Additional Techniques for SC Injection of EXCEDE® in Beef and Dairy Cattle

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Summary

• Two additional techniques were recently approved for SC injection of EXCEDE® Sterile Suspension at the base of the ear (BOE) of cattle.
  o EXCEDE can now be administered SC at the BOE in a rostral direction, toward the eye on the same side of the head as the ear.
  o EXCEDE can also now be administered SC at the BOE in a ventral direction.
• Both additional EXCEDE administration techniques are approved for use in all classes of cattle.
• Both additional BOE injection techniques are approved for use in lactating dairy cows and are preferred in these animals relative to the previously approved 'opposite-eye' method.
• Research has demonstrated that the rostral and ventral BOE injection techniques are safe, well-tolerated, and readily accomplished using normal equipment and restraint.
• The rostral and ventral BOE techniques provide injection outcomes similar to those observed using the previously approved opposite-eye technique.

EXCEDE® Sterile Suspension (ceftiofur crystalline free acid) is the potent single-dose treatment for bovine respiratory disease and foot rot that provides the demonstrated efficacy of ceftiofur in a convenient extended-therapy formulation. EXCEDE is intended for subcutaneous (SC) administration at a dose of 3 mg ceftiofur equivalents (CE) per lb body weight (BW) (or 1.5 mL EXCEDE/100 lb BW). An indication for acute post-partum metritis was recently approved for lactating dairy cows when a 2-dose regimen of EXCEDE is administered 3 days apart.

Previously, EXCEDE was approved for SC injection of cattle (including lactating dairy cows) in the posterior aspect of the ear where it attaches to the head (base of the ear, or ‘BOE’), angled toward the opposite eye. In addition, EXCEDE could be administered in the middle third of the posterior aspect of the ear in beef and non-lactating dairy cattle (not in lactating dairy cows).
Research by Pfizer scientists has resulted in recent FDA approval of two additional BOE injection techniques for EXCEDE, and more specific BOE use instructions for lactating dairy cows. The two additional BOE techniques are:

- **Rostral** direction (toward the eye on the same side of the head);
- **Ventral** direction (pointing ventrally toward the base of the ear).

These two additional BOE techniques are potentially safer and are the preferred methods for using EXCEDE in lactating dairy cows relative to the previously approved opposite-eye technique. The rostral technique (toward the same eye) is particularly useful for many dairy cattle operations. However, because head catches are almost always used for restraint of beef cattle, the rostral method can be problematic when animals pull backwards against the vertical bars of the head catch. Thus, the ventrally directed technique offers a dosing method especially useful for treatment of beef animals.

Figure 1 summarizes the SC injection options for use of EXCEDE, depending on the class and status of cattle being treated. In lactating dairy cattle, SC injection at the BOE can be made using the preferred rostral (Figures 2 and 3) or ventral (Figure 4) injection techniques. For beef and non-lactating dairy cattle, SC injection can accomplished using the rostral, ventral, or opposite-eye (Figure 5) BOE techniques in addition to the middle-third of the ear option (Figure 6).
BOE – rostral (toward the same eye) technique

Figure 3 – Rostral technique (additional). Direction for SC injection of EXCEDE administered rostrally toward the eye on the same side of the head into the loose skin in the caudal aspect of the BOE.

Directions:

• Hold the syringe and needle behind the ear to be dosed so the needle and syringe point in the direction of an imaginary line that would pass through the head toward the eye on the same side of the head (Figures 2 and 3).

• Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (BOE) while maintaining the needle position (Figure 3).
BOE – ventral technique

Figure 4 – Ventral technique (additional). Location and direction for SC injection of EXCEDE administered ventrally into the loose skin in the caudal aspect of the BOE.

Directions:

• 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 (BOE) while pointing ventrally. Care should be taken to not insert the needle through the cartilage of the ear (Figure 4).

• Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (BOE) while maintaining needle position (Figure 4).
BOE – toward the opposite eye technique

**Figure 5** – Toward the opposite eye technique. SC injection of EXCEDE in the posterior aspect of the ear where it attaches to the head (BOE) (previously approved technique).

**Directions:**

- 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 (Figures 2 and 5).
- Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (BOE) while maintaining this angle (Figure 5).
Middle-third of the ear technique

Figure 6 – Middle-third of the ear technique. SC injection of EXCEDE in the middle third of the posterior aspect of the ear (previously approved technique).

