ADVERSE REACTIONS

Swine

In one field study, one out of 40 pigs treated with DRAXXIN Injectable Solution (100 mg/mL) at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

Calves

In one BRD field study, two calves treated with DRAXXIN Injectable Solution (100 mg/mL) at 2.5 mg/kg BW exhibited transient hypersalivation. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

Post Approval Experience

The following adverse events are based on post approval adverse drug experience reporting for DRAXXIN Injectable Solution (100 mg/mL). Not all adverse events are reported to the FDA CVM. It is not possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of reporting frequency in cattle: Injection site reactions and anaphylaxis/anaphylactoid reactions. For a complete listing of adverse reactions for DRAXXIN Injectable Solution or DRAXXIN 25 Injectable Solution reported to the CVM see: www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY

At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophilic than lipophilic media. This solubility profile is consistent with the extracelluar pathogen activity typically associated with the macrolides. Markedly higher tulathromycin concentrations are observed in the lung parenchyma as compared to plasma, and these elevated concentrations can remain in lung tissue for several days beyond that which can be measured in the plasma. However the clinical relevance of these elevated lung concentrations is undetermined.

As a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens. When acting as a cidal compound, they tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the minimum inhibitory concentration (MIC) of the targeted pathogen. Under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial activity. Macrolides also exhibit a post-antibiotic effect (PAE), the duration of which tends to be both drug and pathogen dependent. In general, by increasing the macrolide concentration and the exposure time, the PAE will increase to some maximal duration. Tulathromycin is eliminated from the body predominantly via biliary excretion.


Swine

Following intramuscular (IM) administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is nearly completely absorbed, with peak plasma concentrations achieved within ~0.25 hr. The volume of distribution exceeds 11 L/kg, which is consistent with extensive tissue binding. This large distribution volume results in a long terminal elimination half-life of 60 to 90 hours despite a rapid systemic free drug clearance (187 L/hr/kg). There are no gender differences in swine tulathromycin pharmacokinetics.

Comparative Bioavailability Summary

Despite slightly lower peak concentrations with DRAXXIN 25 Injectable Solution, a single IM dose of 2.5 mg tulathromycin/kg BW of either DRAXXIN Injectable Solution (100 mg/mL) or DRAXXIN 25 Injectable Solution (25 mg/mL) resulted in comparable total systemic tulathromycin exposure. Therefore, DRAXXIN 25 Injectable Solution is considered to be therapeutically equivalent to DRAXXIN Injectable Solution when administered to swine by IM injection at a dose of 2.5 mg tulathromycin/kg BW.

Calves

Following subcutaneous (SC) administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, tulathromycin is nearly completely absorbed, with peak plasma concentrations achieved within ~0.25 hr. The volume of distribution exceeds 11 L/kg, which is consistent with extensive tissue binding. This large distribution volume results in a long terminal elimination half-life of 60 to 90 hours despite a rapid systemic free drug clearance (170 L/hr/kg). No pharmacokinetic differences are observed in castrated male versus female calves.

Comparative Bioavailability Summary

Despite lower peak concentrations with DRAXXIN 25 Injectable Solution, a single SC dose of 2.5 mg tulathromycin/kg BW of either DRAXXIN Injectable Solution (100 mg/mL) or DRAXXIN 25 Injectable Solution (25 mg/mL) resulted in comparable total systemic tulathromycin exposure. Therefore, DRAXXIN 25 Injectable Solution is considered to be therapeutically equivalent to DRAXXIN Injectable Solution when administered to calves by SC injection at a dose of 2.5 mg tulathromycin/kg BW.

* Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.

MICROBIOLOGY

Swine

Tulathromycin has demonstrated in vitro activity against A. pleuropneumoniae, P. multocida, B. bronchiseptica, H. parasuis, and M. hyopneumoniae. The MICs of tulathromycin against indicated pathogens collected from field studies were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI: M31-A and M31-A3). MICs for H. parasuis were determined using Veterinary Fastidious Medium and were incubated up to 48 hours at 35 to 37°C in a CO₂-enriched atmosphere. These values are represented in Table 3, below.

