BRD Antimicrobial Comparison Chart

To find an effective solution for bovine respiratory disease (BRD) on your operation, explore the Zoetis BRD Solutions portfolio, including Draxxin KP, Draxxin, Excede and Advocin.

PRODUCT	Associated with: *Mannheimia haemolytica*		Associated with: *Pasteurella multocida*		Associated with: *Histophilus somni*		Associated with: *Mycoplasma bovis*		DOSAGE (per cwt)	ESTIMATED DURATION	MEAT WITHDRAWAL (days)
	Control	Treat	Control	Treat	Control	Treat	Control	Treat			
Draxxin® KP *(tulathromycin and ketoprofen Injection)*		✓		✓		✓		✓	1.1 mL	14 days[1]	18
Draxxin® *(tulathromycin injection)*	✓	✓	✓	✓	✓	✓	✓	✓	1.1 mL	14 days[2]	18
Excede® *(ceftiofur crystalline free acid)*	✓	✓	✓	✓	✓	✓			1.5 ml	7 days[3]	13
Advocin® *(danofloxacin injection)*	✓	✓	✓	✓					1.5–2 mL	—	4
OTHER PRODUCTS											
Baytril® *(enrofloxacin)*	✓	✓	✓	✓	✓	✓	✓	✓	3.4–5.7 mL	—	28
Micotil® *(tilmicosin)*	✓	✓		✓		✓			1.5–3 mL	—	42
Nuflor® *(florfenicol)*	✓	✓	✓	✓	✓	✓			3–6 mL	—	38 (SC) 28 (IM)
Resflor Gold® *(florfenicol and flunixin meglumine)*		✓		✓		✓		✓	6 mL	N/A	38
Zactran® *(gamithromycin)*	✓	✓	✓	✓		✓		✓	1.82 mL	10 days[4-5]	35
Zuprevo® *(tildipirosin)*	✓	✓	✓	✓	✓	✓			1 mL	—	21

IMPORTANT SAFETY INFORMATION FOR DRAXXIN KP

Draxxin KP has a pre-slaughter withdrawal time of 18 days in cattle. Not for use in female dairy cattle 1 year of age or older, including dry dairy cows. Not for use in beef calves less than 2 months of age, dairy calves, and veal calves. A withdrawal period has not been established for this product in preruminating calves. Do not use in animals previously found to be hypersensitive to tulathromycin and ketoprofen. See full Prescribing Information, attached.

IMPORTANT SAFETY INFORMATION FOR DRAXXIN

Draxxin has a pre-slaughter withdrawal time of 18 days in cattle. Do not use in female dairy cattle 20 months of age or older. Do not use in animals known to be hypersensitive to the product. See full Prescribing Information, attached.

IMPORTANT SAFETY INFORMATION FOR EXCEDE

People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to Excede. Excede is contraindicated in animals with known allergy to ceftiofur or to the ß-lactam group (penicillins and cephalosporins) of antimicrobials. Inadvertent intra-arterial injection is possible and fatal. Do not use in calves to be processed for veal. Pre-slaughter withdrawal time is 13 days following the last dose. See full Prescribing Information, attached.

IMPORTANT SAFETY INFORMATION FOR ADVOCIN

Extra-label use of Advocin in food-producing animals is prohibited. Do not use in cattle intended for dairy production or in calves to be processed for veal. Advocin has a pre-slaughter withdrawal time of four days. See full Prescribing Information, attached.

[1] Data on file, Study Report No. A431N-US-16-418, Zoetis Inc.

[2] Freedom of Information Summary. NADA 141-244 — Draxxin® (*tulathromycin injection*) Injectable Solution. Food and Drug Administration; 2005.

[3] Data on file, Study Report No. 1133R-60-05-489, Zoetis Inc.

[4] Lechtenberg K, Daniels CS, Royer GC, et al. Field Efficacy Study of Gamithromycin for the Control of Bovine Respiratory Disease in Cattle at High Risk of Developing the Disease. *Intern J Appl Res Vet Med.* 2011;9(2):189-197.

[5] Sifferman RL, Wolff WA, Holste JE, et al. Field Efficacy Evaluation of Gamithromycin for Treatment of Bovine Respiratory Disease in Cattle at Feedlots. *Intern J Appl Res Vet Med.* 2011;9(2):166-175.

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Draxxin® KP

(tulathromycin and ketoprofen injection)

INJECTABLE SOLUTION

For subcutaneous injection

Antibiotic: 100 mg of Tulathromycin/mL

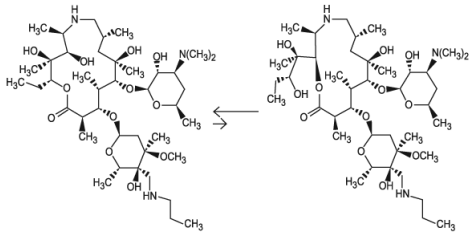
Non-Steroidal Anti-inflammatory Drug: 120 mg Ketoprofen/mL

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

DESCRIPTION

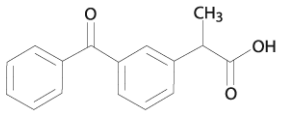
DRAXXIN KP (tulathromycin and ketoprofen injection) Injectable Solution is a ready to use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide and ketoprofen a non-steroidal anti-inflammatory drug. **ACTIVE INGREDIENTS:** Each mL of DRAXXIN KP contains 100 mg of tulathromycin as a free base and 120 mg ketoprofen as a free acid in a 50% propylene glycol vehicle. **INACTIVE INGREDIENTS:** monothioglycerol (5 mg/mL), 2-pyrrolidone (70 mg/mL), citric acid (20 mg/mL) and sodium hydroxide/hydrochloric acid added to adjust pH. DRAXXIN KP contains an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio and a racemic mixture of ketoprofen. The structures of the tulathromycin isomers and ketoprofen are shown below:

Figure 1. Tulathromycin structures



The chemical names of the tulathromycin 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-hexopyranosyl]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 (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl]oxy]-2-[(1S,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

Figure 2. Ketoprofen Structure



The chemical name of ketoprofen is 2-(3-Benzoylphenyl) propanoic acid.

