ONLY ZOETIS OFFERS A DIVERSE RANGE OF ANTIMICROBIALS TO MATCH YOUR BRD CHALLENGES.

When you're dealing with bovine respiratory disease (BRD), antimicrobial selection can be overwhelming. With so many products offering different indications, durations and withdrawal times - which one is right for your operation?

Zoetis makes it simple with the most comprehensive and versatile antimicrobial portfolio available, including products with:

- Three different classes to destroy BRD bacteria in three different ways
- Treatment and control options
- The shortest withdrawal times for greater flexibility at different production stages

PRODUCT	ACTIVE Ingredient	CLASS	BRD CONTROL INDICATIONS CATTLE AT HIGH RISK OF DEVELOPING BRD ASSOCIATED WITH:	BRD TREATMENT INDICATIONS BRD ASSOCIATED WITH:	TREATMENT DICATIONS ASSOCIATED WITH: DOSAGE AND ROUTE OF ADMINISTRATION		ESTIMATED DURATION	MEAT With- Drawal
DRAXXIN®	Tulathromycin	Macrolide	Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis	M. haemolytica, P. multocida, H. somni and M. bovis	1.1 mL/cwt/ subcutaneous (SC) in the neck	10 mL	14 days ^{1,2,3,4}	18 days
EXCEDE ®	Ceftiofur crystalline free acid	Cephalosporin	M. haemolytica, P. multocida and H. somni	M. haemolytica, P. multocida and H. somni	1.5 mL/cwt/ SC in the middle third of ear or base of ear	N/A	7 days⁵	13 days
ADVOCIN®	Danofloxacin mesylate	Fluoroquinolone	M. haemolytica and P. multocida	<i>M. haemolytica</i> and <i>P. multocida</i> P. multocida 2 mL/cwt as a one-timeinjection or1.5 mL/cwt/ SC inthe neck; with thistreatment repeatedonce, 48 hours afterfirst injection		15 mL	**	4 days
Micotil®	Tilmicosin	Macrolide	M. haemolytica	<i>M. haemolytica, P. multocida</i> and <i>H. somni</i> 1.5–3.0 mL/cwt/ SC in the neck		10 mL	**	42 days
Nuflor®	Florfenicol	Amphenicol	<i>M. haemolytica, P. multocida</i> and <i>H. somni</i>	M. haemolytica, P. multocida and H. somni	6 mL/cwt/ SC in the neck or 3 mL/cwt/ intramuscular (IM) in the neck and repeat 48 hours after first injection. Control: 6 mL/ cwt/ SC in the neck	10 mL	**	38 days SC 28 days IM
Nuflor Gold®	Florfenicol	Amphenicol	Not approved for control of BRD	M. haemolytica, P. multocida, H. somni and M. bovis	6 mL/cwt/ SC in the neck	15 mL	*	44 days
Resflor Gold®	Florfenicol and flunixin meglumine	Amphenicol	Not approved for control of BRD	M. haemolytica, P. multocida, H. somni and M. bovis	6 mL/cwt/ SC in the neck	10 mL	*	38 days
Zuprevo™	Tildipirosin	Macrolide	<i>M. haemolytica, P. multocida</i> and <i>H. somni</i>	M. haemolytica, P. multocida and H. somni	1 mL/cwt/ SC in the neck	10 mL	28 days ⁶	21 days
Zactran®	Gamithromycin	Macrolide	<i>M. haemolytica</i> and <i>P. multocida</i>	M. haemolytica, P. multocida, H. somni and M. bovis	1.82 mL/cwt/ SC in the neck	10 mL	10 days ^{7,8}	35 days
Baytril®	Enrofloxacin	Fluoroquinolone	M. haemolytica, P. multocida, H. somni and M. bovis	M. haemolytica, P. multocida, H. somni and M. bovis; multiday therapy is not indicated for M. bovis	3.4–5.7 mL/cwt/ SC in the neck. For multiday therapy: 1.1-2.3 mL/cwt; repeat at 24-hour intervals for three days. Additional treatments may be given on Days 4 and 5 to animals that have shown clinical improvement but not total recovery.	20 mL	**	28 days



IMPORTANT SAFETY INFORMATION FOR DRAXXIN: DRAXXIN has a pre-slaughter withdrawal time of 18 days. 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, on reverse side.

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, on reverse side.

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, on reverse side.

*Not labeled for control of BRD **Data not available in literature.

- ³ Zotetis. Efficacy of DRAXXIN administered to calves 9, 7, 5, 3 n 1 day before challenge with *Mannheimia haemolytica*. *Technical Bulletin No. DRXO6052*, 2006:1-3 ³ Data on file, Study Report No. 1133R-60-09-749, Zoetis Inc.

