A retrospective review of 12 metaphylaxis research studies1-10 was conducted to compile data regarding the success of initial BRD treatment for feedlot/stocker cattle that had previously received arrival metaphylaxis with Draxxin® (tulathromycin).

Most studies compared Draxxin and a single other metaphylaxis product, but 4 studies evaluated 3 metaphylaxis treatment groups (Draxxin vs 2 other agents).

Studies included in the data compilation were high-quality trials conducted by universities or veterinary research/consultant groups and often commissioned by Zoetis or other pharmaceutical companies.

In each study, the Draxxin metaphylaxis treatment group generated a greater BRD first-treatment success rate than the comparative metaphylaxis agent(s).

The success-rate advantages for Draxxin metaphylaxis (in absolute percentages) ranged from 1.0%4 to 22.4%.3

The consistent trend for favorable Draxxin metaphylaxis outcomes in regard to BRD first-treatment success is notable (any anecdotal field perceptions that suggest otherwise were not supported by any of the studies).

In 12 studies,1-10 feedlot cattle that received Draxxin® metaphylaxis demonstrated greater rates of initial BRD treatment success.

The perpetual effort to reduce financial losses associated with bovine respiratory disease (BRD) has prompted many feedlot veterinarians and managers to universally employ metaphylaxis protocols where seemingly healthy animals are treated with an injectable antimicrobial upon arrival at the feedyard. This practice is based on well-established knowledge of BRD etiology, in that pathogen exposure associated with multi-source commingling in concert with shipping stress can often predispose cattle for BRD. By metaphylactically treating these arriving ‘high-risk’ animals for subclinical or potential bacterial infections, respiratory health status is enhanced and rates of early BRD breaks can be greatly reduced.

Though arrival metaphylaxis has been used for years, the strategy has received fresh interest due to the advent of new-generation antimicrobial agents that offer extended durations of activity in cattle. These technological advancements have thus prompted the concept of a prolonged ‘post-metaphylactic interval’ (PMI), which
refers to a period of time after antimicrobial metaphylaxis when no further treatment for BRD is administered. This management model is founded on the rationale that any additional treatment is often of little value if effective levels of an extended-duration medication are still resident in the animal. As a result, a PMI of 3 to 10 days is now often observed at many feedyards. Only after that time period has elapsed will cattle showing clinical signs of BRD be pulled for treatment, usually with a drug from a chemical class different than that used for metaphylaxis.

Feedyard veterinarians are typically tasked with selection of the metaphylaxis antimicrobial, and several products are appropriate candidates (approved for the control of BRD in high-risk animals). Research studies reporting rates of post-metaphylaxis BRD incidence are usually consulted for guidance. However, another often overlooked criterion for metaphylaxis selection is the rate of first-treatment success after an initial BRD episode (occurring subsequent to the PMI). The ability of metaphylactically managed cattle to favorably respond to initial BRD treatment and rejoin penmates at the bunk is often a pivotal factor determining profit or loss, since BRD retreats and chronic can quickly elevate production costs and drain profit potential. The following offers a summary of research studies documenting first-treatment success rates for cattle that received arrival metaphylaxis with Draxxin®.

Data from 12 studies were compiled to evaluate BRD first-treatment success after arrival metaphylaxis with Draxxin® vs other antimicrobials.

**Draxxin® Overview**

Draxxin (tulathromycin) Injectable Solution is a unique antibiotic for the control and treatment of BRD that conveniently delivers a full course of therapy in a single dose. Tulathromycin is a semi-synthetic macrolide compound developed by Zoetis scientists as a highly bioavailable, long-acting antimicrobial for treatment of BRD.11 Administered as a single subcutaneous (SC) injection at 1.1 mL/100 lb body weight (2.5 mg/kg), Draxxin is indicated for the treatment of BRD associated with 4 of the most common bacterial respiratory pathogens of cattle: *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*. These indications make Draxxin particularly well-suited for use in control programs for arriving feedlot cattle, when animals are experiencing stress due to transport, commingling, etc., and are at high risk of BRD pathogen exposure. Draxxin is also indicated for treatment of infectious bovine keratoconjunctivitis associated with *Moraxella bovis*, and bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii*.

**Study Summary Process**

A review of available metaphylaxis research studies was conducted to compile data regarding the success of initial BRD treatment for feedlot/stocker cattle that had previously received arrival metaphylaxis with Draxxin vs animals dosed with another antimicrobial. Twelve studies were identified for inclusion in the retrospective data compilation, high-quality trials conducted by universities or veterinary research/consultant groups and often commissioned by Zoetis or other pharmaceutical companies (Merck, Elanco, Merial).1-10 The trials varied in the number of animals/treatment group, pen numbers, and duration, but health results were usually tracked from arrival through finishing.