INDICATIONS

Draxxin® KP is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis,* and control of pyrexia associated with BRD in beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and replacement dairy heifers. Not for use in reproducing animals over one year of age, dairy calves, or veal calves.

DOSAGE AND ADMINISTRATION

Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg tulathromycin and 3 mg ketoprofen/kg (1.1 mL/100 lb) bodyweight (BW). Do not inject more than 10 mL per injection site. Use this product within 56 days of the first puncture and puncture a maximum of 20 times. If more than 20 punctures are anticipated, the use of automatic injection equipment or a repeater syringe is recommended. When using a draw-off spike or needle with bore diameter larger than 16 gauge, discard any product remaining in the vial immediately after use.

Table 1. DRAXXIN KP Cattle Dosing Guide

Animal Weight (lb)	Dose Volume (mL)
150	1.7
200	2.3
250	2.8
300	3.4
350	4.0
400	4.5
500	5.7
600	6.8
700	8.0
800	9.1
900	10.2
1000	11.4

CONTRAINDICATIONS

The use of DRAXXIN KP Injection is contraindicated in animals previously found to be hypersensitive to tulathromycin and ketoprofen.

WITHDRAWAL PERIODS AND RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 18 days following last treatment with this drug product. Not for use in female dairy cattle 1 year of age or older, including dry dairy cows; use in these cattle may cause drug residues in milk and/or in calves born to these cows or heifers. Not for use in beef calves less than 2 months of age, dairy calves, and veal calves. A withdrawal period has not been established for this product in pre-ruminating calves.

USER SAFETY WARNINGS:

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

The Safety Data Sheet (SDS) provides more detailed occupational safety information. To obtain a Safety Data Sheet contact Zoetis Inc. at 1-888-963-8471.

ANIMAL SAFETY WARNINGS and PRECAUTIONS

The effects of DRAXXIN KP on bovine reproductive performance, pregnancy, and lactation have not been determined. Not for use in reproducing animals over one year of age because reproductive safety testing has not been conducted. Administration of tulathromycin and ketoprofen injection may result in injection site swelling that appears the day after treatment and may persist for at least 32 days post-injection. This may result in trim loss of edible tissue at slaughter.

As a class, cyclo-oxygenase inhibitory NSAIDs (Ketoprofen) may be associated with gastrointestinal, hepatic and renal toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Use judiciously when renal impairment or gastric ulceration is suspected.

Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of DRAXXIN KP with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.

Discontinue use if fecal blood is observed.

ADVERSE REACTIONS

Repeated administration of NSAIDs can result in gastric or renal toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Patients at greatest risk for toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with pre-existing gastric ulcers, renal, cardiovascular, and/or hepatic dysfunction.

CONTACT INFORMATION:

To report suspected adverse drug experiences, to obtain a Safety Data Sheet (SDS) or for technical assistance, contact Zoetis at (888) 963-8471. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ketoprofen is a propionic acid derivate and nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic effects. Ketoprofen inhibits the activity of the enzymes cyclo-oxygenase I and II, resulting in a decreased formation of precursors of prostaglandins and thromboxanes. Ketoprofen also causes a decrease in the formation of thromboxane A2 synthesis, by thromboxane synthase, thereby inhibiting platelet aggregation.

The principal mechanism of action of tulathromycin against bacteria involves direct inhibition of essential protein biosynthesis by selective binding to bacterial 50S ribosomal subunits. Tulathromycin acts by stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process.

Clinical Pharmacology

In a GLP pharmacokinetic study, 60 cattle received one of 3 treatments: 2.5 mg tulathromycin/kg BW, 3 mg ketoprofen/kg BW or a combination of the two active ingredients (2.5 mg tulathromycin and 3 mg of ketoprofen/kg BW) via subcutaneous injection. Blood samples were obtained pre-dose and at 20 min, 40 min, 1, 1.5, 2, 3, 4, 6, 10, 24, 28, 32, 48, 52, 56, 72, 120, 168, 216, 264, 336, and 360 hours after dosing. The samples were analyzed using validated high-performance liquid chromatography-mass spectrometry (LC-MS/MS) methods for tulathromycin and ketoprofen concentrations. The rate of drug exposure was greater for the ketoprofen alone product.

The mean [±standard deviation (SD)] maximum plasma concentration (Cmax) and time to Cmax (tmax) was 6451 (±1342) ng/mL and 0.83 (±0.53) hr, respectively for ketoprofen alone compared to a mean (±SD) Cmax and tmax of 2322 (±1505) ng/mL and 4.0 (±2.93) hr, respectively, for ketoprofen in the combination product. However, the extent of drug exposure was slightly greater and terminal half life (t1/2) was longer for ketoprofen in the combination product. The mean (±SD) area under the drug concentration-time curve between times 0 and the last quantifiable concentration (AUC0-t(last)) was 26458 (±3605) ng*hr/mL for ketoprofen in the combination product and 23106 (±3500) for ng*hr/mL for ketoprofen alone. Similarly, the mean t 1/2 was 6.84 (±2.09) hr for ketoprofen in the combination product and 2.86 (±1.09) hr for ketoprofen alone. Although the mean (±SD) Cmax of tulathromycin in the combination group (373 (±105) ng/mL) was less than tulathromycin alone (653 (±261) ng/mL), based on mean (±SD) AUC0-t(last), the combination (13647 (±2577) ng*hr/mL) and tulathromycin alone (14088 (±4408) ng*hr/mL) groups had similar tulathromycin bioavailability.

Tulathromycin half life was also similar between the combination (93.3 (±27.9) hr) and tulathromycin alone (98.7 (±23.1) hr) groups.

MICROBIOLOGY

Based on data provided for the approval of Draxxin® (tulathromycin injection, NADA 141-244), tulathromycin has demonstrated *in vitro* activity against *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis,* four pathogens associated with BRD.

