EXCEDE® (Ceftiofur Crystalline Free Acid): A New Sustained-Release Injectable Antibiotic for Horses

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EXCEDE® (Zoetis) is a novel, sustained-release formulation of ceftiofur that largely overcomes one of the most important causes of antimicrobial treatment failure: poor compliance. EXCEDE provides 10 days of therapeutic blood levels with only 2 IM injections, thus providing effective treatment with far fewer doses than daily antibiotic formulations. The sustained-release ceftiofur formulation greatly increases the likelihood of successful outcome for one of the most widely used antimicrobials in equine medicine and a mainstay for treating the most common cause of lower respiratory tract (LRT) disease of horses, *Streptococcus equi* subspecies *zooepidemicus* (shorter taxonomic terms are *S. zooepidemicus* as used in this report, *S. zoo*, or *equi* ssp. *zoo*). EXCEDE is the only sustained-release antimicrobial licensed for use in horses.

This report discusses the role of *S. zooepidemicus* in equine LRT disease, ceftiofur as a reliable treatment for this pathogen, the limitations of daily dosing and how simplified dosing (i.e., extended dosing intervals) contributes to compliance, judicious use, and treatment success. Studies providing evidence-based demonstrations of the safety and efficacy of EXCEDE against LRT disease caused by *S. zooepidemicus* are also reviewed.
Ceftiofur and its target pathogen

Ceftiofur has in vitro activity against a variety of Gram-positive and Gram-negative bacteria, including β-lactamase strains, justifying its designation as a broad-spectrum antimicrobial. Ceftiofur is licensed for the treatment of the following respiratory pathogens, *Histophilus somnus*, *Mannheimia haemolytica*, *Pasteurella multocida*, *Streptococcus suis* and *Streptococcus zooepidemicus*. Originally developed as a third-generation cephalosporin for the treatment of respiratory pathogens in cattle, ceftiofur has a single indication in equine medicine – treatment of LRT disease caused by susceptible strains of *S. zooepidemicus*. Ceftiofur is the only cephalosporin licensed for equine use (also available in non-sustained-release form as NAXCEL® (ceftiofur sodium) Sterile Powder, Zoetis).

*S. zooepidemicus* (“Strep zoo”) is an ubiquitous, commensal organism of the equine upper respiratory tract as well as the most frequently isolated bacterial pathogen in equine lower respiratory tract infections. Recent studies have confirmed the predominant role of *S. zooepidemicus* in equine LRT disease of bacterial origin in horses of all ages. For example, a 2008 Canadian study of >1,300 equine clinical cases found that *S. zooepidemicus* was the leading bacterial isolate over a 6-year period from both the upper (trachea) and lower respiratory tracts of horses. Importantly, *S. zooepidemicus* isolates from this extended, large-scale study had a 99% in vitro susceptibility to ceftiofur. This corresponds to comparable ceftiofur susceptibility results reported for other North American equine *S. zooepidemicus* populations. Collectively, these extensive, long-term data establish *S. zooepidemicus* as the leading etiologic agent of bacterial LRT disease in horses and ceftiofur as its reliable antimicrobial treatment.

Non-compliance as a leading cause of treatment failure

Poor compliance is one of the leading causes of antimicrobial treatment failure. When antimicrobials are given at longer than recommended intervals or if doses are missed, the result can be poor therapeutic response, recurrence of infection, and development of bacterial resistance. Compliance is primarily influenced by convenience of the treatment protocol. The more doses that have to be given, the greater the inconvenience and the worse compliance becomes. For example, a European study found that only 44% of dog owners were compliant in administering a 10-day course of daily oral antibiotic treatment. Other investigators found a significant reduction in compliance when duration of oral antibiotic therapy in human pediatric patients was >7 days. Recent Pfizer market research confirmed that compliance shortfalls are a commonplace feature of equine antimicrobial therapy, with missed doses typically occurring as the result of route of administration or dosing frequency (see box). Treatments which are easy to give and have a simple dosing regimen help ensure that the patient receives a complete course of therapy, leading to optimum case outcomes.

NAXCEL, the previously licensed, non-sustained-release ceftiofur equine formulation, is recommended for daily IM dosing at 1 to 2 mg/lb (2.2 to 4.4 mg/kg) for up to 10 consecutive days. Using this regimen, plasma concentrations greater than the minimum inhibitory concentration (MIC) for the target pathogen are maintained for virtually the entire 24-hour dosing interval. Like other β-lactam antimicrobials, ceftiofur is a time-dependent agent, meaning that its efficacy correlates to duration of exposure of the pathogen to the drug at a concentration above its MIC. For β-lactams to have an antibacterial effect, time of concentration >MIC should be at least 50% of the dosing interval. Thus, adhering to the daily dosing interval for a non-sustained-release ceftiofur formulation is critical for maintaining time of concentration >MIC. However, this imposes the burden of daily administration and introduces the element of inconvenience, especially for longer courses of treatment. EXCEDE was developed specifically to overcome the need for daily dosing of
antimicrobials. When given by IM injection at a dosage of 3.0 mg/lb (6.6 mg/kg), EXCEDE maintains a therapeutic blood level of 0.2 µg/mL for an average of 4.7 days. A full, 10-day course of treatment consists of 2 doses, administered 4 days apart. When EXCEDE is administered by the attending veterinarian, compliance is virtually assured.

Study shows that equine injectable antimicrobials are especially prone to noncompliance

A market research study conducted by Zoetis confirmed that injectable antimicrobials are associated with a high rate of compliance shortfalls. Multi-dose regimens and the extended duration of the typical course of antimicrobial therapy in horses contribute to inconvenience, a key driver of irregular compliance. Study participants included 199 horse owners or professional caretakers who had administered oral or injectable antimicrobials to their animals for at least 5 days during the previous 5 years. Findings included the following:

- 32% of participants said their horses experienced side effects associated with injectable antimicrobials, the most common of which was injection-site pain or swelling.
- 26% of participants said their horses experienced side effects associated with oral antimicrobials, the most common of which was loss of appetite.
- Injectable antimicrobials were prescribed once (62%) or twice (38%) daily, and in 77% of cases the participants were instructed to administer the medication for 5 to 10 days, a regimen that imposes the element of inconvenience.
- 31% of owners and 22% of caretakers (26% of all participants) reported they missed at least 1 dose of an injectable antimicrobial.
- 48% of owners and 26% of caretakers (37% of all participants) reported they missed at least 1 dose of an oral antimicrobial.

- More than half of owners and caretakers reported that a horse reacted negatively (displaying pain, apprehension, or resistance) to injectable antimicrobial administration, and 1 in 4 said that the horse became more difficult to inject with successive doses.
- 50% of owners and caretakers reported that a horse reacted negatively (difficult to medicate, loss of appetite, spitting out of medication) to oral antimicrobial administration, and more than half reported that oral antibiotics required additional daily care.
- 41% and 34% of participants reported that giving an injectable or oral antimicrobial respectively to a horse was not a positive experience.

Brief profile for EXCEDE

- **Indication** – For the treatment of LRT disease in horses caused by susceptible strains of *Streptococcus equi ssp. zooepidemicus*.
- **Presentation** – Supplied as a ready-to-use sterile suspension packaged in a multi-dose 100 mL vial.
- **Dosage and administration** – Administered as 2 IM injections at a dose of 3.0 mg/lb (6.6 mg/kg) of bodyweight 4 days apart. Therapeutic drug concentrations are maintained for 6 days after the second injections (for a total of 10 days from beginning of treatment) against *S. zooepidemicus*.
- **Dose-volume equivalent** – Administered at a dose of 1.5 mL per 100 lbs bodyweight, with a maximum dose of 20 mL per injection site.
- **Storage** – Does not require refrigeration; Store at room temperature (68-77º F). Twelve (12) week broached vial stability.