- ⁴ Zoetis. Efficacy of DRAXXIN, followed by a 7-, 10-, or 14-day post-treatment intervals, against naturally occurring bovine respiratory disease in high-risk calves to close. *Technical Bulletin No. DRX06053*, 2007:1-5.
 ⁵ Zoetis. Bryson WL, Dame KJ, Hibbard B, et al. Outcomes of 3-, 5-, or 7-day post-treatment intervals after a single dose of EXCEDE. *Technical Bulletin No. EXD06112*, 2006:1-3.
- ⁶ 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.
- ⁸ 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* 201;9(2):171-180.





¹ Freedom of Information Summary. NADA 141-244. Available at: http://www.fda.gov/downloads/animalveterinary/products/approvedanimaldrugproducts/foiadrugsummaries/ucm118061.pdf. Accessed June 19, 2014



Injectable Solution

Antibiotio 100 mg of tulathromycin/mL

For use in beef cattle (including suckling calves), non-lactating dairy cattle (including dairy calves), veal calves, and swine. 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 Inject . ctable Solution is a ready-to-use sterile parenteral preparation DRAXMM injectable Solution is a ready-to-use stelline parelineral preparation containing dutationity on, a semi-synthetic macrolide antibiotic of the subclass triamilide. Each mL of DRAXXIN contains 100 mg of tutathromycin 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.



The chemical names of the isomers are (2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-13-[[2,6 didexy-3-C-methyl-3-O-methyl-4-C-[(propylamino) methyl)-oc-1-nbo-hexopyrano-sylloxy]-2-et 3,4,10-thydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-diimethylamino];-Po-xylo-hexopyranosy]-0,0y1-1-oxa6-acaza(copentadecan-15-one and (2R, 3R, 5R, 8R, 9R, 9R, 10S, 11S, 12R) 11-[[2,6-dideoxy-3-C-methyl-4-C-[(propylamino)]methyl]-oc-1-nbo-hexopyrano-syll 0y2;-[(11,2R, 1)-2.dihydroxy--1-methylu+0-[-4]-(0xroy-3,68,10,1-2)-entamethyl=4](3,4,6-tri oxy-3-(dimethylamino)- β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respect -2-ethyl INDICATIONS

Beef and Non-Lactating Dairy Cattle BRD – DRAXXIN Iniectable Solution is indicated for the treatment of bovine respiratory disease (BRD) Beer ann Work-actaining Jarry Caute BRD – DRAXOIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD associated with Mannheimia haemolytica, Pasteurella multocida, Histophilus sommi, 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 sommi, and Mycoplasma bovis. IBK – DRAXOII Injectable Solution is indicated for the treatment of Infectious bovine keratoconjunctivits (IBK) associated with Moraxella bovis. Foot Rot – DRAXOII Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with Posobacterium mecophorum and Porphyromonas levii. Suckling Calves, Dairy Calves, and Veal Calves BRO - DRAXOII Injectable Solution is indicated for the treatment of BRD associated with M. Inaemolytica, P. multocida, H. sommi, and M. bovis.

m. itermolytica, r. minucoda, rr. summ, an w. boxs. Swine DRAXXIN Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with Actinobacillus pleuropneumoniae, Pasteurella multicoida, Bordetella bronchiseptica, Haemophilus parasuis, and Mycoplasma hypopneumoniae; and for the control of SRD associated with Actinobacillus pleuropneumoniae, Pasteurella multicoida, and Mycoplasma hypopneumoniae in group of pigs where SRD has been diagnosed. DOSAGE AND ADMINISTRATION

 $\begin{array}{l} \label{eq:cattle} \mbox{Cattle} \\ \mbox{Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1.1 mL/100 lb) body \\ \mbox{weight (BW)}. Do not inject more than 10 mL per injection site. \end{array}$

Jable 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					

Inject intramuscularly as a single dose in the neck 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	Dose Volume
(Pounds)	(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

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



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

CAUTION Federal (USA) lav CAUTION Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal Law pro extra-label use of this drug in cattle for disease prevention purposes; at unaproved doss; trequencies, dura or routes of administration; and in unapproved major food producting species/production classes.

Of lowers of manufacture of the second secon

Utility of an anticipation of the second sec



INDICATIONS EXCEDE Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD, shipping fever, response in the second start with Mannheimia haemolvitica, Pasteurella multicida, and Histophilus somni in beel, non-EVLECE some occurs of the Manheimia haenolylica, Pasteurne menocane, mo-bacting durin, and lactating dary catle. EVCRC Some Some Soperation is also indicated for the control of respicatory disease in bed and non-hectating EVCRC Source Source (and a source of the control of respicatory of the methods) and H. some data and the source of the associated with Fiscobacterium necrophorum and Porphyremonas lewl in bed, non-lactating dairy, and lactating associated with Fiscobacterium necrophorum and Porphyremonas lewl in bed, non-lactating dairy, and lactating associated with Fiscobacterium necrophorum and Porphyremonas lewl in bed, non-lactating dairy, and lactating associated with Fissobacterium necrophorum and Proprycennes are a social of the social

DOSAGE

Administer as a single subclaterous injection in the posterior aspect of the ear where it attaches to the head (asso of the ear) to call at a dosage of 30 mg celtifour equivalents (CE)/tb (6.6 mg CEAg) body weight (SW) (1.5 mL startie suspension per 100.0 B W). (1-4) mit settre subpension per 100 b BW). In beel and non-licitating dary cattle, EXCEDE Stenie Suspension may also be administered as a langle exception of the setting of the setting of the setting of the set of the setting of the setting Most animals will respond to realment within three to five days. If no improvement is observed the discussion should be realmented.

Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension via middle third of the art injection of sub of the art injection directed towards the opposite eye, intra-arterial injection of EXCEDE Sterile Suspension is likely to result in sudden deals of the animal. During the conduct of clinical studies, there injection. No other aviewes systemic affects were noted for either the antibiotic or formulation during any of the clinical and traget animal safety studies. Control of BRD subcutaneous injection either in the middle third of the posterior aspect of the ear or in the the ear where it attaches to the head (base of the ear) to beef and non-lactating dairy cattle at C2Hb (6 5 mg CE/kg) BW (1.5 mL sterile suspension per 100 h BW). indicate that administration of EXCEDE Sterile Suspension is effective for the control of clinical and larger eliminations, and the cellifold of th

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 Swine Swine intended for human consumption must not be slaughtered within 5 days from the last treatmen

PRECAUTIONS

Cattle

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

Swine The effects of DRAXXIN on porcine reproductive performance, pregnancy, and lactation have not been determined. Intranuscular 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

Swine In one field study, one out of 40 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation in the sector of the four hours

CLINICAL PHARMACOLOGY CLINICAL PHARMACDLOGY At physiological BH, lutahromycin (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 macrolices. Markedly hipher lutahromycin concentrations are observed in the lungs as compared to the plasma. The extent to which lung concentrations represent free activity 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 Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been characterized, as a class, macrolides tend to be primarily bacterisotial, but may be bacterioidal against some pathogens². They also tend to exhibit concentration independent killing: the rate of bacterial eradication does not charge once server drug concentrations reach 2 to 3 times the minimum inhibitory concentration (MIC) of the targeted pathogen. Under these conditions, the time that sum concentrations remain above the MIC becomes the major determinant of autimicrobial 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 concentrations and the exposure time, the PAE will increase to some maximud duration. Of the vorvaribles, concentration 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. Inflect. Dis., **27**:28-32.
² Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Intect. Dis., J., **6**:483-443.

Cattle Following subcutaneous administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW.

Following subcutaneous administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, lutathromycin is rapidly and nearly completely absorbed. Peak plasma concentrations generally occur within 1.5 minutes after dosing and product relative bioavailability exceeds 90%. Total systemic clearance is approximately 170 mL/hr/kg. Tutathromycin distributes extensively into body tissues, as evidenced by volume of distribution si targely responsible for the long elimination half-life of this compound (approximately 2.75 days for total lung concentrations gluesd on data from healthy animals). Inter aphrameotic size of the size of approximately for the 2.75 days for total systemic mg/kg BW. No pharmacokhenic 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. Swine

source Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed (T_{mx} = 0.25 hour). Subsequently, the drug rapidly distributes introbody tissues, achieving a volume of distribution exceeding 15 L/kg. The free drug is rapidly cleared from the systemic circulation ($CL_{minute} = 187 mL/hkg$). However, the tas 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 plarmacokinetics. MICROBIOLOGY

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

The MCs of utahromycin 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). AII MIC values were determined using the 3:1 isomer ratio of this compound.

All MC values were determined using the 9.1 somer ratio of this compound. BRD - The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and 4-risk field studies in the U.S. in 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngaal swabs from all study calves, and from lung swabs or lung tissue of saline-treated calves that diel. In the 4-risk studies, isolates were obtained from nasopharyngaal swabs of saline-treated con-responders, and from lung swabs or lung tissue of saline-treated calves that died. In the 4-risk studies, isolates were obtained from calves enrolled in IBK field studies in the U.S. in 2004. Isolates were obtained from calves enrolled in IBK field studies in the U.S. in 2004. Isolates were obtained from treatment conjunctival swabs of calves with clinical signs of IBK enrolled in the DRAXNI and saline-treated groups. The results are shown in Table 3.

proups. The results are drawn in neuron of Pool Ref. The MICs of hubitromyrini were determined for *Fusobacterium necrophorum* and *Porphyrononas levi* obtained from cattle enrolled in foot rot field studies in the U.S. and Canada in 2007. Isolates were obtained from por-treatment intervingilal 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

istration for Sase 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 tomard the based of the ear. The needle will be inserted into the isone skin in the posterior aspect of the ear where it attacks to be head (base of the early while pointing ventral). Case should be taken to not insert insert the needle through the losse skin in the posterior aspect of the ear where it attacks to the head in-way of the early while maintaining needle position. See Figure 7.

FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. Keep out of reach of children.