TARGET ANIMAL SAFETY

Thirty-two (16 male and 16 female) growing cattle were enrolled in a margin of safety study. Calves were injected subcutaneously with either saline, DRAXXIN KP at the label dose 2.5 mg tulathromycin/3 mg ketoprofen/kg BW, DRAXXIN KP at 3 times the label dose, or DRAXXIN KP at 5 times the label dose. Calves received three doses at a 14-day interval between doses. Daily clinical observations were conducted by a veterinarian as well as daily general health observations and injection site evaluations. Samples were collected for urinalysis, fecal occult blood, hematology, serum chemistry and coagulation and for pharmacokinetics. At the conclusion of the study, all animals were euthanized and necropsied for gross pathology and histopathology evaluation. Injection site lesion volumes for the first injection site was calculated. Injection site reactions were noted in all DRAXXIN KP-treated animals and the size and incidence of injection site lesions were greater in the 3X and 5X treatment groups.

Test article-related differences in serum chemistry parameters were lower alkaline phosphatase in the 5X group; lower albumin in the 3X and 5X groups; lower total protein (TP) and serum calcium in the 1X, 3X and 5X groups; and higher creatine kinase (CK) in the 1X, 3X, and 5X groups. The changes for serum calcium and albumin were considered clinically insignificant because all values were within the normal reference range on the days with statistical differences. The changes for TP were considered secondary to the differences in albumin and clinically insignificant because the albumin changes were considered clinically insignificant. In addition, the only TP values that were outside of the normal reference range were only 0.1 g/dL below the normal reference range. The differences in neutrophil values might be secondary to test article-associated injection site inflammation and the differences in CK values are directly associated with injection site reactions.There were non-quantifiable ketoprofen plasma concentrations prior to the second and third doses, while there was a modest accumulation for tulathromycin (mean ≤16.5%) with the 14-day dosing interval. There was dose proportional increase in tulathromycin AUC0-t(last) with an increase in dose, while there was slightly greater than dose proportional increase in ketoprofen AUC0-t(last). A single calf in Group T04 had test article-associated positive fecal occult blood samples on Days 15 and 29. Microscopic mucosal erosions of the pylorus of the abomasum were present in the 3X (2/8) and 5X (1/8) groups and was considered test article-related. Renal interstitial inflammation and minimal multifocal degeneration and regeneration occurred at similar incidence and severity in treated and control calves. Subcutaneous injection of cattle with tulathromycin-ketoprofen at the label dose was well tolerated.

EFFECTIVENESS

A multi-location field study was conducted to evaluate the effectiveness of Draxxin® KP for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis,* and control of pyrexia associated with BRD. A total of 819 cattle with clinical signs of BRD (moderate depression and respiratory distress, and a rectal temperature ≥104.5 °F) were enrolled and treated with either saline (0.025 mL/kg BW), tulathromycin (2.5 mg/kg BW) or Draxxin® KP (2.5 mg tulathromycin/kg BW and 3 mg ketoprofen/kg BW) administered by subcutaneous injection. Rectal temperatures were measured six hours later and animals were observed for clinical signs of BRD through 14 days post-treatment. An animal was classified as a treatment success for treatment of BRD if it was not classified as a failure prior to Day 14, and had normal or mild depression and respiratory distress scores and a rectal temperature <104.5 °F on Day 14. An animal was classified as a treatment success for control of pyrexia associated with BRD if it displayed a ≥2 °F reduction in rectal temperature at 6-hours post-treatment compared to pre-treatment. The Draxxin® KP-treated group had a significantly different (P=0.0020) and numerically higher success rate (76.2%) for the treatment of BRD compared to the saline-treated group (31.6%), and the success rate in the Draxxin® KP-treated group was statistically non-inferior to that in the group receiving tulathromycin alone. The success rate (back-transformed estimate) for pyrexia associated with BRD in the Draxxin® KP-treated group was significantly different (P=0.0010) and numerically higher (83.8%) at 6 hours post-treatment than the success rate in the saline-treated group (2.4%). The success rate (back-transformed estimate) for pyrexia associated with BRD in the Draxxin® KP-treated group was significantly different (P=0.0032) and numerically higher (83.9%) at 6 hours post-treatment than the success rate in the tulathromycin-treated group (5.4%). A sufficient number of *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis* were isolated from cattle in the study to demonstrate that these BRD pathogens were contributing to the observed disease.

HOW SUPPLIED

DRAXXIN KP Injection is available in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

STORAGE CONDITIONS

Store at or below 25°C (77°F), with excursions up to 40°C (104°F). Protect from freezing.

APPROVED BY FDA under NADA # 141-543

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Product of Spain

May 2021

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FULL PRESCRIBING INFORMATION FOR USE IN CATTLE ONLY

Draxxin®

(tulathromycin injection)

Injectable Solution

Antibiotic

100 mg of tulathromycin/mL

For use in beef cattle (including suckling calves), non-lactating dairy cattle (including dairy calves) and veal calves. Not for use in female dairy cattle 20 months of age or older.

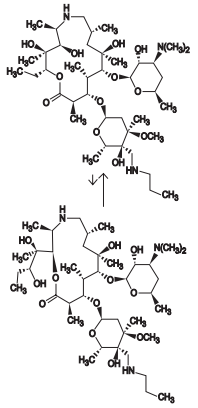
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

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, 500 mg propylene glycol, 19.2 mg citric acid and 5 mg monothioglycerol. Sodium hydroxide or hydrochloric acid may be 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 (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyrano-syl] 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-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS

Beef and Non-Lactating Dairy Cattle

BRD – DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis*; and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis.*

IBK – DRAXXIN Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis.*

Foot Rot – DRAXXIN Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii,*

Suckling Calves, Dairy Calves, and Veal Calves

BRD - DRAXXIN Injectable Solution is indicated for the treatment of BRD associated with *M. haemolytica, P. multocida, H. somni,* and *M. bovis.*

DOSAGE AND ADMINISTRATION

Cattle

Inject subcutaneously as a single dose in the neck 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

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. This drug is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows.

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.

ADVERSE REACTIONS

Cattle

In one BRD 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.

POST APPROVAL EXPERIENCE

The following adverse events are based on post approval adverse drug experience reporting. Not all adverse events are reported to the FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of reporting frequency in cattle: Injection site reactions and anaphylaxis/anaphylactoid reactions. For a complete listing of adverse reactions for DRAXXIN (tulathromycin injection) Injectable Solution reported to the CVM see: http://www.fda.gov/AnimalVeterinary.

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 minimum inhibitory concentration (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.