*Equine Antibiotics: Compliance and Barriers to Administration. Ipsos Forward Research, May 2008.*
**Unique formulation designed for sustained-release**

The sustained-release properties of EXCEDE are the result of the placement of the crystallization form of ceftiofur (ceftiofur crystalline free acid or CCFA) into a unique oil-based formulation composed of high-purity miglyol and cottonseed oil. This formulation creates a depot of CCFA following IM administration. The depot at the injection site, when metabolized, slowly releases ceftiofur, which is rapidly metabolized into its primary active metabolite desfuroylceftiofur (DFC). Thus, a sustained therapeutic blood level of DFC is achieved. The efficacy of EXCEDE has been previously demonstrated in the antimicrobial treatment of cattle.12-14 The efficacy of miglyol, a pharmaceutical-grade fatty-acid derivative that maintains stability over a wide temperature range, as an extended-release model for lipophilic drugs has also been reported.15 A sustained-release formulation greatly reduces labor and increases the prospects for improved compliance versus daily dosing.

**Mode of action**

Ceftiofur is bactericidal, deriving its antimicrobial effect from disruption of cell-wall synthesis. This activity occurs in the peptidoglycan layer of the bacterial cell wall, which maintains cell rigidity. β-lactam agents bind to penicillin-binding proteins (PBPs), enzymes which are involved in the synthesis of peptidoglycan precursors. Binding of PBPs inhibits cell-wall synthesis and ultimately causes cell lysis. This activity occurs both in Gram-negative and Gram-positive pathogens, although the PBPs involved are different depending on the bacterial species. Because peptidoglycan synthesis occurs on a continuing basis, a therapeutic level of antimicrobial must be maintained for an extended period until bacterial cell death occurs. Thus, ceftiofur has a time-dependent (rather than concentration-dependent) mode of action.

**Pharmacokinetic parameters and their clinical relevance**

**Ceftiofur MIC and susceptibility breakpoint for S. zooepidemicus**

An antimicrobial’s MIC and susceptibility breakpoints (sometimes called the clinical breakpoints) are closely related but not synonymous terms that refer to the susceptibility of a pathogen to an antimicrobial. The in vitro susceptibility of a bacterial pathogen is derived from clinical samples, and usually expressed as MIC<sub>50</sub> or MIC<sub>90</sub> values, the antimicrobial concentration that inhibits 50% or 90% of the organisms in the sample population. An antimicrobial’s susceptibility breakpoint is the concentration at which a pathogen is classified as susceptible, intermediate, or resistant. In other words, MIC is a purely quantitative value while as a clinical breakpoint for comparing clinical efficacy of EXCEDE to NAXCEL against S. zooepidemicus in pharmacokinetic studies breakpoint is a qualitative value based on a quantitative component.

The MIC is one of the factors taken into consideration by Clinical Laboratory Standards Institute (CLSI) in calculating a breakpoint, but CLSI evaluates other criteria as well. These include results of clinical trials involving different populations of the target pathogen, the range of MIC values for various population samples, and the pharmacokinetic properties of the antimicrobial (e.g., its distribution at the site of infection). A breakpoint is relevant only for a specific pathogen, antimicrobial, and organ system. The CLSI breakpoint for ceftiofur against lower respiratory tract infections caused by S. zooepidemicus is 0.25 µg/mL. The MIC<sub>90</sub> of ceftiofur against S. zooepidemicus is 0.12 µg/mL. Based on the MIC<sub>90</sub> and other relative factors, the FDA’s Center for Veterinary Medicine (CVM) chose 0.2 µg/mL as a clinical breakpoint for comparing clinical efficacy of EXCEDE to NAXCEL against S. zooepidemicus in pharmacokinetic studies.

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Ceftiofur MIC values for *S. zooepidemicus* were determined prior to the 1994 approval for use in horses. Additional MIC testing was performed for contemporaneous isolates of *S. zooepidemicus*. The MIC\(_{50}\) value for isolates collected from 2005-2007 averaged ≤0.12 μg/mL (range ≤0.015 to 0.5 μg/mL),\(^b\) well below the current breakpoint. The MIC values have remained unchanged since the approval of NAXCEL. Breakpoints have been determined in horses for only a relatively few antimicrobials and specific equine infections. Ceftiofur has the advantage of having an equine-specific clinical breakpoint against *S. zooepidemicus*, the most important bacterial respiratory pathogen of horses. While breakpoints are not a guarantee of clinical efficacy, they are a strong predictor of a favorable treatment response. Breakpoints derived from human data or other animal species are not reliable indicators of treatment efficacy in horses when antimicrobials are used off-label.

**Plasma concentration-over-time study**

A study was conducted to compare the pharmacokinetic (PK) behavior in horses that were given EXCEDE in 2 doses administered 96 hours (4 days) apart versus horses given 10 doses of NAXCEL, the non-sustained-release ceftiofur formulation, at 24-hour intervals. Both formulations were administered at their recommended IM doses of 6.6 mg/kg for EXCEDE and 2.2 mg/kg for NAXCEL. There were 12 horses in each of the respective test groups. Figure 1 shows the mean plasma concentrations at each time point for the respective formulations and their relation to the FDA clinical breakpoint of 0.2 μg/mL.

Both formulations reached a plasma concentration greater than clinical breakpoint and maximum plasma concentration (C\(_{\text{max}}\)) in <2 hours after IM administration of the initial dose. The C\(_{\text{max}}\) for EXCEDE was 0.78 μg/mL versus 4.31 μg/mL for NAXCEL, a 5-fold difference. The area under the concentration-over-time curve (AUC\(_{0-\infty}\)), the measure of total drug exposure extrapolated to 0-10 days, was

\(^{157}\) μg•hr/mL for EXCEDE versus 353 μg•hr/mL for NAXCEL, a 2-fold difference. The time that plasma concentrations of DFC, the active metabolite of ceftiofur, remained above the clinical breakpoint of 0.2 μg/mL for *S. zooepidemicus* for 10 days (240 hours), although plasma concentration for EXCEDE is maintained at a more consistent level. (NOTE: The y-axis is a logarithmic scale and does not show a linear relationship in plasma concentration values.)

In the case of time-dependent antimicrobials such as ceftiofur, the goal of therapy is to maximize time >MIC. There is no therapeutic benefit if the C\(_{\text{max}}\) or AUC of NAXCEL is multi-fold higher than that for EXCEDE as long as the plasma concentrations remain >MIC.

The key finding of the PK studies comparing the sustained-release and non-sustained-release formulations was that the plasma concentration of EXCEDE remained above the MIC for *S. zooepidemicus* throughout the 10-day course of therapy and that it did so with only 2 IM doses versus 10 doses for NAXCEL. Importantly, other studies have shown that concentrations of ceftiofur equivalents in lung tissue at 12 and 24 hours are only slightly less than plasma concentration in the same horses.\(^c\) Thus, ample distribution of the drug to the site of lower respiratory-tract infection occurs following IM administration.

\(^{a}\)Data on file. Study 1552N-60-06-209, Zoetis Inc.
How EXCEDE contributes to judicious antimicrobial use

Judicious use of antimicrobials consists of their conservative application to maximize therapeutic efficacy, to minimize adverse effects on animal or human health, and to minimize potential for emergence of resistant bacterial strains. Specific guidelines for judicious use have been issued by the American College of Veterinary Internal Medicine. In general terms, judicious use is the selection of the most appropriate drug, dose, dosing interval, and duration of therapy, and avoidance of inappropriate or excessive use of antimicrobials. Because of its formulation and proven antibacterial profile for *S. zooepidemicus*, EXCEDE supports judicious antimicrobial use.

Overdosing of non-sustained-release ceftiofur (NAXCEL) has been a long-standing practice enabled by the drug’s exceptional safety. In non-sustained-release form, ceftiofur has a short half-life and is rapidly excreted, necessitating daily dosing. These factors have led to 3 forms of non-judicious use – administration by the IV route to achieve immediate therapeutic blood levels, deliberate overdosing, and administration at shorter than recommended intervals on the erroneous assumption that efficacy will be enhanced by elevating blood plasma levels well above the MIC level. For a time-dependent antimicrobial such as ceftiofur, there is no therapeutic benefit to any of these practices. In fact, enterocolitis due to alterations in intestinal flora has been observed when ceftiofur is given at excessive dose or frequency. In addition, IV administration results in a more rapid decline in plasma concentrations (to <MIC at <20 hours) and a reduced AUC compared to what occurs following IM administration. All of these consequences are avoided by the sustained-release formulation in EXCEDE.

