EXCEDE® for Lactating Dairy Cows: Overview of Research Supporting a 2-Dose Regimen for Treatment of Metritis

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KEY POINTS
• A 2-dose regimen of EXCEDE® Sterile Suspension (ceftiofur) was recently approved for the treatment of acute metritis (0-10 days postpartum) in lactating dairy cows.

• A study characterized the pharmacokinetics of 2 EXCEDE treatments given 3 days apart, with each dose administered at the rate of 3 mg CE/lb BW.
  • Two treatments with EXCEDE provided plasma drug concentrations comparable to a 5-day regimen of ceftiofur (1 mg CE/lb BW/day). The secondary peak in plasma levels likely helps achieve higher and longer drug concentrations in uterine tissues.

• An extensive 15-site clinical study evaluated the efficacy of a 2-dose EXCEDE regimen for treatment of metritis in lactating dairy cows.
  • A significantly greater ($P < 0.0001$) metritis cure rate was achieved in cows treated with EXCEDE (74.3%) vs non-medicated control cows (55.3%).
  • Cows treated with EXCEDE demonstrated significantly lower ($P \leq 0.0004$) rectal temperatures than controls for 5-6 days post-treatment.

• A milk residue study confirmed that a 2-dose EXCEDE regimen can be safely administered to lactating dairy cows with no milk discard.

• EXCEDE is highly effective for the treatment of acute postpartum metritis in dairy cows.
Metritis is an inflammation of the uterus caused by bacterial infection, and is a common, costly, even life-threatening disease of dairy cows. Clinical metritis most commonly occurs in the first 10 days post-calving, and affected cows may subsequently exhibit poor reproductive performance with irregular estrous cycles, lower conception rates, and greater intervals from calving to pregnancy.

Clinical metritis is characterized by fever, fetid vulvar discharge, depression, inappetence, and a uterus with excess fluid and lacking tone. The literature demonstrates that infection of the uterus with *Escherichia coli* appears to predispose animals for subsequent infection with other bacteria that further contribute to the condition. An average case of metritis is estimated to cost dairy producers between $304 and $354 due to culling, reduced milk production and fertility/reproductive performance, treatment costs, and milk discard. The disease can be very difficult to treat, and the treatment of choice has been a 5-day regimen of EXCENEL® RTU (ceftiofur HCl) plus appropriate supportive therapy.

EXCEDE® Sterile Suspension (ceftiofur crystalline free acid) is the potent single-dose treatment for bovine respiratory disease and foot rot in lactating dairy cattle. Furthermore, dairy producers often prefer EXCEDE because it can be used with no milk discard. EXCEDE provides the demonstrated efficacy of ceftiofur in a convenient extended-therapy formulation designed for SC administration at the base of the ear in lactating dairy cows at a dose of 3 mg ceftiofur equivalents (CE) per lb body weight (BW) (or 1.5 mL EXCEDE/100 lb BW).

As the result of an extensive research and development program conducted by Zoetis scientists, a 2-dose regimen of EXCEDE has been recently approved for the treatment of acute metritis (0-10 days postpartum) in lactating dairy cows. Summaries of studies that led to the new metritis indication for EXCEDE follow, highlighting the rationale, efficacy, and safety of this significant therapeutic advance for dairy veterinarians and their clients.

**Pharmacology of EXCEDE**

The pharmacokinetic rationale for using a 2-dose EXCEDE regimen in the treatment of acute metritis was established by studies that investigated the fate of ceftiofur in dairy cows.

**Single-dose pharmacokinetics**

In an early study, ceftiofur concentrations in uterine tissues (caruncle) were compared after dairy cows received either a single dose of EXCEDE (3 mg CE/lb BW) or 5 sequential daily doses of conventional ceftiofur (EXCENEL RTU, 1 mg CE/lb BW/day). Caruncle tissue was assayed for ceftiofur concentration at 1, 3, and 5 days after initial dose administration. A ceftiofur minimum inhibitory concentration (MIC) of 0.2 μg/mL has often been used for bacterial respiratory pathogens susceptible to ceftiofur, and a MIC of 0.5 μg/mL has been determined for many *E. coli* isolates involved in metritis cases.

