PRODUCT FEATURES

- EQUISUL-SDT is proven effective in horses for the treatment of lower respiratory tract infections caused by susceptible strains of *Streptococcus equi* subsp. *zooepidemicus* in controlled field trials.
- EQUISUL-SDT safety was demonstrated in a controlled study in horses at 1X, 3X and 5X the recommended dose for 30 days.
- Easy-to-use liquid formulation.
- Significantly higher bioavailability on a mg-to-mg basis compared to an existing approved paste product, based on a pharmacokinetic crossover study.
- Low incidence of side effects in our controlled safety studies.

“EQUISUL-SDT liquid oral suspension is a better choice than Uniprim® and human SMZ/TMP tablets because we see a faster response to treatment and improved ease of administration for our clients. We are confident our patients receive the proper dose with EQUISUL-SDT.”

— Barb Page, DVM, Colorado Equine Clinic, 303-638-3835
EQUISUL-SDT is produced using Aurora Pharmaceutical’s patented drug product formulation. The product demonstrated 20% increased bioavailability over an existing paste product in a pharmacokinetic crossover study.

Administer EQUISUL-SDT orally at the dosage of 24 mg combined active ingredients per kilogram body weight (10.9 mg/lb.) twice daily for 10 days. EQUISUL-SDT can be administered by volume at 2.7 mL per 45.4 kg (2.7 mL/100 lb.) body weight. The product is available in 900 mL, 560 mL and 135 mL bottles.

**Efficacy**

In a controlled field efficacy study of EQUISUL-SDT in horses with lower respiratory tract infections caused by *Streptococcus equi* subsp. *zooepidemicus*, 59% (66/112) of the horses receiving EQUISUL-SDT were successfully treated, showing complete resolution of clinical symptoms within seven days after completion of treatment. In contrast, only 15% of the negative control horses demonstrated improvement during the same period. Additionally, transtracheal wash samples taken before and after treatment demonstrated that EQUISUL-SDT further indicated complete bacterial clearance of *Streptococcus equi* subsp. *zooepidemicus* in 66% of the treated animals. The incidences of adverse events associated with EQUISUL-SDT treatment during this study were comparable to those seen in the saline control group and were largely self-limiting. Diarrhea was seen in only 1.1% of the animals treated and resolved without treatment.

**Take Home Message From Efficacy Study**

Horses with lower respiratory tract infections caused by *Streptococcus equi* subsp. *zooepidemicus* were treated with EQUISUL-SDT at a dosage of 24 mg/kg twice daily for 10 days. Improved bioavailability allows a 20% lower dose than previously published. 1 EQUISUL-SDT effectively treated the clinical signs of respiratory infection and eliminated the infection from the respiratory tract.


**Safety**

In a controlled safety study, horses were administered up to five times the recommended dose of EQUISUL-SDT twice daily for 30 consecutive days. While a higher incidence of loose stool was seen in animals treated with the higher dose of EQUISUL-SDT, in all cases, the incidents were self-limiting and resolved without treatment. EQUISUL-SDT is the only sulfadiazine/trimethoprim product for horses to be tested according to modern FDA requirements.

**Take Home Message From Safety Study**

EQUISUL-SDT had no serious adverse effects on clinical or laboratory parameters and no significant changes were seen in the representative tissues of mature horses when administered at up to five times the intended combined dosage of 24 mg/kg twice daily for 30 consecutive days.

**Clinical Pathology**

There were no significant clinical changes in clinical pathology parameters related to the administration of EQUISUL-SDT.
Pharmacology

Simplified pathway for the action of sulfonamide-trimethoprim combinations.

Sulfadiazine and trimethoprim have been used to treat infection in horses for many years. The suspension used in this study is a novel formulation with high bioavailability. When given twice daily at a dose of 24 mg/kg body weight over a 10-day dosing period, blood plasma levels remain above the MIC90 for *Streptococcus equi* subsp. *zooepidemicus* greater than 98% of the time. As with all antibiotics, it is important to follow label directions including the full 10-day dose be administered to optimize the antimicrobial value, limit the potential development of resistance, and to follow the AVMA policy on judicious use of antimicrobials.

