ADVERSE REACTIONS

Cattle

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

POST APPROVAL EXPERIENCE

The reported adverse events are based on post approval drug adverse event reporting. 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 between product exposure and adverse events. The following adverse events are listed, in decreasing order of frequency reporting in cattle: injection site reactions and pain, anaphylactic/anaphylactoid reactions. For a complete list of adverse reactions, see the CONTRAINDICATIONS and WARNINGS sections.

APPLICATION OF DRAXXIN (tulathromycin injection) Injectable Solution reported to the CVM can be found at: http://www.fda.gov/vets/animals.

CLINICAL PHARMACOLOGY

At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophobic than hydrophilic media. This solubility profile is consistent with the inclusion of this antibiotic principally associated with membranes. Markedly higher tulathromycin concentrations are observed in the plasma compared to the exudate. The exudate drug concentration has been found to be below the minimum inhibitory concentration (MIC) of the targeted pathogen. Therefore, the clinical relevance of these elevated lung concentrations is undetermined.

Although the relationship between tulathromycin and the characteristics of its antimicrobial activity has not been fully characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens. They also tend to exhibit concentration-dependent killing, the rate of killing or 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 bacterial concentrations remain below the MIC becomes the major determinant of antimicrobial activity. Macrolides also exhibit a post-antibiotic effect (PAE), a period of time during which bacterial killing continues in the absence of free drug, is not known. Therefore, the clinical relevance of these elevated lung concentrations is undetermined.

Following subcutaneous administration into the neck of fodder calves at a dosage of 2.5 mg/kg BW, tulathromycin is rapidly and nearly completely absorbed. Peak plasma concentrations generally occur within 2 to 3 hours after dosing and product relative bioavailability exceeds 90%. Total systemic clearance is approximately 100 mL/h/kg. Tulathromycin distributes extensively to body tissues, as evidenced by volume distribution of volumes of 11 L/kg in healthy ruminating cattle. This extensive volume of distribution is largely responsible for the long elimination half-life of this compound (approximately 2.5 days in the plasma (based on quantifiable terminal plasma drug concentrations) versus 6.75 days in the lungs). The protein binding in plasma is near maximal (98% to 99%). Macrolides are observed with subcutaneous dosages ranging from 1.27 mg/kg BW to 5 mg/kg BW. No pharmacokinetic differences are observed in castrated male versus intact male cattle.

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

MICROBIOLOGY

Cattle

Tulathromycin has demonstrated in vitro activity against Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and Mycoplasma bovis, four pathogens associated with BRD, against Moraxella bovis associated with IBK, and against Fusobacterium necrophorum and Porphyromonas levii associated with bovine foot rot.

The MICs of tulathromycin against indicated BRD and IBK pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI). Briefly, MICs were determined using methods recommended by the CLSI (M11-A6). All MIC values were determined using the 91% isosensitive ratio of this compound.

BRD - The MICs of tulathromycin were determined for BRD isolates obtained from calves in risk studies conducted in the U.S. in 1999. In the therapeutic studies, isolates were obtained from post-treatment nasopharyngeal swabs and infections were caused by Moraxella bovis. The MIC endpoint for all isolates was defined as the fluid concentration required to inhibit bacterial growth. In the M11-A6. All MIC values were determined using the 91% isosensitive ratio of this compound.

IBK - The MICs of tulathromycin were determined for IBK isolates obtained from calves in risk studies conducted in the U.S. in 2004. Isolates were obtained from post-treatment nasopharyngeal swabs and infections were caused by Moraxella bovis. The MIC endpoint for all isolates was defined as the fluid concentration required to inhibit bacterial growth. In the M11-A6. All MIC values were determined using the 91% isosensitive ratio of this compound.