Results summarized in Figure 1 show that ceftiofur concentrations in the caruncle fell below 0.5 μg/g by day 3 for cows treated with a single dose of EXCEDE, and approached 0.2 μg/g by day 5. In contrast, uterine tissue...
concentrations gradually accumulated in cows that received 5 doses of ceftiofur and remained near or above the MIC benchmarks of 0.2 to 0.5 μg/g. These outcomes suggested that a single dose of EXCEDE would likely be insufficient for the treatment of acute metritis and that a second dose after 3 days might provide the additional coverage required for efficacy. Results of this study and other research thus prompted investigation of the pharmacokinetic behavior of a 2-dose EXCEDE regimen for metritis therapy.

Two-dose pharmacokinetics

A study was conducted to characterize the pharmacokinetics of 2 EXCEDE treatments given 3 days apart, with each dose administered at the rate of 3 mg CE/lb BW. The study involved 12 lactating Holstein dairy cows that received EXCEDE as a SC injection at the base of the ear, with the second dose administered in the base of the opposite ear approximately 72 hours after the first injection. Blood samples were obtained prior to the first injection and at specified time points up to 14 days after the first injection, and assayed to determine concentrations of ceftiofur and active metabolites.

Pharmacokinetic parameters calculated from collected data are summarized in Table 1, and Figure 2 shows the resulting plasma concentrations observed over the course of the study. Figure 2 also includes projected plasma levels for 5 sequential daily doses of conventional ceftiofur (EXCENEL RTU) when administered at 1 mg CE/lb BW. Investigators were most interested in estimates of maximum drug concentration (C_{max}) and the area under the drug depletion curve (AUC). Study results indicated that ceftiofur exposure in lactating cows following 2 doses of EXCEDE (3 mg CE/lb BW) administered 72 hours apart was statistically similar to that provided by 5 sequential daily doses of ceftiofur (1 mg CE/lb BW). The second dose of EXCEDE provided a secondary peak in plasma that would likely help achieve higher and longer concentrations of active drug in uterine tissues. These results provided the pharmacokinetic rationale to suggest that 2 doses of EXCEDE could provide efficacy against acute metritis in lactating dairy cows.

### Table 1 – Mean pharmacokinetic parameters of ceftiofur in cows when administered as EXCEDE in 2 doses of 3 mg CE/lb BW 3 days apart.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (µg/mL)</td>
<td>5.98</td>
</tr>
<tr>
<td>AUC_{0-LOQ} (µg•h/mL)</td>
<td>651</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>77.1</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>55.7</td>
</tr>
<tr>
<td>t_{&gt;0.2} (h)</td>
<td>341</td>
</tr>
</tbody>
</table>

C_{max} = maximum plasma concentration; AUC_{0-LOQ} = area under the plasma concentration vs time curve from time of injection to the limit of quantitation (LOQ) of the assay; t_{max} = time after injection when C_{max} occurs; t_{1/2} = terminal phase biological half life; t_{>0.2} = time plasma concentrations remain above 0.2 µg.

Figure 2 – Ceftiofur/metabolite concentration (LS means) in plasma after 2 doses of EXCEDE (3 mg CE/lb BW, 3 d apart) or 5 sequential daily doses of EXCENEL RTU (1 mg CE/lb BW).

### Metritis Efficacy: Experiment Design

An extensive clinical field study evaluated the effectiveness of a 2-dose EXCEDE regimen for the treatment of acute metritis in lactating dairy cows under commercial production conditions. The multicentric study was conducted at 15 dairies in the West, Northeast, Midwest, and Southwest regions of the US, with an identical experiment protocol followed at each site.

Plasma levels from 2 doses of EXCEDE were similar to 5 sequential daily doses of EXCENEL RTU.

The 2nd dose of EXCEDE provides a secondary plasma peak that helps achieve effective drug levels in uterine tissues.
The study involved 1023 lactating Holstein dairy cows that had calved within 10 days of study initiation. Cows were managed according to the normal husbandry, health, and management practices of each particular dairy operation. Cows included in the study were housed with cows not enrolled in the study and often moved between pens consistent with normal animal flow in the dairy, while at some sites cows remained in the fresh-cow pen.