Pencilinis and cophaloporties can cause alreger reactions in sceneral molecular and the penciline product and the severe alreger reactions in sceneral molecular. Repeated on the severe alreger reactions in sceneral molecular. Repeated on the severe alreger reactions in sceneral molecular. Repeated on the severe alreger reactions in sceneral molecular. Repeated on the severe alreger reactions in sceneral molecular. Repeated on the severe alreger reactions in sceneral molecular. Repeated on the severe alreger reactions in sceneral molecular reactions in the severe alreger reaction is sceneral molecular reactions in the severe alreger reaction is sceneral molecular. The severe alreger reaction is sceneral molecular reaction and the severe alreger reaction cocors (i.e., alst nash, these, difficult is reacted alregical barder contains molecular mole

ARNINGS Following belo use as either a single-dose or 2-dose regimen, a 13-day pre-slaughter withdrawal period is required after the last teatment. Following labeli use as either a single-dose or 2-dose regimen, no milk discard period is minimat for this modult

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/Ib (6.6 mg CE/kg) BW or administration by unap-proved routes (subcutaneous injection in the neck or intramuscular injection) may cause

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

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 less of disclose the several stagnation. In previous practice that 20 may. In the middle threit of the ear, may result may end that the several stagnation of the several stage of the several stage of the several stage of the several may end the several stage of the several may be affected or the sever reproductive performance, pregnancy, and lactation have not been

utaneous injection in the middle third of the posterior aspect of the ear, thickening and s septic cellular infiltrate) of the ear may occur. As with other parenteral injections, lo rial infections may result in abscess formation. Attention to hygienic procedures can m

metabolite. Subcutaneous administration of certifolur crystalline free rior aspect of the ear (middle third of the ear, MOE) of beef and non-vect of the ear where it attaches to the head (base of the ear, BOE) of faily cattle, provides therapeutic concentrations of certiform and plasma above the lowest minimum inhibitory concentration for the second se

A withdrawal period has not been established for this product in pre-ruminating ca
 Do not use in calves to be processed for yeal.

CONTRAINDICATIONS As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals prev hvoersensitive to the drug.

Indicated pathogen	Date isolated	No. of isolates	MICso ** (µg/mL)	MIC90** (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 Ievii	2007	103	8	128	≤ 0.25 to > 128

Swine

ulathromycin has been demonstrated against Actinobacillus pleuropneu ida, Bordetella bronchiseptica, Haemophilus parasuis, and Mycoplasm

hyopneumoniae. The MICs of Utabitnomycin against indicated SRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A and M31-A3). MICs for Haemophilus parasuls were determined using Veterinary Fastidious Medium and were incubated up to 48 hours as 35 or 37°C in a Co-meriched atmosphere. All MIC values were determined using the 91 isomer ratio of this compound. Isolates obtained in 2000 and 2002 were from lung samples from saline-treated pips annoth-rated santhel pips enrolled in Treatment of SRD field studies in the U.S. and Canada. Isolates obtained in 2007 and 2008 were from lung samples from saline-treated on DRAXIM-treated pips and on-treated santhel pips enrolled in Treatment of SRD field studies in and DRAXIM-treated pips and on-treated pips field studies in the U.S. and Canada. The results are shown in Table 4.

Table 4. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating SRD in the U.S. and Canada.

Indicated	Date	No. of	MIC _{so} **	MIC ₉₀ **	MIC range
pathogen	isolated	isolates	(µg/mL)	(µg/mL)	(µg/mL)
Actinobacillus	2000-2002	135	16	32	16 to 32
pleuropneumoniae	2007-2008	88	16	16	4 to 32
Haemophilus parasuis	2000-2002	31	1	2	0.25 to > 64
Pasteurella	2000-2002	55	1	2	0.5 to > 64
multocida	2007-2008	40	1		≤ 0.03 to 2
Bordetella bronchiseptica	2000-2002	42	4	8	2 to 8

* 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, respect EFFECTIVENESS

Cattle

BRD - In a multi-location field study, 314 calves with naturally occurring BRD were treated with BAXUN. 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 \leq 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 one treatment asopharyngeal svabs. 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 superior more treatment tailures in the BRD treatment supersection in wurp.

(28.8%) calves were categorized as trastment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were treatement failures. A Bayesian meta-analysis was conducted to compare the BPD treatment failures. A Bayesian meta-analysis was conducted to compare the BPD treatment failures. A Bayesian meta-analysis was conducted to compare the BPD treatment success rate in young calves (calves weighing 200 be or less and 1d primarily a milk-based diely treated with DRAXNI he analysis included data from four BPD treatment effectiveness studies conducted for the approval to DRAXNI he used with DRAXNI he analysis included data from four BPD treatment effectiveness studies conducted for the approval to DRAXNI he use. San onite contemporaneous studies conducted in the DR treatment success rate in US. and nite contemporaneous studies conducted in the BPD treatment success rate in young calves was all east as good as the BPD treatment success rate in US. An onite contemporaneous studies conducted in ED treatment BPD treatment success rate in young calves was all east as good as the BPD treatment success rate in US. An onite contemporaneous calves was all east as good as the BPD treatment success rate in US. An onite contemporaneous calves was allowed in the BPD treatment of BPD reatment success rate in young to DRAXNI he and Suck sing (2014). They compared to saline-treated calves (53%). Effectiveness evaluation was based on scored clinical signs of normal attitude/activity, normal respiration, and a rectal therperature of 2 - 04% ron Day 14. There were no BPD-related datasts in the DRAXNI heraet calves compared to two BRD-related datasts. They asing barbar barba