![Figure 1](image-url) – General design of 12 studies that reported BRD first-treatment success rates for different arrival metaphylaxis treatment groups.
In each study, arriving cattle at high risk for BRD received metaphylaxis with DRAXXIN (2.5 mg/kg) or label doses of another agent:
- Micotil® (tilmicosin, Elanco);
- Zactran® (gamithromycin, Merial);
- Zuprevo® (tildiopirosin, Merck);
- Nuflor® (florfenicol, Merck);
- Oxytetracycline (OTC).

Most studies compared DRAXXIN and a single other product, but 4 studies evaluated 3 metaphylaxis treatment groups (DRAXXIN vs 2 other agents).

A PMI ranging from 3 to 10 days was a component of the arrival metaphylaxis protocol for most studies (Figure 1). Thereafter, cattle exhibiting clinical signs of BRD were pulled and treated according to standard criteria for each study/operation. The same BRD treatment protocol was used for each treatment group in a particular study, and the antimicrobial agent used for metaphylaxis varied across the 12 studies, and included label doses of EXCEDE® (ceftiofur, Zoetis), Nuflor, A180® (danofloxacin, Zoetis), Baytril® (enrofloxacin, Bayer), or OTC.

For each study, the percent of BRD pulls that successfully responded to a single BRD treatment was extracted from the study report or publication (cattle requiring 2 or more BRD treatments were ‘failures’ under these criteria). Outcomes were then compared for each metaphylaxis treatment group in the study (DRAXXIN metaphylaxis vs other-drug metaphylaxis). This analysis was based on the rationale that superior metaphylaxis should help reduce costly BRD retreats (enhanced respiratory health status can help reduce the severity of a BRD episode and, thus, encourage a favorable treatment response).

**Results**

The various designs, features, and outcomes for the 12 studies are summarized in Table 1. Notably, in each study, the DRAXXIN metaphylaxis treatment group generated a greater BRD first-treatment success rate than the comparative metaphylaxis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>Study source</th>
<th>Avg. hd(reps)/ group</th>
<th>Avg. start wt. (lb)</th>
<th>Approx. duration (d)</th>
<th>PMI (d)</th>
<th>1st-pull drug</th>
<th>1st-pull treatment success (%)</th>
<th>by metaphylaxis drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>A’</td>
<td>2005</td>
<td>CO</td>
<td>Zoetis</td>
<td>250 (5)</td>
<td>548</td>
<td>228</td>
<td>3/3</td>
<td>OTC</td>
<td>70.2%</td>
<td>60.0%</td>
</tr>
<tr>
<td>B’</td>
<td>2005</td>
<td>ID</td>
<td>Zoetis</td>
<td>250 (5)</td>
<td>531</td>
<td>223</td>
<td>3/3</td>
<td>OTC</td>
<td>73.6%</td>
<td>51.8%</td>
</tr>
<tr>
<td>C’</td>
<td>2005</td>
<td>TX</td>
<td>Zoetis</td>
<td>250 (5)</td>
<td>505</td>
<td>194</td>
<td>3/3</td>
<td>A180</td>
<td>73.3%</td>
<td>55.1%</td>
</tr>
<tr>
<td>D’</td>
<td>2007</td>
<td>Alberta</td>
<td>Zoetis</td>
<td>3305 (10)</td>
<td>610</td>
<td>230</td>
<td>3/3</td>
<td>Nuflor</td>
<td>77.0%</td>
<td>61.5%</td>
</tr>
<tr>
<td>E’</td>
<td>2008</td>
<td>KS</td>
<td>KSU</td>
<td>146 (12)</td>
<td>482</td>
<td>43</td>
<td>3/3</td>
<td>Baytril</td>
<td>71.9%</td>
<td>49.5%</td>
</tr>
<tr>
<td>F’</td>
<td>2008</td>
<td>Alberta</td>
<td>Elanco</td>
<td>2247 (10)</td>
<td>603</td>
<td>218</td>
<td>10/5</td>
<td>Nuflor</td>
<td>90.0%</td>
<td>89.0%</td>
</tr>
<tr>
<td>G’</td>
<td>2010</td>
<td>TX</td>
<td>Cactus</td>
<td>787 (8)</td>
<td>715</td>
<td>196</td>
<td>10/3</td>
<td>Excede</td>
<td>95.0%</td>
<td>81.0%</td>
</tr>
<tr>
<td>H’</td>
<td>2012</td>
<td>TX</td>
<td>Zoetis</td>
<td>1184 (13)</td>
<td>589</td>
<td>231</td>
<td>10/10</td>
<td>Excede</td>
<td>74.5%</td>
<td>68.4%</td>
</tr>
<tr>
<td>I’</td>
<td>2012</td>
<td>Alberta</td>
<td>Merck</td>
<td>3358 (6)</td>
<td>close</td>
<td>3/3</td>
<td>na</td>
<td>79.3%</td>
<td>76.8%</td>
<td>2.5%</td>
</tr>
<tr>
<td>J’</td>
<td>2013</td>
<td>NM</td>
<td>KSU / NMSU</td>
<td>193 (10)</td>
<td>404</td>
<td>56</td>
<td>na</td>
<td>Excede</td>
<td>100.0%</td>
<td>97.4%</td>
</tr>
<tr>
<td>K’</td>
<td>2013</td>
<td>TX</td>
<td>Zoetis</td>
<td>457 (12)</td>
<td>626</td>
<td>200</td>
<td>10/10</td>
<td>Excede</td>
<td>70.0%</td>
<td>63.0%</td>
</tr>
<tr>
<td>L’</td>
<td>2013</td>
<td>KS/NE</td>
<td>KSU / Merial</td>
<td>1265 (17)</td>
<td>502</td>
<td>180</td>
<td>na</td>
<td>Nuflor</td>
<td>60.5%</td>
<td>58.5%</td>
</tr>
</tbody>
</table>