Cow were enrolled in the randomized-block study (day 0) when they demonstrated clinical signs of acute postpartum metritis defined as a fetid vaginal discharge (thin, serous, or watery, red/pink to brown in color, with or without pieces of necrotic tissue) and rectal temperature ≥103°F. Pairs of qualifying animals were blocked based on order-of-entry within dairies without regard to parity, and randomly assigned to either of 2 treatment groups:

- **EXCEDE (2 doses):** 1.5 mL/100 lb BW (3 mg CE/lb BW) administered SC at the base of the ear on day 0, followed by a second SC dose at the base of the opposite ear 3 days later (day 3) (n=514);
- **Non-medicated control (vehicle; 2 doses):** 1.5 mL/100 lb BW administered SC at the base of the ear on day 0, followed by a second SC dose at the base of the opposite ear 3 days later (day 3) (n=509).

Each cow was observed daily on study days 1 to 13 for any abnormal clinical signs, and rectal temperature was recorded on days 1 to 5 or 6. On study day 5/6, each cow was examined to determine if severe clinical signs of acute postpartum metritis necessitated removal from the study. Cows removed from the study for worsening metritis during days 1 to 14 were classified as a treatment failure and were administered alternate therapy. On day 14, each remaining cow was examined, rectal temperature recorded, and vaginal discharge was scored (0 to 4 scale, 0=no discharge, 4=fetid discharge) to determine metritis cure or treatment failure. The condition of cow ears (where treatments were administered) and ease/success of the base-of-ear SC administration procedure were also assessed on days 5/6, 14, and 57 (study conclusion). Personnel conducting all clinical evaluations were blinded to treatment assignments.

Data collected during the study were statistically analyzed using appropriate standard methods (including computation of least squares means), with significance declared when \( P \leq 0.05 \). The primary parameter was ‘cure rate’ defined as a non-fetid vaginal discharge score (<4) and rectal temperature <103°F on day 14. Temperature <103°F on day 14.

**Two treatments of EXCEDE successfully resolved metritis in 74.3% of clinical cases.**

**Cows treated with EXCEDE had lower rectal temperatures than controls for 5-6 days after treatment.**

**Figure 3 – Metritis cure rate (back-transformed LS means) 14 days after initial dose; 2 doses of EXCEDE (3 mg CE/lb BW, 3 d apart) vs non-medicated vehicle (control).**

**Figure 4 – Rectal temperature (LS means) on study days 0 to 5/6; 2 doses of EXCEDE (3 mg CE/lb BW, 3 d apart) vs non-medicated vehicle (control).**
Metritis Efficacy: Results

A total of 41 cows were not included in statistical analyses for treatment efficacy due to medical events unrelated to metritis (25 cows) or protocol deviations (16 cows).

Two treatments of EXCEDE administered 3 days apart proved successful in resolving clinical metritis. As shown in Figure 3, a significantly greater ($P < 0.0001$) metritis cure rate was achieved in cows treated with EXCEDE (74.3%) than in control cows that received non-medicated vehicle (55.3%). Thus, EXCEDE improved cure rate by 34.4% compared to controls.

EXCEDE also favorably impacted rectal temperature of cows with clinical metritis (Figure 4). Cows treated with EXCEDE demonstrated significantly lower ($P \leq 0.0004$) rectal temperatures than controls on each of days 1 to 5/6. These results suggest that medicated cows rapidly responded to EXCEDE therapy.

Data collected regarding treatment administration at the base-of-ear SC site were also summarized. Equipment routinely used to restrain cows (neck lock-up and halter) was adequate to allow injection at the base of the ear for $\geq97.8\%$ of administered injections, $\geq96.8\%$ of all injections were completed without need for re-injection due to animal movement, and no post-injection problems (bleeding and/or leakback) were observed in $\geq78.5\%$ of doses administered. Normal ear carriage (vs droopy ears) was observed in about 98% of all ears at day 14, and no apparent differences existed between treatment groups in regard to injection site irritation (mostly swelling) at day 57 ($>96\%$ normal).

Results of this study demonstrate that EXCEDE is effective for treatment of acute metritis of lactating dairy cows occurring within 10 days of calving. The 2-dose EXCEDE regimen administered SC at the base of the ears quickly lowered rectal temperatures and cured metritis in 74.3% of affected cows.

Milk Discard and Tissue Residue Studies

The advent of a 2-dose EXCEDE regimen for lactating dairy cows raised milk discard and tissue residue implications that required investigation before FDA approval could be attained.