*[1] Carbon, C. 1998. Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis., **27**:28-32.*

*[2] Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J., **16**:438-443.*

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.

[3] Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.

MICROBIOLOGY

Cattle

Tulathromycin has demonstrated *in vitro* activity against *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis,* four pathogens associated with BRD; against *Moraxella bovis* associated with IBK; and against *Fusobacterium necrophorum* and *Porphyromonas levii* associated with bovine foot rot.

The MICs of tulathromycin against indicated BRD and IBK pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A2). The MICs against foot rot pathogens were also determined using methods recommended by the CLSI (M11-A6). All MIC values were determined using the 9:1 isomer ratio of this compound.

BRD - The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and at-risk field studies in the U.S. in 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves, and from lung swabs or lung tissue of saline-treated calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders, and from lung swabs or lung tissue of saline-treated calves that died. The results are shown in Table 3.

IBK - The MICs of tulathromycin were determined for *Moraxella bovis* isolates obtained from calves enrolled in IBK field studies in the U.S. in 2004. Isolates were obtained from pre-treatment conjunctival swabs of calves with clinical signs of IBK enrolled in the DRAXXIN and saline-treated groups. The results are shown in Table 3.

Foot Rot - The MICs of tulathromycin were determined for *Fusobacterium necrophorum* and *Porphyromonas levii* obtained from cattle enrolled in foot rot field studies in the U.S. and Canada in 2007. Isolates were obtained from pre-treatment interdigital biopsies and swabs of cattle with clinical signs of foot rot enrolled in the DRAXXIN and saline-treated groups. The results are shown in Table 3.

Table 3. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating BRD and IBK in the U.S. and from foot rot field studies in the U.S. and Canada.

Indicated pathogen	Date isolated	No. of isolates	MIC_{50}** (μg/mL)	MIC_{90}** (μg/mL)	MIC range (μg/mL)
Mannheimia haemolytica	1999	642	2	2	0.5 to 64
Pasteurella multocida	1999	221	0.5	1	0.25 to 64
Histophilus somni	1999	36	4	4	1 to 4
Mycoplasma bovis	1999	43	0.125	1	≤ 0.063 to > 64
Moraxella bovis	2004	55	0.5	0.5	0.25 to 1
Fusobacterium necrophorum	2007	116	2	64	≤ 0.25 to > 128
Porphyromonas levii	2007	103	8	128	≤ 0.25 to > 128

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.

** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

EFFECTIVENESS

Cattle

BRD – 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 ($P \leq 0.05$) 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. Fifty-two DRAXXIN-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *Mycoplasma bovis* identified in cultures from pre-treatment nasopharyngeal swabs.

Of the 52 DRAXXIN-treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were treatment failures.

A Bayesian meta-analysis was conducted to compare the BRD treatment success rate in young calves (calves weighing 250 lbs or less and fed primarily a milk-based diet) treated with DRAXXIN to the success rate in older calves (calves weighing more than 250 lbs and fed primarily a roughage and grain-based diet) treated with DRAXXIN. The analysis included data from four BRD treatment effectiveness studies conducted for the approval of DRAXXIN in the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate in young calves was at least as good as the BRD treatment success rate in older calves. As a result, DRAXXIN is considered effective for the treatment of BRD associated with *M. haemolytica, P. multocida, H. somni,* and *M. bovis* in suckling calves, dairy calves, and veal 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. Fifty saline-treated calves classified as non-responders in this study had *Mycoplasma bovis* identified in cultures of post-treatment nasopharyngeal swabs or lung tissue.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN against *Mycoplasma bovis*. A total of 166 calves were inoculated intratracheally with field strains of *Mycoplasma bovis*. When calves became pyrexic and had abnormal respiration scores, they were treated with either DRAXXIN (2.5 mg/kg BW) subcutaneously or an equivalent volume of saline. Calves were observed for signs of BRD for 14 days post-treatment, then were euthanized and necropsied. In both studies, mean lung lesion percentages were statistically significantly lower in the DRAXXIN-treated calves compared with saline-treated calves (11.3% vs. 28.9%, $P = 0.0001$ and 15.0% vs. 30.7%, $P < 0.0001$).

IBK – Two field studies were conducted evaluating DRAXXIN for the treatment of IBK associated with *Moraxella bovis* in 200 naturally-infected calves. The primary clinical endpoint of these studies was cure rate, defined as a calf with no clinical signs of IBK and no corneal ulcer, assessed on Days 5, 9, 13, 17, and 21. Time to improvement, defined as the first day on which a calf had no clinical signs of IBK in both eyes, provided that those scores were maintained at the next day of observation, was assessed as a secondary variable. At all time points, in both studies, the cure rate was significantly higher ($P < 0.05$) for DRAXXIN-treated calves compared to saline-treated calves. Additionally, time to improvement was significantly less ($P < 0.0001$) in both studies for DRAXXIN-treated calves compared to saline-treated calves.

Foot Rot - The effectiveness of DRAXXIN for the treatment of bovine foot rot was evaluated in 170 cattle in two field studies. Cattle diagnosed with bovine foot rot were enrolled and treated with a single subcutaneous dose of DRAXXIN (2.5 mg/kg BW) or an equivalent volume of saline. Cattle were clinically evaluated 7 days after treatment for treatment success, which was based on defined decreases in lesion, swelling, and lameness scores. In both studies, the treatment success percentage was statistically significantly higher in DRAXXIN-treated calves compared with saline-treated calves (60% vs. 8%, $P < 0.0001$ and 83.3% vs. 50%, $P = 0.0088$).

ANIMAL SAFETY

Cattle

Safety studies were conducted in feeder calves receiving a single subcutaneous dose of 25 mg/kg BW, or 3 weekly subcutaneous doses 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 and two of six calves administered 15 mg/kg BW.

A safety study was conducted in preruminant 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.

STORAGE CONDITIONS

Store below 25°C (77°F), with excursions up to 40°C (104°F). Use this product within 45 days of the first puncture and puncture a maximum of 20 times. If more than 20 punctures are anticipated, the use of automatic injection equipment of a repeater syringe is recommended. When using a draw-off spike or needle with bore diameter larger than 16 gauge, discard any product remaining in the vial immediately after use.