na = not available
Conclusions

Results of this retrospective review of 12 metaphylaxis research studies support the use of DRAXXIN for arrival metaphylaxis. In each study, feedlot cattle that received DRAXXIN metaphylaxis demonstrated greater rates of subsequent initial BRD treatment success than cattle that received some other metaphylactic agent. The consistently improved rates of initial BRD treatment success suggest that respiratory health status was enhanced in animals that received DRAXXIN metaphylaxis at arrival.

These outcomes further differentiate DRAXXIN as the choice antimicrobial for arrival metaphylaxis. DRAXXIN offers feedlot veterinarians and managers the opportunity to help reduce medical expenses, performance losses, and input costs related to recurring BRD, thus helping optimize the profit potential of their operations.

DRAXXIN IMPORTANT SAFETY INFORMATION: DRAXXIN has a pre-slaughter withdrawal time of 18 days. Do not use in dairy cattle 20 months of age or older. Do not use in animals known to be hypersensitive to the product. See full Prescribing Information.

EXCEDE IMPORTANT SAFETY INFORMATION: As with all drugs, the use of EXCEDE is contraindicated in animals with known allergy to cefotiofur or to the β-lactam group (penicillins and cephalosporins) of antimicrobials. Though safe in cattle when properly administered, inadvertent intra-arterial injection is possible and fatal. EXCEDE has a pre-slaughter withdrawal time of 13 days in cattle. Do not use in calves to be processed for veal. See full Prescribing Information.
DRAXXIN consists of an equilibrated mixture of two isomeric with citric and hydrochloric acids added to adjust pH. A 50% propylene glycol vehicle, monothioglycerol (5 mg/mL), macrolide antibiotic of the subclass triamilide. Each mL of preparation containing tulathromycin, a semi-synthetic

DESCRIPTION

DRAXXIN Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide. Each mL of DRAXXIN contains 100 mg of tulathromycin as the free base in a 50% propylene glycol vehicle, monothioglycerol (5 mg/mL), with citric and hydrochloric acids added to adjust pH. DRAXXIN consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 1:1 ratio. Structures of the isomers are shown below.

Figure 1.

The chemical names of the isomers are [2R,3S,4R,5R,8R,10R, 11R,12S,13S,14R]-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl- 4-C-(propionyl) methyl]-L-rho-hexahexanyuronosyl]oxy]- 2-ethyl-3,4,10-tri hydroxy-3,5,8,10,12,14-hexamethyl-11- [[3,6-dideoxy-3-(dimethylamino)-D-xyl-hexahexanyuronosyl]- oxy]-(1-oxa-4-azacyclotetradecan-13-one, one, respectively.

INDICATIONS

Beef and Non-Lactating Dairy Cattle

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

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

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

Suckling Calves, Dairy Calves, and Veal Calves

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

Swine

DRAXXIN Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, Haemophilus parasuis, and Mycoplasma hyopneumoniae; and for the control of SRD associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, and Mycoplasma hyopneumoniae in groups of pigs where SRD has been diagnosed.