The original labeling for single-dose EXCEDE administration dictated a 13-day pre-slaughter withdrawal period, but no milk discard period (0-day withdrawal). Additional studies were conducted by Zoetis scientists to evaluate the depletion of ceftiofur metabolites in milk and body tissues following 2 doses of EXCEDE (3 mg CE/lb BW) administered 3 days apart via SC administration at the base of the ear in lactating dairy cows.

A milk residue study monitored drug levels for up to 216 hours (9 days) after the 2 doses of EXCEDE in 40 lactating Holstein cows. The average peak level of ceftiofur metabolites in milk was 0.0433 ppm at 108 hours post treatment, less than half the tolerance level of 0.1 ppm, with all other average levels below this peak value. Since EXCEDE clearly does not accumulate in milk, the 2-dose regimen retains the ‘no milk discard’ benefit that producers desire. Thus, the 2-dose EXCEDE regimen can be safely administered to lactating dairy cows with no milk discard.

Another study addressed ceftiofur residues in body tissues of cattle slaughtered for human consumption. Drug levels in kidneys (the target tissue for such evaluations) were monitored for up to 16 days after the 2-dose EXCEDE regimen was administered to 16 lactating Holstein cows. No drug could be detected at 12 or 16 days after administration of the second EXCEDE dose. Thus, the existing 13-day pre-slaughter withdrawal period was again deemed appropriate for the 2-dose EXCEDE regimen (13 days after administration of the second dose).
Human Safety

As part of the pre-approval safety evaluation process, FDA considers the potential impact on human health of antimicrobial drugs used in food-producing animals. The FDA believes that human exposure through the ingestion of antimicrobial resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to bacteria that have emerged or been selected as a consequence of antimicrobial drug use in animals. Thus, a risk assessment is required for all antimicrobial drugs used in food-producing animals.

To address these concerns, EXCEDE was given a prescription-only (Rx) marketing status, restricted for parenteral injection only into individual animals with clinically recognizable symptoms of metritis, and designated for continued monitoring in the National Antimicrobial Resistance Monitoring System. Based on additional research, FDA found there was no need to determine a microbiological acceptable daily intake since the amount of microbiologically active residues of EXCEDE that reach the human colon would most likely not cause adverse effects on the intestinal flora of consumers.

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

An extensive body of scientific research has resulted in FDA approval of a 2-dose EXCEDE regimen for treatment of acute postpartum metritis in lactating dairy cows. A pharmacokinetics study showed that a 2-dose EXCEDE regimen provides a secondary drug peak in plasma, supporting the rationale for higher and longer concentrations of ceftiofur and its metabolites in uterine tissues. A subsequent 15-site clinical field study involving 1023 lactating dairy cows demonstrated that a 2-dose EXCEDE regimen quickly reduced rectal temperatures and cured metritis in 74.3% of sick cows compared to a cure rate of only 55.3% for non-medicated control animals. Subcutaneous injection of EXCEDE via the base-of-ear route was readily accomplished, and almost all injection site reactions were transient and resolved with time. Additional research confirmed that the 2-dose EXCEDE regimen can be used in lactating dairy cows with no milk discard, and a 13-day pre-slaughter withdrawal period was reconfirmed.

A 2-dose EXCEDE regimen offers dairy practitioners and their clients a valuable new tool for treating metritis in lactating dairy cows, thus circumventing financial losses due to poor performance and mortality in these very highvalue animals.

References

For subcutaneous administration 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 where it attaches to the head (base of the ear) in 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.

**DESCRIPTION**
EXCEDE Sterile Suspension is a ready-to-use formulation that contains the crystalline free acid of ceftiofur, which is a broad-spectrum, potent, beta-lactamase, and Gram-negative bacteria including beta-lactamase-producing strains. Like other cephalosporins, EXCEDE Sterile Suspension is a member of the cephalosporin class of antibiotics. EXCEDE Sterile Suspension subcutaneously in the middle third of the posterior aspect of the ear where it attaches to the head (base of the ear) in non-lactating dairy cattle. Not for use in calves to be processed for veal.

**INDICATIONS**
- Control of BRD in non-lactating dairy, and lactating dairy cattle.
- Control of BPP in non-lactating dairy, and lactating dairy cattle.
- Control of BRS in non-lactating dairy, and lactating dairy cattle.
- Control of subclinical BRS in non-lactating dairy, and lactating dairy cattle.
- Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension in the middle third of the posterior aspect of the ear where it attaches to the head (base of the ear) in non-lactating dairy cattle.