HOW SUPPLIED

DRAXXIN Injectable Solution is available in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

NADA 141-244, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

To report a suspected adverse reaction or to request a safety data sheet call **1-888-963-8471.** For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

For additional DRAXXIN product information call: **1-888-DRAXXIN** or go to **www.DRAXXIN.com**

TAKE TIME OBSERVE LABEL DIRECTIONS

Made in Spain

Revised: June 2018

EXCEDE®
(Ceftiofur Crystalline Free Acid)
Sterile Suspension

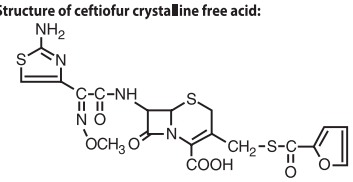
For subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle. For subcutaneous injection in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) in beef and non-lactating dairy cattle. Not for use in calves to be processed for veal.

CAUTION
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits extra-label use of this drug in cattle for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

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 caprylic/capric triglyceride 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*.

EXCEDE Sterile Suspension is also indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef, non-lactating dairy, and lactating dairy cattle.

EXCEDE Sterile Suspension is also indicated for treatment of acute metritis (0-10 days post-partum) associated with bacterial organisms susceptible to ceftiofur in lactating dairy cattle.

DOSAGE
Treatment of BRD and bovine foot rot

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 ceftiofur equivalents (CE)/lb (6.6 mg CE/kg) body weight (BW) (1.5 mL sterile suspension per 100 lb BW).

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) BW (1.5 mL sterile suspension per 100 lb BW).

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

Control of BRD

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) BW (1.5 mL sterile suspension per 100 lb BW).

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).

Treatment of Acute Metritis

Administer as a subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) to lactating dairy cattle at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW). Repeat this dose in the contra-lateral (opposite) ear approximately 72 hours following the initial dose.

Table 1. Dosing Schedule for EXCEDE Sterile Suspension.

Weight (lb)	Dose Volume (mL)	Weight (lb)	Dose Volume (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.

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

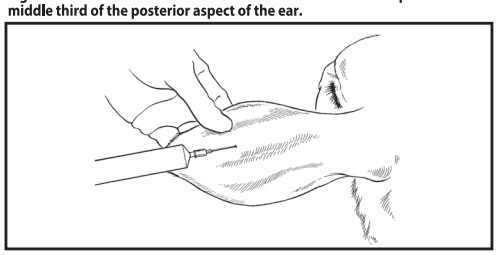
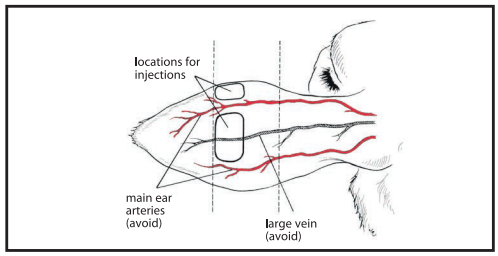


Figure 3. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.



ADMINISTRATION FOR BASE OF THE EAR
In lactating dairy cattle the injection techniques for subcutaneous (SC) injection in the posterior aspect of the ear where it attaches to the head (base of the ear) can be made by the rostral or ventral injection techniques.

In beef and non-lactating dairy cattle the SC injection in the base of the ear can be made by the rostral, ventral or toward the opposite eye injection techniques.

- **Shake well before using.** Please read the complete package insert before administering EXCEDE Sterile Suspension subcutaneously in the posterior aspect of the ear where it attaches to the head (base of the ear).
- The subcutaneous (SC) injection may be made using the toward the opposite eye, rostral, or ventral techniques. Hold the syringe and needle and insert the needle as described below.
- Deliver the entire contents of the syringe.
- Do not administer EXCEDE Sterile Suspension in the neck.

Administration for the Base of the Ear: Toward the Opposite Eye Technique
- 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.

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

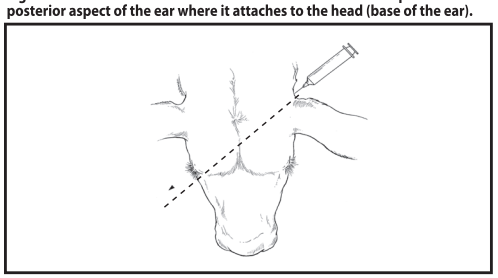
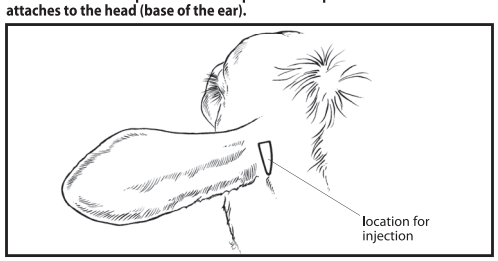
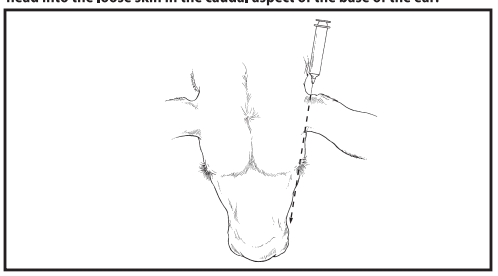


Figure 5. Injection location for the subcutaneous administration of EXCEDE Sterile Suspension in the posterior aspect of the ear where it attaches to the head (base of the ear).



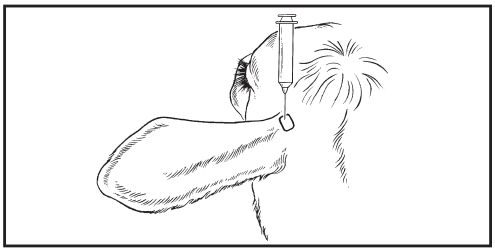
Administration for the Base of Ear: Toward the Same Eye Technique or Rostral Direction
- Hold the syringe and needle behind the ear to be dosed so the needle and syringe point in the direction of an imaginary line that would pass through the head toward the eye on the same side of the head. See Figures 5 and 6.
- 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 the needle position. See Figure 6.

Figure 6. Diagram of head showing the direction for the base of ear injections administered rostrally toward the eye on the same side of the head into the loose skin in the caudal aspect of the base of the ear.