Gradual antimicrobial release occurs only when EXCEDE is given by the IM route, and sustained-release above MIC for 4 days following a single dose precludes the need for excessive dose volume or frequency.

Efficacy

EXCEDE was evaluated in a pivotal field efficacy study involving 373 horses ranging in age from 4 months to 20 years at 7 study sites in the U. S. and 2 in Canada. All horses evaluated in the study had naturally acquired LRT disease involving laboratory-confirmed *S. zooepidemicus* or other relevant bacterial pathogens. Enrollment was based on presence of fever >100.6°F and a scoring system (0=normal, 1 to 2 or 3 for overt clinical signs) for each of 4 clinical signs: depression, dyspnea, coughing, and nasal discharge. Horses received 2 IM injections of either EXCEDE at a dose of 6.6 mg/kg (n=278) or sterile saline placebo (n=95) administered 96 hours apart in a randomized, controlled, blinded format. EXCEDE and placebo were administered in an approximate 3:1 ratio. Clinical cure was defined as temperature ≤100.6°F and clinical score ≤1 nasal discharge and cough and clinical score of zero for depression and dyspnea on treatment days 15 and 25. This resulted in 136 EXCEDE-treated cases and 57 placebo-treated cases for statistical analysis.

Horses with moderate to severe LRT disease involving *S. zooepidemicus* had a day 25 clinical cure rate of 69.12%, significantly better (p=0.0215) than the 31.58% rate for placebo-treated horses.

Iowa test site clinical trial experience

The field trial conducted by one of the authors (Dr. McClure) at the Iowa test site was a demonstration of product efficacy under clinically challenging conditions. All horses were yearlings obtained from Midwestern sale barns, then shipped to a single site where they were monitored for LRT disease during a 10-week period from November to January. The stress of transportation, commingling and close confinement, and exposure to cold, wet weather virtually ensured an outbreak of clinical pneumonia in a population of young, susceptible horses. A total of 60 horses that met the inclusion criteria were enrolled, 43 (71.7%) of which were positively cultured for *S. zooepidemicus*. Diagnosis was based on

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Data on file. Study 1552N-60-08-218, Zoetis Inc.

Data on file. Study 1153C-60-06-208, Zoetis Inc. 136.
clinical evaluation of depression, dyspnea, cough, nasal discharge, and fever, confirming that each enrolled horse was a valid test animal for the randomized, blind study.

Three EXCEDE-treated horses were removed from the study due to conditions other than LRT disease, and were not counted in the efficacy determination. The remaining EXCEDE-treated horses had a 93% (39/42) clinical cure rate, based on study completion without requiring additional therapy, versus a 47% (7/15) rate in placebo horses. Treatment efficacy against LRT disease caused by *S. zooepidemicus* was noteworthy in view of the fact that culture results indicated mixed infections in a majority of the horses, all of which were treated with EXCEDE given as monotherapy. In clinical practice, horses with pneumonia would often be treated with a β-lactam antimicrobial such as ceftiofur given as co-therapy with a drug from another antimicrobial class such as an aminoglycoside or an anti-inflammatory agent.¹

Adverse post-administration effects were evaluated daily. Injection-site reactions were absent in most horses and clinically insignificant in the others. The 2 doses of EXCEDE were administered in opposite sides of the neck, left then right.

The most severe post-treatment sequelae were lesions resulting from collection of the transtracheal specimens. Localized inflammation was sometimes observed at the site of tracheal centesis as a result of withdrawal of infectious material. The relatively low dose volume administered to the yearling horses may explain the very minimal incidence of injection-site reactions.

**Safety**

Safety of EXCEDE was evaluated in multiple studies, including the pivotal field efficacy study described above. In addition, studies were conducted that specifically evaluated systemic dose tolerance, gastrointestinal safety, and local injection-site tolerance in horses.

**Field safety**

A total of 120 adverse events (AEs) were reported in 104 of the 373 study animals; however, the majority of these were unrelated to treatment. For example, 6.6% of the treated horses (15% of those with AEs) experienced sequelae associated with transtracheal centesis to obtain aspirates for diagnostic evaluation.² Five horses treated with EXCEDE died or were euthanized during the study, 4 with severe respiratory disease and one with cranial mesenteric arteritis, Clostridium perfringens colitis, and bronchopneumonia that was observed prior to treatment. Visible injection-site reactions were the most commonly reported adverse event (AE), occurring in 10 of 278 (3.6%) of horses given EXCEDE and 1 of 95 (1.1%) of placebo horses. These resolved in 1 to 20 days. Diarrhea or soft (“cowpie”) stools were observed in 25 of 278 (9%) EXCEDE-treated horses and 7 of 95 (7%) placebo horses. The diarrhea or soft stools resolved in 1 to 6 days with minimal or no treatment.³

**Gastrointestinal safety**

The gastrointestinal (GI) safety of EXCEDE given repeatedly at higher than recommended doses was evaluated in 4 groups of 8 horses each. EXCEDE was administered 6 times (3 times the number of recommended doses per course of therapy) to respective groups at IM doses of 6.6 mg/kg (1x), 13.2 mg/kg (2x) or 19.8 mg/kg (3x).

A control group was given sterile saline by IM injection. All doses of EXCEDE were systemically well tolerated. No clinical observations or laboratory findings indicated that GI adverse events resulted from EXCEDE, even when repeated doses were given in multiple-dose sizes.

**Injection-site tolerance**

Injection-site reactions were a special focus of the EXCEDE safety studies due to the product’s unique CCFA-in-oil formulation. In addition to the safety component of the field efficacy study noted above, injection-site tolerance was evaluated in separate, controlled studies.

¹Data on file. Study 1552N-60-06-209, Zoetis Inc.
²Data on file. Study 11563C-60-06-208, Zoetis Inc.
In the first study, injection-site reactions were compared in horses given 10 doses of NAXCEL at daily intervals at the recommended dose of 2.2 mg/kg, or EXCEDE given in 2 doses 96 hours apart at 0.5, 1, or 2 times the recommended dose of 6.6 mg/kg. Twelve adult horses were randomly assigned to each group and were evaluated daily for up to 15 days after the final dose. The NAXCEL formulation of ceftriaxone sodium produced no injection-site edema on any study day. The EXCEDE formulation of CCFA in oil was generally well tolerated at all dose sizes but was associated with mild, local reactions at the injection site. At the recommended dose of 6.6 mg/kg, EXCEDE produced edema at the injection site 1 to 5 days after injection. These reactions averaged ≤0.4 cm³ at day 3 and decreased to <0.2 cm³ by study day 15 (10 days after the second injection). Injection-site reactions tended to be more pronounced when dose volume was ≥10 mL or as a consequence of the second dose. Localized reactions occasionally produced edema and neck stiffness at the injection site. Two horses treated with EXCEDE had small (<0.3 cm³), firm injection-site reactions that did not completely resolve by day 15. Adverse health effects, erythema, heat, tissue necrosis, or drainage from the injection sites were not observed. Histopathology evaluations of injection-site reactions in necropsied horses in the group given 6.6 mg/kg in some cases revealed discoloration in the muscle or fascia and variable eosinophilic inflammation, granulomas, and fibrosis. In the second study, a more rigorous test of injection-site reactions, groups of 8 horses each were given 6 consecutive doses at 96-hour intervals of saline placebo or EXCEDE at 1, 2, and 3 times the recommended dose of 6.6 mg/kg. Mild, local reactions at the injection sites were commonly observed within 2 days after injection in horses given 6.6 mg/kg, including in all horses after the second dose. The most common reaction was edema, firmness at the injection site, mild localized sensitivity, and stiffness of the neck. In horses given the recommended dose, edema was generally greatest on day 6 (2 days after the second injection. Edema resolved within 3 days, and other manifestations within 1 to 18 days. At the conclusion of the 6-dose series, histopathology evaluations in some horses given the 6.6 mg/kg dose revealed mild to moderate local eosinophilic inflammation with variable fibrosis, granulomas, and in some cases hemorrhage. No erythema, necrosis, drainage, or tissue damage was observed.