DOSEAGE AND ADMINISTRATION

Cattle

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

<table>
<thead>
<tr>
<th>Animal Weight (Pounds)</th>
<th>Dose Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1.1</td>
</tr>
<tr>
<td>200</td>
<td>2.3</td>
</tr>
<tr>
<td>300</td>
<td>3.4</td>
</tr>
<tr>
<td>400</td>
<td>4.5</td>
</tr>
<tr>
<td>500</td>
<td>5.7</td>
</tr>
<tr>
<td>600</td>
<td>6.8</td>
</tr>
<tr>
<td>700</td>
<td>8.0</td>
</tr>
<tr>
<td>800</td>
<td>9.1</td>
</tr>
<tr>
<td>900</td>
<td>10.2</td>
</tr>
<tr>
<td>1000</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Swine

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>
<thead>
<tr>
<th>Animal Weight (Pounds)</th>
<th>Dose Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0.2</td>
</tr>
<tr>
<td>30</td>
<td>0.6</td>
</tr>
<tr>
<td>50</td>
<td>0.8</td>
</tr>
<tr>
<td>70</td>
<td>1.0</td>
</tr>
<tr>
<td>110</td>
<td>1.3</td>
</tr>
<tr>
<td>130</td>
<td>1.5</td>
</tr>
<tr>
<td>150</td>
<td>1.7</td>
</tr>
<tr>
<td>170</td>
<td>1.9</td>
</tr>
<tr>
<td>190</td>
<td>2.2</td>
</tr>
<tr>
<td>210</td>
<td>2.4</td>
</tr>
<tr>
<td>230</td>
<td>2.6</td>
</tr>
<tr>
<td>250</td>
<td>2.8</td>
</tr>
<tr>
<td>270</td>
<td>3.1</td>
</tr>
<tr>
<td>290</td>
<td>3.3</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS

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

WARNINGS

FOR USE IN ANIMALS ONLY.

NOT FOR HUMAN USE.

KEEP OUT OF REACH OF CHILDREN.

NOT FOR USE IN CHICKENS OR TURKEYS.

RESIDUE WARNINGS

Cattle

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

Swine

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

PRECAUTIONS

Cattle

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

Swine

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

ADVERSE REACTIONS

Cattle

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

Swine

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

CLINICAL PHARMACOLOGY

At physiological pH, tulathromycin (a weak base) is more than four hours.

In one field study, one out of 40 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited transient hypersalivation. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

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CLINICAL PHARMACOLOGY

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

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

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

The MICs of tulathromycin against indicated BRD and IBK pathogens were determined using methods recommended by the CLSI (M31-A2). The MICs against foot rot pathogens were also determined using methods recommended by the CLSI (M11-A6). All MIC values were determined using the 9:1 isomer ratio of this compound.
**BRD** - The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and at-risk field studies in the U.S. In 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves, and from lung swabs or lung tissue of saline-treated calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders, and from young swabs or lung tissue of saline-treated calves that died. The results are shown in Table 3.

**Foot Rot** - The MICs of tulathromycin were determined for Fusobacterium necrophorum and Porphyrormonas levii isolated from cattle enrolled in foot rot field studies in the U.S. and Canada. In 2004. Isolates were obtained from pre-treatment conjunctival swabs of cattle with clinical signs of IBK enrolled in the DRAXXIN and saline-treated groups. The results are shown in Table 3.

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

<table>
<thead>
<tr>
<th>Indicated pathogen</th>
<th>Date isolated</th>
<th>No. of isolates</th>
<th>MIC (µg/mL)</th>
<th>MIC range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannheimia haemolytica</td>
<td>1999</td>
<td>642</td>
<td>2</td>
<td>0.5 to 64</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>1999</td>
<td>221</td>
<td>0.5</td>
<td>0.25 to 1</td>
</tr>
<tr>
<td>Hectophilus somni</td>
<td>1999</td>
<td>36</td>
<td>4</td>
<td>1 to 4</td>
</tr>
<tr>
<td>Mycoplasma bovis</td>
<td>1999</td>
<td>43</td>
<td>0.125</td>
<td>≤ 0.063</td>
</tr>
<tr>
<td>Moraxella bovis</td>
<td>2004</td>
<td>55</td>
<td>0.5</td>
<td>0.25 to 1</td>
</tr>
<tr>
<td>Fusobacterium necrophorum</td>
<td>2007</td>
<td>116</td>
<td>2</td>
<td>0.25 to &gt; 128</td>
</tr>
<tr>
<td>Porphyrormonas levii</td>
<td>2007</td>
<td>103</td>
<td>8</td>
<td>128 to &gt; 128</td>
</tr>
</tbody>
</table>

**EFFECTIVENESS**

**Cattle**
**BRD** - In a multi-location field study, 314 calves with naturally occurring BRD were treated with DRAXXIN. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal activity/attitude, normal respiration, and a rectal temperature of < 104°F on Day 14. The cure rate was significantly higher (P < 0.05) in DRAXXIN-treated calves (78%) compared to saline-treated calves (24%). There were two BRD-related deaths in the DRAXXIN-treated calves compared to nine BRD-related deaths in the saline-treated calves. Fifty-two DRAXXIN-treated calves and 27 saline-treated calves from the multi-location field study were enrolled in the BRD treatment study. Moraxella bovis was isolated from pre-treatment nasopharyngeal swabs. Of the 52 DRAXXIN-treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were categorized as treatment failures.