EFFECTIVENESS

Cattle

BRD - In a multi-location field study, 314 calves with naturally occurring BRD were treated with DRAXXIN. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal rectal temperature, normal respiration, and a total score of ≤ 104°F on Day 14. The cure rate was significantly higher (P < 0.05) for calves treated with DRAXXIN compared to saline controls (49% compared to 24%). Tulathromycin was also associated with a significantly longer time to clinical improvement as compared to saline controls. No drug-related clinical signs or other adverse events were observed in either group. The analysis included data from four BRD treatment effectiveness studies conducted in Europe and the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate was significantly higher (P < 0.001) in both US studies compared to saline-treated calves. Fifty-seven DRAXXIN-treated calves compared to 78 saline-treated calves developed as clinical responders in these studies. Fifty-seven DRAXXIN-treated calves compared to 78 saline-treated calves developed as clinical responders in these studies. Fifty-seven DRAXXIN-treated calves compared to 78 saline-treated calves developed as clinical responders in these studies. Fifty-seven DRAXXIN-treated calves compared to 78 saline-treated calves developed as clinical responders in these studies.

A Bayesian meta-analysis was conducted to compare the BRD treatment success rate in young calves (calves weighing 250 lbs or less fed primarily a milk-based diet) and calves (calves weighing more than 250 lbs and fed primarily a roughage and grain-based diet) treated with DRAXXIN. The analysis included data from four BRD treatment effectiveness studies conducted in Europe and the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate was significantly higher (P < 0.001) in both US studies compared to saline-treated calves. Fifty-seven DRAXXIN-treated calves compared to 78 saline-treated calves developed clinical responses. In both studies, the cure rate was significantly higher (P < 0.05) for DRAXXIN-treated calves compared to saline-treated calves. Time to improvement was significantly less (P < 0.001) in both studies for DRAXXIN-treated calves compared to saline-treated calves. Fifty-seven DRAXXIN-treated calves compared to 78 saline-treated calves developed as clinical responders in these studies.

Foot Rot - The effectiveness of DRAXXIN for the treatment of bovine foot rot was evaluated in 170 cattle in two field studies. Cattle diagnosed with bovine foot rot were enrolled and treated with a single subcutaneous dose of DRAXXIN (2.5 mg/kg BW) or an equivalent volume of saline. Cattle were clinically evaluated 7 days after treatment for treatment success, which was based on defined decreases in lesion, swelling, and lameness scores. In both studies, mean lesion improvement was statistically significant (P < 0.001). At all time points, in both studies, the cure rate was significantly higher (P < 0.05) for DRAXXIN-treated calves compared to saline-treated calves. The time to improvement was significantly less (P < 0.001) in both studies for DRAXXIN-treated calves compared to saline-treated calves.

ANIMAL SAFETY

Cattle

Safety studies were conducted in feeder calves receiving a single subcutaneous dose of DRAXXIN (at the 2.5 mg/kg BW) or an equivalent volume of saline. 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 skin at the injection site, and atrophies of the skin at the injection site were also noted. No changes were seen in animals in all dosage groups. Lesions showed signs of resolution within 30 days. No other drug-related lesions were observed macroscopically or microscopically.

An exploratory study was conducted in feeder calves receiving a single subcutaneous dose of DRAXXIN (2.5 mg/kg BW) or an equivalent volume of saline. No lesions were observed. (Microscopically), minimal to mild myositis and scarring 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 2.5 mg/kg BW of DRAXXIN and saline treatments. Lesions were observed macroscopically or microscopically. A minimal to mild injection site reactions, no drug-related clinical signs or other adverse events were observed macroscopically or microscopically.

STORAGE CONDITIONS

Store below 25°C (77°F), with excursions up to 40°C (104°F). This product can tolerate an extended cold storage temperature of 2 hours at a temperature up to 25°C (77°F). When using a drive-off needle or needle with more than 16 gauge, discard any product remaining in the immediately after use.

HOW SUPPLIED

Draxxin Injectable Solution is available in the following package sizes: 50 mL vial 100 mL vial 250 mL vial 500 mL vial NADA 141-244, Approved by FDA

Manufactured by: Zoetis, Inc. Kalamazoo, MI 49007 To report a suspected adverse reaction to or request a safety data sheet call 1-888-DRAXXIN or visit http://www.fda.gov/vets/animals/Safety/HealthInfo. For additional product information call 1-888-DRAXXIN.