15.0% vs. 30.7%, P < 0.0001).</p>
IBK – Two field studies were conducted evaluating DRAXXIN for the treatment of IBK associated with Moraxelia Dovin 100 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 uicer, 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. All time points, in both studies, the cure rate was significantly teach hipher (P < 0.05) for DRAX(NI-treated calves compared to saline-treated calves. Additionally, time to compared to saline-treated calves.

Foot Rot - The effectiveness of DRAXXIN for the treatment of bovine foot rot was evaluated in 170 Foot Ref - The effectiveness of DRAXXIM for the treatment of bovine foot rot was evaluated in T/O cattle in two field studies. Cattle diagnosed with bovine foot rot were conciled and treated with a single subcataneous dose of DRAXXIM (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).

Swine In a multi-location field study to evaluate the treatment of naturally occurring SRD, 266 pigs were treated with DRAXXIN. Responses to treatment were compared to saline-treated controls. Success was defined as a jp with normal attitude, normal respiration, and rectal temperature of <104°F on Day 7. The treatment success rate was significantly greater ($P \le 0.05$) in DRAXXIN-treated pigs (70.5%) compared to saline-treated pigs (46.15%). *M hopneumoniae* was isolated from 106 saline-treated and non-treated sentinel pigs in this study.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN against *M*. hypopreumoniae. Ten days after inoculation intranasally and initiatracheally with a field strain of *M*. hypopreumoniae, the days after inoculation intranasally and initiatracheally with a field strain of *M*. hypopreumoniae, 144 pigs were trated with either DRAXXIN (25 mg/kg BW) intramuscularly or an equivalent volume of saile. Pigs were entitated and necrospice 10 days post-treatment. The mean percentage of gross pneumonic lung lesions was statistically significantly lower (P < 0.0001) for DRAXXIM-treated pigs than for sailen-treated pigs in both studies (8.52% vs. 23.62% and 11.31% vs. 26.42%).

The effectiveness of DRAXXIN for the control of SRD was evaluated in a multi-location natura The energy energy and the control of SRD was evaluated in a multi-location natural infection field study. When at least 15% of the study candidates showed clinical signs of SRD, al pigs were enrolled and treated with DRAXXIN (226 pigs) or saline (227 pigs). Responses to treatment were evaluated on Day 7. Success was defined as a pig with normal attitude, normal respiration, and rectai temperature of 104°F. The treatment success rate was significantly gratest (P < 0.05) in DRAXXIN-treated pigs compared to saline-treated pigs (59.2% vs. 41.2%). ANIMAI SAFFTY

Cattle

Canne Safety studies were conducted in feeder calves receiving a single subcutaneous dose of 25 mg/kg BW, of 3 weekly subcutaneous doses of 25, 75, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including had shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site and corresponding histo-pathologic changes were seen in animals in all dosage groups. These Jesions showed signs of resolving over time. No other drug-related lesions were observed macroscopically or microscopically and the intervention of the subcutaneous time to be a substance and each of 10.

An exploratory study was conducted in feeder calves receiving a single subctanaeous does 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. Swine

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 pain after injection were sen, including reatlessness and exessive vocalization. Tremors occur briefly in one animal receiving 7.5 mg/kg BW. Discoloration ad edema of injection site tissues a corresponding histopathologic changes were seen in animals at all dosages and resolved over time No other drug-related lesions were observed macroscopically or microscopically.

Store at or below 25°C (77°F)

HOW SUPPLIED RAXXIN 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



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



Made in Brazil

032908ZOA&P Revised: February 2014

Subcutaneous administration of EXCEDE uspension in the middle third of the aspect of the ear.