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

In another multi-location field study with 399 calves at high risk of developing BRD, administration of DRAXXIN resulted in a significantly reduced incidence of BRD (11%) compared to saline-treated calves (28.9%). Effectiveness evaluation was based on scored clinical signs of normal attitude/activity, normal respiration, and a rectal temperature of < 104°F on Day 14. There were no BRD-related deaths in the DRAXXIN-treated calves compared to two BRD-related deaths in the saline-treated calves. A total of 166 calves were inoculated intratracheally with field strains of M. hyopneumoniae. When calves became pyroxic and had abnormal respiration scores, they were treated either with 2.5 mg/kg BW of DRAXXIN subcutaneously or an equivalent volume of saline. Saline was observed for signs of BRD for 14 days post-treatment, then they were euthanized and necropsied. In both groups, mean lesion scores were similar. However, DRAXXIN was significantly lower in the DRAXXIN-treated calves compared with saline-treated calves (11.3% vs. 28.9%, P = 0.0001 and 15.0% vs. 30.7%, P < 0.0001).

**IBK** - Two field studies were conducted evaluating DRAXXIN for the treatment of IBK associated with Moraxella bovis in 200 naturally-infected calves. The primary clinical endpoint of these studies was cure rate, defined as a calf with no clinical signs of IBK and no corneal ulcer, assessed on Days 5, 9, 13, 17, and 21. Time to improvement, defined as the first day on which those scores were maintained at the next day of observation, was assessed as a secondary variable. At all time points, in both studies, the cure rate was significantly higher (P < 0.05) for DRAXXIN-treated calves compared to saline-treated calves. Additionally, time to improvement was significantly less (P < 0.05) in calves administered 7.5 mg/kg BW of DRAXXIN compared to saline-treated calves.

**Foot Rot** - The effectiveness of DRAXXIN for the treatment of bovine foot rot was evaluated in 170 cattle in two field studies. Cattle diagnosed with bovine foot rot were enrolled and treated with a single subcutaneous dose of DRAXXIN (2.5 mg/kg BW) or an equivalent volume of saline. Cattle were clinically evaluated 7 days after treatment for treatment success, which was based on defined decreases in lesion, swelling, and lameness scores. In both studies, the treatment success percentage was significantly higher (P < 0.05) in DRAXXIN-treated calves compared with saline-treated calves (60% vs. 8%, P < 0.0001 and 83.3% vs. 50%, P = 0.008).

**Swine**
In vitro activity of tulathromycin has been demonstrated against Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, Haemophilus parasuis, H. somni, and Mycoplasma hyopneumoniae.

The MICs of tulathromycin against SRD pathogens were determined using methods recommended by the Clinical Laboratory Standards Institute (CLSI, M31-A and M31-A3). MICs for Haemophilus parasuis were determined using Veterinary Fastidious Medium and were incubated up to 48 hours at 35 to 37°C in a CO2-enriched atmosphere. All MIC values were determined using 9.1% isomer ratio of this compound. Isolates obtained in 2000 and 2002 were from lung samples from saline-treated pigs and non-treated sentinel pigs 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 and DRAXXIN-treated pigs enrolled in the Control of SRD field study 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.

<table>
<thead>
<tr>
<th>Indicated pathogen</th>
<th>Date isolated</th>
<th>No. of isolates</th>
<th>MIC (µg/mL)</th>
<th>MIC range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinobacillus pleuropneumoniae</td>
<td>2000-2002</td>
<td>139</td>
<td>16</td>
<td>2 to 128</td>
</tr>
<tr>
<td></td>
<td>2007-2008</td>
<td>88</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Haemophilus parasuis</td>
<td>2000-2002</td>
<td>31</td>
<td>2</td>
<td>0.25 to &gt; 64</td>
</tr>
<tr>
<td></td>
<td>2007-2008</td>
<td>40</td>
<td>2</td>
<td>0.5 to &gt; 128</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>2000-2002</td>
<td>55</td>
<td>5</td>
<td>0.25 to &gt; 64</td>
</tr>
<tr>
<td></td>
<td>2007-2008</td>
<td>40</td>
<td>2</td>
<td>0.5 to &gt; 128</td>
</tr>
<tr>
<td>Bordetella bronchiseptica</td>
<td>2000-2002</td>
<td>42</td>
<td>4</td>
<td>2 to 8</td>
</tr>
</tbody>
</table>

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

**Animal Safety**

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

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

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

**Storage Conditions**

Store at or below 25°C (77°F)

**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

Distributed by: Zoetis Inc. Kalamazoo, MI 49007

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

Made in Brazil

0229082OA&P

Revised: February 2014
For subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle. For subcutaneous injection in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) in beef and non-lactating dairy cattle. Not for use in calves to be processed for veal.

