### 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.

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>Associated with: Mannheimia haemolytica</th>
<th>Associated with: Pasteurella multocida</th>
<th>Associated with: Histophilus somni</th>
<th>Associated with: Mycoplasma bovis</th>
<th>DOSAGE (per cwt)</th>
<th>ESTIMATED DURATION</th>
<th>MEAT WITHDRAWAL (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draxxin® KP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1 mL</td>
<td>14 days1</td>
<td>18</td>
</tr>
<tr>
<td>(tulathromycin and ketoprofen Injection)</td>
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<tr>
<td>Draxxin®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1 mL</td>
<td>14 days2</td>
<td>18</td>
</tr>
<tr>
<td>(tulathromycin injection)</td>
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<tr>
<td>Excede®</td>
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<td></td>
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<td>1.5 mL</td>
<td>7 days3</td>
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<tr>
<td>(ceftiofur crystalline free acid)</td>
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<td>Advocin®</td>
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<td></td>
<td></td>
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<td>1.5–2 mL</td>
<td>—</td>
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<tr>
<td>(danofloxacin injection)</td>
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</tr>
</tbody>
</table>

**OTHER PRODUCTS**

- **Baytril®** (enrofloxacin)
  - Dose: 3.4–5.7 mL
  - MEAT WITHDRAWAL: 28 days

- **Micotil®** (tilmicosin)
  - Dose: 1.5–3 mL
  - MEAT WITHDRAWAL: 42 days

- **Nuflor®** (florfenicol)
  - Dose: 3–6 mL
  - MEAT WITHDRAWAL: 38 days (SC) 28 days (IM)

- **Resflor Gold®** (florfenicol and flunixin meglumine)
  - Dose: 6 mL
  - MEAT WITHDRAWAL: N/A 38 days

- **Zactran®** (gamithromycin)
  - Dose: 1.82 mL
  - MEAT WITHDRAWAL: 10 days4 5 35 days

- **Zuprevo®** (tildipirosin)
  - Dose: 1 mL
  - MEAT WITHDRAWAL: 21 days

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**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 β-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.

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The chemical names of the tulathromycin isomers are (2R,3S,4R,5R,8R,[(propylamino)methyl]-O,[(propylamino)methyl]-10R,11R,12S,13S,14R)-13-[2,6-dideoxy-3-C-methyl-3,a non-steroidal anti-inflammatory drug. Semi-synthetic macrolide antibiotic of the subclass triamilide and ketoprofen a ready to use sterile parenteral preparation containing tulathromycin, a DRAXXIN KP (tulathromycin and ketoprofen injection) Injectable Solution is for veterinarian Non-Steroidal Anti-inflammatory Drug: 100 mg of Tulathromycin/mL of the tulathromycin isomers and ketoprofen are shown below:

Figure 1. Tulathromycin structures

The chemical names of tulathromycin isomers are (2S,3R,4S,5S,8S,[(propylamino)methyl]-O,[(propylamino)methyl]-10S,11S,12R,13R,14S)-13-[2,6-dideoxy-3-C-methyl-3-D-xylo,D-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10-trihydroxy-

Figure 2. Ketoprofen Structure

The chemical name of ketoprofen is 2-(3-Benzoylphenyl) propionic 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 cows, and replacement dairy heifers. Not for use in reproducing animals over one year of age, dairy calves, or veal calves.

DOSEAGE AND ADMINISTRATION

Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg of tulathromycin/kg and 3 mg of ketoprofen/kg (1 mL/100 lb) by 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 used with disposable needles 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

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<th>Animal Weight (lb)</th>
<th>Dose Volume (mL)</th>
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<td>7501-8000</td>
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</table>

CLINICAL PHARMACOLOGY

A GLP pharmacokinetic study, 60 cattle received one of three treatments: 2.5 mg tulathromycin/kg BW, 3 mg ketoprofen/kg BW or a combination of the two. Blood samples were obtained immediately before and at 1, 2, 3, 4, 5, 6, 24, 28, 32, 48, 72, 96, 120, 144, 168, 240, 336, 408, and 576 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 principal mechanism of action of tulathromycin against bacteria involves decreased formation of precursors of prostaglandins and thromboxanes. Tulathromycin halflife was also similar between the combination (93.3 (±27.9) hr) and tulathromycin alone (87.8 (±16.1) hr) groups.

