Clinical trial of client preferences, compliance and satisfaction following treatment of equine bacterial infections with oral trimethoprim-sulfonamide or injectable EXCEDE® (ceftiofur crystalline free acid) Sterile Suspension

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KEY POINTS

• Attending veterinarians gave their clients the choice of two anti-infective (AIF) treatments that represented a difference in cost and convenience: trimethoprim-sulfonamide (TMS) given orally by the client b.i.d. for 10 days or two doses of ceftiofur crystalline free acid (EXCEDE®, Zoetis LLC) given intramuscularly (IM) by the veterinarian four days apart.

• Pretreatment cost estimates for a 1,000-pound horse were $56.66 for TMS versus $124.63 for EXCEDE. Despite the wide variance in pretreatment cost estimates, 93.1% of clients selected EXCEDE (n=122) versus TMS (n=9).

• Compliance at Day 4 was 100% (122/122) for the EXCEDE horses and 75% (6/8) for TMS. Veterinarians’ efficacy scores on Days 4 and 10 were equivalent for the two treatment regimens.

• Actual drug charges varied considerably from the pretreatment estimates. Average per-case medication costs were $86.54 for TMS and $107.34 for EXCEDE.

• A post-treatment survey confirmed that clients judged convenience to be more important than cost in their value perception and as the basis for their choice of an AIF drug.
Veterinarians often make the logical assumption that their clients will prefer the lowest-cost treatment option if it provides equivalent efficacy to higher-priced alternatives. However, this assumption does not consider whether the client views cost as more important than convenience in making a treatment choice.

There are few published studies on treatment compliance (adherence) in veterinary medicine, and to the authors’ knowledge there are none involving equine practice. Experts consider a compliance rate of 70% to 80% to be the norm.1,2 In view of the history of medication compliance shortfalls, the EXCEDE-TMS preference trial provided an opportunity to evaluate whether there was an appreciable difference in compliance between the oral multidose regimen versus a parenteral two-dose regimen.

**Study Design**

Twenty-seven veterinarians from 11 equine practices in various regions of the U.S. participated in the trial. Participating veterinarians enrolled 132 horses that were considered suitable for AIF treatment of injuries and clinical infections, or in a small minority of cases, for other reasons. Clients were given the choice of either of two AIF regimens: IM injection with EXCEDE administered by the attending veterinarian on Day 1 and Day 4, or client administration of TMS given orally in tablet form twice daily for 10 consecutive days. Veterinarians did not express a treatment preference to clients who agreed to participate in the trial, nor did they discuss compliance criteria or indicate that compliance would be assessed. Veterinarians did explain the dosage schedule and estimated costs of each therapeutic regimen prior to treatment in order to enable clients to make a cost-benefit assessment and an informed treatment choice. Veterinarians who had not previously used EXCEDE were excluded from the trial.

All horses were examined on Day 4 to evaluate treatment response, administer the second IM dose of EXCEDE to horses in that group and, in the case of the TMS group, to verify compliance in administering oral AIF medication. Costs for each case were calculated when treatment was completed. At the conclusion of the trial, each veterinarian completed a survey of 10 items related to client treatment preferences, compliance and satisfaction. Survey responses were based on dialog between the veterinarian and client regarding the case outcomes.

**Results**

Participating veterinarians submitted an average of 4.6 cases for inclusion in the trial (range 1 to 36). By a wide margin, clients selected veterinarian-administered parenteral treatment with two doses of EXCEDE instead of twice-daily oral treatment administered by the horse owner for 10 days with TMS, 122 (93.1%) versus 9 cases (6.9%), respectively.

Average treatment response scores for the two AIF regimens were comparable at Days 0 and 10. Full treatment compliance (122/122 cases) was achieved for horses treated with EXCEDE versus 75% compliance (6/8 cases) for those treated with TMS (one of the nine TMS-treated horses had an unknown compliance history and was excluded from the compliance calculation).

There was a wide divergence in the veterinarian’s pretreatment estimate of the cost of AIF treatment to treat a horse, with the estimated cost of EXCEDE more than double that of TMS (Table 1). However, the pretreatment estimate differed markedly from the actual AIF costs incurred. When the actual per-horse AIF costs incurred in the study are compared, average costs for EXCEDE were $20.80 greater than for the TMS group. Convenience was judged to be more important than price in the clients’ perception of value, with mean scores of 4.3 versus 3.5, respectively. The item with the greatest score differential was convenience, where EXCEDE had a
near-perfect average score of 4.8 versus 3.0 for TMS. Overall client satisfaction when EXCEDE was selected as the treatment choice had a mean score of 4.7, approaching the maximum possible score of 5.0 (Figure 1).

**Discussion and Conclusions**

The central finding of the trial was that horse owners overwhelmingly chose the most convenient therapeutic option even though pretreatment cost estimates for EXCEDE were more than double those for TMS (Table 1). Treatment compliance was 100% for the 122 EXCEDE cases. This was not surprising in view of the fact that the ceftiofur crystalline free acid injections were administered by the attending veterinarian. The perfect compliance outcome for EXCEDE was still noteworthy given the relatively large number of patients and the fact that redosing was at the client’s discretion.

Results of the EXCEDE-TMS preference trial have several implications for equine practitioners. Chief among these is that veterinarians should not assume that cost is the most critical factor in their clients’ choice of antimicrobial treatment. For most horse owners, convenience is more important.

**Acknowledgement**

The authors acknowledge the contribution of Mark Dana of Scientific Communications Services, LLC and Dr. Ed Blach with data collection.