ぼ

ed needle insertion locations. f EXCEDE Sterile Suspension inter-

1

large vei

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

M

location f

injections administered rostrally the same side of the head into the caudal aspect of the base of

arteries

n of 6.6 mg CE/kg BW administered 72 hours apart is req

netabolitas for the 2-dose regimen in 12 cows is shown in Figure 9 rs for the 2-dose regimen are provided in Table 3. Figure 9. LS-Mean DCA Plasma Concentration Time Profile Following Two Subcuta EXCEDE 72 hours apart at a Dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW in 12 lactating cow



24 48 72 96 120 144 168 192 216 240 284 288 Time from First Dose (h)



C_{nax} (µg/ml CROBIOLOGY Cefficitur has

MICROBIOLOFY Catfolur has demonstrated in vitro activity against Mannhelmia haemolyticz, Pasteurella multipocia, and Histophilas sonmi, three major pathogens associated with borno fort of. Popyhromnosa Win associated with borno fort of. A summary of the susceptibility of BHD and foot regulatogene is persential in Table A EDD isolate wave and the susceptibility of BHD and foot regulatogene is persential in Table A EDD isolate wave clositoses were obtained from cattle emoletic in histle study ondered in the billed States and Catada that were diagnosed with foot rcl. Susceptibility testing was conducted according to the Clinical and Laboratory Standards Institute (CSS) MF-A and MH-36 statestist or BHD and foot rolloads, respectively.

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

Indicated pathogen	Year of isolation	Number of isolates	MIC (µg/mL)	MIC (µg/mL)	MIC range (µg/mL)
fannheimia haemolytica	1996 to 1997	75	0.008	0.015	0.001 to 0.015
asteurella multocida	1996 to 1997	43	0.004	0.004	0.001 to 0.015
listophilus somni	1996 to 1997	11	0.004	0.004	0.002 to 0.015
usobacterium necrophorum	2006 to 2007	148	≤ 0.25	0.5	≤ 0.25 to >128
ornhvromonas levii	2006 to 2007	141	< 0.25	2.0	< 0.25 to 16

ction of EXCEDE Sterile S caue was evaluated in a separate study. The systemic safety of celtofur 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

The orotes of administration are therapendically equivalent. To support systemic target animal step for the 2-does metritis regimen. Nor projected daily doese of NXOEL Strate Powder (adhitor sodium) at 2.2 mg/g BW vere compared pharmacokinetically with PXCXDE dominiseted 2 lines at 2 hour interval 4.6 mg/g BW. The pack concentration (Luc) and the extent of exposure (ALU) after two doese of DXCEDE were statistically no higher than the exposure following five daily doese of NXOEL Statie Powder in the attrate. Interstigning of Intra-Arterial and Intra-mosts lightion In approximative (ROO) annuals emetide in the BEO circles at the time ellipschon. The exact case was sognitissing and the staties were within 30 minutes of the time ellipschon. The exact case was sognitissing and the other staties are stating ellipschon and the staties ellipschon in the static case was sognitissing of the horomogen carried (exit) artissis in a attrate allegion at the line of the location resulting direct administration or the other static ellipschon in the static staties (exit) artissis and death.

EXCED® Starling Supprisonan-confirmed in three animats. These details resultion runs manufactures and the series of the series



cattle have had cor. cattle have experie dehornino¹ res (such as castration Treatment of Acute Metritis

Administer as a subcutaneous injection in the posterior aspect of the ear where it attaches to th of the ear) to lactating dairy cattle at a dosage of 3.0 mg CE/b (6.6 mg CE/bg) BW (1.5 mL sterile su 100 lb BW). Repeat this dose in the contra-lateral (opposite) ear annimimately 79 hours following at the contra-lateral (opposite) ear annimimately 79 hours following at the contra-lateral (opposite) ear annimimately 79 hours following at the contra-lateral (opposite) ear annimimately 79 hours following at the contra-lateral (opposite) ear annimimately 79 hours following at the contra-lateral (opposite) ear annimimately 79 hours following at the contra-lateral (opposite) ear annimimately 79 hours following at the contra-lateral (opposite) ear annihility of the contra-lateral (opposite) ea

Weight (Ib)	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

ackage insert before administering EXCEDE Steril

us bleb of EXCEDE Sterile Suspension will appear.

ION FOR BASE OF THE EAR

- staching unity claim the injection transpose in standards of col, injection in the prosine aspect to the ref attaches to the that adds add the early can be made by the rotation restinal particular behaviour. Set beef and non-acculating dairy cattle the SC injection in the base of the sar can be made by the rostal, vertical dot the opcosite equation the higher. States will before using. Plase read the magnetic package inset before administrating PCCVE Setup Segmention substanting PCCVE setup.
- subcutaneous (SC) injection may be made using the toward the opposite eye, rostral, or ventral ingues. Hold the syringe and needle and insert the needle as described below. er the entire contents of the syringe. or dominister EXCEDE Sterile Suspension in the neck.