Directions:

• Deposit as a single SC injection in the middle third of the posterior aspect of the ear, avoiding all blood vessels (Figure 6).

• Adjust the needle insertion point to avoid any blood vessels, previous implants, ear tags, or ear-tag holes. Do not administer intra-arterially.

• When administered correctly, a subcutaneous bleb of EXCEDE will appear.

• When withdrawing the needle, apply pressure to the needle insertion point, and massage toward the base of the ear.
Injection Technique Field Studies

Two field studies were conducted to gain experience on the practicality and acceptability of the additional rostral and ventral BOE injection techniques in dairy and beef cattle.

Lactating dairy cows

A field study involving 197 lactating dairy cows compared injection procedures and site reactions for BOE injections of EXCEDE directed toward the opposite eye with those directed either rostrally or ventrally. Healthy lactating cows were enrolled in the study across 2 commercial dairy sites. The rostral and opposite-eye techniques were compared at one site (4 different treatment administrators, consistent needle length), while the rostral and ventral routes were used at the other site (2 different treatment administrators, 5/8- or 1-inch needle lengths). All cows received a single SC injection of EXCEDE at the approved dose of 3 mg CE/lb BW. At administration, animals were scored for restraint, injection procedure, and post-injection problems. Cows were observed for injection site reactions on days 14 and 28 post-injection.

Results summarized in Table 1 indicate that no relevant differences were observed in restraint, re-injection, leak-back, or excessive bleeding between the 3 techniques. By day 28, 73% of injection sites were scored as normal using the rostral technique, compared to 87.8% using the ventral technique and 64.6% using the opposite-eye technique. Needle length did not affect injection procedures or site reactions.

This study demonstrated that BOE administration of EXCEDE using the additional rostral or ventral SC injection techniques was safe, well-tolerated, and readily accomplished in lactating dairy cows using normal equipment and restraint. Injection outcomes were similar to those observed using the previously approved ‘opposite-eye’ technique.

Feedlot heifers

A similar field study involving 199 feedlot heifers (750 lb BW) evaluated injection procedures and site reactions for BOE injections of EXCEDE performed using the ventral technique. Healthy cattle were enrolled in the study at a commercial feedlot and treated with EXCEDE at the approved dose of 3 mg CE/lb BW. Ventrally directed BOE injections were administered by 2 different people using 5/8- or 1-inch needle lengths. At administration, animals were scored for restraint, injection procedure, and post-injection problems. Cattle were observed for injection site reactions on days 14 and 28 post-injection.

Study results show that few problems were observed relative to restraint, re-injection, leak-back, or excessive bleeding (Table 2). By day 28, 92.5% of injection sites were scored as normal using the ventral technique. Needle length did not affect injection procedures or site reactions.

This study demonstrated that BOE administration of EXCEDE using the ventrally directed SC injection technique was safe, well-tolerated, and readily accomplished in feedlot cattle using normal equipment and restraint.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rostral</th>
<th>Ventral</th>
<th>Opposite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cows</td>
<td>100</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>No added restraint (%)</td>
<td>98.0</td>
<td>89.8</td>
<td>100.0</td>
</tr>
<tr>
<td>No re-injection (%)</td>
<td>97.0</td>
<td>87.8</td>
<td>100.0</td>
</tr>
<tr>
<td>No leak back (%)</td>
<td>99.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>No excessive bleeding (%)</td>
<td>99.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Day 14 normal sites (%)</td>
<td>32.0</td>
<td>46.9</td>
<td>47.9</td>
</tr>
<tr>
<td>Day 28 normal sites (%)</td>
<td>73.0</td>
<td>87.8</td>
<td>64.6</td>
</tr>
</tbody>
</table>

Table 1 – Injection parameters and site outcomes in lactating dairy cows after BOE injection of EXCEDE using rostral, ventral, or opposite-eye SC techniques.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ventral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of heifers</td>
<td>199</td>
</tr>
<tr>
<td>No added restraint (%)</td>
<td>95.5</td>
</tr>
<tr>
<td>No re-injection (%)</td>
<td>93.5</td>
</tr>
<tr>
<td>No leak back (%)</td>
<td>99.0</td>
</tr>
<tr>
<td>No excessive bleeding (%)</td>
<td>100.0</td>
</tr>
<tr>
<td>Day 14 normal sites (%)</td>
<td>65.3</td>
</tr>
<tr>
<td>Day 28 normal sites (%)</td>
<td>92.5</td>
</tr>
</tbody>
</table>

Table 2 – Injection parameters and site outcomes in beef heifers after ventrally directed BOE injection.
Important Safety Information: As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug. Though safe in cattle when properly administered, inadvertent intra-arterial injection in the ear is possible and is fatal. EXCEDE has a pre-slaughter withdrawal period of 13 days.