**CAUTION**

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

**DESCRIPTION**

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

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

**Figure 1. Structure of ceftiofur crystalline free acid:**

![Chemical structure of ceftiofur](image)

Chemical name of ceftiofur crystalline free acid:

7-[[2-(2-Amino-4-thiazolyl)-2-(methylamino)acetamido]-3-[[2-(furanylcarbonyl)thio]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene 2-carboxylic acid

**INDICATIONS**

EXCEDE Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni in beef, non-lactating dairy, and lactating 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 Pasteurella multocida, P. haemolytica, and H. somni.

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

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

**DOSAGE**

**Treatment of BRD and bovine foot rot**

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

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

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

**Control of BRD**

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

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

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

**Treatment of Acute Metritis**

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

**Table 1. Dosing Schedule for EXCEDE Sterile Suspension.**

<table>
<thead>
<tr>
<th>Weight (lb)</th>
<th>Dose Volume (mL)</th>
<th>Weight (lb)</th>
<th>Dose Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1.5</td>
<td>1100</td>
<td>16.0</td>
</tr>
<tr>
<td>200</td>
<td>3.0</td>
<td>1200</td>
<td>18.0</td>
</tr>
<tr>
<td>300</td>
<td>4.5</td>
<td>1300</td>
<td>19.5</td>
</tr>
<tr>
<td>400</td>
<td>6.0</td>
<td>1400</td>
<td>21.0</td>
</tr>
<tr>
<td>500</td>
<td>7.5</td>
<td>1500</td>
<td>22.5</td>
</tr>
<tr>
<td>600</td>
<td>9.0</td>
<td>1600</td>
<td>24.0</td>
</tr>
<tr>
<td>700</td>
<td>10.5</td>
<td>1700</td>
<td>25.5</td>
</tr>
<tr>
<td>800</td>
<td>12.0</td>
<td>1800</td>
<td>27.0</td>
</tr>
<tr>
<td>900</td>
<td>13.5</td>
<td>1900</td>
<td>28.5</td>
</tr>
<tr>
<td>1000</td>
<td>15.0</td>
<td>2000</td>
<td>30.0</td>
</tr>
</tbody>
</table>

**ADMINISTRATION**

**ADMINISTRATION FOR THE MIDDLE THIRD OF THE EAR**

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

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

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

**ADMINISTRATION FOR BASE OF THE EAR**

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

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

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

**Administration for the Base of the Ear: Toward the Opposite Eye Technique**

- **Hold the syringe and needle behind the ear to be dosed so the needle and syringe point in the direction of an imaginary line that would pass through the head toward the animal’s opposite eye.** See Figures 4 and 5.
- **Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining this angle.** See Figure 4.

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

**Figure 5. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.**

**Figure 6. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.**

**Figure 7. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.**

**Figure 8. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.**

**Figure 9. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.**
Figure 6. Diagram of head showing the direction for the base of ear injections administered rostrally toward the eye on the same side of the head into the loose skin in the caudal aspect of the base of the ear.

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

Administration for the Base of Ear: Toward the Same Eye Technique or Rostral Direction
• Hold the syringe and needle behind the ear to be dosed so that the needle and syringe point in the direction of an imaginary line that would pass through the head toward the eye on the same side of the head. See Figures 5 and 6.
• Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining the needle position. See Figure 6.

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

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

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

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

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

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

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

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

ADVERSE EFFECTS
Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension via middle third of the ear injection or base of the ear injection directed towards the opposite eye. Intra-arterial injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal. During the conduct of clinical studies, there was a low incidence of acute death (see ANIMAL SAFETY) confirmed to be the result of inadvertent intra-arterial injection. No other adverse systemic effects were noted for either the antibiotic or formulation during any of the clinical and target animal safety studies.

CLINICAL PHARMACOLOGY
Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder), ceftiofur hydrochloride (EXCENEL® RTU Sterile Suspension), or ceftiofur crystalline free acid (EXCEDE Sterile Suspension) is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Subcutaneous administration of ceftiofur crystalline free acid, either in the middle third of the posterior aspect of the ear (middle third of the ear, MOE) of beef and non-lactating dairy cattle, or in the posterior aspect of the ear where it attaches to the head (base of the ear, BOE) of beef, non-lactating dairy, and lactating dairy cattle, provides therapeutic concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma above the lowest minimum inhibitory concentration to encompass 90% of the most susceptible isolates (MIC90) for the labeled BRD pathogens, Pasteurella multocida, Mannheimia haemolytica and Histophilus somni, for generally not less than 150 hours after a single administration (See Figure 8).