**IMPORTANT SAFETY INFORMATION:**

People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to EXCEDE. EXCEDE is contraindicated in animals with known allergy to ceftiofur or to the β-lactam group (penicillins and cephalosporins) of antimicrobials. Do not use 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. See full Prescribing Information, attached.

**References**


### Table 1: Costs of anti-infective (AIF) treatment with EXCEDE®
or trimethoprim-sulfonamide (TMS)

<table>
<thead>
<tr>
<th>Cost Factor</th>
<th>Average Estimated or Actual AIF Cost</th>
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</thead>
<tbody>
<tr>
<td>Pretreatment estimated charge per 1,000-pound horse</td>
<td>$124.63    $56.66</td>
</tr>
<tr>
<td>Actual charge per case (all weights)</td>
<td>$107.34    $86.54</td>
</tr>
</tbody>
</table>
Figure 1 – A post-treatment survey of attending veterinarians who participated in the antibiotic preference trial evaluated five outcome factors: relative importance of price versus convenience, treatment convenience, cost versus benefit, overall satisfaction and efficacy. Individual responses were scored on a five-point scale from low to high. Mean responses favored convenience over price as a contributor to value. Mean scores for the other outcome factors favored EXCEDE versus trimethoprim-sulfonamide (TMS). The greatest variance in scores was for the convenience of EXCEDE (4.8) versus TMS (3.0), a 1.8-point differential.
EXCEDE Sterile Suspension

Cefetiofur 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. Federal Law prohibits extra-labelling of this drug in cattle for disease prevention purposes; at unauthorized sites; or in unapproved species.

DESCRIPTION
EXCEDE Sterile Suspension is a ready-to-use formulation that contains the crystalline free acid of cefetiofur, which is a broad-spectrum cephalosporin antibiotic active against Gram-positive and Gram-negative bacteria, including 8-lactamase-producing strains. Other cephalosporins, cephalosporin antibiotics, or cephalosporin metabolites have been isolated from the clinical material used as the starting material for the preparation of EXCEDE Sterile Suspension.

Each ml of this ready-to-use sterile suspension contains cefetiofur crystalline free acid equivalent to 200 μg cefetiofur, in a capecrylocaprylyl glycerophosphate (Miglyol®) and cottonseed oil based suspension.

Figure 1. Structures of cefetiofur acid free base:

Chemical name of cefetiofur crystalline free acid: 7-[2-[[2-Benzyl-4-thiazolidine-3-carboxylic acid]aminomethyl]imino]methoxy)-8-oxo-5-aza-1-
aza-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 subsp. equi-pneumoniae.

DOSE AND ADMINISTRATION
Shake well before use.

Administer free 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 concentrations are maintained for 6 days after the second injection (or a total of 10 days from the beginning of treatment) against Streptococcus equi subsp. equi-pneumoniae.

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 subsp. equi-pneumoniae.

Table 1. Dosing Schedule for EXCEDE Sterile Suspension.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Dose (mg/lb)</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horse</td>
<td>3.0</td>
<td>Intramuscular</td>
</tr>
</tbody>
</table>

ANTIBACTERIAL WARNINGS
Use of antibiotic drugs in the absence of a susceptible bacterial infection is unlikely to provide benefit to treated animals and may contribute to the development of drug-resistant bacteria.

PRECAUTIONS
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 treatment should be initiated.

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, firmness, swelling, and/or sensitivity were observed in at least one injection site in all horses treated at the label dose. The use of cefetiofur has not been evaluated in horses less than 4 months of age and in breeding, pregnant, or lactating horses.

ADVERSE REACTIONS
The injection of EXCEDE Sterile Suspension in the horse may cause firmness, swelling, sensitivity, and/or edema at the site of injection. This adverse reaction may be related to the development of drug-resistant bacteria.

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 equi subsp. equi-pneumoniae. In the study, a total of 278 horses were treated with EXCEDE and 65 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 by Day 7, resolution of the clinical signs by Day 15, and no recurrence of clinical signs by Day 25 after relapse dosing. EXCEDE was superior to the saline control. Table 5 summarizes the clinical success rates obtained 15 and 25 days after the first dose.

Table 5. Clinical success rates at Day 15 and 25.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathotype From Isolates</th>
<th>Treatment Outcome</th>
<th>Time of Sample Collection</th>
<th>WBC/mcL</th>
<th>MIC, μg/mL</th>
<th>MIC Range, μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus equi subsp. equi-pneumoniae</td>
<td>Success</td>
<td>Post-Treatment</td>
<td>0.06</td>
<td>0.5-1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>Pre-Treatment</td>
<td>0.06</td>
<td>0.5-1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* One horse cultured Streptococcus equi subsp. equi-pneumoniae (successfully treated) and is not represented in the table.

ANIMAL SAFETY
This has been 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.

A study of healthy adult horses received 6 intramuscular (lateral neck) injections of EXCEDE Sterile Suspension at a dose of 100 mL vial (100 mL vial 3X). One hundred forty six horses (33 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 by Day 7, resolution of the clinical signs by Day 15, and no recurrence of clinical signs by Day 25 after relapse dosing. EXCEDE steroid was superior to the saline control. Table 5 summarizes the clinical success rates obtained 15 and 25 days after the first dose.

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>
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The material safety data sheet (MSDS) contains more detailed occupational safety information. To obtain a material safety data sheet (MSDS), you should contact the manufacturer or distributor of the product.

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