Conclusions

EXCEDE can be administered SC at the BOE of cattle by two additional options, directed rostrally toward the eye on the same side of the head, or directed ventrally. Both BOE injection techniques are approved for use in lactating dairy cows and are preferred in these animals relative to the previously approved opposite-eye method. For beef cattle and non-lactating dairy animals, the additional rostral and ventral BOE injection techniques join the previously approved SC methods (middle-third of the ear or BOE toward the opposite eye) as options for administering EXCEDE.
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 be by or on the order of a licensed veterinarian.

DESCRIPTION

EXCEDE Sterile Suspension is a ready-to-use formulation that contains the crystalline free acid, which is a broad-spectrum, beta-lactam antibiotic effective against Gram-positive and Gram-negative bacteria including E. coli and P. multocida. Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Use of antibacterial drugs in the absence of a susceptible bacterial infection is unproved routes (subcutaneous injection in the neck or intraocular injection) may cause visceral irritation. Use of dosages in excess of 3.0 mg CE/lb (6.6 mg CE/kg) BW or parenteral other with As occur. may result in the direction for the base of ear injections when administered ventrally into the loose skin in the caudal aspect of the base of the ear.

Figure 6. Diagram of head showing the direction for base of ear injections in the middle third of the posterior aspect of the ear.

Figure 9. 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 10. Diagram of head showing the direction for the base of ear injections administered cranially toward the opposite eye on the same side of the head into the loose skin in the caudal aspect of the base of the ear.

As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously known 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 exposure to such antimicrobials, including orf, may result in 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 mucous membranes. 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 skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction results (e.g., skin, eye, nose, nasal, rhinitis, throat distress) call medical attention. The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet please call 1-800-733-1950. To report any adverse event please call 1-800-366-5288. Intra-ocular 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 eye. Intra-ocular injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal.

RESIDUE WARNINGS

- Following label use as either a single-dose or 2-dose regimen, a 13-day pre-slaughter withdrawal period is required after the last treatment.
- Following label use as either a single-dose or 3-dose regimen, a 42-day discard period is required for this product.
- Use of dosages in excess of 3.0 mg CE/lb (6.6 mg/kg) BW or administration by unsupervised routes (subcutaneous injection in the neck or intraocular injection) may cause visceral irritation.
- A withdrawal period has not been established for this product in pre-nursing cattle.
- 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, for any adverse reactions, signs of inflammation may persist at least 13 days post administration resulting in trim loss of edible tissue at slaughter. Injection of volumes greater than 20 mL, in the middle third of the ear, may result in open draining lesions in a small percentage of cattle. The effects of ceftiofur on bovine reproductive performance, pregnancy, and lactation have not been determined.

ADVERSE EFFECTS

Intra-ocular 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 eye. Intra-ocular injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal. During the conduct of clinical trials, there was a low incidence of acute death (see AMARIL SAFETY) confirmed to be due to inadvertent intra-ocular injection. No other adverse systemic effects were noted for either the antibiotic or pharmacological delivery system. Clinical effect: ceftiofur free acid
Table 2. Average (n = 12/group) pharmacokinetic parameters for ceftiofur and desfuroylceftiofur metabolites calculated after a single subcutaneous administration of EXCEDE Sterile Suspension to either the middle third of the ear or the base of the ear.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Ear/Ear Base</th>
<th>Mean ± Standard Deviation</th>
<th>Ear/Ear Base</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftiofur</td>
<td>6.20 ± 2.68</td>
<td>6.39 ± 1.79</td>
<td>4.44 ± 1.65</td>
<td>4.63 ± 1.75</td>
</tr>
<tr>
<td>Desfuroylceftiofur</td>
<td>4.55 ± 2.97</td>
<td>4.67 ± 2.56</td>
<td>3.43 ± 1.58</td>
<td>3.53 ± 1.75</td>
</tr>
<tr>
<td>Neisseria</td>
<td>370 ± 66</td>
<td>363 ± 53</td>
<td>317 ± 55</td>
<td>315 ± 52</td>
</tr>
<tr>
<td>Porphyromonas</td>
<td>181 ± 40</td>
<td>191 ± 49</td>
<td>173 ± 51</td>
<td>180 ± 50</td>
</tr>
<tr>
<td>Coxiella</td>
<td>24.5 ± 4.5</td>
<td>25.6 ± 4.5</td>
<td>20.5 ± 4.5</td>
<td>20.3 ± 3.8</td>
</tr>
<tr>
<td>Mannheimia</td>
<td>62.3 ± 13.5</td>
<td>62.7 ± 13.5</td>
<td>43.2 ± 9.8</td>
<td>43.5 ± 9.2</td>
</tr>
</tbody>
</table>

