estimated using compartmental pharmacokinetic techniques.
$t_{>0.2,\ nca}$ (h) = the time plasma concentrations remain above 0.2 µg CE/mL (in hours), estimated using noncompartmental pharmacokinetic techniques.
$t_{1/2}$ (h) = terminal phase biological half life (in hours)
NE = Not estimated

CLINICAL MICROBIOLOGY

Ceftiofur has demonstrated in vitro activity against Mannheimia haemolytica, P. multocida and H. somni, the major pathogenic bacteria associated with BRD (Pneumonia, shipping fever).

A summary of minimum inhibitory concentrations (MIC) for various cattle pathogens is presented in Table 3. Isolates were obtained in the United States and Canada. Testing followed the Clinical and Laboratory Standards Institute (CLSI) Guidelines.[1] Quality control strains were included in each run and results were within acceptable ranges.

Table 3. Ceftiofur MIC values from field studies evaluating BRD in the US (1997-1998)

Organisms*	N	MIC Range (µg/mL)	MIC_{90}** (µg/mL)	Date tested
Mannheimia haemolytica	110	≤0.03–0.25	≤0.06	1997–1998
Pasteurella multocida	107	≤0.03–0.25	≤0.03	1997–1998
Histophilus somni	48	≤0.03–0.25	≤0.03	1997–1998

* Clinical isolates supported by clinical data and indications for use.
**The minimum inhibitory concentration for 90% of the isolates.

Based on pharmacokinetic and clinical effectiveness studies of ceftiofur in cattle after a single administration of 6.6 mg CE/kg (3 mg CE/lb) BW and the MIC and disk (30 µg) diffusion data, the following breakpoints are recommended by the Clinical and Laboratory Standards Institute.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤2.0	(S) Susceptible
18-20	4.0	(I) Intermediate
≤17	≥ 8.0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The 30 µg ceftiofur sodium disk and the ceftiofur sodium standard reference powder (or disk) should provide MIC values and zone diameters for the reference strains as presented in Table 4. Ceftiofur sodium disks or powder reference standard are appropriate for all forms of ceftiofur (sodium, hydrochloride and free acid).

Table 4. Acceptable quality control ranges for ceftiofur against Clinical and Laboratory Standards Institute recommended American Type Culture Collection (ATCC) reference strains

Organism (ATCC No.)	MIC (µg/mL)	Zone Diameter (mm)
Escherichia coli (ATCC 25922)	0.25 -1.0	26-31
Staphylococcus aureus (ATCC 29213)	0.25 -1.0	—
S. aureus (ATCC 25923)	—	27-31
Pseudomonas aeroginosa (ATCC 27853)	16.0 -64.0	14-18

CLINICAL EFFECTIVENESS

A field dose confirmation study for the treatment of BRD evaluated the effectiveness of single doses of 2 and 3 mg CE/lb BW (4.4 to 6.6 mg CE/kg) for the treatment of the bacterial component of BRD under field conditions. All treatments were administered SC in the middle third of the posterior aspect of the ear. Cattle were clinically evaluated on days 2-4, 14 and 28 and were observed on all other study days. The 6.6 mg CE/kg (3 mg CE/lb) EXCEDE Sterile Suspension dose significantly ($P \leq 0.05$) increased day 14 treatment success rate, defined as animals that did not require any ancillary treatment and had a rectal temperature of <104°F, normal respiration index, and had no or mild depression on that day.

The effectiveness of a single dose of EXCEDE Sterile Suspension for the control of BRD in feedlot cattle was evaluated in a nine-location field effectiveness study. In addition to standard processing on arrival at feedlots, cattle (n=3911) considered to be at high risk for BRD were assigned to one of four arrival treatments, including EXCEDE Sterile Suspension at 2 or 3 mg CE/lb BW (4.4 or 6.6 mg CE/kg) or negative control. Effectiveness evaluation was based on the incidence of clinical BRD within 28 days following arrival processing. Administration of a single dose of EXCEDE Sterile Suspension administered SC in the middle third of the posterior aspect of the ear at arrival processing significantly reduced the incidence of BRD in high risk feedlot cattle in the 28-day period after arrival processing compared to negative controls.