Microbiology

Based on data provided for the approval of Draxxin® Injection, n/a/2021, tulathromycin has demonstrated in vitro activity against Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and Mycoplasma bovis, four pathogens associated with BRD.

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 meat. Milk derived from 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. KETOPROFEN IS 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 3 days post-injection. This may result in thin loss of edible tissue at slaughter. As a class, cyclooxygenase inhibitory NSAIDs (Ketoprofen) may be associated with gastrointestinal, hepatic and renal toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with pre-existing glomerular, renal, cardiovascular, and/or hepatic dysfunction.

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 events 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 glomerular, 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 animals, contact the FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalmed.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ketoprofen is a propionic acid derivative and nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic effects. Ketoprofen inhibits the activity of the enzymes cyclooxygenase I and II, resulting in a decreased formation of precursors of prostaglandins and thromboxanes. Tulathromycin 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 inhibition of essential protein biosynthesis by selective binding to bacterial 50S ribosomal subunits, thereby inhibiting bacterial protein synthesis.

APPLICATION OF RESULTS

The changes for TP, 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 related to the injection site.
ADVERSE REACTIONS

Cattle

In one BRD field study, two calves treated with DRAXXIN at 2.5 mg/kg BW exhibited transient decreased weight gain. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

POST APPROVAL EXPERIENCE

There have been no adverse events reported on post approval 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 between product exposure and an adverse event.

The following adverse events are listed in decreasing order of reporting frequency in cattle: injection site reactions and pneumonia/abscess/swabs of saline-treated non-responders. For a complete list of reported adverse events for DRAXXIN (tulathromycin injection) Injectable Solution reported to the CVM see: http://www.fda.gov/vetmanual/ adverseeffects.html

CLINICAL PHARMACOLOGY

At physiological pH, tulathromycin is a weak base that is approximately 50 times more soluble in hydrophilic than in hydrophobic media. This solubility profile is consistent with this macrolide antibiotic being readily associated with anionic macromolecules. Markedly higher tulathromycin concentrations are observed in the plasma to a much lesser extent compared to the lung. The extent of lung concentration compared to plasma is dependent on the route of administration and may not be significant where free drug alone was not administered e.g. intranasal. Therefore, the clinical relevance of these elevated lung concentrations is undetermined.

Although the relationship between tulathromycin and the characteristics of its antibacterial effects has not been characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens. They also tend to show concentration-dependent killing, the rate of killing of bacteria is related to the extent of cell wall deactivation. They do 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 for 50% of the macromolecules to reach the targeted pathogen will be

The chemical names of the isomers are (2S,3S,6S,8S,9R,10R,12R,13S,14R)-3,6-dideoxy-3-C-methyl-4-C-[(propylamino)methyl]-10-oxa-6-azacyclotridecan-13-one and (2R,3R,6R,8R,9R,10S,11S,12R)-11-[2,6-dideoxy-3-C-methyl-4-C-[(propylamino)methyl]-10-oxa-6-azacyclotridecan-13-one, respectively. Structures of the isomers are shown below.

DRAXXIN consists of an equilibrated mixture of two isomeric forms of tulathromycin or hydrochloric acid may be added to adjust pH.

The use of DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and Mycoplasma bovis, for the treatment of foot rot due to Porphyromonas levii, 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.

The MICs of tulathromycin against indicated BRD and IBK pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI). MICs are reported in μg/mL. The MIC range represents the range of MICs 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 cattle.

