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

February 2012

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 Pfizer 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

![Caruncle drug concentration (µg/g)](image)

**Figure 1** – Ceftiofur/metabolite concentration in uterine caruncle tissue after a single dose of EXCEDE (3 mg CE/lb BW) or 5 sequential daily doses of EXCENEL RTU (1 mg CE/lb BW).

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 ceftriaxone 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 ceftriaxone (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 ceftriaxone 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_D-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_D-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.

### 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.

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.

**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 ≥97.8% of administered injections, ≥96.8% of all injections were completed without need for re-injection due to animal movement, and no post-injection problems (bleeding and/or leak-back) were observed in ≥78.5% 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.
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 a valuable new tool for treating metritis in lactating dairy cows, thus circumventing financial losses due to poor performance and mortality in these very high-value animals.

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.
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 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 forveal.

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, which is a beta-lactam antibiotic and is bactericidal against Gram-positive and Gram-negative bacteria including E. coli and Pasteurella multocida, and anaerobic bacteria in vitro, in vivo, and resulting from inhibition of cell wall synthesis.


INDICATIONS

EXcede Sterile Suspension is indicated for treatment of bovine respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni strains. Like other respiratory disease agents, ceftiofur is effective for the control of respiratory disease in beef and non-lactating dairy cattle.

Administration of EXcede Sterile Suspension into ear arteries is likely to be fatal.

EXcede Sterile Suspension is also indicated for treatment of acute bovine bronchopneumonia caused by Pasteurella multocida associated with Pseudomonas aeruginosa and Porphyromonas levii in beef, non-lactating dairy, and lactating dairy cattle.

Each mL of this ready-to-use sterile suspension contains ceftiofur crystalline free acid equivalent to 200 mg, in a caprylic/capric triglyceryl ([Mg(2+)Cl2]12 and condensed base suspension.

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 poster Ear area and the recommended needle insertion locations. Administration of EXcede Sterile Suspension into ear arteries is likely to be fatal.

Figure 4. Subcutaneous administration of EXcede Sterile Suspension in the middle third of the posterior aspect 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 cranially toward the eye on the same side of the head into the loose skin in the caudal aspect of the base of the ear.
**Table 4. Ceftiofur minimum inhibitory concentration (MIC) values* of indicated pathogens.**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>MIC range (μg/mL)</th>
<th>n</th>
<th>MEC (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannheimia haemolytica</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*These criteria are only intended for use when CLSI-A2 standards are used. They may not be appropriate for other susceptibility tests.*

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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disk Potency</th>
<th>Zone Diameter (mm)</th>
<th>MBC Breakpoint (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus subtilis</td>
<td>9</td>
<td>≥ 21</td>
<td>S</td>
</tr>
</tbody>
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**Figure 8. Average (n=12/group) plasma concentrations of ceftiofur and its metabolites (μg/mL) following two subcutaneous injections of EXCEDE Sterile Suspension at a dose rate of 3.0 mg CE/lb (6.6 mg CE/kg) BW in dairy cattle.**

**Figure 9. 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 in Dairy Cattle.**

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**Table 3. Average (n = 12/group) pharmacokinetic parameters for cattle and dairy calves calculated after a single subcutaneous administration of EXCEDE Sterile Suspension at a dose rate of 2.0 mg CE/lb (4.4 mg CE/kg) BW to 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>Average</th>
<th>Standard Deviation</th>
<th>Beef - Base of the Ear</th>
<th>Average</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (μg/mL)</td>
<td>5.5 ± 1.7</td>
<td></td>
<td></td>
<td>6.9 ± 2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>0.9 ± 0.2</td>
<td></td>
<td></td>
<td>1.0 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0-24 (μg h/mL)</td>
<td>18 ± 3</td>
<td></td>
<td></td>
<td>21 ± 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2. Average (n = 12/group) pharmacokinetic parameters for cattle and dairy calves calculated after a single subcutaneous administration of EXCEDE Sterile Suspension at a dose rate of 2.0 mg CE/lb (4.4 mg CE/kg) BW to either the middle third of the ear or the base of the ear.**

<table>
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<tr>
<th>Pharmacokinetic Parameter</th>
<th>Base of the Ear</th>
<th>Average</th>
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<tbody>
<tr>
<td>Cmax (μg/mL)</td>
<td>8.9 ± 2.0</td>
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**Figure 10. Average (n=12/group) plasma concentrations of ceftiofur and its metabolites (μg/mL) following two subcutaneous injections of EXCEDE Sterile Suspension at a dose rate of 3.0 mg CE/lb (6.6 mg CE/kg) BW in dairy cattle.**

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**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

Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

www.EXCEDE.com or call 1-866-387-2387

Revised: December 2011

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**References**

5. Data on file, Study Report No. 1133C-60-06-509, Pfizer Inc.