Base of the ear administration (beef and non-lactating dairy cattle) and middle third of the ear administration (lactating dairy cattle) were compared to the middle third of the ear pharmacokinetic data for beef and non-lactating dairy cattle and were found to be therapeutically equivalent.

ANIMAL SAFETY

After parenteral administration, EXCEDE Sterile Suspension, ceftiofur sodium and ceftiofur hydrochloride accede to the same principal metabolite, desfuroylceftiofur. Therefore, studies conducted with ceftiofur sodium are adequate to evaluate the systemic safety of EXCEDE Sterile Suspension. Results from a five-day tolerance study conducted with ceftiofur sodium in normal feeder calves indicated that ceftiofur was well tolerated at 25 mg CE/lb/day for five consecutive days, approximately 8 times the highest approved dose of EXCEDE Sterile Suspension (3 mg CE/lb). Ceftiofur administered parenterally had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were administered ceftiofur sodium intramuscularly at 0 (vehicle control), 1, 3, 5 or 10 mg CE/lb/day thus, evaluating up to 3.3 times the highest recommended dose of EXCEDE Sterile Suspension of 3.0 mg CE/lb/day. There were no adverse systemic effects, indicating that ceftiofur has a wide margin of safety when injected intramuscularly into feeder calves. Local tissue tolerance to subcutaneous injection of EXCEDE Sterile Suspension in the posterior ear of cattle was evaluated in a separate study.

In approximately 6,000 tested animals, nine animals have died following injection of EXCEDE Sterile Suspension. All deaths were within 30 minutes of the time of injection. The exact cause was confirmed in three animals. These deaths resulted from inadvertent intra-arterial injection of this oil-based suspension into one of the two major auricular (ear) arteries. Intra-arterial injection at this location resulted in direct administration of the oil-based formulation into the arterial blood supply of the brain resulting in embolism and death.

Since intra-arterial injection was confirmed in three animals that died following injection of EXCEDE Sterile Suspension, the consequences of purposeful intra-arterial injection of EXCEDE Sterile Suspension were investigated in feeder cattle. Two heifers (body weight approximately 225 kg) were given a single 6.6 mg CE/kg bolus dose of EXCEDE Sterile Suspension in the middle auricular artery. Both heifers collapsed immediately and died within approximately eight minutes of injection. Intra-arterial injection of EXCEDE Sterile Suspension in the ear will result in death and must be avoided.

Since subcutaneous injection in the ear may potentially result in inadvertent intravenous administration of an injectable product, the consequences of purposeful intravenous injection of EXCEDE Sterile Suspension were investigated in feeder cattle. Three heifers and 3 steers (body weight range 197-223 kg) were given a single 6.6 mg CE/kg bolus dose of EXCEDE Sterile Suspension in the jugular vein and were monitored for adverse effects following injection. One steer and one heifer had transient (2-5 minutes) increases in heart rate without any other untoward signs in these or the other cattle. Intravenous injection of EXCEDE Sterile Suspension is an unacceptable route of administration.

Subcutaneous administration in the middle third of the posterior aspect of the ear

A study was designed and conducted to specifically address tissue tolerance in cattle when EXCEDE Sterile Suspension was administered as a single subcutaneous injection into the posterior aspect of the ear of cattle at the recommended dose of 3 mg CE/lb body weight (6.6 mg CE/kg). Results from this study indicate that the subcutaneous injection of EXCEDE Sterile Suspension into the middle third of the posterior aspect of the ear of cattle is well tolerated and characterized by a biphasic thickening of the ear. The initial increase in thickness is attributed to the space required for the volume of injected material. Additional increases in thickness were observed through day 14 after injection. After day 14, post injection ear thickness decreased in all animals. One animal carried an injected ear in a drooping position for 7 days post injection. At necropsy, subcutaneous areas of discoloration and some foci of hemorrhage were observed in ears of injected cattle. The discoloration was markedly reduced in size by the end of the study. Ears are inedible tissues in the US (9 CFR 301.2). No signs of irritation were observed on the edible portions of the carcass around the base of the ear.

