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 8-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 250 mg ceftiofur, in a caprylic/capric triglyceride (Miglyol®) and cottonseed oil based suspension.

Figure 1. Structure of ceftiofur crystalline free acid

Chemical name of ceftiofur crystalline free acid:


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

EXCEDE Sterile Suspension is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with M. haemolytica, P. multocida, and H. somni.

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

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

DOSEAGE
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. Not for use in calves to be processed for veal.

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>16.5</td>
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<tr>
<td>200</td>
<td>3.0</td>
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<td>300</td>
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<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>
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<tr>
<td>700</td>
<td>10.5</td>
<td>1700</td>
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</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. Injection location for the subcutaneous administration of EXCEDE Sterile Suspension in the posterior aspect of the ear where it attaches to the head (base of the ear).

Administration for the Base of Ear: Toward the Same Eye Technique or Rostral Direction
- Hold the syringe and needle behind the ear to be dosed so 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 6. Diagram 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 ear.

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 pointing ventrally. See Figure 7.

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

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

WARNINGS
FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE.

Keep out of reach of children.

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

PRECAUTIONS
Following subcutaneous injection in the middle third of the posterior aspect of the ear, thickening and swelling (characterized by aseptic cellular infiltrate) of the ear may occur. As with other parenteral injections, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence. Following injection in the posterior aspect of the ear where it attaches to the head (base of the ear), areas of discoloration and signs of inflammation may persist at least 13 days post administration resulting in thin loss of edible tissue at slaughter. Injection of volumes greater than 20 mL, in the middle third of the ear, may result in open draining lesions in a small percentage of cattle. The effects of ceftiofur on bovine reproductive performance, pregnancy, and lactation have not been determined.

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

CLINICAL PHARMACOLOGY
Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder), ceftiofur hydrochloride (EXCENEL® RTU Sterile Suspension), or ceftiofur crystalline free acid (EXCEDE Sterile Suspension) is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Subcutaneous administration of ceftiofur crystalline free acid, either in the middle third of the posterior aspect of the ear (middle third of the ear, DOE) 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 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</th>
<th>Mean Value ± Standard Deviation</th>
<th>Beef - Base of the Ear</th>
<th>Mean Value ± Standard Deviation</th>
<th>Dairy Cow - Base of the Ear</th>
<th>Mean Value ± Standard Deviation</th>
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</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>
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<tr>
<td>tmax (h)</td>
<td>12.0 ± 6.2</td>
<td>19.8 ± 5.81</td>
<td>19.0 ± 6.02</td>
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<tr>
<td>AUC (0-LOQ) (μg•h/mL)</td>
<td>276 ± 66.1</td>
<td>412 ± 67.3</td>
<td>313 ± 85.5</td>
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<tr>
<td>t0.2, model (h)</td>
<td>163 ± 49.8</td>
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<td>NE</td>
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<tr>
<td>t0.2, no (h)</td>
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<td>t1/2 (h)</td>
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<tr>
<td>Cmax (μg CE/mL)</td>
<td>maximum plasma concentration</td>
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<td>tmax (h)</td>
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<td>Cmax occurs (in hours)</td>
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<td>the time plasma concentrations</td>
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<td>remain above 0.2 μg CE/mL</td>
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<td>life (in hours)</td>
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<td>Not estimated</td>
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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 two-dose regimen in 12 cows is shown in Figure 9 below. The pharmacokinetic parameters for the 2-dose regimen are provided in Table 3.
he effectiveness of EXCEDE Sterile Suspension for the treatment of bovine foot rot was evaluated in a 15-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 regression of swelling, lameness, temperature, and rectal temperature and vaginal discharge score recorded. A total of 160 beef and dairy cattle were included in the analysis. There was a statistically significant difference (p = 0.0054) in treatment success for EXCEDE-treated cattle (58.4%) compared to vehicle-treated control cattle (13.2%).

The effectiveness of EXCEDE Sterile Suspension for the treatment of acute metritis was evaluated in a 15-location field effectiveness study. A total of 1023 cows with a febrile vaginal discharge and a rectal temperature of a 103 °F were enrolled in the study and treated with either a two-dose regimen of EXCEDE Sterile Suspension (6.6 mg CE/kg BW) or an equivalent volume of vehicle control, administered approximately 7 hours apart at the base of the ear. At 14 days after treatment, a total of 151 cows was treated with EXCEDE and 141 cows were treated with the vehicle control. The effectiveness of EXCEDE Sterile Suspension against the middle third of the ear 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 systemic safety of ceftiofur concentrations resulting from product administration at the base of the ear was established via a pharmacokinetic comparison of the two routes of administration (base of the ear versus middle third of the ear). Based on the results of this relative bioavailability study, it was determined that the route of administration had no effect on systemic safety.

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

In vivo mean pharmacokinetic parameters following a single dose of EXCEDE Sterile Suspension at a dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW are presented in Table 1. The mean ± standard deviation plasma concentration-time profiles following subcutaneous injection of EXCEDE Sterile Suspension at a dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW at a 72 Hour Interval are shown in Figure 9.

**EFFECTIVENESS**

A field dose confirmation study for the treatment of BRD evaluated the effectiveness of single doses of 2.0 and 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW for the treatment of the bacterial component of BRD under field conditions. All treatments were administered subcutaneously in the middle third of the ear. Cattle were clinically evaluated on Days 2 to 4, 14 and 28 and were observed on all other study days. The 3.0 mg CE/lb (6.6 mg CE/kg) BW EXCEDE Sterile Suspension dose significantly (p < 0.0001) increased Day 14 treatment success rate, defined as cattle that did not require any ancillary treatment and had a rectal temperature of <104°F, normal respiration index, and had no other signs of illness on that day.

The effectiveness of a single dose of EXCEDE Sterile Suspension for the control of bovine foot rot was evaluated in a 15-location field effectiveness study. In addition to standard processing on arrival at feedlots, cattle (n=1911) considered to be at high risk for BRD were assigned to one of four treatment groups, including EXCEDE Sterile Suspension at 2.0 or 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW or negative control. Effectiveness evaluation was based on the incidence of clinical BRD within 28 days following arrival processing. Administration of a single dose of EXCEDE Sterile Suspension administered subcutaneously in the middle third of the posterior aspect of the ear at ear arrival processing significantly reduced the incidence of BRD in high-risk feedlot cattle in the 28-day period after arrival processing compared to negative controls.

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

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

A pivotal tissue residue decline study was conducted in dairy cattle. In this study, cows received a single injection of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as the kidney, liver and muscle by 13 days after dosing. These data collectively support that no milk discard period is required for this product.

Two-Dose Residue Decline Studies

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

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

STORAGE CONDITIONS

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

HOW SUPPLIED

EXCEDE Sterile Suspension is available in the following package sizes:

- 100 mL vial
- 250 mL vial

NADA #141-209, Approved by FDA