Figure 10. LS-Mean DCA Plasma Concentration Time Profile Following Two Subcutaneous Injections of EXCEDE Sterile Suspension at a Dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW at 72 hours after injection.

Table 3. Average (n = 12/group) 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 72 hours after injection.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Ear/Ear Base</th>
<th>Mean ± Standard Deviation</th>
<th>Ear/Ear Base</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftiofur</td>
<td>651 ± 119</td>
<td>651 ± 119</td>
<td>575 ± 44</td>
<td>575 ± 44</td>
</tr>
<tr>
<td>Desfuroylceftiofur</td>
<td>7.3 ± 3.34</td>
<td>7.3 ± 3.34</td>
<td>5.93 ± 2.51</td>
<td>5.93 ± 2.51</td>
</tr>
</tbody>
</table>

Microbiology

Ceftiofur has demonstrated in vitro activity against Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni in vitro. The in vitro activity of ceftiofur has been associated with the metabolic breakdown of ceftiofur and BRD, as reflected by resistance to BRD and Pasteurella multocida-associated lethality in vivo.

A summary of the susceptibility of BRD and foot rot pathogens is presented in Table 1, which shows the MIC of ceftiofur for 100% of the most susceptible isolates (MIC50) for the labeled BRD pathogens, Porphyromonas, Mannheimia haemolytica, and Histophilus somni, as well as the MIC range for each strain. These results were obtained from the MIC range for each strain, as determined by the Clinical and Laboratory Standards Institute (CLSI) MT-A3 and MT-A1 standards for BRD and foot rot isolates, respectively.

Table 4. Ceftiofur minimum inhibitory concentration (MIC) values* of indicated pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Year of Collection</th>
<th>MIC (μg/mL)</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannheimia haemolytica</td>
<td>1996 to 1997</td>
<td>75</td>
<td>0.003 ± 0.001</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>1996 to 1997</td>
<td>11</td>
<td>0.004 ± 0.001</td>
</tr>
<tr>
<td>Histophilus somni</td>
<td>1996 to 1997</td>
<td>11</td>
<td>0.004 ± 0.001</td>
</tr>
<tr>
<td>Pasteurella aerogenes</td>
<td>2006 to 2007</td>
<td>15</td>
<td>0.3 ± 0.25</td>
</tr>
<tr>
<td>Pasteurella haemolytica</td>
<td>2006 to 2007</td>
<td>15</td>
<td>0.3 ± 0.25</td>
</tr>
</tbody>
</table>

*These interpretive criteria are only intended for use when CLSI M31-A2 performance standards are used. Interpretive criteria for isolates with MIC values of less than 150 hours after a single administration (See Figure 8).

Table 5. CLSI-accepted interpretive criteria* for ceftiofur against cattle foot rot organisms.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disk diameter (mm)</th>
<th>Zone diameter (mm)</th>
<th>MIC breakpoint (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannheimia haemolytica</td>
<td>16</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>16</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Histophilus somni</td>
<td>16</td>
<td>18</td>
<td>2</td>
</tr>
</tbody>
</table>

*These interpretive criteria are only intended for use when CLSI M31-A2 performance standards are used.
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 tissue 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

Distributed by Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017
www.EXCEDE.com or call 1-866-387-2287

Revised: December 2011
References

1. Data on file, Study Report No. 1437C-60-09-768, Pfizer Inc.
2. Data on file, Study Report No. 1437C-60-09-769, Pfizer Inc.