In a multi-location field study with 39 calves at high risk of developing BRD, administration of DRAXXIN resulted in a significantly reduced incidence of BRD (11% compared to saline-treated calves (56%). Efficacy evaluation was based on scored clinical signs of normal attitude/activity, normal respiration, and a respiratory score of > 10% 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-six saline-treated calves classified as non-responders in this study had Mycoplasma bovis identified in cultures of post-treatment nasopharyngeal swabs.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN. Two field studies were conducted evaluating DRAXXIN for the treatment of foot rot associated with Moraxella cathohonica in 2004. The primary clinical endpoint of these studies was cure rate, defined as a calf with no clinical signs of foot rot for 4 consecutive days. The overall cure rate in the DRAXXIN-treated calves was significantly higher than in the saline-treated calves (P < 0.0001) in both studies for DRAXXIN-treated calves compared to saline-treated calves (60% vs. 8%, P < 0.0001 and 83% vs. 30%, P < 0.0001).

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 size, swelling, and overall sheep score. The percentage of healed lesions at the end of the treatment success was statistically significantly higher in DRAXXIN-treated calves compared with saline-treated calves (60% vs. 8%, P < 0.0001 and 83% vs. 30%, P < 0.0001).

A pilot study was conducted in feeder calves receiving a single subcutaneous dose of DRAXXIN (2.5 mg/kg BW) in 27 saline-treated calves. In all groups, transient indications of pain after injection were seen, including head shaking and pacing at the ground. Injection site swellings, discoloration of the skin at the injection site and corresponding histological changes were seen in animals in all dosage groups. These lesions showed signs of resolution at the end of the study, to other drug-related lesions were observed macroscopically or microscopically.

An exploratory study was conducted in feeder calves receiving a single subcutaneous dose of DRAXXIN (2.5 mg/kg BW) in 11 groups, transient indications of pain after injection were seen, including head shaking and pacing at the ground. Injection site swellings, discoloration of the skin at the injection site and corresponding histological changes were seen in animals in all dosage groups. These lesions showed signs of resolution at the end of the study, to other drug-related lesions were observed macroscopically or microscopically.

Storage conditions

Store below 25° C (77°F), with excursions up to 40° C (104°F). Use product within 24 hours of opening. Store vials in upright position. Discard unused portions if more than 20 punctures are anticipated. The use of automatic injection equipment of a repeater syringe is recommended. When using a drone-off needle or needle with bore size less than 18 gauge, discard any remaining product in the immediate 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

Made in Spain

Made in Spain

Made in Spain

Made in Spain

Made in Spain

Made in Spain

Made in Spain

Made in Spain

Made in Spain

Made in Spain

Made in Spain

Made in Spain
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 base of the ear in beef and non-lactating dairy cattle. Not for use in calves to be processed for veal.

Chemical name of ceftiofur crystalline free acid: 7-(2-[(4-anilino-3-carboxyphenylamino)carboxamido]-3-[(2-furylcarbonyl)-thio)methyl]-8-oxo-9xa-th1-azacyclo[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 acute mastitis (lactating dairy cattle).

EXCEDE Sterile Suspension is also indicated for treatment of acute mastitis (lactating dairy cattle). 

DOSAGE

The subcutaneous injection may be made using the needle as described below.

• Insert the needle through the skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while pointing ventrally toward the base of the ear.
• 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 not to 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 needle is inserted 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 with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing protective clothing, including gloves. Persons with a known hypersensitivity to penicillins or cephalosporins should avoid exposure to this product.

Cattle may be exposed to, or exposed to this product, but not for use in pregnant or lactating dairy cattle. For subcutaneous injections, flush with water for 15 minutes. In cases 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 effects, please call 1-888-963-8471.

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

RESIDUE WARNINGS

Follow ing label use as either a single dose or 2-dose regimen, a 13-day pre-slaughter withdrawal period is required after the last treatment.

Follow ing 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 CEI/kg (6.6 mg CEI/lb) 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 entire ear may occur. As with other parenteral injections, localized post-injection bacterial infections may result in abscess formation. Attention to hygiene procedures can minimize these conditions.

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 for at least 1 day. Local administration resulting in this loss of edible 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 reproduction performance, pregnancy, and lactation have not been determined.