Overall results of the injection-site safety studies indicate that mild to moderate local reactions characterized by localized edema, firmness, and sensitivity occurred in the majority of horses given EXCEDE at the recommended dose of 6.6 mg/kg. Visual identification of injection-site reactions was generally possible for 24 to 48 hours after injection, and thereafter only by palpation. The reactions usually resolved within 7 days of the second injection.

**Drug testing interference**

In an independent study conducted by investigators at Ohio State University and the University of California-Davis, EXCEDE was evaluated to determine if it would mimic the presence of prohibited drugs in exercised horses. A positive result would indicate that EXCEDE could interfere with the ability to correctly identify these compounds in horses following maximal or submaximal exercise. Four thoroughbred horses were used as test animals. Blood and urine samples were obtained from each horse at 5 intervals: 24 hours before administration of EXCEDE (baseline), and 24, 48, 72, and 96 hours after administration. Horses were exercised immediately before sample collection at 3 intervals: 24 hours before administration of EXCEDE and 24 and 72 hours after administration. Exercise sessions consisted of 3 20-minute incremental treadmill workouts designed to simulate race training. Samples were analyzed for the presence of 850 compounds, including prohibited substances identified by the California Horse Racing Board, the Fédération Équestre Internationale, and the U. S. Equestrian Federation. These included anabolic steroids, corticosteroids,
diuretics, non-steroidal anti-inflammatory drugs, narcotic analgesics, local anesthetics, stimulants, and depressants. Immunoassay screening of the samples was followed by confirmatory testing using gas or liquid chromatography with mass spectrometry. This combination of technologies is considered to be 99.9% reliable in detecting a target analyte, and meets racing industry standards for forensic testing of horses at Graded Stakes races. The analyses did not detect the presence of any prohibited substance in any of the 20 blood or 20 urine samples. Pfizer is one of the few manufacturers to proactively evaluate a new equine product for its potential to interfere with drug testing.

Tissue concentration study

A study was conducted to determine tissue concentrations of DFC, the principal active metabolite of CCFA, in horses following parenteral administration of EXCEDE at the recommended dose of 6.6 mg/kg. EXCEDE was given in 2 doses 4 days apart, and DFC tissue concentrations were measured at 24, 48, 72, and 96 hours after the second dose. Each of 16 healthy horses was randomly allocated to 1 of 4 treatment groups, with 2 males and 2 females assigned to each group. One group was euthanized at each post-treatment interval. In addition to plasma, the tissue and body fluid samples shown in Table 1 were collected and DFC concentrations in parts-per-million were determined by an independent laboratory.

Except for the skin/subcutaneous fat samples, the mean concentration of DFC declined somewhat in all tissue samples from the 24-hour to the 96-hour intervals. The results indicated that DFC concentrations were achieved at multiple sites in the equine host and that DFC concentrations at 96 hours

Table 1 – Ceftiofur concentration in equine tissue following a single dose of EXCEDE®

<table>
<thead>
<tr>
<th>Tissue*</th>
<th>24 hrs</th>
<th>48 hrs</th>
<th>72 hrs</th>
<th>96 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>0.022</td>
<td>0.018</td>
<td>0.018</td>
<td>0.013</td>
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<tr>
<td>Lung</td>
<td>0.352</td>
<td>0.368</td>
<td>0.252</td>
<td>0.269</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.480</td>
<td>1.115</td>
<td>0.875</td>
<td>0.794</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.456</td>
<td>0.251</td>
<td>0.260</td>
<td>0.297</td>
</tr>
<tr>
<td>Lymph node</td>
<td>0.326</td>
<td>0.230</td>
<td>0.193</td>
<td>0.204</td>
</tr>
<tr>
<td>Lung</td>
<td>0.352</td>
<td>0.368</td>
<td>0.252</td>
<td>0.269</td>
</tr>
<tr>
<td>Liver</td>
<td>1.227</td>
<td>1.041</td>
<td>0.697</td>
<td>0.605</td>
</tr>
<tr>
<td>Fat</td>
<td>0.303</td>
<td>0.313</td>
<td>0.188</td>
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<td>Skin with fat</td>
<td>0.253</td>
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<tr>
<td>Synovial fluid</td>
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<td>0.351</td>
<td>0.214</td>
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<td>Kidney</td>
<td>1.480</td>
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<td>Uterus</td>
<td>0.456</td>
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<td>0.260</td>
<td>0.297</td>
</tr>
</tbody>
</table>

Mean DFC concentration (ppm) at post-treatment interval

CSF = cerebrospinal fluid; DFC = desfuroylceftiofur; ppm = parts per million.
*Uterine samples were obtained from 2 horses; all other samples were obtained from 4 horses.

Zoetis does not endorse the use of EXCEDE other than for the label indication.
were maintained at levels ≥50% of the 24-hour level in all tissues evaluated. During the interval from 24 to 96 hours, the mean DFC concentration in the lung declined by 23.6%, from 0.352 ppm to 0.269 ppm. The relative concentration of DFC in lung tissue was much more prolonged over the 96-hour EXCEDE post-treatment period compared to what occurs with a non-sustained-release formulation of ceftiofur. In a prior study, the mean lung concentration of DFC declined by nearly 90% from 1 to 24 hours in adult horses (n=12) after IM administration of NAXCEL.16

Clinical perspectives

S. zooepidemicus is universally present as part of the normal flora of the equine upper respiratory tract. This organism becomes pathogenic when it invades the lower respiratory tract as a secondary, bacterial cause of pneumonia. S. zooepidemicus is the most frequently isolated bacterial pathogen in equine lower respiratory tract infections.8 Ceftiofur and its primary metabolite DFC are both highly active against Streptococcus spp, as well as various other Gram-positive and Gram-negative pathogens.1,2

As one of the few antimicrobials and the only cephalosporin licensed for equine use, ceftiofur has the additional advantages of low toxicity, a high margin of safety, and a long history of successful use in horses as a non-sustained-release formulation given at daily intervals (NAXCEL). These beneficial characteristics have invited administration of ceftiofur at higher-than-recommended doses or redosing at shorter intervals than recommended – 2 forms of non-judicious, extra-label use. Not only does this practice have no impact on efficacy of a time-dependent antimicrobial such as ceftiofur, but it potentially contributes to onset of antimicrobial-induced enterocolitis. The goal of therapy with a concentration-dependent antimicrobial (e.g., fluoroquinolones, aminoglycosides) is to maximize the intensity of exposure, or Cmax. There is no benefit to excess dosing of a time-dependent antimicrobial such as ceftiofur, where the goal of therapy is to maximize time >MIC. The EXCEDE sustained-release formulation ensures gradual antimicrobial release that minimizes abrupt increases in plasma levels resulting from an excess dosage, a form of non-judicious use.

The sustained-release feature of EXCEDE is made possible by the formulation of CCFA suspended in a purified oil vehicle. The oil-based EXCEDE formulation creates a depot in situ that has some potential for injection-site reactions. The low rate of injection-site reactions in the clinical field trial (3.6%) was in contrast to higher rates in the injection-site tolerance studies. The likely explanation is that the latter studies involved adult horses given large doses up to 20 mL. Many of the field trial horses were small or younger horses, for example the yearlings used at the Iowa test site. These animals required relatively smaller doses that were not as conducive to injection-site reactions. The collective experience from the safety studies suggests that injection-site reactions are more frequent when the dosage size is ≥10 mL.

As a sustained-release formulation of ceftiofur, EXCEDE overcomes the most important limitation of the non-sustained-release formulation, namely the need for daily dosing. Studies show that 2 injections of EXCEDE given 4 days apart maintain blood levels above the MIC for a 10-day course of treatment (Figure 1), and that this regimen is as clinically effective as multiple daily injections of non-sustained-release ceftiofur. This efficacy profile eliminates the inconvenience of daily dosing that is a principal cause of non-compliance, and discourages overdosing that often accompanies the use of non-sustained-release ceftiofur formulations. As the field efficacy trial demonstrated, avoidance of excessive dosing is accomplished without compromising the efficacy of EXCEDE. The administration of only 2 doses for a 10-day course of therapy means that treatment can be easily administered by the attending veterinarian, helping ensure full compliance with the recommended dosing guidelines. Eliminating the need for daily injections also minimizes the pain and relationship disruption between horse and handler that can result from repeated injections.