In *Streptococcus equi* subsp. *zooepidemicus* samples isolated from lower respiratory tract infections in horses from 1989 to 2008, the MIC90 of potentiated sulfonamides has not increased, indicating that they remain valuable antimicrobials in the treatment of lower respiratory disease in horses. In our study, the suspension was shown to be safe, with very few adverse events noted over the 10-day treatment period.

Aurora Pharmaceutical is an FDA-inspected facility and manufactures under cGMP standards. All USP grade materials are tested according to compendial standards, including tests for potency and impurities of active ingredients. Aurora products are required to pass testing prior to release for sale, thus guaranteeing batch consistency. Aurora products are tested on stability to assure quality through labeled expiration.
administration of potentiated sulfonamides. EQUISUL-SDT should be discontinued if prolonged clotting times, or decreased platelet, white blood cell or red blood cell counts are observed.

Sulfonamides should be used with caution in horses with impaired hepatic function. Although rare, sulfonamide use has been associated with fulminant hepatic necrosis in humans.

Neurologic abnormalities have been reported in several species following administration of potentiated sulfonamides. In horses, potentiated sulfonamides have been associated with gait alterations and behavior changes that resolved after discontinuation of the drug.

The safe use of EQUISUL-SDT has not been evaluated in horses less than 1 year of age.

ADVERSE REACTIONS

Adverse reactions reported during a field study of 270 horses of various breeds, ranging from 1 to 25 years of age, that had been treated with either EQUISUL-SDT (n = 182) or with a saline control (n = 88) are summarized in Table 1. At least one episode of loose stool was observed in 69 of 182 (38%) of the EQUISUL-SDT-treated horses, and 29 of 88 (33%) saline control horses. Of those animals experiencing loose stool, 2 of 182 (1.1%) of the EQUISUL-SDT-treated horses and 0 of 88 (0%) placebo-treated horses were removed from the study due to diarrhea (as defined at least one episode of watery stool). Both cases of diarrhea in this study were self-limiting and resolved without treatment within 5–10 days after discontinuation of EQUISUL-SDT.

Table 1. Number of Horses with Adverse Reactions During the Field Study with EQUISUL-SDT

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>EQUISUL-SDT (n=182)</th>
<th>Saline control (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loose stool (including diarrhea)</td>
<td>69 (38%)</td>
<td>25 (33%)</td>
</tr>
<tr>
<td>Colic</td>
<td>3 (1.6%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (1.1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Aurora Pharmaceutical LLC at 888-215-1256 or www.aurorapharmaceutical.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

CLINICAL PHARMACOLOGY

Following oral administration, EQUISUL-SDT is rapidly absorbed and widely distributed throughout body tissues. Sulfadiazine levels are usually highest in the kidney and liver than in the blood. Sulfadiazine and trimethoprim are both eliminated primarily by renal excretion, both by glomerular filtration and tubular secretion. Urine concentrations of both trimethoprim and sulfadiazine are several-fold higher than blood concentrations. Sulfadiazine and trimethoprim are 20% and 35% bound to plasma protein, respectively. Administration of sulfadiazine and trimethoprim with food decreases the absorption of trimethoprim but there is no apparent effect on sulfadiazine absorption.

Based on a study in fed horses, trimethoprim concentrations following repeated oral administration of 24 mg/kg EQUISUL-SDT to horses reached peak concentration in 1.96-5.31 h. The median plasma elimination half-life for sulfadiazine was approximately 7.80 h, with a range of 6.78 to 10.73 h. Only minor accumulation of both drugs was observed following repeat oral administration of EQUISUL-SDT and both drugs reached steady state by Day 3. Sulfadiazine and trimethoprim key state parameters associated with administration in 6 fed horses over a period of 7 days are found in Table 2.

Table 2. Median (Range) of sulfadiazine and trimethoprim pharmacokinetics parameters following repeat dosing of 24 mg/kg bid EQUISUL-SDT for 7 days to six horses in fed condition

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sulfadiazine</th>
<th>Trimethoprim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (hr)</td>
<td>1.00–12.00</td>
<td>0.50–12.00</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>17.63</td>
<td>0.78</td>
</tr>
<tr>
<td>AUC 0–12 (last dose) (µg*h/mL)</td>
<td>159.35</td>
<td>5.47</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>7.80</td>
<td>3.00</td>
</tr>
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</table>

MICROBIOLOGY

EQUISUL-SDT is the combination of the sulfonamide sulfadiazine and trimethoprim. These two drugs block sequential steps in nucleic acid biosynthesis. Sulfadiazine inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by reversibly inhibiting dihydrofolate reductase. The effect of the dual action is to reduce the minimum inhibitory concentration of each agent (synergism) and to convert a bacteriostatic action to a bactericidal action.

