Two additional techniques were recently approved for SC injection of EXCEDE Sterile Suspension at the base of the ear (BOE) of cattle.

- 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.
- 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 singledose treatment for bovine respiratory disease and foot rot that provides the demonstrated efficacy of ceftiofur in a convenient extendedtherapy 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 Zoetis 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).

Figure 1 – SC injection technique options for administration of EXCEDE.

Figure 2 – BOE injections. Injection location for SC administration of EXCEDE in the posterior aspect of the ear where it attaches to the head (BOE).
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.

Results summarized in Table 2 indicate that no relevant differences were observed in restraint, re-injection, leak-back, or excessive bleeding between the 3 techniques. By day 28, 93% of injection sites were scored as normal using the ventral technique, compared to 91% using the rostral technique and 95% 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 feedlot heifers using normal equipment and restraint. Injection outcomes were similar to those observed using the previously approved ‘opposite-eye’ technique.

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**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>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 2 – Injection parameters and site outcomes in beef heifers after ventrally directed BOE injection.**

<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>
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.

**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.

**References**

EXCEDE® Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD), shipping fever, pneumonic associated with Mannheimia haemolytica, Pasteurella multocida, and Fusobacterium necrophorum in beef, non-lactating dairy cattle, and calves. EXCEDE® Sterile Suspension is also indicated for the treatment of bovine bronchopneumonia caused by Pasteurella multocida and Neospora caninum in non-lactating dairy cattle.

INDICATIONS
EXCEDE Sterile Suspension is indicated for the control of respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with Mannheimia haemolytica, Pasteurella multocida, and Fusobacterium necrophorum. EXCEDE Sterile Suspension is indicated for the treatment of bovine respiratory disease in the middle third of the posterior aspect of the ear.

ADDITIONAL USES
• Excision of abscesses
• Excision of aural polyps
• Management of pyostomatitis

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

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 development of drug-resistant bacteria.
• Do not use in calves to be processed for veal.

PRECAUTIONS
Excessive or prolonged use of antibacterials may lead to drug resistance or the emergence of drug-resistant strains.

ADVERSE EFFECTS
• Drug-resistant bacteria
• Drug-related metabolites after administration of EXCEDE Sterile Suspension may be excreted via renal or non-renal routes.

ADVERSE REACTIONS
The effects of ceftiofur on bovine reproductive performance, pregnancy, and lactation have not been determined.

ADVERSE EFFECTS
• Anterior uveitis may occur during administration of EXCEDE Sterile Suspension as a result of the drug's immunostimulatory properties.

SUSPENSIONS
The physical properties of the two subcutaneous locations of injection (MDE and BOE) as shown in Table 3. Statistical analyses of the data from these non-subcutaneous injection sites (MDE and BOE) demonstrate that they are bioequivalent.

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The effects of ceftiofur on bovine reproductive performance, pregnancy, and lactation have not been determined.

CLINICAL PHARMACOLOGY
Ceftiofur is a broad-spectrum, time-dependent antimicrobial agent against a wide range of Gram-positive and Gram-negative bacteria, including Pseudomonas aeruginosa, Staphylococcus aureus, and Enterobacteriaceae. It is metabolized by the liver to a number of active metabolites, including desfuroylceftiofur, desfuroylceftiofur oxime, and desfuroylceftiofur lactone. These metabolites are responsible for the therapeutic effect of ceftiofur and are responsible for the observed pharmacological effects.

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These interpretive criteria are only intended for use when CLSI M31-A2 performance standards are used to determine antimicrobial susceptibility. Interpretive criteria for ceftriaxone are as follows:

\[
C_{\text{MIC}} = \text{MIC value}\times 10^{\text{CoP} (\text{mg/L})}
\]

**Table 5. CLSI-accepted interpretive criteria**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CoP</th>
<th>C_{\text{MIC}}</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>20</td>
<td>200</td>
<td>Intermediate</td>
</tr>
<tr>
<td><em>Salmonella enterica</em></td>
<td>10</td>
<td>100</td>
<td>Sensitive</td>
</tr>
<tr>
<td><em>Shigella flexneri</em></td>
<td>10</td>
<td>100</td>
<td>Sensitive</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td>10</td>
<td>100</td>
<td>Sensitive</td>
</tr>
</tbody>
</table>

**AUC0-LOQ**

The area under the curve from time 0 to the last quantifiable concentration (\(C_{\text{LOQ}}\)) is the area under the curve from time 0 to the limit of quantification of the assay (\(C_{\text{LOQ}}\)).

**Table 3. AUC0-LOQ and 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>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-LOQ (μg/mL h)</td>
<td>651 ± 119</td>
</tr>
<tr>
<td>Peak concentration (μg/mL)</td>
<td>90</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>4.6 ± 1.6</td>
</tr>
</tbody>
</table>

**EFFICACY**

A FDA dose confirmation study for the treatment of BRD evaluated the effectiveness of single and repeated doses of EXCEDE Sterile Suspension in the treatment of the bacterial component of BRD under field conditions. All treatments were administered subcutaneously at the base of the ear of 200 dairy cows (average weight of 600 kg) in a field trial conducted in Washington State in 1996 to 1997 (19). Over 80% of cows that were tested had a confirmed diagnosis of BRD. Ceftiofur was effective, significantly reducing the incidence of clinical disease in treated cows.

**Table 4. Mean ± Standard Deviation Characteristics of ear infection before and after EXCEDE Sterile Suspension treatment.**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>MIC concentration (μg/mL)</th>
<th>Before EXCEDE</th>
<th>After EXCEDE</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>2</td>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>1</td>
<td>1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**ANIMAL SAFETY**

**Tissue and Milk Residue Depletion**

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 97.8% of dairy cattle using the excentric injection technique. Normal restraint was adequate for ≥ 97.8% of cattle at all observation times after treatments. Milk residue data from this study supports that no milk residue was detected at 72 hour post-injection.

**Storage Conditions**

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

**How Supplied**

EXCEDE Sterile Suspension is available in the following packages:

- 100 mL
- 250 mL

**Revised: December 2011**

**Distributed by Pfizer Inc, NY, NY 10017**