- nummer churche other adaptement in en intext. Terr the Base of the Example Terr bard does not be adapted and syninge point in the direction of syninge and needle behind the ear to be doesd so the needle and syninge point in the direction of the main of the terr and other strength in the terr and the animal's adopted terr by See Figures 4 and 5. The any intert and terr and the main of the adopted terr and the main of the terr intert in the direction of the same yields maintaining this angle. See Figure 4.
- (used on ere ary mine instantiaming instantia): ever mine 4. Instantian for the base of lear. Trevent the Same For Technique or Restral Direction Hold the symptom and seedle shift of the ear to be doad so the needle and symptom point in the direction Figures 5 and 6. Insert the needle through the loose skin in the posterior aspect of the ear where it attacks to the head (used or the early while miniating) the needle position. See Figure 5.

lates (MIC₆₀) for the labeled BRD pathogens, Pasteurella multocida, somni, tor generally not less than 150 hours after a single ous locations of injection (MOE and BOE) are found in utaneous injection sites (MOE and BOE) demonstrate Table Figure 8. Average (n=12/group) plasma concentrations of cettiolur and desturoy/cettiolur-rater administration of EXCEDE Sterile Suspension at 3.0 mg CE/b (6.6 mg CE/b) (9.6 mg CE/b) (

third of the posterior as the posterior as , and lactating metabolites in





218 ± 45.5 40.7 ± 11.2 205 ± 35.7 43.92 ± 9.84 ncentration (in µg CE/mL) n when C.... occurs (in ho μg CE/mL) maximum plasma co the time after injection the area under the plasma concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 yp G2/mL). the time plasma concentrations remain above 0.2 yp G2/mL (in hours), estimated using compartmental pharmacokinetic techniques.

t_{,0.2, model} (h)

t₁₂ (h) NF

ns remain above 0.2 μg CE/mL (in hours), estimated macokinetic techniques

The correlation between in vitro The lowest MIC to encompass 5 bility data and clinical effectiveness is unknown 3.0 mg CE/lb (6.6 mg CE/kg) BW and the N for BRD pathogens by CLSI.



 These interpret to determine ant established. EFFECTIVENESS

Terretretes: Here the second second

scores. A total of 169 beef and dairy cattle were included in the analysis. There was a statistically significant difference (p=0.054) in treatment success for EXCEDE-treated cattle (58.4%) compared to vehicle-treated control cattle (17.2%). centrel cattle (13.25). The effectiveness of PCECEE Service Supportion for the treatment of a out method was evoluted to a 15-location field effectiveness study. A tradi of 1023 cores with a feld vaginal discharge and a recta imperature of 103 verse remained in the study and retated with effert a volue over genime of PCECEE (6 ef ng CECEW) an equivalent volume of vehicle control, administered approximately 72 hours agart at the base of opposite easts. Al 14 days post-treatment, each our remaining in the study area canning and recta themperature and vaginal discharge score were recorded. Course with a non-feld discharge, and a recta imperature (103 ⁺, and that did non-feld discharge, score were recorded. Course with a non-feld discharge, and a recta imperature 103 ⁺, and that did non-feld discharge score were recorded. Course with a non-feld discharge, and a recta imperature and vaginal discharge score were recorded. Course with a non-feld discharge, and a recta imperature and vaginal discharge score were recorded. Course with a non-feld discharge, and a recta imperature and vaginal discharge score were recorded. Course with a non-feld discharge, and a recta imperature and vaginal discharge score were recorded. Course with a non-feld discharge, and a recta imperature and vaginal discharge score were recorded. Course with a non-feld discharge, and a recta imperature and vaginal discharge score were recorded. Course with a non-feld discharge, and a rectar imperature and vaginal discharge score were recorded. Course with a flags of the score score flags. Course in flags of the score s

ANIMAL SAFETY Systemic Safety Studies alline free acid (as EXCEDE Sterile S

Youm: any contract of the second s tolerate Sterile Suspense effects. In a 15-day safety/t ""m intramuscularly " of EXC 15-day safety/toxicity study, five steer and five halfer cakes per group were administere tramuscularly at 0 (vehicle control), 1. 3, 5 or 10 mg CE/tb/day fluss, evaluating up to 3.3 does of DXCEDE Starle Suspension of 3.0 mg CE/tb/day (6.6 mg CE/tb) PW. There were effects, indicating that cellibolt has a wide margin of safety when injected intramuscularly

Supersonics is an unacceptable route of administration. **Starty Status**: The set of the CHAC Mark Status is a based characterized to specifically address tissue toteraces in cattle when EXEEP Steries supersonics was deministered as a single subcharacterized in the heposterior aspect of the ear of cattle the recommended case of 3.0 mg CzPb (6.6 mg CZFkg) EW. Results from this study indicate that the subcharacterized interface and characterized by a babaast. This characterized and the supersonice aspect of the ear of cattle the recommended case of 3.0 mg CzPb (6.6 mg CZFkg) EW. Results from this study indicate that the subcharacterized and characterized by a babaast. This characterized and the supersonic multi-set of the supersonic transmission of the memory of the supersonic transmission of the term of the case of the supersonic transmission of the term of the case of the supersonic transmission of the term of the case of the supersonic transmission of the term of the case of the case of the supersonic transmission of the term of the case of the supersonic transmission of the term of the term of the case of the term of the term of the case of the term of the term of the case of the term of t of their lacks where topolend in 32-34 of elem. Constrained the set of the carbon se