The two drugs act synergistically, reducing the minimum inhibitory concentration of each drug and increasing bactericidal action of each separately to a bacteriostatic action when combined.

EQUISUL-SDT administered as a combined sulfadiazine-trimethoprim dose of 24 mg/kg body weight twice daily for 2 days provided concentrations of sulfadiazine and trimethoprim with T>MIC of 95% values of 100% and 98% respectively. The minimum inhibitory concentration (MIC) values for EQUISUL-SDT against indicated pathogens isolated from lower respiratory tract infections in horses enrolled in a 2010–2011 effectiveness field study are presented in Table 3. All MICs were determined in accordance with the Clinical and Laboratory Standards Institute (CLSI) Approved Standard M3-A3 using a broth microdilution system and 3% lysed horse blood.

Table 3. Trimethoprim/sulfadiazine minimum inhibitory concentration (MIC) values* of isolates recovered from horses with lower respiratory infection caused by Streptococcus equi subspp. zooepidemicus treated with EQUISUL-SDT in the U.S. (2010–2011)

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of isolates</td>
<td>65</td>
<td>46</td>
</tr>
<tr>
<td>Time of Sample Collection</td>
<td>Pre-treatment</td>
<td>Pre-treatment</td>
</tr>
<tr>
<td>MIC 50 (µg/mL)</td>
<td>0.254-7.5</td>
<td>0.254-7.5</td>
</tr>
<tr>
<td>MIC 90 (µg/mL)</td>
<td>0.254-7.5</td>
<td>0.254-7.5</td>
</tr>
<tr>
<td>MIC Range (µg/mL)</td>
<td>0.122/4</td>
<td>to 0.595</td>
</tr>
</tbody>
</table>

* The correlation between in vitro susceptibility data and clinical effectiveness is unknown.

ANIMAL SAFETY

In a target animal safety study, EQUISUL-SDT was administered orally to 32 healthy adult horses at 0 X, 24 X, 72 X, or 120 (5X) mg/kg twice daily for 30 days. Loose stool was the most common abnormal observation. Observations of loose stool (pillets with liquid or unformed/ceaseable stool) occurred more often in horses treated with EQUISUL-SDT with the incidence of loose stool increasing in a dose related manner. All incidents of loose stool were self-limiting and resolved without treatment.

In horses in all EQUISUL-SDT groups demonstrated statistically significantly higher mean serum creatinine concentrations, and those in the 3X and 5X groups demonstrated statistically significantly higher mean serum albumin concentrations. Statistically significantly higher mean neutrophil and mean serum gamma glutamyl transferase (GGT) activity were seen in the 1X and 5X groups. In addition, mean creatinine, GGT, and albumin concentrations remained within the reference range. Individual animal elevations in absolute neutrophil counts ranged from 7.08 to 10.73 x10^9/mL (reference range: 1.96-5.31 x10^9/mL).

Based upon blood concentrations obtained during the study, it was noted that the sulfadiazine and trimethoprim plasma concentrations did not increase in proportion to dose. For sulfadiazine, a 3X and 5X dose resulted in an average exposure of 2.0X and 2.6X the concentration observed for a 1X dose. In comparison, the corresponding values were 2.5X and 3.5X as compared to the 1X dose. Furthermore, marked variability in serum sulfadiazine, resulted in substantial overlap of individual subject blood levels across the three dosing groups.

STORAGE CONDITIONS

Store at 59°–86°F (15°–30°C). Brief periods up to 104°F (40°C) are permissible from the freezing.

HOW SUPPLIED

EQUISUL-SDT is available in the following package sizes:

- 150 mg amber glass bottle containing 153 mL
- 625 mg amber glass bottle containing 580 mL
- 950 mL amber glass bottle containing 900 mL