Administration for Base of the Ear: Ventral Technique
- Hold the syringe and needle above the ear to be dosed so that the needle and syringe are pointing ventrally toward the base of the ear. The needle will be inserted into the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while pointing ventrally. Care should be taken to not insert the needle through the cartilage of the ear. See Figure 7.
- 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 needle position. See Figure 7.

Figure 7. Diagram of head showing the direction of base of ear injections when administered ventrally into the loose skin in the caudal aspect of the base of the ear.



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 protective 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 or to report any adverse event please call 1-888-963-8471.

Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension via middle third of the ear injection or base of the ear injection directed towards the opposite eye. Intra-arterial injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal.

RESIDUE WARNINGS
- **Following label use as either a single-dose or 2-dose regimen, a 13-day pre-slaughter withdrawal period is required after the last treatment.**
- **Following label use as either a single-dose or 2-dose regimen, no milk discard period is required for this product.**
- **Use of dosages in excess of 3.0 mg CE/lb (6.6 mg CE/kg) BW 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.**

ANTIBACTERIAL WARNINGS
Use of antibacterial drugs in the absence of a susceptible bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant bacteria.

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 injection in 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
Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension via middle third of the ear injection or base of the ear injection directed towards the opposite eye. Intra-arterial injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal. During the conduct of clinical studies, there was a low incidence of acute death (see ANIMAL SAFETY) 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
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 lowest minimum inhibitory concentration to encompass 90% of the most susceptible isolates (MIC_{90}) for the labeled BRD pathogens, *Pasteurella multocida, Mannheimia haemolytica* and *Histophilus somni*, for generally not less than 150 hours after a single administration (See Figure 8).

Single Dose Regimen

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 8. Average (n=12/group) plasma concentrations of ceftiofur and desfuroylceftiofur-related metabolites after administration of EXCEDE Sterile Suspension at 3.0 mg CE/lb (6.6 mg CE/kg) BW 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.

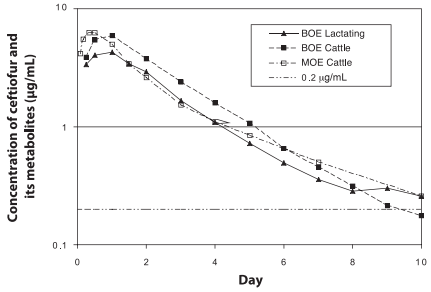


Table 2. Average (n = 12/group) pharmacokinetic parameters for ceftiofur and desfuroylceftiofur metabolites calculated after a single subcutaneous administration of 3.0 mg CE/lb (6.6 mg CE/kg) BW of EXCEDE Sterile Suspension in either the middle third of the ear or the base of the ear.

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 CE/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 CE/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

Two-Dose Regimen

A two-dose regimen of 6.6 mg CE/kg BW administered 72 hours apart is required for the treatment of acute metritis in lactating cows. The mean plasma concentration vs. time profile for ceftiofur and desfuroylceftiofur-related metabolites for the 2-dose regimen in 12 cows is shown in Figure 9 below. The pharmacokinetic parameters for the 2-dose regimen are provided in Table 3.

Figure 9. LS-Mean DCA Plasma Concentration Time Profile Following Two Subcutaneous Injections of EXCEDE 72 hours apart at a Dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW in 12 lactating cows.

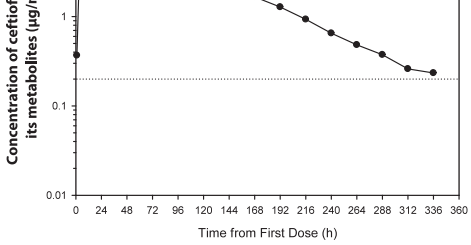


Table 3. Average (n = 12) Pharmacokinetic Parameters Following Two Subcutaneous Injections of EXCEDE Sterile Suspension at a Dose 3.0 mg CE/lb (6.6 mg CE/kg) BW at a 72 Hour Interval.

PK Parameter	Mean ± Standard Deviation
$AUC_{0\text{-}LOQ}$ (µg•h/mL)	651 ± 119
$t_{1/2}$ (h)	55.7 ± 4.84
$t_{>0.2}$ (h)	341 ± 34.0
T_{max} (h)	77.1 ± 33.4
C_{max} (µg/mL)	5.98 ± 2.51

MICROBIOLOGY

Ceftiofur has demonstrated *in vitro* activity against *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni,* three major pathogens associated with BRD, and against *Fusobacterium necrophorum* and *Porphyromonas levii* associated with bovine foot rot.

A summary of the susceptibility of BRD and foot rot pathogens is presented in Table 4. BRD isolates were obtained from cattle enrolled in a field study conducted in the United States that were diagnosed with BRD. Foot rot isolates were obtained from cattle enrolled in a field study conducted in the United States and Canada that were diagnosed with foot rot. Susceptibility testing was conducted according to the Clinical and Laboratory Standards Institute (CLSI) M7-A3 and M11-A6 standards for BRD and foot rot isolates, respectively.

Table 4. Ceftiofur minimum inhibitory concentration (MIC) values* of indicated pathogens isolated from cattle with naturally occurring BRD or foot rot.

Indicated pathogen	Year of isolation	Number of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	1996 to 1997	75	0.008	0.015	0.001 to 0.015
Pasteurella multocida	1996 to 1997	43	0.004	0.004	0.001 to 0.015
Histophilus somni	1996 to 1997	11	0.004	0.004	0.002 to 0.015
Fusobacterium necrophorum	2006 to 2007	148	≤ 0.25	0.5	≤ 0.25 to >128
Porphyromonas levii	2006 to 2007	141	≤ 0.25	2.0	≤ 0.25 to 16

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

Based on pharmacokinetic and clinical effectiveness studies of ceftiofur in cattle after a single administration of 3.0 mg CE/lb (6.6 mg CE/kg) BW and the MIC and susceptibility data, the following breakpoints are recommended for BRD pathogens by CLSI.

Table 5. CLSI-accepted interpretive criteria* for ceftiofur against cattle respiratory pathogens.

