Key Points

• The pharmacokinetics of EXCEDE® (ceftiofur crystalline free acid) Sterile Suspension, whether administered at the base of the ear (BOE) in adult dairy cattle or in the middle one-third of the posterior ear in beef cattle, are therapeutically equivalent.1,2 Base of the ear is the approved site for injection of EXCEDE in lactating dairy cows.

• Susceptibility of targeted respiratory pathogens to ceftiofur in vitro continues to be exceptional.

• Proven effectiveness for bovine respiratory disease (BRD) organisms shows a single dose of EXCEDE provides extended therapy in cattle, now available for lactating dairy cattle.

• Milk does not need to be discarded from cows treated with EXCEDE following appropriate administration.

Introduction

EXCEDE is a ready-to-use formulation that contains the crystalline free acid of ceftiofur, which is a broad-spectrum cephalosporin active against Gram-positive and Gram-negative bacteria, including some β-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal, in vitro, resulting from inhibition of cell wall synthesis. Clinical efficacy of EXCEDE for treatment of BRD in beef and non-lactating dairy cattle is well established.3,4 Now approved for lactating dairy cows, EXCEDE is a single-administration, extended-therapy product that preserves the proven clinical efficacy of ceftiofur and continues to support the tenants of Beef Quality Assurance.

Pharmacology

EXCEDE was originally approved for subcutaneous (SC) administration in the middle one-third of the posterior aspect of the ear in beef and non-lactating dairy cattle. To obtain approval for use of EXCEDE in lactating dairy cattle, Pfizer evaluated the pharmacokinetic parameters after SC administration at a new site, the base of the ear. Statistical analyses were used to compare the pharmacokinetic values for middle one-third of ear administration with BOE administration. The approved site for injection of EXCEDE in lactating dairy cows is at the base of the ear.
Lactating Holsteins (1,206 to 1,916 lb) in their first to sixth lactation, and ≥40 days into the current lactation, were randomly assigned to receive a single injection of EXCEDE (1.5 cc per cc). Twelve cows received the SC injection at the base of the ear. Plasma was harvested from samples of blood collected at 0.6, 12, 24 and 36 hours, and then daily through Day 10. The concentration of ceftiofur and desfuroylceftiofur acetamide (HPLC-DCA), a metabolite that serves as an indicator for total ceftiofur activity.

Figure 1. Plasma Concentrations of 5 Daily Doses of NAXCEL (0.5 mg CE/lb) or 1 Dose of EXCEDE (3.0 mg CE/lb) in the Lactating Dairy Cow

A single dose of EXCEDE (blue) can be expected to maintain circulating concentrations above the therapeutic threshold (0.2 µg DCA/mL) for targeted BRD pathogens longer than five, 0.5 mg CE/lb daily doses of NAXCEL (red). Curves represent the best-fit simulated concentration-time course of DCA, based on respective data. Desfuroylceftiofur acetamide (DCA) is a metabolite that serves as an indicator for total ceftiofur activity.

Figure 2. Plasma Concentrations of 5 Daily Doses of NAXCEL (1.0 mg CE/lb) or 1 Dose of EXCEDE (3.0 mg CE/lb) in the Lactating Dairy Cow

A single dose of EXCEDE (blue) can be expected to maintain circulating concentrations above the therapeutic threshold (0.2 µg DCA/mL) for targeted BRD pathogens for longer than five, 1.0 mg CE/lb daily doses of NAXCEL (red). Curves represent the best-fit simulated concentration-time course of DCA, based on respective data. Desfuroylceftiofur acetamide (DCA) is a metabolite that serves as an indicator for total ceftiofur activity.

Microbial Susceptibility

Clinical isolates of the targeted respiratory pathogens (M. haemolytica, P. multocida and H. somni) have remained exceptionally susceptible to ceftiofur. A summary of minimum inhibitory concentrations (MIC) is presented in Table 2. Isolates were obtained in the U.S. and Canada, and testing followed Clinical and Laboratory Standards Institute (CLSI, formerly National Committee for Clinical Laboratory Standards or NCCLS) Guidelines. The CLSI-approved breakpoints for susceptible BRD pathogens are MIC ≤2.0 µg/mL, with a zone diameter of ≥21 mm.