The local tolerance of the ear of cattle to a single SC injection of EXCEDE Sterile Suspension was also evaluated in a large multilocation field efficacy study. None of the 1927 animals treated with EXCEDE Sterile Suspension were removed from this trial due to ear irritation although swelling was noted at some injection sites. Leak back and/or bleeding from the injection site was observed in a small fraction of the treated animals immediately after administration. It was concluded that administration of EXCEDE Sterile Suspension in the posterior aspect of the ear was well tolerated and was acceptable under feedlot conditions.

A study evaluated the 56-day feedlot performance of beef steers administered EXCEDE Sterile Suspension alone, EXCEDE Sterile Suspension with a growth promoting implant, growth promoting implant alone, or neither product, in a total of 207 Angus and Angus crossbred steers. The administration of EXCEDE Sterile Suspension in the posterior aspect of the ear with or without growth promoting implants was well tolerated by cattle and did not adversely affect feedlot cattle performance. Based upon the results of this study, the location of implants administered after EXCEDE Sterile Suspension may need to be adjusted slightly within the boundaries of the middle third of the ear in some animals.

Subcutaneous administration in the posterior aspect of the ear where it attaches to the head (base of the ear)

Base of the ear injection in beef cattle: The systemic safety of ceftiofur concentrations resulting from product administration at the base of the ear was established via a pharmacokinetic comparison of the two routes of administration (base of the ear versus middle third of the ear). Based upon the results of this relative bioavailability study, it was determined that the two routes of administration are therapeutically equivalent.

The local tolerance of the ear to a single SC injection at the posterior aspect of the ear where it attaches to the head (base of the ear) of EXCEDE Sterile Suspension was evaluated in a multi-location field study in 2926 beef cattle. Normal restraint was adequate for administration of EXCEDE Sterile Suspension for 99.8% of cattle. No post injection problems (excessive bleeding or leak back) were observed in 99.8% of cattle. On Days 28 and 56 post-injection, 97.8% and 98.9% of the cattle had "normal" (no observed swelling) ears.

In a residue study, 72 beef cattle were injected in the posterior aspect of the ear where it attaches to the head (base of the ear) with EXCEDE Sterile Suspension at a dose rate of 6.6 mg CE/kg BW. Injection sites were observed daily from treatment to necropsy (4, 7, 10, or 13 days post-injection) for swelling and drooping, and evaluated grossly at necropsy, using skinning and trimming procedures similar to slaughterhouse practices. All animals had injection site swelling during the study; swelling resolved prior to euthanasia in 23 of 72 animals. None of the animals showed ear drooping. At necropsy, signs of inflammation (hemorrhage, congestion, and firmness of tissue) and presence of drug material were seen in the area around the injection site and on the carcass. At 13 days post-injection, gross lesions were found in the inedible portions of the base of the ear in all 18 animals, and in the exposed carcass tissue in 11 of 18 animals.

Base of the ear injection in dairy cattle: The local tolerance of the ear to a single SC injection at the posterior aspect of the ear where it attaches to the head (base of the ear) of EXCEDE Sterile Suspension was evaluated in a multi-location field study in 114 adult dairy cattle. Successful injection in the base of the ear was achieved in 97.4% of cattle using normal facilities and restraint equipment. No leak back or excessive bleeding was observed following injection for 99.1% of cattle, with injection volumes ranging from 15 to 30 mL. On Days 28 and 56 following injection of EXCEDE Sterile Suspension in the base of the ear, 95.6% and 100% of ears, respectively, were observed as normal with no injection site swelling.