Pathogen	Disk potency	Zone diameter (mm)			MIC breakpoint (µg/mL)		
		S	I	R	S	I	R
Mannheimia haemolytica *Pasteurella multocida* *Histophilus somni*	30 µg	≥ 21	18 to 20	≤ 17	≤ 2.0	4.0	≥ 8.0
S – Susceptible I – Intermediate R – Resistant							

* These interpretive criteria are only intended for use when CLSI M31-A2 performance standards are used to determine antimicrobial susceptibility. Interpretive criteria for bovine foot rot pathogens have not been established.

EFFECTIVENESS

A field dose confirmation study for the treatment of BRD evaluated the effectiveness of single doses of 2.0 and 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW for the treatment of the bacterial component of BRD under field conditions. All treatments were administered subcutaneously in the middle third of the posterior aspect of the ear. Cattle were clinically evaluated on Days 2 to 4, 14 and 28 and were observed on all other study days. The 3.0 mg CE/lb (6.6 mg CE/kg) BW 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 2.0 or 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW 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 subcutaneously 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.

The effectiveness of EXCEDE Sterile Suspension for the treatment of bovine foot rot was evaluated in a six-location field effectiveness study. Cattle diagnosed with bovine foot rot were enrolled and treated with EXCEDE Sterile Suspension, administered by subcutaneous injection in the base of the ear as a single dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW or an equivalent volume of a vehicle control. Cattle were clinically evaluated 7 days post-treatment for treatment success, which was based on defined decreases in lesion, swelling and lameness scores. A total of 169 beef and dairy cattle were included in the analysis. There was a statistically significant difference ($p = 0.0054$) in treatment success for EXCEDE-treated cattle (58.4%) compared to vehicle-treated control cattle (13.2%).

The effectiveness of EXCEDE Sterile Suspension for the treatment of acute metritis was evaluated in a 15-location field effectiveness study. A total of 1023 cows with a fetid vaginal discharge and a rectal temperature of ≥ 103 °F were enrolled in the study and treated with either a two-dose regimen of EXCEDE (6.6 mg CE/BW) or an equivalent volume of vehicle control, administered approximately 72 hours apart at the base of opposite ears. At 14 days post-treatment, each cow remaining in the study was examined and rectal temperature and vaginal discharge score were recorded. Cows with a non-fetid discharge, and a rectal temperature < 103 °F, and that did not require alternate ("escape") therapy during the 14_day observation period were classified as a cure. The cure rate was significantly higher ($p < 0.0001$) in EXCEDE-treated cows (362/493, 74.3%) than in vehicle-treated cows (271/489, 55.3%). One cow died 15 to 20 minutes after the second administration of EXCEDE. Necropsy findings determined the probable cause of death to be intra-arterial injection.

ANIMAL SAFETY

Systemic Safety Studies

After parenteral administration, ceftiofur crystalline free acid (as EXCEDE Sterile Suspension), ceftiofur sodium and ceftiofur hydrochloride are rapidly metabolized to 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 approved dose of EXCEDE Sterile Suspension 3.0 mg CE/lb (6.6 mg CE/kg) BW. 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 approved dose of EXCEDE Sterile Suspension of 3.0 mg CE/lb/day (6.6 mg CE/kg) BW. 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.

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.

To support systemic target animal safety for the 2-dose metritis regimen, five projected daily doses of NAXCEL Sterile Powder (ceftiofur sodium) at 2.2 mg/kg BW were compared pharmacokinetically with EXCEDE administered 2 times at a 72 hour interval at 6.6 mg/kg BW. The peak concentration (C_{max}) and the extent of exposure (AUC) after two doses of EXCEDE were statistically no higher than the exposure following five daily doses of NAXCEL Sterile Powder in beef cattle.

Investigation of Intra-Arterial and Intravenous Injection

In approximately 6000 animals enrolled in the BRD clinical studies, nine animals 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 3.0 mg CE/lb (6.6 mg CE/kg) BW 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 three steers (body weight range 197-223 kg) were given a single 3.0 mg CE/lb (6.6 mg CE/kg) BW 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 to 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.

Safety Studies in Beef Cattle

Middle of the ear injection:

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 3.0 mg CE/lb (6.6 mg CE/kg) BW. 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 subcutaneous injection of EXCEDE Sterile Suspension was also evaluated in a large multi-location effectiveness 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 cross-bred 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.

Base of the ear injection:

The local tolerance of the ear to a single subcutaneous injection at the 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 base of the ear with EXCEDE Sterile Suspension at a dose rate of 3.0 mg CE/lb (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.

The ventral base of the ear injection technique was evaluated in a conditions of use study in 200 beef cattle. Each animal received a single injection of EXCEDE Sterile Suspension at a dose of 6.6 mg CE/kg BW at the base of the ear using the ventral injection technique. Normal restraint was adequate for 95.5% of animals in the study. Injection site scores were normal for 65.3% and 92.5% of cattle on Days 14 and 28, respectively. One animal had an unusually large swelling on Day 7 which reduced to a size comparable to other study animals by Day 14.

Safety Studies in Lactating Dairy Cattle

The local tolerance of the ear to a single subcutaneous injection at the 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, six dairy cows were injected in the base of the ear at a dose rate of 3.0 mg CE/lb (6.6 mg CE/kg) BW 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 observation times after treatment. Cows were slaughtered 10 days after injection. At necropsy, all six cows showed evidence of injection site inflammation (discoloration of fat tissue/fascia) and four of six 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.

Injection site safety for base of the ear administration was evaluated in the metritis effectiveness study described above. Normal restraint was adequate for ≥ 97.8% of injections administered. Injection site scores were normal in 50.3%, 73.2%, and 96.4% at 2 or 3, 11, and 54±3 days after the second injection, respectively.

The ventral and rostral base of the ear injection techniques were compared with the toward the opposite eye technique in a conditions of use study in 197 lactating dairy cattle. Normal restraint was adequate for 89.8% (ventral), 98% (rostral), and 100% (opposite eye) of animals in the study. Injection site scores were normal for 32% (rostral), 46.9% (ventral), and 47.9% (opposite eye) of cattle on Day 14, and 73% (rostral), 87.8% (ventral), and 64.6% (opposite eye) of cattle on Day 28, respectively.

