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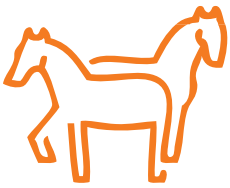

Clinical trial of client preferences, compliance and satisfaction following treatment of equine bacterial infections with oral trimethoprim-sulfonamide or injectable EXCEDE® (*ceftiofur crystalline free acid*) Sterile Suspension

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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

1 Claxton AJ, Cramer J, Pierce C. A systematic review of the association between dose regimens and medication compliance. *Clin Therap.* 2001;23:1296-1310.

2 Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. *Epilepsy Behav.* 2002;3:38-42.

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

Cost Factor	Average Estimated or Actual AIF Cost	
	EXCEDE	TMS
Pretreatment estimated charge per 1,000-pound horse	$124.63	$56.66
Actual charge per case (all weights)	$107.34	$86.54

Figure 1 – Client Value Perception

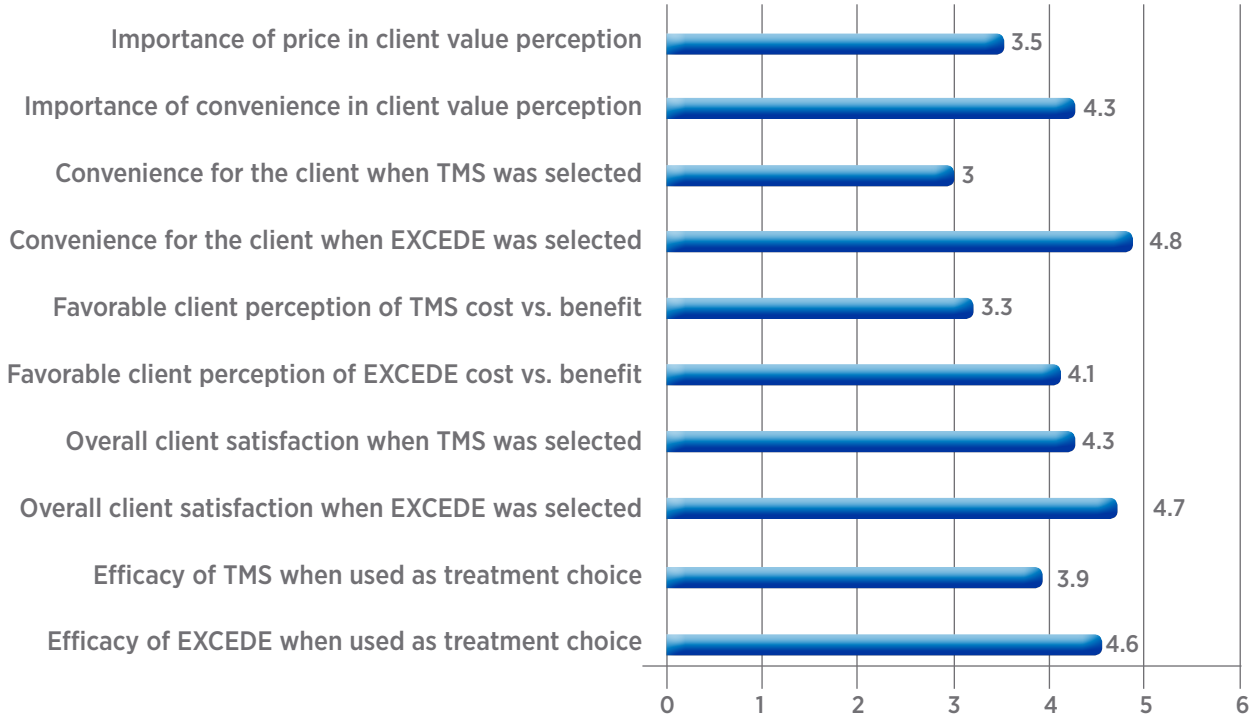


Figure 1 – A post-treatment survey of attending veterinarians who participated in the antibiotic preference trial evaluated five outcome factors: relative importance of price versus convenience, treatment convenience, cost versus benefit, overall satisfaction and efficacy. Individual responses were scored 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®
(Ceftiofur Crystalline Free Acid)
Sterile Suspension

For intramuscular injection in the horse.