**Important Safety Information**

As with all drugs, the use of EXCEDE is contraindicated in animals with known allergy to ceftiofur or to the β-lactam group (penicillins and cephalosporins) of antimicrobials. Do not use EXCEDE in horses intended for human consumption. The administration of antimicrobials in horses under conditions of stress may be associated with diarrhea, which may require appropriate veterinary therapy. Though safe in cattle when properly administered, inadvertent intra-arterial injection is possible and fatal. EXCEDE has a pre-slaughter withdrawal time of 13 days in cattle. Do not use in calves to be processed for veal. For complete details, refer to the full prescribing information.

**Acknowledgement**

The authors acknowledge the contribution of Mark Dana of Scientific Communications Services in the writing and editing of this report.

**References**

EXCEDE®
(Ceftiofur Crystalline Free Acid)
Sterile Suspension

For intramuscular injection in the horse.

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 cephalosporin antibiotic active against Gram-positive and Gram-negative bacteria including β-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal, in vitro, resulting from inhibition of cell wall synthesis. Each mL of this ready-to-use sterile suspension contains ceftiofur crystalline free acid equivalent to 200 mg ceftiofur, in a caprylic/capric triglyceride (Miglyo®) and cottonseed oil based suspension.

Figure 1. Structure of ceftiofur crystalline free acid:

Chemical name of ceftiofur crystalline free acid:
7-[[2-(2-Amino-4-thiazolyl)-2-[(methoxyimino)acetyl]amino]-3-[[2-(furanylcarbonyl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene 2-carboxylic acid

INDICATION
EXCEDE Sterile Suspension is indicated for the treatment of lower respiratory tract infections in horses caused by susceptible strains of Streptococcus equi ssp. zooepidemicus.

Dosage and Administration
Shake well before using. Administer two intramuscular injections to horses, 4 days apart, at a dose of 3.0 mg/lb (6.6 mg/kg). A maximum of 20 mL per injection site may be administered. Therapeutic drug concentrations are maintained for 6 days after the second injection (or a total of 10 days from the beginning of treatment) against Streptococcus equi ssp. zooepidemicus.

Table 1. Dosing Schedule for EXCEDE Sterile Suspension

<table>
<thead>
<tr>
<th>Weight (lb)</th>
<th>Dose Volume (mL)</th>
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</thead>
<tbody>
<tr>
<td>100</td>
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<tr>
<td>200</td>
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<td>900</td>
<td>13.5</td>
</tr>
<tr>
<td>1000</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Table 2. Number of Horses with Adverse Reactions During the Field Study with EXCEDE

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EXCEDE (n=278)</th>
<th>Placebo (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea/Soft Stool</td>
<td>25 (9%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Injection Site Swelling</td>
<td>10 (4%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

The material safety data sheet (MSDS) contains more detailed occupational safety information. To obtain a material safety data sheet, please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

CLINICAL PHARMACOLOGY
Ceftiofur is a beta-lactam antibiotic from the cephalosporin class. Beta lactams exert their inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins, which are essential for synthesis of the bacterial wall. Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder) or ceftiofur crystalline free acid (EXCEDE Sterile Suspension) is rapidly metabolized to desfuroylceftiofur, the primary metabolite with antimicrobial activity. Two intramuscular injections of EXCEDE Sterile Suspension at a dose of 6.6 mg/kg body weight in the horse provide concentrations of ceftiofur and desfuroylceftiofur related metabolites in plasma above the therapeutic target of 0.2 µg/mL for the entire 96 hour (4 day) dosing interval and for 6 days after the second injection (or a total of 10 days from the beginning of treatment) (see Figure 2 and Table 3).

Figure 2. Average plasma concentration of ceftiofur and desfuroylceftiofur related metabolites in horses following the intramuscular administration of either EXCEDE Sterile Suspension at a dose of 3.0 mg/lb (6.6 mg/kg) administered twice at a 96 hour interval or NAXCEL Sterile Powder at a dose of 1.0 mg/lb (2.2 mg/kg BW) once daily for 10 consecutive days.

CONTRAINdications
EXCEDE Sterile Suspension is contraindicated in horses with known allergy to ceftiofur or to β-lactam (penicillins and cephalosporins) group antimicrobials. Due to the extended exposure in horses, based on the drug’s pharmacokinetic properties, adverse reactions may require prolonged care.

WARNINGS
Not for use in humans. For use in animals only. Keep this and all drugs out of reach of children. Consult a physician in case of accidental human exposure.

Do not use in horses intended for human consumption.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposure to such antimicrobials, including ceftiofur, may elicit mild to 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 clothing. Sensitization of the skin may be avoided by wearing protective gloves. Persons with a known sensitivity to penicillins or cephalosporins should avoid exposure to this product. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g. skin rash, hives, difficult breathing) seek medical attention.

PRECAUTIONS
Prescribing antibacterial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the treated animal and may increase the risk of development of drug-resistant animal pathogens.

The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that can be fatal. If acute diarrhea is observed, additional doses of EXCEDE should not be administered and appropriate therapy should be initiated.

Due to the extended exposure in horses, based on the drug’s pharmacokinetic properties, adverse reactions may require prolonged care. EXCEDE is slowly eliminated from the body, with approximately 17 days needed to eliminate 97% of the dose from the body. Animals experiencing adverse reactions may need to be monitored for this duration of time.

The use of ceftiofur has not been evaluated in horses less than 4 months of age and in breeding, pregnant, or lactating horses. The long term effects on injection sites have not been evaluated.

ADVERSE REACTIONS
The injection of EXCEDE Sterile Suspension in the horse may cause firmness, swelling, sensitivity, and/or edema at the injection site (see ANIMAL SAFETY).

A total of 373 horses of various breeds, ranging in age from 4 months to 20 years, were included in the field study safety analysis. Adverse reactions reported in horses treated with EXCEDE and the placebo control are summarized in Table 2.

Injection site swelling (edema) was reported in 10 of 278 (3.6%) EXCEDE-treated horses and 1 of 95 (1%) of the placebo-treated horses. Of the 10 EXCEDE-treated horses with injection site swelling, 8 horses had swellings of 4 cm or less in diameter, one horse had a 10 cm diameter swelling and one horse had injection site reactions to both injections measuring 25 x 12 cm each. The injection site reactions in EXCEDE-treated horses resolved over 1 to 20 days.

At least one episode of diarrhea, loose, soft, or cowpie stools were observed in 25 of 278 (9%) of the EXCEDE-treated horses and 7 of 95 (7%) of the placebo-treated horses. The duration of episodes in EXCEDE-treated horses ranged from a single observation of loose stool to observations lasting 6 days. All cases were self-limiting and resolved with minimal (a single dose of loperamide) or no treatment.
Table 3. Pharmacokinetic parameters measured after either two intramuscular injections of EXCEDE Sterile Suspension at a dose of 3.0 mg/lb (6.6 mg/kg) BW at a 96 hour interval or NAXCEL Sterile Powder at a dose of 1.0 mg/lb (2.2 mg/kg) BW once daily for 10 consecutive days are summarized in the following table.

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>CCFA-SS at 6.6 mg/kg BW administered twice 96 h apart (Mean ± SD; n=12)</th>
<th>Cefiotur sodium at 2.2 mg/kg BW once daily for 10 days (Mean ± SD; n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC∞(µg-h/mL)</td>
<td>157 (19.1)</td>
<td>353 (44.9)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>262 (29.0)</td>
<td>ND</td>
</tr>
<tr>
<td>Dose 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.78 (0.19)</td>
<td>2.0 (3.3)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>21.6 (5.8)</td>
<td>15.6 (6.3)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>16.0 (3.1)</td>
<td>1.0 (0.24)</td>
</tr>
<tr>
<td>Cmin (µg/mL)</td>
<td>4.31 ± 0.78</td>
<td>3.99 (1.23)</td>
</tr>
</tbody>
</table>

Table 4. Activity of EXCEDE Against Pathogens Isolated from Horses Treated With EXCEDE in Field Studies in the U.S. During 2007-2008

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Treatment Outcome</th>
<th># of Isolates</th>
<th>Time of Sample Collection</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; µg/mL</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; µg/mL</th>
<th>MIC Range µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Respiratory Tract Infection</td>
<td>Streptococcus equispor. zooepidemicus</td>
<td>Success</td>
<td>93</td>
<td>Pre-Treatment</td>
<td>0.06</td>
<td>0.12</td>
<td>0.03-0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Failure</td>
<td>42</td>
<td>Pre-Treatment</td>
<td>0.06</td>
<td>0.25</td>
<td>0.03-0.5</td>
</tr>
</tbody>
</table>

* One horse cultured Staphylococcus aureus (successfully treated) and is not represented in the table.