Table 1. Pharmacokinetic Parameters for EXCEDE Administered at the Base of the Ear of the Lactating Dairy Cattle

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>4.44 ± 1.65</td>
<td></td>
</tr>
<tr>
<td>tmax (h)</td>
<td>19.00 ± 8.02</td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>313 ± 85.5</td>
<td></td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>205 ± 35.7</td>
<td></td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>43.92 ± 9.98</td>
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</tbody>
</table>

One dose of EXCEDE provides extended therapy comparable to 5 daily doses of NAXCEL* (ceftiofur sodium) Sterile Powder, as depicted in Figures 1 and 2. Pharmacokinetic analyses demonstrated that a single dose of EXCEDE administered in the BOE of lactating dairy, non-lactating dairy, or beef cattle provides therapeutic concentrations for targeted BRD pathogens.

Table 2. Minimum Inhibitory Concentrations (MIC) for Ceftiofur Against Clinical Isolates Supported by Clinical Data and Indications for Use

<table>
<thead>
<tr>
<th>Organisms</th>
<th>MIC Range (µg/mL)</th>
<th>MIC* (µg/mL)</th>
<th>Date Tested</th>
</tr>
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<tbody>
<tr>
<td>Mannheimia haemolytica</td>
<td>110</td>
<td>≤0.03-0.25</td>
<td>≤0.06</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>1320</td>
<td>≤0.03-0.25</td>
<td>≤0.03</td>
</tr>
<tr>
<td>Haemophilus somni (formerly Haemophilus somnus)</td>
<td>1577</td>
<td>≤0.03-0.25</td>
<td>≤0.03</td>
</tr>
</tbody>
</table>

The minimum inhibitory concentration for 90% of the isolates

Efficacy and Management Considerations

Statistical analyses of pharmacokinetics from middle one-third of ear and BOE injection sites in beef and dairy cattle, respectively, demonstrate that they are therapeutically equivalent. The efficacy of a single dose of EXCEDE for treatment of BRD in beef and non-lactating dairy cattle was previously demonstrated in multiple studies. 2 3 4 8 One multi-location study evaluated the feasibility of using 3-, 5-, or 7-day post-treatment intervals (PTI), during which no additional antimicrobial treatment was allowed, as a management option (Figure 3). The Day 28 treatment success rate was significantly greater by 12 percent-age points in the 7-day PTI group than in the 3-day PTI group (Figure 4). Mortality due to BRD was not analyzed statistically but was numerically lower for the 7-day PTI group. Average daily gain was similar for all treatment groups. A single dose of EXCEDE provided extended therapy without increasing mortality or decreasing weight gain.

Residue Depletion in Milk

Milk was collected from healthy Holstein cows in their first to sixth lactation, and ≥40 days into the current lactation. Animals in the study were all producing at least 50 lb/day for the 3 to 6 days prior to receiving EXCEDE. No clinical mastitis was present by visual inspection of the milk and udder for the 18 to 21 days before treatment. All cows were free of subclini-cal mastitis as defined by all milk having <400,000 somatic cells per mL in 4-quarter composite samples taken just prior to the beginning of the study. Twelve (12) cows received EXCEDE (1.5 mg CE/lb BW) by SC injection at the base of the ear. Production of milk was monitored for 13 days before EXCEDE was administered through 7 days afterwards. Samples of milk were obtained twice daily for the first 6 days and once on Day 7 after administration to deter-mine the concentrations of ceftiofur and metabolites using the validated HPLC-DCA assay, which has a limit of quantification of 50 ppb and a limit of detection of 15 ppb. None of the samples contained residues above the tolerance established for milk (100 ppb). These data support no milk discard.

Conclusions

A single dose of EXCEDE administered to lactating dairy cows at the base of the ear provided therapeutic concentrations of ceftiofur and metabolites for an extended period with no milk discard. Susceptibility of targeted respiratory pathogens in vitro continues to be exceptional.

As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously found to be hypersensi-tive to the drug. Though safe in cattle when properly given, inadvertent intra-arterial injection in the ear is possible and is fatal. EXCEDE has a pre-slaughter withdrawal time of 13 days.

Figure 3. Study Design

Figure 4. 28-Day Treatment-Success Rates

References