ADVERSE EFFECTS

Intra-articular injection may occur during administration of EXCEDE Sterile Suspension via middle third of the ear injection or base of the ear injection directed toward the opposite ear. Intra-articular injection is likely to result in sudden death of the animal. During the conduct of clinical studies, there may have been adverse events (see ANIMAL SAFETY) confirmed to be the result of inadvertent intra-articular 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 \textsuperscript{TM} Sterile Powder), ceftiofur hydrochloride (EXCEDE \textsuperscript{TM} RTU Sterile Suspension), or ceftiofur crystalline free acid (EXCEDE \textsuperscript{TM} 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 injection) or in the posterior aspect of the ear (base of the ear injection) directed toward the opposite ear, may result in open draining lesions in a small percentage of cattle. Intra-articular injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal.

Simple Dose Regimen

The pharmacokinetic parameters for the two subcutaneous locations of injection (middle third of the ear and base of the ear) are found in Table 2. Statistical analyses of the data from these two subcutaneous injection sites (MOE and BOE) of beef have not been determined.

Table 1. Dosing Schedule for EXCEDE Sterile Suspension.

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<th>DOSE Volume (mL)</th>
<th>Weight (lb)</th>
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Table 2. Thrombosis End Point Summary.

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</tr>
<tr>
<td>Test 2</td>
<td>30</td>
</tr>
<tr>
<td>Test 3</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 4. Administration for Base of the Ear: Toward the Opposite Eye Technique.

<table>
<thead>
<tr>
<th>Location for injection</th>
<th>Dose (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500</td>
<td>22.5</td>
</tr>
<tr>
<td>1300</td>
<td>19.5</td>
</tr>
<tr>
<td>1100</td>
<td>16.5</td>
</tr>
<tr>
<td>900</td>
<td>13.5</td>
</tr>
<tr>
<td>700</td>
<td>10.5</td>
</tr>
<tr>
<td>500</td>
<td>8.0</td>
</tr>
<tr>
<td>300</td>
<td>5.0</td>
</tr>
<tr>
<td>200</td>
<td>3.0</td>
</tr>
<tr>
<td>100</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Figure 8. Diagram of head showing the direction of base of ear injections when needle is inserted ventrally into the loose skin in the posterior aspect of the ear.

Figure 9. Diagram of head showing the direction of base of ear injections when needle is inserted ventrally into the base of the ear.
**Microbiology**

M. haemolytica, P. multocida, H. somni, F. necrophorum, and P. levii were recovered from clinical isolates, and F. necrophorum was the most frequent isolate. Ceftiofur has demonstrated activity against M. haemolytica, P. multocida, and F. necrophorum.

**Clarithromycin**

Clarithromycin (250 mg/mL) was used as a positive control. The MICs of clarithromycin were 2.5 ± 0.6 μg/mL for M. haemolytica, 1.25 ± 0.25 μg/mL for P. multocida, and 0.031 ± 0.007 μg/mL for F. necrophorum. These results indicate that clarithromycin is effective against these bacteria.

**Safety Studies in Beef Cattle**

Ceftiofur is approved by the FDA under NADA #141-209 for use in beef cattle. Ceftiofur is an injectable antibiotic that is effective against a wide range of Gram-negative and Gram-positive bacteria. It is administered intramuscularly or intravenously as a single dose or as a multi-dose regimen. Ceftiofur is also available as a long-acting injectable implant for use in cattle.

**Conclusion**

Overall, the data presented in this study suggest that Marcam (ceftiofur sodium) is effective and safe for use in treating and controlling bovine respiratory diseases in beef cattle. The use of Marcam (ceftiofur sodium) can potentially reduce the incidence and severity of bovine respiratory diseases, leading to improved animal health and economic benefits for producers.
ADOVICIN™
(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: ADOVICIN is a sterile injectable solution containing danofloxacin mesylate, a synthetic fluorquinolone antimicrobial agent. Danofloxacin mesylate is the mesylate designation for (1S)-1-cyclopropyl-4-fluoro-1,4-dihydro-7-(3-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-4-oxo-3-quinolonic acid monomethanesulfonate. The empirical formula is C_{19}H_{24}N_{2}O_{7}S_2 and the molecular weight is 434.42.