EXCEDE group were euthanized due to laminitis. Clinical signs of foot pain (stiff front limbs and increased heat and pulses in feet) affected more horses, for a longer period of time, in all EXCEDE-treated groups as compared to the NAXCEL-treated group. The study housing (multi-horse pens on concrete slabs) and diet (free choice alfalfa/grass mix and once a day pellets) may have contributed to the development of foot pain. The prevalence and severity of injection site reactions in EXCEDE-treated horses may also have contributed to the development of a stiff gait. A causal relationship between cefiotur and foot pain could not be definitively determined.

**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 size: 100 mL vial


NADA #141-209, Approved by FDA

www.EXCEDE.com or call 1-866-387-2287

©2007-2009 Pfizer Inc, NY, NY 10017

Revised October 2009 10423900

**MICROBIOLOGY**

Cefiotur is a cephalosporin antibiotic. Like other β-lactam antimicrobials, cefiotur exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial wall. Cefiotur is not active against Pseudomonas spp. and enterococci.

The minimum inhibitory concentration (MIC) values for cefiotur against label-claim pathogens isolated from lower respiratory tract infections in horses enrolled in a 2007-2008 field effectiveness study are presented in Table 4. All MICs were determined in accordance with the Clinical and Laboratory Standards Institute (CLSI) standards.

**EFFECTIVENESS**

A double masked, randomized, negative control, field study evaluated the effectiveness of two intramuscular doses of 6.6 mg/kg EXCEDE Sterile Suspension administered 4 days apart for the treatment of lower respiratory infections caused by Streptococcus equispor. zooepidemicus in the horse. In this study, a total of 278 horses were treated with EXCEDE, and 95 horses were treated with saline injections. One hundred ninety-three horses (136 EXCEDE and 57 saline placebo) were included in the statistical analysis. Therapeutic success was characterized by no worsening of clinical signs at Day 4, clinical improvement at Day 9, resolution of the clinical signs by Day 15, and no recurrence of clinical signs by Day 25 after initial dosing. EXCEDE was superior to the saline control. Table 5 summarizes the clinical success rates obtained 15, 25 days after the first dose.

**ANIMAL SAFETY**

Two studies, a target animal safety (TAS) study and a pharmacokinetic (PK) study (see CLINICAL PHARMACOLOGY section), were conducted to assess the safety of EXCEDE in the horse.

In the TAS study, healthy adult horses received 6 intramuscular (lateral neck) injections of EXCEDE Sterile Suspension at doses of either 3.0 (1X), 6.0 (2X) or 9.0 (3X) mg/lb with a 4 day interval between each injection. In the PK study, there were no treatment related gastrointestinal findings for the three EXCEDE Sterile Suspension treatment groups. In the PK study, one horse treated with 6.0 mg/lb (2X) EXCEDE experienced a mild episode of colic the day after the second injection of EXCEDE. The horse recovered without treatment.

Injection sites were observed in both studies. In both studies, the largest injection volume administered was 20 mL per injection site. There were no observations of erythema, necrosis or drainage at the injection sites in these studies. Firmness, swelling, and/or sensitivity were observed in at least one injection site in all horses treated at the label dose. In the TAS study, injection site reaction measurements ranged from no measurable reaction to 16 x 33 x 1.5 cm. In the PK study, the largest area of edema associated with the injection site ranged from no detectable reaction to a 30 x 36 cm area of edema. Injection site reactions developed within 2 days of injection and resolved within 1-18 days. In the PK study, 2 horses had small areas of firmness that had not resolved at the end of the study (21 days after injection). In both studies, a greater incidence of injection site reactions occurred after the second injection, and in several horses, swelling at the injection site resolved then recurred 1-5 days later.

In the PK study, several horses developed clinical signs consistent with foot pain (stiff in the front limbs when turned in tight circles, and increased pulses and heat to the front feet). One horse in the NAXCEL group and one horse in the 6.0 mg/lb (2X) EXCEDE group were euthanized due to laminitis. Clinical signs of foot pain (stiff front limbs and increased heat and pulses in feet) affected more horses, for a longer period of time, in all EXCEDE-treated groups as compared to the NAXCEL-treated group. The study housing (multi-horse pens on concrete slabs) and diet (free choice alfalfa/grass mix and once a day pellets) may have contributed to the development of foot pain. The prevalence and severity of injection site reactions in EXCEDE-treated horses may also have contributed to the development of a stiff gait. A causal relationship between cefiotur and foot pain could not be definitively determined.

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EXCEDE®
(Ceftiofur Crystalline Free Acid)
Sterile Suspension

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 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 cephalosporin antibiotic active against Gram-positive and Gram-negative bacteria including β-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal, in vitro, resulting from inhibition of cell wall synthesis.

Each mL of this ready-to-use sterile suspension contains ceftiofur crystalline free acid equivalent to 200 mg ceftiofur, in a caprylic/capric triglyceride (Miglyol®) and cottonseed oil based suspension.

Figure 1. Structure of ceftiofur crystalline free acid:

Chemical name of ceftiofur crystalline free acid:
7-[[2-(2-Amino-4-thiazolyl)-2-(methoxyimino)acetyl]amino]-3-[[2-(furylacryloyl)thio]methyl] di-oxo-5-thia-1- azabicyclo[4.2.0]oct-2-ene 2-carboxylic acid

INDICATIONS
EXCEDE Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD), shipping fever, pneumonia associated with Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni in beef, non-lactating dairy, and lactating dairy cattle.

EXCEDE Sterile Suspension is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with M. haemolytica, P. multocida, and H. somni.

EXCEDE Sterile Suspension is also indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with Fusobacterium necrophorum and Porphyromonas levii in beef, non-lactating dairy, and lactating dairy cattle.

DOSEAGE
Treatment of BRD and bovine foot rot

Administer as a single subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) to cattle at a dosage of 3.0 mg ceftiofur equivalents (CE)/lb (6.6 mg CE/kg) body weight (BW) (1.5 mL sterile suspension per 100 lb BW).

In beef and non-lactating dairy cattle, EXCEDE Sterile Suspension may also be administered as a single subcutaneous injection in the middle third of the posterior aspect of the ear at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW).

Most animals will respond to treatment within three to five days. If no improvement is observed, the diagnosis should be reevaluated.

Control of BRD

Administer as a subcutaneous injection either 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) to beef and non-lactating dairy cattle at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW).

Clinical studies indicate that administration of EXCEDE Sterile Suspension is effective for the control of respiratory disease in beef and non-lactating dairy cattle at “high risk” of developing BRD. One or more of the following factors typically characterizes calves on arrival at high risk of developing BRD:

- Cattle are from multiple farm origins,
- Cattle have had extended transport times (that may have included few if any rest stops),
- Ambient temperature change from origin to arrival of 30° F or more,
- Cattle have had continued exposure to extremely wet or cold weather conditions,
- Cattle have experienced excessive shrink or excessive arrival processing procedures (such as castration, dehorning).

Table 1. Dosing Schedule for EXCEDE Sterile Suspension

<table>
<thead>
<tr>
<th>Weight (lb)</th>
<th>Dose Volume (mL)</th>
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<tbody>
<tr>
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<tr>
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<td>30.0</td>
</tr>
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</table>

ADMINISTRATION FOR THE MIDDLE THIRD OF THE EAR
- Shake well before using. Please read the complete package insert before administering EXCEDE Sterile Suspension subcutaneously in the posterior ear of cattle.
- Deposit as a single subcutaneous injection in the middle third of the posterior aspect of the ear, avoiding all blood vessels. See Figures 2 and 3.
- Adjust the needle insertion point to avoid any blood vessels, previous implants, ear tags or ear tag holes. Do not administer intra-arterially.
- Deliver the entire contents of the syringe.
- When administered correctly, a subcutaneous bleb of EXCEDE Sterile Suspension will appear.
- When withdrawing the needle, apply pressure to the needle insertion point, and massage toward the base of the ear.