<table>
<thead>
<tr>
<th>Indicated pathogen</th>
<th>Date isolated</th>
<th>No. of isolates</th>
<th>MIC_C (μg/mL)</th>
<th>MIC_C (μg/mL)</th>
<th>MIC range (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinobacillus pleuropneumoniae</td>
<td>2002-2006</td>
<td>135</td>
<td>4</td>
<td>16</td>
<td>16 to 32</td>
</tr>
<tr>
<td>Haemophilus parasuis</td>
<td>2002-2006</td>
<td>78</td>
<td>4</td>
<td>8</td>
<td>4 to 32</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>2000-2007</td>
<td>55</td>
<td>2</td>
<td>0.25 to &gt; 8</td>
<td></td>
</tr>
<tr>
<td>Actinobacillus pleuropneumoniae</td>
<td>2000-2007</td>
<td>40</td>
<td>2</td>
<td>0.5 to &gt; 4</td>
<td></td>
</tr>
<tr>
<td>Brachyspira bronchiseptica</td>
<td>2000-2007</td>
<td>42</td>
<td>0.03 to 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. hyopneumoniae</td>
<td></td>
<td>0.2 to 2</td>
<td></td>
<td></td>
<td></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.

** The correlation between in vitro susceptibility data and clinical effectiveness is unknown.
Table 4. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating BRD in the U.S.

<table>
<thead>
<tr>
<th>Indicated pathogen</th>
<th>Date isolated</th>
<th>No. of isolates</th>
<th>MIC&lt;sub&gt;G&lt;/sub&gt; (μg/mL)</th>
<th>MIC&lt;sub&gt;S&lt;/sub&gt; (μg/mL)</th>
<th>MIC range (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannheimia haemolytica</td>
<td>1999</td>
<td>642</td>
<td>2</td>
<td>2</td>
<td>0.5 to 64</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>1999</td>
<td>221</td>
<td>0.5</td>
<td>1</td>
<td>0.25 to 64</td>
</tr>
<tr>
<td>Histophilus somni</td>
<td>1999</td>
<td>36</td>
<td>4</td>
<td>4</td>
<td>1 to 4</td>
</tr>
<tr>
<td>Mycoplasma bovis</td>
<td>1999</td>
<td>43</td>
<td>0.125</td>
<td>1</td>
<td>≤ 0.063 to &gt; 64</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.

EFFECTIVENESS

Swine

Plasma concentrations of tulathromycin administered as DRAXXIN Injectable Solution (100 mg/mL) or as DRAXXIN 25 Injectable Solution (100 mg/mL) support the effectiveness for DRAXXIN 25 Injectable Solution. In a multi-location field study to evaluate the treatment of naturally occurring SRD, 266 pigs were treated with DRAXXIN Injectable Solution (100 mg/mL). Responses to treatment were compared to saline-treated controls. Success was defined as a pig with normal activity, normal respiration, and rectal temperature of <104°F on Day 7. The treatment success rate was significantly greater (P ≤ 0.05) in DRAXXIN-treated pigs compared to saline-treated pigs in both studies (85.2% vs. 23.82% and 11.31% vs. 26.42%).

The effectiveness of DRAXXIN Injectable Solution (100 mg/mL) for the control of SRD was evaluated in a multi-location natural infection field study. When at least 15% of the study candidates showed clinical signs of SRD, all pigs were enrolled and treated with DRAXXIN (226 pigs) or saline (227 pigs). Responses to treatment were evaluated on Day 7. Success was defined as a pig with normal activity, normal respiration, and rectal temperature of <104°F. The treatment success rate was significantly greater (P < 0.05) in DRAXXIN-treated pigs compared to saline-treated pigs (59.2% vs. 41.2%).

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN Injectable Solution (100 mg/mL) against M. hyopneumoniae. Ten days after inoculation intratracheally and intratransversely with a field strain of M. hyopneumoniae, 144 pigs were treated with either DRAXXIN (2.5 mg/kg BW) intramuscularly or an equivalent volume of saline. Pigs were euthanized and necropsied 10 days post-treatment. The mean percentage of gross pneumonic lung lesions was statistically significantly lower (P < 0.001) for DRAXXIN-treated pigs than for saline-treated pigs in both studies (8.52% vs. 23.82% and 11.31% vs. 26.42%).