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

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Beef - Middle Third of the Ear Mean Value ± Standard Deviation</th>
<th>Beef - Base of the Ear Mean Value ± Standard Deviation</th>
<th>Dairy Cow - Base of the Ear Mean Value ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (μg CE/mL)</td>
<td>6.90 ± 2.68</td>
<td>6.39 ± 1.79</td>
<td>4.44 ± 1.65</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>12.0 ± 6.2</td>
<td>19.8 ± 5.81</td>
<td>19.00 ± 6.02</td>
</tr>
<tr>
<td>AUC 0-LOQ (µg•h/mL)</td>
<td>37.6 ± 14.1</td>
<td>412 ± 87.3</td>
<td>313 ± 85.5</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>62.3 ± 13.5</td>
<td>40.7 ± 11.2</td>
<td>43.92 ± 9.84</td>
</tr>
<tr>
<td>t&gt;0.2, nca (h)</td>
<td>246 ± 48.5</td>
<td>218 ± 45.5</td>
<td>205 ± 35.7</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>62.3 ± 13.5</td>
<td>40.7 ± 11.2</td>
<td>43.92 ± 9.84</td>
</tr>
</tbody>
</table>

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

Two-Dose Regimen
A two-dose regimen of 6.6 mg CE/kg BW administered 72 hours apart is required for the treatment of acute metritis in lactating cows. The mean plasma concentration vs. time profile for ceftiofur and desfuroylceftiofur-related metabolites for the 2-dose regimen in 12 cows is shown in Figure 9 below. The pharmacokinetic parameters for the 2-dose regimen are provided in Table 3.
Figure 9. LS-Mean DCA Plasma Concentration Time Profile Following Two Subcutaneous Injections of EXCEDE 72 hours apart at a Dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW in 12 lactating cows.

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

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-24 hr)</td>
<td>661 ± 119</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>55.7 ± 4.84</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>341 ± 34.0</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>77.1 ± 33.4</td>
</tr>
<tr>
<td>Cmin (μg/mL)</td>
<td>5.98 ± 2.51</td>
</tr>
</tbody>
</table>

**MICROBIOLOGY**

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

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

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

<table>
<thead>
<tr>
<th>Indicated pathogen</th>
<th>Year of isolation</th>
<th>Number of isolates</th>
<th>MIC of ceftiofur sodium (μg/mL)</th>
<th>MIC of ceftiofur hydrochloride (μg/mL)</th>
<th>MIC range (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mannheimia haemolytica</em></td>
<td>1996 to 1997</td>
<td>75</td>
<td>≤0.25</td>
<td>&lt;0.004</td>
<td>0.004 to 0.015</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>1996 to 1997</td>
<td>43</td>
<td>≤0.25</td>
<td>&lt;0.004</td>
<td>0.004 to 0.015</td>
</tr>
<tr>
<td><em>Histophilus somni</em></td>
<td>1996 to 1997</td>
<td>11</td>
<td>≤0.25</td>
<td>&lt;0.004</td>
<td>0.004 to 0.015</td>
</tr>
<tr>
<td><em>Fusobacterium necrophorum</em></td>
<td>2006 to 2007</td>
<td>148</td>
<td>≤0.25</td>
<td>≤0.025</td>
<td>≤0.025 to 0.125</td>
</tr>
<tr>
<td><em>Porphyromonas levii</em></td>
<td>2006 to 2007</td>
<td>141</td>
<td>≤0.25</td>
<td>≤0.025</td>
<td>≤0.025 to 0.16</td>
</tr>
</tbody>
</table>

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

**ANIMAL SAFETY**

Systemic Safety Studies

After parenteral administration, ceftiofur crystalline free base (as EXCEDE Sterile Suspension), ceftiofur sodium (as EXCEDE and EXCEDE Sterile Suspension), and ceftiofur sodium (as derogard) were given a single 3.0 mg CE/lb (6.6 mg CE/kg) BW bolus dose of EXCEDE Sterile Suspension in the middle third of the posterior aspect of the ear. The initial increase in thickness is attributed to the space required for the volume of injected material, and had no or mild depression on that day.

The effectiveness of EXCEDE Sterile Suspension for the treatment of bovine foot rot was evaluated in a six-location field effectiveness study. Cattle diagnosed with bovine foot rot were enrolled and treated with EXCEDE Sterile Suspension, administered by subcutaneous injection in the base of the ear as a single dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW or an equivalent volume of a vehicle control. Cattle were clinically evaluated 7 days post-treatment for treatment success, which was based on defined decreases in lesion, swelling and lameness indexes. A total of 168 beef and dairy cattle were enrolled in this study. There was a statistically significant difference (p = 0.0054) in treatment success for EXCEDE-treated cattle (58.4%) compared to vehicle-treated control cattle (13.2%).