Figure 2. Subcutaneous administration of EXCEDE Sterile Suspension in the middle third of the posterior aspect of the ear.

ADDITIONAL RECOMMENDATIONS
- Cattle with clinical signs of respiratory disease may benefit from simultaneous administration of an intra-arterial injection of EXCEDE Sterile Suspension and a subcutaneous injection of EXCEDE Sterile Suspension. Clinical evaluation is essential to determine whether a subcutaneous injection alone is sufficient in all cases.

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<td>4.5</td>
</tr>
<tr>
<td>400</td>
<td>6.0</td>
</tr>
<tr>
<td>500</td>
<td>7.5</td>
</tr>
<tr>
<td>600</td>
<td>9.0</td>
</tr>
<tr>
<td>700</td>
<td>10.5</td>
</tr>
<tr>
<td>800</td>
<td>12.0</td>
</tr>
<tr>
<td>900</td>
<td>13.5</td>
</tr>
<tr>
<td>1000</td>
<td>15.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (lb)</th>
<th>Dose Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1100</td>
<td>16.5</td>
</tr>
<tr>
<td>1200</td>
<td>18.0</td>
</tr>
<tr>
<td>1300</td>
<td>19.5</td>
</tr>
<tr>
<td>1400</td>
<td>21.0</td>
</tr>
<tr>
<td>1500</td>
<td>22.5</td>
</tr>
<tr>
<td>1600</td>
<td>24.0</td>
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<tr>
<td>1700</td>
<td>25.5</td>
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<tr>
<td>1800</td>
<td>27.0</td>
</tr>
<tr>
<td>1900</td>
<td>28.5</td>
</tr>
<tr>
<td>2000</td>
<td>30.0</td>
</tr>
</tbody>
</table>

ADMINISTRATION FOR THE BASE OF THE EAR
- Shake well before using. Please read the complete package insert before administering EXCEDE Sterile Suspension subcutaneously at the posterior aspect of the ear where it attaches to the head (base of the ear).
- 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. See Figures 4 and 5.
- Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining this angle. See Figure 4.
- Deliver the entire contents of the syringe.
- Do not administer EXCEDE Sterile Suspension in the neck.

Figure 4. Subcutaneous administration of EXCEDE Sterile Suspension at the posterior aspect of the ear where it attaches to the head (base of the ear).
CONTRAINDICATIONS
As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously found 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 exposures to such antimicrobials, including ceftiofur, may elicit mild to 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 clothing. 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 eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet please call 1-800-366-5289.

Injection of EXCEDE Sterile Suspension into the arteries of the ear is likely to result in sudden death to the animal.

RESIDUE WARNINGS
- Following label use as a single treatment, a 13-day pre-slaughter withdrawal period is required.
- Following label use as a single treatment, no milk discard period is required for this product.
- Use of dosages 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 residue hazards.
- A withdrawal period has not been established for this product in pre-running ruminants.
- Do not use in calves to be processed for veal.

PRECAUTIONS
Following subcutaneous injection in the middle third of the posterior aspect of the ear, thickening and swelling (characterized by aseptic cellular infiltrate) of the ear may occur. As with other parenteral injections, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

Following injection at the posterior aspect of the ear where it attaches to the head (base of the ear), areas of discoloration and 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
Administration of EXCEDE Sterile Suspension into the ear arteries is likely to result in sudden death in cattle. During the conduct of clinical studies, there was a low incidence of acute death (nine out of approximately 6000 animals). Three of these deaths were confirmed to be the result of inadvertent intra-arterial injection. No other adverse systemic effects were noted for either the antibiotic or formulation during any of the clinical and target animal safety studies.

CLINICAL PHARMACOLOGY
Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder), ceftiofur hydrochloride (EXCENEL® RTU Sterile Suspension), or ceftiofur crystalline free acid (EXCEDE Sterile Suspension) is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Subcutaneous administration of ceftiofur crystalline free acid, either in the middle third of the posterior aspect of the ear (middle third of the ear, MOE) of beef and non-lactating dairy cattle, or in the posterior aspect of the ear where it attaches to the head (base of the ear, BOE) of beef, non-lactating dairy, and lactating dairy cattle, provides therapeutic concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma above the lowest minimum inhibitory concentration to encompass 90% of the most susceptible isolates (MIC90) for the labeled BRD pathogens, Pasteurella multocida, Mannheimia haemolytica and Histophilus somni, for generally not less than 150 hours after a single administration (See Figure 6).

The pharmacokinetic parameters for the two subcutaneous locations of injection (MOE and BOE) are found in Table 2. Statistical analyses of the data from these subcutaneous injection sites (MOE and BOE) demonstrate that they are therapeutically equivalent.

Table 2. Pharmacokinetic parameters measured after a single subcutaneous administration of 3.0 mg CE/lb (6.6 mg CE/kg) BW of EXCEDE Sterile Suspension in 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>Beef - Base of the Ear</th>
<th>Dairy Cow - Base of the Ear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg CE/mL)</td>
<td>6.90 ± 2.68</td>
<td>6.39 ± 1.79</td>
<td>4.44 ± 1.65</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>12.0 ± 6.2</td>
<td>19.8 ± 5.81</td>
<td>19.0 ± 8.02</td>
</tr>
<tr>
<td>AUC (µg*hr/ML)</td>
<td>376 ± 66.1</td>
<td>412 ± 67.3</td>
<td>313 ± 85.5</td>
</tr>
<tr>
<td>t1/2, α (h)</td>
<td>183 ± 40.8</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>t1/2, β (h)</td>
<td>246 ± 48.5</td>
<td>218 ± 45.5</td>
<td>205 ± 35.7</td>
</tr>
<tr>
<td>t1/2, nca (h)</td>
<td>623.3 ± 13.5</td>
<td>407 ± 11.2</td>
<td>43.92 ± 9.84</td>
</tr>
</tbody>
</table>

Table 3. Ceftiofur minimum inhibitory concentration (MIC) values* of indicated pathogens isolated from cattle with naturally occurring BPD or foot rot.

<table>
<thead>
<tr>
<th>Indicated pathogen</th>
<th>Year of isolation</th>
<th>Number of isolates</th>
<th>MIC** (µg/mL)</th>
<th>MIC*** (µg/mL)</th>
<th>MIC range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannheimia haemolytica</td>
<td>1996 to 1997</td>
<td>75</td>
<td>0.008</td>
<td>0.015</td>
<td>0.001 to 0.015</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>1996 to 1997</td>
<td>43</td>
<td>0.004</td>
<td>0.004</td>
<td>0.001 to 0.015</td>
</tr>
<tr>
<td>Histophilus somni</td>
<td>1996 to 1997</td>
<td>11</td>
<td>0.004</td>
<td>0.004</td>
<td>0.002 to 0.015</td>
</tr>
<tr>
<td>Fusobacterium nigerorum</td>
<td>2005 to 2007</td>
<td>148</td>
<td>≤0.25</td>
<td>≤0.25</td>
<td>≤0.25 to 1.28</td>
</tr>
<tr>
<td>Porphyromonas levii</td>
<td>2006 to 2007</td>
<td>141</td>
<td>≤0.25</td>
<td>≤0.25</td>
<td>≤0.25 to 16</td>
</tr>
</tbody>
</table>

* The correlation between in vitro susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

Based on pharmacokinetic and clinical effectiveness studies of ceftiofur in cattle, the administration of 3.0 mg CE/lb (6.6 mg CE/kg) BW and the MIC and susceptibility data, the following breakpoints are recommended for BPD pathogens by CLSI.