In a residue study, 6 dairy cows were injected in the posterior aspect of the ear where it attaches to the head (base of the ear) at a dose rate of 6.6 mg CE/kg of EXCEDE Sterile Suspension. No animals exhibited drooping ears at any time after treatment but all animals had signs of swelling at the injection site at all observations times after treatment. Cows were slaughtered 10 days after injection. At necropsy, all 6 cows showed evidence of injection site inflammation (discoloration of fat tissue/fascia) and 4 of 6 cows had discoloration of tissue dorsal and posterior to the ear canal on the carcass. In addition to discoloration, tan nodules and a milky white fluid exudate were also present at the sectioned surface.

TISSUE RESIDUE DEPLETION

A radiolabeled residue metabolism study established tolerances for ceftiofur residues in cattle kidney, liver and muscle. These tolerances of ceftiofur residues are 0.4 ppm in kidney, 2.0 ppm in liver, 1.0 ppm in muscle, and 0.1 ppm in milk.

A pivotal tissue residue decline study was conducted in dairy cattle. In this study, cows received a single injection of 6.6 mg of ceftiofur per kg body weight (3.0 mg per pound). Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as the kidney, liver and muscle by 13 days after dosing. These data collectively support a 13-day pre-slaughter withdrawal period.

A pivotal milk residue decline study was conducted in lactating dairy cattle. In this study, cows received a single injection of 6.6 mg of ceftiofur per kg body weight (3.0 mg/pound). Ceftiofur residues in milk were less than tolerances at all time points after treatment. These data collectively support that no milk discard period is required for this product.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP]. Shake well before using. Contents should be used within 12 weeks after the first dose is removed.

HOW SUPPLIED

EXCEDE Sterile Suspension is available in the following package size: 100 mL vial

Figure 2. Subcutaneous administration of EXCEDE Sterile Suspension in the middle third of the posterior aspect of the ear.

Figure 3. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.

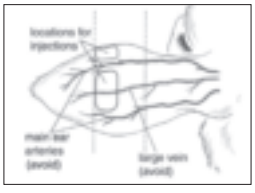


Figure 4. Subcutaneous administration of EXCEDE Sterile Suspension at the posterior aspect of the ear where it attaches to the head (base of the ear).

Figure 5. Injection location for the subcutaneous administration of EXCEDE Sterile Suspension at the posterior aspect of the ear where it attaches to the head (base of the ear).

1 National Committee for Clinical Laboratories Standards (now Clinical and Laboratories Standards Institute). Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard. NCCLS Document M31-A (ISBN 1-56238-377-9) CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1832, 1999.

U.S. Patent No. 5,721,359 and other patents pending.

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A180®
(danofloxacin mesylate)

Sterile Antimicrobial Injectable Solution

180.0 mg of danofloxacin as the mesylate salt/mL

For subcutaneous use in cattle only

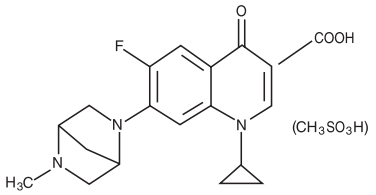
Not for use in cattle intended for dairy production or in calves to be processed for veal.

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)-1cyclopropyl-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 $C_{19}H_{20}FN_3O_3 \bullet CH_3SO_3H$ and the molecular weight is 453.49.

Figure 1. The chemical structure of danofloxacin mesylate.



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 mesylate) 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

Cattle Weight (lb)	6 mg/kg, given twice, 48 hours apart 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. The material safety data sheet (MSDS) contains more detailed occupational safety information. To obtain a MSDS, please call 1-800-733-5500. To report any adverse events, please 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 (VDss) 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 q 48h-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]VDss	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. AUC_{0-24} = 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 VDss 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
Mannheimia (Pasteurella) haemolytica	363	≤0.015–0.12	0.06
Pasteurella multocida	301	≤0.015–0.12	0.015
Haemophilus somnus*	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 inappetance, 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

Distributed by:

Pfizer Animal Health
Exton, PA 19341, USA
Div. of Pfizer Inc
New York , NY 10017

Use Only as Directed

TAKE TIME OBSERVE LABEL DIRECTIONS

DRX06011