The effectiveness of EXCEDE Sterile Suspension for the treatment of acute metritis was evaluated in a 15-location field effectiveness study. A total of 1023 cows with a cervical vaginal discharge and a rectal temperature of ≥103 °F were enrolled in the study and treated with either a two-dose regimen of EXCEDE (6.6 mg CE/BW) or an equivalent volume of vehicle control, administered approximately 72 hours apart at the base of opposite ears. At 14 days post-treatment, each cow remaining in the study was examined and rectal temperatures and a non-invasive discharge score were recorded. Cows scoring a non-discharge and a rectal temperature <103 °F, and that did not require alternate ("escape") therapy during the 14-day observation period were classified as a cure. The cure rate was significantly higher (p < 0.0001) in EXCEDE-treated cows (562/693, 79.4%) than in vehicle-treated cows (271/489, 55.3%). One cow died 15 to 20 minutes after the 1st injection of EXCEDE. Necropsy findings determined the probable cause of death to be intra-arterial injection.
Base of the ear injection:
The local tolerance of the ear to a single subcutaneous injection at the base of the ear of EXCEDE Sterile Suspension was evaluated in a multi-location field study in 2926 beef cattle. Normal restraint was adequate for administration of EXCEDE Sterile Suspension for 99.8% of cattle. No post injection problems (excessive bleeding or leak back) were observed in 99.8% of cattle. On Days 28 and 56 post-injection, 97.3% and 98.9% of the cattle had “normal” (no observed swelling) ears.

In a residue study, 72 beef cattle were injected in the base of the ear with EXCEDE Sterile Suspension at a dose rate of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Injection sites were observed daily from treatment to necropsy (4, 7, 10, or 13 days post-injection) for swelling and drooping, and evaluated grossly at necropsy, using skinning and trimming procedures similar to slaughterhouse practices. All animals had injection site swelling during the study; swelling resolved prior to euthanasia in 23 of 72 animals. None of the animals showed ear drooping. At necropsy, signs of inflammation (hemorrhage, congestion, and firmness of tissue) and presence of drug material were seen in the area around the injection site and on the carcass. At 13 days post-injection, gross lesions were found in the inedible portions of the base of the ear in all 18 animals, and in the exposed carcass tissue in 11 of 18 animals.

The ventral base of the ear injection technique was evaluated in a conditions of use study in 200 beef cattle. Each animal received a single injection of EXCEDE Sterile Suspension at a dose of 6.6 mg CE/kg BW at the base of the ear using the ventral injection technique. Normal restraint was adequate for 95.6% of animals in the study. Injection site scores were normal for 65.3% and 92.5% of cattle on Days 14 and 28, respectively. One animal had an unusually large swelling on Day 7 which reduced to a size comparable to other study animals by Day 14.

Safety Studies in Lactating Dairy Cattle

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

In a residue study, six dairy cows were injected in the base of the ear at a dose rate of 3.0 mg CE/lb (6.6 mg CE/kg) BW of EXCEDE Sterile Suspension. No animals exhibited drooping ears at any time after treatment but all animals had signs of swelling at the injection site at all observation times after treatment. Cows were slaughtered 10 days after injection. At necropsy, all six cows showed evidence of injection site inflammation (discoloration of fat tissue/fascia) and four of six cows had discoloration of tissue dorsal and posterior to the ear canal on the carcass. In addition to discoloration, tan nodules and a milky white fluid exudate were also present at the sectioned surface.

Injection site safety for base of the ear administration was evaluated in the metritis effectiveness study described above. Normal restraint was adequate for 97.8% of injections administered. Injection site scores were normal in 50.3%, 73.2%, and 96.4% at 2 or 3, 11, and 54a3 days after the second injection, respectively.

The ventral and rostral base of the ear injection techniques were compared with the toward the opposite eye technique in a conditions of use study in 197 lactating dairy cattle. Normal restraint was adequate for 89.8% (ventral), 98% (rostral), and 100% (opposite eye) of animals in the study. Injection site scores were normal for 32% (rostral), 46.9% (ventral), and 47.9% (opposite eye) of cattle on Day 14, and 73% (rostral), 87.8% (ventral), and 64.8% (opposite eye) of cattle on Day 28, respectively.

TISSUE AND MILK RESIDUE DEPLETION

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

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

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

Two-Dose Residue Decline Studies

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

A pivotal milk residue decline study was conducted in lactating dairy cattle. In this study, cows received two injections of 3.0 mg CE/lb (6.6 mg CE/kg) BW with a 72 hour interval between injections. Milk residue decline data from this study supports that no milk discard period is required for this product.

STORAGE CONDITIONS

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

HOW SUPPLIED

EXCEDE Sterile Suspension is available in the following package sizes:

- 100 mL vial
- 250 mL vial

NADA #141-209, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

www.EXCEDE.com or call 1-888-963-8471

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References


