Ceftiofur is a cephalosporin antibiotic. Like other β-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) (e.g., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial cell wall. Ceftiofur is not active against ß-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal, i.e., killing bacteria rather than inhibiting bacterial growth.

The minimum inhibitory concentration (MIC) values for ceftiofur against label-claim pathogens isolated from 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.

MICROBIOLOGY

Excessive plasma 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 interfered with bacterial cell wall synthesis. This interference is primarily due to its covariant binding to the penicillin-binding proteins (PBPs) (e.g., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial cell wall. Ceftiofur is not active against ß-lactamase-producing strains.

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Outcome</th>
<th>% Success</th>
<th>% Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic</td>
<td>Exced</td>
<td>Success</td>
<td>97*</td>
<td>3*</td>
</tr>
<tr>
<td>Nasal</td>
<td>Exced</td>
<td>success</td>
<td>95*</td>
<td>5*</td>
</tr>
<tr>
<td>Conjunctival</td>
<td>Exced</td>
<td>failure</td>
<td>3*</td>
<td>97*</td>
</tr>
</tbody>
</table>

* One horse cultured Streptococcus 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 subsp. zooepidemicus in the horse. In this study, a total of 278 horses were treated with EXCEDE, and 95 horses were treated with saline placebo. 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 23 following 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.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Effectiveness parameter</th>
<th>EXCEDE</th>
<th>Saline Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic</td>
<td>Clinical success Day 15</td>
<td>73.53%</td>
<td>38.60%</td>
<td>0.0015</td>
</tr>
<tr>
<td>Nasal</td>
<td>Clinical success Day 25</td>
<td>69.12%</td>
<td>31.58%</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

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 X10, 6.0 X2 or 9.0 X3 mg/kg 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/kg (2X) EXCEDE experienced a mild episode of colic the day after the second injection of EXCEDE. The horse recovered without treatment.

In the PK study, one horse was obtained 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 PK study, injection site reactions 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 over the injection site resolved but 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 pain upon standing and to the front foot). One horse in the NAXCEL group and one horse in the 6.0 mg/kg (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 saline placebo group. The study housed (mulithorse 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 CEFTIOFUR-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 use. 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 mg/2 ml vial
- 250 mg/5 ml vial
- NADA #141-209, Approved by FDA

Zoetics

Distributed by: Zoetis Inc.
Kalamazoo, MI 49007

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

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