TISSUE AND MILK RESIDUE DEPLETION

A radiolabeled residue metabolism study established tolerances for ceftiofur residues in cattle kidney, liver and muscle. A separate study established the tolerance for ceftiofur residues in milk. The tolerances for 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 3.0 mg CE/lb (6.6 mg CE/kg) BW. 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 3.0 mg CE/lb (6.6 mg CE/kg) BW. 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.

Two-Dose Residue Decline Studies

A pivotal tissue residue decline study was conducted in dairy cattle. In this study, cows received two injections of 3.0 mg CE/lb (6.6 mg CE/kg) BW with a 72 hour interval between injections. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in the kidney by 13 days after the second dose. These data collectively continue to support a 13-day pre-slaughter withdrawal period after the last dose.

A pivotal milk residue decline study was conducted in lactating dairy cattle. In this study, cows received two injections of 3.0 mg CE/lb (6.6 mg CE/kg) BW with a 72 hour interval between injections. Milk residue decline data from this study supports 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). 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 sizes:
100 mL vial
250 mL vial

Approved by FDA under NADA # 141-209

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007
www.EXCEDE.com or call 1-888-963-8471

Revised: January 2020
40029632A&P

ADVOCIN™
(danofloxacin injection)

Sterile Injectable Solution
Antimicrobial

180 mg of danofloxacin as the mesylate salt/mL

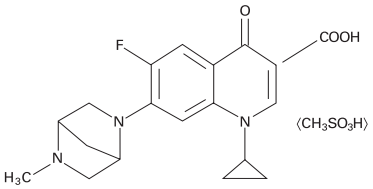
For subcutaneous use in beef cattle.

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 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 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 $C_{19}H_{20}FN_3O_3 \cdot CH_3SO_3H$ and the molecular weight is 453.49.

Figure 1. The chemical structure of danofloxacin mesylate.



Each mL contains 180 mg of danofloxacin as the mesylate salt, 200 mg 2-pyrrolidone, 50 mg povidone, 20.3 mg heavy magnesium oxide, 2.5 mg phenol, 5 mg monothioglycerol, hydrochloric acid or sodium hydroxide as needed to adjust pH, nitrogen headspace and water for injection, q.s.

INDICATIONS: For the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica* and *Pasteurella multocida* in beef cattle and for the control of BRD in beef cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

DOSAGE AND ADMINISTRATION: Care should be taken to dose accurately. Administered dose volume should not exceed 15 mL per injection site.

Single-Dose Therapy (BRD Treatment and Control in Cattle at High Risk): Administer subcutaneously at 8 mg/kg of body weight (2 mL/100 lb) as a one-time injection.

Multi-Day Therapy (BRD Treatment): Administer subcutaneously at 6 mg/kg of body weight (1.5 mL/100 lb) with this treatment repeated once approximately 48 hours following the first injection.

ADVOCIN Dosage and Treatment Schedule

Cattle Weight (lb)	Dose Volume (mL) 6 mg/kg, given twice, 48 hours apart (treatment)	8 mg/kg given once (treatment and control in cattle at high risk)
50	0.75	1
100	1.5	2
150	2.25	3
200	3	4
250	3.75	5
300	4.5	6
400	6	8
500	7.5	10
600	9	12
700	10.5	14
800	12	16*
900	13.5	18*
1000	15	20*

* Administered dose volume should 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 one or more of the following risk factors:

- Commingling from multiple sale barns/sources
- Extended transport times and shrink
- Exposure to wet or cold 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 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 Safety Data Sheet (SDS), 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 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 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 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) in cattle 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 negligible accumulation was observed when animals were dosed twice, 48 hours apart.

Danofloxacin is rapidly absorbed and is highly bioavailable when administered as a subcutaneous injection in the neck. Linear pharmacokinetics has been demonstrated when danofloxacin is administered to cattle by subcutaneous injection at doses between 1.25 to 10 mg/kg. No statistically significant gender difference was observed in peak or total systemic exposure following a single subcutaneous administration of danofloxacin to heifers and steers at a dose of 6 mg/kg body weight (Table 1).

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

		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] $T_{½}$	hr	4.8	18	4.2	7

[a] 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] Bioavailability (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 by either a subcutaneous or intravenous injection.
[c] Statistically significant differences in T_{max} were detected between genders. Given the similarity in C_{max} values, these differences are not expected to have any clinical relevance.
[d] Clearance (CL) and Volume of distribution at steady state (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, 1996–1997, were determined using the standardized microdilution technique (Sensititre/Alamar, Accumed International), and are shown in Table 2.

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

Indicated Pathogen	Number of Isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC Range (µg/mL)
Mannheimia haemolytica	106	0.06	0.06	≤0.015 to 0.12
Pasteurella multocida	94	≤0.015	0.06	≤0.015 to 0.12

* The correlation between in vitro susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

Table 3. Danofloxacin minimum inhibitory concentration (MIC) values* of indicated pathogens isolated from 2013 pivotal field studies in the U.S. and Canada for the control of BRD in cattle at high risk of developing BRD.

Indicated Pathogen	Number of Isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC Range (µg/mL)
Mannheimia haemolytica	507	0.03	0.06	≤0.008 to >8
Pasteurella multocida	324	≤0.008	0.12	≤0.008 to 1.0

* The correlation between in vitro susceptibility data and clinical effectiveness is unknown.
**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 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 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 (86.0%) was statistically significantly (p=0.0068) greater than that of saline-treated calves (76.3%) (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 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: 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 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 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. When using a draw-off spike or needle with bore diameter larger than 16 gauge, discard any product remaining in the vial immediately after use.

100 mL vial: Use this product within 28 days of the first puncture and puncture a maximum of 7 times. If more than 7 punctures are anticipated, the use of automatic injection equipment or a repeater syringe is recommended.

250 mL vial: Use this product within 28 days of the first puncture and puncture a maximum of 17 times. If more than 17 punctures are anticipated, the use of automatic injection equipment or a repeater syringe is recommended.

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

Approved by FDA under NADA # 141-207

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 SDS or for technical assistance, call Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

TAKE TIME OBSERVE LABEL DIRECTIONS

100 mL: Revised: June 2019
8713834A&P

250mL: Revised: June 2019
8713844A&P