tal fiscalesci) and four of six cores han discursarian is a new mile with fauld exudate were also present at the sectioned surface. In discoloration, han nodeles and a miley with fauld exudate were also present at the sectioned surface. The section of the ear administration was evaluated in the metritis effectiveness study described above. Normal restantive adequate for s 29 % of injections administered. Injection site scores were normal in 305, 77, 78, and 36 % at 20 × 11, and 34-34 gave, the second injection, respectively. The vental and relate base of the ear injection istemices were compared with the toward the opposite get (vental), 38% (vental), and 100% (opposite yet) of annias in the subs/, nigicion is stores were normal or 32% (vental), 40,40% (vental), and 100% (opposite yet) of cattle on Day 14, and 75% (opposite yet) of annias in the self, nigicion is the soft nigicion of 45 % (opposite yet) of cattle on Day 25 (section), 87,8% (ventral), and 17,8% (ventral), and

allo 64 by (tipposite over a series of the second s A radiableate resource measurement and a function of the study established the tolerances for certitour sidues are 4 ppm in kideny. 24 ppm in kiner, 10 ppm in muscle and 11 ppm in mick. A pholat lissue resolve define study was and conclustent in ally calls. In this study, cours received a single piction of 30 mg CEIR (65 mg CEAR) EW. Celtour resolutes in tissues were less than the tolerances for fully picture and the study of the study of the study of the study. Cours received a study are study the study of the study of the study. Cours received a study of the study course study and the study course study of the study. Cours received a study of the study. Cello and the study of the study course study of the study. Cours received a study of the study. Cours received and the study. Cours Thou'r eisdiwes in tissues stour a o ne wenny, we can a store a store of the store

poins after treatment. These data collectively support that no milk discard period is required for this product. <u>The "Code Reider documents Studies</u> <u>A</u> photol tissue residue dione Study was acconducted in divident attention to extra the study converticed that the study of the study of

STORAGE CONDITIONS Store at controlled room temperature 20° to 25°C (68° to 77°F). Shake well before using. Cont sed within 12 weeks after the first dose is removed.

IOW SUPPLIED EXCEDE Sterile Suspension is available in the following package sizes:

100 mL vial 250 mL vial

NADA #141-209, Approved by FDA zoetis

Distributed by: Zoetis Inc. Kalamazoo, MI 490 ww.EXCEDE.com or call 1-888-963-8471 Revised: August 2013

ure 7. Diagram of head showing the direction of e of ear injections when administered ventrally o the loose skin in the caudal aspect of the base he ear



Sterile Injectable Solution Antimicrobial

180 mg of danofloxacin as the mesvlate 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 danfloxacin mesylate, a synthetic flooroquinolone 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 pirical formula is $C_{19}H_{20}FN_3O_3 \bullet CH_3SO_3H$ and the molecular weight

Figure 1. The chemical structure of danofloxacin mesylate.

is 453.49.



Each mL contains 180 mg of danofloxacin as the mesylate salt, 200 mg 2-pyrrolidone, 50 mg polyvinyl pyrrolidone, 20.3 mg héavy 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, a.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

	Dose Volume (mL)			
Cattle Weight (Ib)	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		



* 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

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 during the second secon

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 during the starting in the start start of the starting of the starting the starting of the starting of the starting in the starting start starting and starting starting and starting s 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 hc 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 $T_{\rm M}$ 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	%CVe	Mean	%CV		
a AUC, 24	µg x hr/mL	9.4	10	8.8	9		
^b F%		92	5	87	3		
a C	µg/mL	1.25	16	1.27	13		
a,c T	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		
$UC_{n,24}$ = area under the plasma concentration versus time curve from hr zero to hr 24							

* AUC_{3,24} = area under the plasma concentration versus time curve from hr zero to hr 24 postdose. $C_{max} = maximum observed concentration. T_{max} = time to <math>C_{max} = b^{10}$ isovailability (F_{0}^{0}) = extent of drug absorption following subcutaneous administration Within subject F values were determined as the ratio of AUC₄₀₀₀ values estimated following a 6 mg/kg dose administered by either a subcutaneous or intravenous injection. * 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 error in hibition of DNA gyrase is lethal to bacteria and danofloxacin has been shown to be rapidly bactericidal. Danofloxacin is active against gram-negative and grampositive 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.

3100163111116-0.0.						
Indicated Pathogen	Number of Isolates	MIC ₅₀ ** (µg/mL)	MIC₀ [™] (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 isola respectively.

Canada for the control of BRD in cattle at high risk of developing BRD.

	Indicated Pathogen	Number of Isolates	MIC₅₀** (µg/mL)	MIC₀" (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), atxia (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. Recumber 2 day 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 addy du daves. 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 crythema, and developed nasal crythema after treatment that may or may not have been treatment

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.

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

NADA #141-207, Approved by FDA

ZOEtis Distributed by: Zoetis Inc. Kalamazoo, MI 49007

Use Only as Directed

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



Revised: May 2014 Made in France 8713843A&P