Figure 1. The chemical structure of danofloxacin mesylate.

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 persist for a few minutes to hours. This reaction often subsides if the animal is not restrained during the injection. 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 in growing animals of various species. Refer to Animal Safety for information specific to cartilage.

ADVERSE REACTIONS: A hypersensitivity reaction was noted in 2 healthy calves treated with ADOVICIN in a laboratory study. In one location of a multi-site field trial, one out of the 41 calves treated with 6 mg/kg in 60 mg/kg was sham treated on Day 6 only. In this same field trial, none of the 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 field trial developed lameness on the last day of the study.

CLINICAL PHARMACOLOGY:
(a) Pharmacokinetics: Danofloxacin distributes extensively throughout the body, as evidenced by a steady state volume of distribution (VSS) in cattle estimated at 160 L/kg. Danofloxacin localized within the bone marrow. Plasma levels marked 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 the single dose 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/kg of danofloxacin/kg body weight.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male (µg/mL)</th>
<th>Female (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max}</td>
<td>12.3</td>
<td>12.7</td>
</tr>
<tr>
<td>T_{max}</td>
<td>3.2</td>
<td>3.4</td>
</tr>
<tr>
<td>AUC</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>Vdss</td>
<td>18.6</td>
<td>17.6</td>
</tr>
</tbody>
</table>

(b) Microbiology: Danofloxacin exerts its activity by inhibiting the bacterial DNA gyrase enzyme, thereby blocking DNA replication. Inhibition of DNA gyrase 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 Pasteurella multocida 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 U.S.

<table>
<thead>
<tr>
<th>Indicated Pathogen</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannheimia haemolytica</td>
<td>106</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>94</td>
</tr>
</tbody>
</table>

*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 the USA, and no clinical infections isolated in the clinical field trial were provided in the Microbiology section.

The effectiveness of ADOVICIN 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 ADOVICIN at a dosage rate of 8 mg/kg of body weight or an equivalent volume of 0.9% 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 ADOVICIN-treated calves (86.0%) was statistically significantly (p=0.0069) greater than that of saline-treated calves (78.3%) (based on back-transformed least squares means). No adverse events associated with ADOVICIN 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 4 consecutive days, and 18, 24, 40, 60 and 30 mg/kg for 3 consecutive days. No clinical signs of toxicity were observed at doses of 10 and 20 mg/kg when administered for 5 days, or at doses of 18 and 24 mg/kg when administered for 3 days. Articular cartilage lesions, consistent with fluorquinolone 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 (2b), ataxia (2b), tremors (2b), mystematis (1b), exophoria (2b), and recumbency (2b) 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. The only clinical sign at the injection site was transient lameness. Safety was also evaluated in 21-day-old calves. In one group, these immature animals were given injections of 8 mg/kg on study days 2, 3, 5, 6, and 8. A second group of animals received injections of 18 mg/kg for a total of 6 days. 48 hours post-treatment, the only treatment-related change was erythema of the nasal pad in 3 of 6 calves that received 18 mg/kg. One calf in the 8 mg/kg group had pre-treatment scleral erythema, and developed nasal discharge. Treatment failure rates 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 when rodent doses were up to 10,000 times (100 mg/kg bw/day) or 100 times (10 mg/kg bw/day) or in rats at the highest tested dose of 15 mg/kg bw/day. A three-generation rat reproductive toxicity study established a NOEL of 8.25 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 microbial community of the consumer or the environment.

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 22G, subcutaneous administration may result in trim loss of edible tissue at slaughter. 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 22G, subcutaneous administration may result in trim loss of edible tissue at slaughter. To report suspected adverse effects and/or reactions, call 1-888-963-8471.

Approved by FDA under NADA #141-287

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CONTACT INFORMATION: To report suspected adverse effects and/or (copy of the SDS) or for technical assistance, call Zoetis Inc. at 1-800-442-9330. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalads.

100 ml: 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: 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: ADOVICIN (180 mg danofloxacin/ml) is supplied in 100- and 250-ml amber-glass, sterile, multi-dose vials.

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