Table 4. CLSI-accepted interpretive criteria* for ceftiofur against cattle respiratory pathogens.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disk Potency</th>
<th>Zone Diameter</th>
<th>MIC Breakpoint (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannheimia haemolytica</td>
<td>S</td>
<td>I</td>
<td>R</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>S</td>
<td>I</td>
<td>R</td>
</tr>
<tr>
<td>Histophilus somni</td>
<td>S</td>
<td>I</td>
<td>R</td>
</tr>
</tbody>
</table>

* These interpretive criteria are only intended for use when CLSI M1-A2 performance standards are used to determine antimicrobial susceptibility. Interpretive criteria for bovine foot rot pathogens have not been established.

Figure 5. Injection location for the subcutaneous administration of EXCEDE Sterile Suspension at the posterior aspect of the ear where it attaches to the head (base of the ear).

Figure 6. Average plasma concentrations of ceftiofur and desfuroylceftiofur-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 two different locations of the ear, 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.
EFFECTIVENESS
A field dose confirmation study for the treatment of BRD evaluated the effectiveness of single doses of 2.0 and 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW for the treatment of the bacterial component of BRD under field conditions. All treatments were administered subcutaneously in the middle third of the ear at the base of the ear. A total of 3,387 cattle were evaluated on Days 2 to 4, 11 and 28 and were observed on all other study days. The 3.0 mg CE/lb (6.6 mg CE/kg) BW EXCEDE Sterile Suspension dose significantly (p < 0.05) increased Day 14 treatment success rate, defined as not requiring any ancillary treatment and had a normal temperature of ≤ 104°F, normal respirations index, and had no or mild depression on that day.

The effectiveness of a single dose of EXCEDE Sterile Suspension for the control of BRD in feedlot calf disease-location field study. In addition to standard processing on arrival at feedlots, cattle (n=3191) considered to be at high risk for BRD were assigned to one of four arrival treatments, including EXCEDE Sterile Suspension at 2.0 or 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW or a negative control. Effectiveness was based on the incidence of clinical BRD within 28 days following arrival processing. Administration of a single dose of EXCEDE Sterile Suspension administered subcutaneously in the middle third of the ear at arrival processing 3.0 mg CE/lb/day for five consecutive days, approx-imately 8 times the approved dose of EXCEDE Sterile Suspension 3.0 mg CE/kg (6.6 mg CE/kg) BW. Cefiofur administered parenterally had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were administered cefiofur sodium intramuscularly at 0 (vehicle control), 1, 3, 5 mg CE/lb/day, and were monitored for adverse systemic effects, indicating that cefiofur has a wide margin of safety when injected intramuscularly into feeder calves. Local tissue tolerance to subcutaneous injection of EXCEDE Sterile Suspension in the posterior ear of cattle was evaluated in a separate study. In approximately 6,000 tested animals, nine animals have died following injection of EXCEDE Sterile Suspension. All deaths were within 30 minutes of the time of injection. The exact cause was confirmed in three animals. These deaths resulted from inadvertent intravenous administration of the product administration at the base of the ear was established via a pharmacokinetic comparison of the two routes of administration (base of the ear versus jugular vein). Administration of EXCEDE Sterile Suspension in the middle auricular artery. Both heifers collapsed immediately and died within approximately 8 minutes of injection. These data collectively support a 13-day pre-slaughter withdrawal period.

A pivotal milk residue study was conducted in lactating dairy cattle. In this study, cows received a single injection of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Cefiofur residues in tissues were less than the tolerances for cefiofur residues in tissues such as the kidney, liver and muscle by 13 days after dosing. These data collectively support a 13-day pre-slaughter withdrawal period.

The effectiveness of EXCEDE Sterile Suspension for the treatment of bovine foot rot was evaluated in a six-location field effectiveness study. Cattle diagnosed with bovine foot rot were enrolled and treated with EXCEDE Sterile Suspension, administered by subcutaneous injection in the middle third of the ear. Cattle were evaluated 7 days post-treatment for treatment success, which was based on defined decreases in lesion, swelling and lameness scores. A total of 169 beef and dairy cattle were evaluated in this study, and significant statistical significance (p = 0.0054) in treatment success for EXCEDE-treated cattle (58.4%) compared to vehicle-treated control cattle (13.2%).

ANIMAL SAFETY
After parental administration, cefiofur crystalline free acid (as EXCEDE Sterile Suspension), cefiofur sodium and cefiofur hydrochloride are rapidly metabolized to desfuroylceftiofur. Therefore, studies conducted with cefiofur sodium are adequate to evaluate the systemic safety of EXCEDE Sterile Suspension. Results from a five-day tolerance study conducted with cefiofur sodium indicated that cefiofur was well tolerated at 25 mg CE/lb/day for five consecutive days, approxim-ately 8 times the approved dose of EXCEDE Sterile Suspension 3.0 mg CE/kg (6.6 mg CE/kg) BW. Cefiofur administered parenterally had no adverse systemic effects. There were no adverse systemic effects, indicating that cefiofur has a wide margin of safety when injected intramuscularly into feeder calves. Local tissue tolerance to subcutaneous injection of EXCEDE Sterile Suspension in the posterior ear of cattle was evaluated in a separate study. In approximately 6,000 tested animals, nine animals have died following injection of EXCEDE Sterile Suspension. All deaths were within 30 minutes of the time of injection. The exact cause was confirmed in three animals. These deaths resulted from inadvertent intravenous administration of the oil-based suspension into one of the two major auricular (ear) arteries. Intra-arterial injection at this location resulted in direct administration of the oil-based formulation into the arterial blood supply of the brain resulting in embolism and death. Since intra-arterial injection was confirmed in three animals that died following injection of EXCEDE Sterile Suspension, the consequences of purposeful intra-arterial injection of EXCEDE Sterile Suspension in the middle third of the ear at the base of the ear was established via a pharmacokinetic comparison of the two routes of administration (base of the ear versus jugular vein). Intra-arterial injection of EXCEDE Sterile Suspension in the ear will result in death and must be avoided.

Since subcutaneous injection in the ear may potentially result in inadvertent intravenous administration of injectable product, the consequences of purposeful intravenous injection of EXCEDE Sterile Suspension were investigated in feeder cattle. Two heifers (body weight 42x344) were injected intra-arterially with 3.0 mg CE/lb (6.6 mg CE/kg) BW bolus dose of EXCEDE Sterile Suspension in the jugular vein and were monitored for adverse effects following injection. One steer and one heifer had transient (2 to 5 minutes) increases in heart rate without any other untoward signs in these or the other cattle. Intravenous injection of EXCEDE Sterile Suspension is an unacceptable route of administration.

Subcutaneous administration in the middle third of the posterior aspect of the ear
A study was designed and conducted to specifically address tissue tolerance in cattle when EXCEDE Sterile Suspension was administered as a single subcutaneous injection into the posterior ear of cattle at the recommended dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Results from this study indicate that EXCEDE Sterile Suspension into the middle第三 of the posterior aspect of the ear of cattle is well tolerated and characterized by a biphasic thickening of the ear. The initial increase in thickness is attributed to tissue/fascia) and four of six cows had discoloration of tissue dusol and posterior to the ear canal on the carcass. In addition to discoloration, tan nodules and a milky white fluid exudate were also present at the sectioned surface.

TISSUE RESIDUE DEPLETION
A radiolabeled residue metabolism study established tolerances for cefiofur residues in cattle kidney, liver and muscle. A separate study established the tolerance for cefiofur residues in milk. The tolerances for cefiofur residues are 0.4 ppm in kidney, 2.0 ppm in liver, 1.0 ppm in muscle and 0.1 ppm in milk.

A pivotal tissue residue decline study was conducted in dairy cattle. In this study, cows received a single injection of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Cefiofur residues in tissues were less than the tolerances for cefiofur residues in tissues such as the kidney, liver and muscle by 13 days after dosing. These data collectively support a 13-day pre-slaughter withdrawal period.

A pivotal milk residue study was conducted in lactating dairy cattle. In this study, cows received a single injection of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Cefiofur residues in milk were less than tolerances at all time points after treatment. These data collectively support 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 size: 100 mL vial


NADA #141-209, Approved by FDA

Revized October 2009

10423900

www.EXCEDE.com or call 1-866-387-2287

Distributed by Pfizer Inc., NY, 10017

Pharmacia & Upjohn Company