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 always 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: http://www.fda.gov/AnimalVeterinary

CLINICAL PHARMACOLOGY

As a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens.2 When acting as a bacterial antibiotic, this concentration range is the ratio of bacterial eradication to 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 antibacterial activity. Macrolides also exhibit a post-antibiotic effect (PAE), the duration of which varies from one drug to another. The PAE of tulathromycin is the longest of those reported for macrolides and is generated by the inhibition of DNA gyrase, which is a bacterial enzyme crucial to the replication of bacterial DNA. The PAE for tulathromycin is related to the concentrations of the drug that are achieved in serum and can exceed 48 hours.3 Tulathromycin exposure time, the PAE will increase to some maximal duration.1 Tulathromycin is eliminated from the body unchanged via biliary excretion.


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, M2-A1 and M3-A3). MICs for A. pleuropneumoniae were determined using Veterinary Fastidious Medium and were interpreted up to 48 hours at 35°F in a CO2 enriched atmosphere. These values are represented in Table 3. below.

Mycobacteria bronchiseptica

Tulathromycin has demonstrated in vitro activity against M. haemolytica, P. multocida, H. somni, and M. bovis, four pathogens associated with BRD. The MICs of tulathromycin against indicated pathogens collected from field studies using DRAXXIN Injectable Solution (100 mg/mL) were determined using methods recommended by the CLSI (M2-A1). These values are represented in Table 4. below.

Table 3. Minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating SRR in the U.S. and Canada.

<table>
<thead>
<tr>
<th>Indicated pathogen</th>
<th>Date isolated</th>
<th>MIC range (µg/mL)</th>
<th>No. of isolates</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/mL)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinobacillus pleuropneumoniae</td>
<td>2000-2002</td>
<td>4 to 32</td>
<td>135</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Haemophilus parasuis</td>
<td>2000-2002</td>
<td>0.25 to &gt; 64</td>
<td>88</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>2000-2002</td>
<td>0.03 to 2</td>
<td>59</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mycoplasma bronchiseptica</td>
<td>2000-2002</td>
<td>2.68</td>
<td>42</td>
<td>8</td>
<td>2</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 gross and microscopic findings in the DRAXXIN 25-treated group were consistent post-injection. No heat, sensitivity, firmness, necrosis, drainage, or swelling was observed at any injection sites. Injection site observations included two instances of erythema in the DRAXIN 25-treated group on Day 1 and Day 14. 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 head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site 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.

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, the treatment success rate was significantly greater (P<0.05) in DRAXXIN-treated pigs (70.5%) compared to saline-treated pigs (46.1%). M. hyopneumoniae was isolated from 106 saline-treated and non-treated sentinel pigs in this study.

In all multi-location field study, the cure rate was significantly higher (P<0.001) for DRAXXIN-treated pigs than for saline-treated pigs in both studies. The effectiveness of DRAXXIN Injectable Solution (100 mg/mL) against M. haemolytica, M. hyopneumoniae, and M. parahaemolytica was evaluated in a multi-location natural infection field study. When at least 15% of the study candidates showed clinical signs of SRD, the treatment success rate was significantly greater (P<0.05) in DRAXXIN-treated pigs compared to saline-treated pigs (9.2% vs. 41.2%).

Calves 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 effectiveness 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 head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site 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. Microscopically, 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 preruminant 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 subsequently. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.

Sixteen growing cattle were injected 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.

**Table 4. Tulathromycin minimum inhibitory concentration (MIC) values**

<table>
<thead>
<tr>
<th>Indicated pathogen</th>
<th>Date isolated</th>
<th>No. of isolates</th>
<th>MIC** (pg/mL)</th>
<th>MIC** (pg/mL)</th>
<th>MIC range (pg/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.

** MIC

** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

---

**ANIMAL SAFETY**

**Swine**

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 effectiveness 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 head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site 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. Microscopically, 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 preruminant 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 subsequently. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.

Sixteen growing cattle were injected 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.

**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
- 100 mL vial
- 250 mL vial

NADA 141-349, Approved by FDA

**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 http://www.fda.gov/AnimalVets/SafetyHealth.

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

Made in Brazil

0600054AAAAP

Revised: September 2014