CAUTION

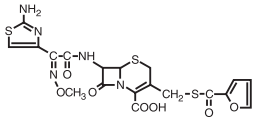
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal Law prohibits extra-label use of this drug in cattle for disease prevention purposes; at unapproved doses; frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

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 ß-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-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.

Weight (lb)	Dose Volume (mL)
100	1.5
200	3.0
300	4.5
400	6.0
500	7.5
600	9.0
700	10.5
800	12.0
900	13.5
1000	15.0

Weight (lb)	Dose Volume (mL)
1100	16.5
1200	18.0
1300	19.5
1400	21.0
1500	22.5
1600	24.0
1700	25.5
1800	27.0
1900	28.5
2000	30.0

CONTRAINDICATIONS

EXCEDE Sterile Suspension is contraindicated in horses with known allergy to ceftiofur or to ß-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 penicillin or cephalosporins should avoid exposure to this product. In the 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.

ANTIBACTERIAL WARNINGS

Use of antibacterial drugs in the absence of a susceptible bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of 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 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 2. Number of Horses with Adverse Reactions During the Field Study with EXCEDE.

Adverse Reaction	EXCEDE (n=278)	Placebo (n=95)
Diarrhea/Soft Stool	25 (9%)	7 (7%)
Injection Site Swelling	10 (4%)	1 (1%)

The material safety data sheet (MSDS) contains more detailed occupational safety information. To obtain a material safety data sheet or to report any adverse event please call 1-888-963-8471.

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.

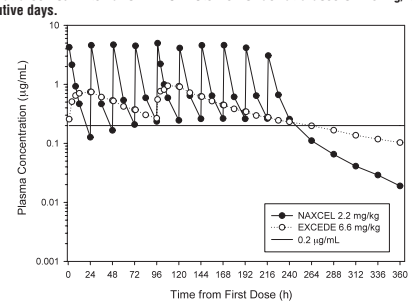


Table 3. Pharmacokinetic parameters measured after either two intramuscular injections of EXCEDE Sterile Suspension at a dose of 3.0 mg/lb (6.6 mg/kg) BW at a 96 hour interval or NAXCEL Sterile Powder at a dose of 1.0 mg/lb (2.2 mg/kg) BW once daily for 10 consecutive days are summarized in the following table.

PK Parameter	CCFA-SS at 6.6 mg/kg BW administered twice 96 h apart (Mean ± SD; n=12)		Ceftiofur sodium at 2.2 mg/kg BW once daily for 10 days (Mean ± SD; n=11)	
$AUC_{0-\infty}$ (µg•h/mL)	157 (19.1)		353 (44.9)	
$t_{\frac{1}{2}\beta}$ (h)	262 (29.0)		ND	
	Dose 1	**Dose 2**	**Dose 1**	**Dose 10**
T_{max} (h)	21.6 (5.8)	15.6 (6.3)	1.0	2.0 (3.3)
C_{max} (µg/mL)	0.78 (0.19)	1.0 (0.24)	4.31 ± 0.78	3.99 (1.23)

MICROBIOLOGY

Ceftiofur is a cephalosporin antibiotic. Like other ß-lactam antimicrobials, ceftiofur 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. Ceftiofur is not active against *Pseudomonas* spp. and enterococci.

The minimum inhibitory concentration (MIC) values for ceftiofur 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.

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

Disease	Pathogen	Treatment Outcome	# of Isolates	Time of Sample Collection	MIC_{50} µg/mL	MIC_{90} µg/mL	MIC Range µg/mL
Lower Respiratory Tract Infection	*Streptococcus equi* ssp. *zooepidemicus*	Success	93*	Pre-Treatment	0.06	0.12	0.03-0.5
		Failure	42	Pre-Treatment	0.06	0.25	0.03-0.5

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

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 equi* ssp. *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 and 25 days after the first dose.

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

Effectiveness parameter	EXCEDE	Saline Control	P-value
Clinical success Day 15	73.53%	38.60%	N/A
Clinical success Day 25	69.12%	31.58%	0.0215

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 TAS 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 ceftiofur 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 sizes:
100 mL vial
250 mL vial

NADA #141-209, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

www.EXCEDE.com or call 1-888-963-8471

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