The effectiveness of DRAXXIN Injectable Solution (100 mg/mL) against M. haemolytica, P. multocida, H. somni, and M. bovis was confirmed in two induced infection model studies. When calves became pyrexic and had abnormal respiration scores, they were treated with DRAXXIN Injectables Solution (100 mg/mL). Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal activity, normal respiration, and rectal temperature of ≤104°F. The treatment success rate was significantly higher (P ≤ 0.05) in DRAXXIN-treated pigs compared to saline-treated pigs (78% vs. 24%).

Sixteen growing cattle were infected with either saline (eight animals) as a single injection of 11.5 mL or DRAXXIN 25 Injectable Solution (eight animals) as a single injection of either 2.5 mg/kg BW or a dose volume of 11.5 mL (whichever volume was higher). One calf in the DRAXXIN 25-treated group was observed to have firmness at the injection site for a single day. Two DRAXXIN 25-treated calves exhibited injection site swelling. In one calf, the swelling resolved within 48 hours. In the other calf, the swelling was observed over a three-day period, after which the calf underwent a scheduled necropsy, preventing further injection site observations. No injection site swelling was observed in saline-treated animals. At necropsy, three of the saline-treated calves and five of the DRAXXIN 25-treated calves had altered tissue present at the injection site. The gross and microscopic findings in the DRAXXIN 25-treated group were consistent with inflammatory changes induced by injections, were considered to be mild to marked, and progressed to macroscopic resolution and microscopic resolution by Day 42 post-injection.

Calves

Plasma concentrations of tulathromycin administered as DRAXXIN Injectable Solution (100 mg/mL) or as DRAXXIN 25 Injectable Solution support the effectiveness for DRAXXIN 25 Injectable Solution. Therefore effectiveness studies conducted with DRAXXIN Injectable Solution support the systemic safety for DRAXXIN 25 Injectable Solution. Plasma concentrations of tulathromycin administered as DRAXXIN Injectable Solution (100 mg/mL) or as DRAXXIN 25 Injectable Solution were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore effectiveness studies conducted with DRAXXIN Injectable Solution support the systemic safety for DRAXXIN 25 Injectable Solution. Plasma concentrations of tulathromycin administered as DRAXXIN Injectable Solution (100 mg/mL) or as DRAXXIN 25 Injectable Solution were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore effectiveness studies conducted with DRAXXIN Injectable Solution support the systemic safety for DRAXXIN 25 Injectable Solution.

A safety study was conducted in feeder calves receiving DRAXXIN Injectable Solution (100 mg/mL) as a single subcutaneous dose of 25 mg/kg BW, or 3 weekly subcutaneous doses of 2.5, 7.5, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including restlessness and excessive vocalization. Tremors were observed briefly in one animal receiving 7.5 mg/kg BW. Discoloration and edema of injection site tissues and corresponding histopathologic changes were seen in animals in all dosage groups. These lesions showed signs of resolving over time. No other drug-related lesions were observed macroscopically or microscopically.

An exploratory study was conducted in feeder calves receiving DRAXXIN Injectable Solution (100 mg/mL) as a single subcutaneous dose of 10, 12.5, or 15 mg/kg BW. Macroscopically, no lesions were observed. Macroscopically, minimal to mild myocardial degeneration was seen in one of six calves administered 12.5 mg/kg BW and two of six calves administered 15 mg/kg BW.

A safety study was conducted in prepubertal calves 13 to 27 days of age receiving DRAXXIN Injectable Solution (100 mg/mL) at 2.5 mg/kg BW or 7.5 mg/kg BW once subcutaneously. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.

Storage Conditions:

Store at or below 25°C (77°F). Use within 90 days of first vial puncture.

How Supplied:

DRAXXIN 25 Injectable Solution is available in the following package sizes:
- 50 mL vial
- 250 mL vial

Approved by FDA under NADA # 141-349

Distributed by:

Zoetis Inc.
Kalamazoo, MI 49007

To report a suspected adverse reaction or to request a safety data sheet call 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

For additional DRAXXIN 25 product information call: 1-888-DRAXXIN or go to www.DRAXXIN.com

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