**CONTRAINDICATIONS**
As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously treated with the same or related cephalosporins.

**WARNINGS**
For use in animals only. Not for human use. Keep out of reach of children.

**PRECAUTIONS**
- Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe sensitization to the product, skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing protective gloves.
- Persons with a known hypersensitivity to penicillins or cephalosporins should avoid exposure to this product.

**ADVERSE EFFECTS**
- Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension in the middle third of the posterior aspect of the ear where it attaches to the head (base of the ear). Intra-arterial injection may result in sudden death of the animal.

**RESIDUE WARNINGS**
- Following label use as either a single-dose or 2-dose regimen, a 15-day pre-slaughter withdrawal period is required after the last treatment.
- Following label use as either a single-dose or 2-dose regimen, no milk withdrawal period is required for this product.
- Use of doses in excess of 3.0 mg CE/lb (6.6 mg CE/kg) BW or administration by unapproved routes (subcutaneous injection in the neck or intramuscular injection) may cause volunteer residues.

**ADDITIONAL INFORMATION**
- Use of medicinal 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.

**REFERENCES**
- Administration of ceftiofur crystalline free acid in the middle third of the posterior aspect of the ear where it attaches to the head (base of the ear) in non-lactating dairy cattle may result in open draining lesions in a small percentage of cattle.
- The effects of topical ceftiofur on bovine reproductive performance, pregnancy, and lactation have not been determined.

**CLINICAL PHARMACOLOGY**
Cefitiofur administered as either oral sulfadiazine (ZEPHYL* Sulfa Powder), cefitiofur hydrochloride (EXCEDE* RY/EXCEDE Sterile Suspension), or cefitiofur crystalline free acid (ZEPHYL* RY) is metabolized rapidly to dehydrocephalosporin, the primary metabolite. Subcutaneous administration of ceftiofur crystalline free acid, either in the middle third of the posterior aspect of the ear (MOE) of the non-lactating dairy cattle, or in the posterior aspect of the ear where it attaches to the head (base of the ear) of pre-ruminating calves, does not appear to elicit a significant hemicidal effect. As with all drugs, the use of this product in animals previously treated with the same or related cephalosporins is contraindicated.

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

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<thead>
<tr>
<th>Weight (lb)</th>
<th>Dose Volume (mL/kg)</th>
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<tr>
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<td>10000</td>
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**Figure 1. Structure of ceftiofur crystalline free acid.**

**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.**

**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).**

**Figure 6. Diagram of head showing the direction for the base of ear injections administered normally toward the eye on the same side of the head as the base of the ear.**

**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.**

**Figure 8. Average in (±)200 mg plasma concentrations of cefitiofur and desfurfuryl-related metabolites after administration of EXCEDE Sterile Suspension at 3.0 mg CE/lb (6.6 mg CE/kg) BW via subcutaneous injection into one of the ears of non-lactating dairy cattle, middle third of the ear (MOE Cattle) and base of the ear (BOE Cattle) in beef cattle as well into the base of the ear (BOE Lactating) in lactating dairy cattle.**
Pharmacokinetic Parameter

<table>
<thead>
<tr>
<th>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>
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<td>Cmax (µg/mL)</td>
<td>271 ± 85.5</td>
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<td>AUC0-LOQ (µg•h/mL)</td>
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<td>210 ± 41.5</td>
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<tr>
<td>t1/2 (h)</td>
<td>6 ± 2.0</td>
<td>6 ± 2.0</td>
<td>9 ± 3.0</td>
</tr>
</tbody>
</table>

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

1.0 ppm in muscle and 0.1 ppm in milk.

In a residue study, 72 beef cattle were injected in the base of the ear with EXCEDE Sterile Suspension at a dose of 6.6 mg CE/kg BW at the base of the ear using the intravenous injection technique. These cattle were slaughtered 3, 11, and 54±3 days after the second injection, respectively.

In a local tolerance study conducted with ceftiofur sodium in normal feeder calves indicated that cattle were well tolerated at 25 mg CE/kg for the dosage and the extent of exposure (AUC) after two doses of CE/lb (6.6 mg CE/kg) BW EXCEDE Sterile Suspension dose significantly (p ≤0.05) increased antibiotic treatment during the 14-day post-injection period. Successful injection in the base of the ear was achieved in 97.4% of cattle using normal injection techniques.

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