Draxxin™
(tulathromycin)
Injectable Solution

Antibiotic
100 mg of tulathromycin/mL

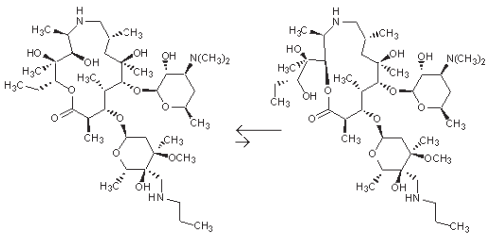
For subcutaneous injection in beef and non-lactating dairy cattle and intramuscular injection in swine only.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
DRAXXIN Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass; triamilide. Each mL of DRAXXIN contains 100 mg of tulathromycin as the free base in a 50% propylene glycol vehicle, monothioglycerol (5 mg/mL), with citric and hydrochloric acids added to adjust pH.

DRAXXIN consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio. Structures of the isomers are shown below.

Figure 1.



The chemical names of the isomers are (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyrano-syl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2S,3S,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribohexopyranosyl]oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylohexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS
Cattle
DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni (Haemophilus somnus),* and for the control of respiratory disease in cattle at high risk of developing BRD, associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni (Haemophilus somnus).*

Swine
DRAXXIN Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica* and *Haemophilus parasuis.*

DOSAGE AND ADMINISTRATION
Cattle
Inject subcutaneously as a single dose in the neck of cattle at a dosage of 2.5 mg/kg (1.1 mL/100 lb) body weight (BW). Do not inject more than 10 mL per injection site.

Table 1. DRAXXIN Cattle Dosing Guide

Animal Weight (Pounds)	Dose Volume (mL)
100	1.1
200	2.3
300	3.4
400	4.5
500	5.7
600	6.8
700	8.0
800	9.1
900	10.2
1000	11.4

Swine
Inject intramuscularly as a single dose in the neck of swine at a dosage of 2.5 mg/kg (0.25 mL/22 lb) BW. Do not inject more than 2.5 mL per injection site.

Table 2. DRAXXIN Swine Dosing Guide

Animal Weight (Pounds)	Dose Volume (mL)
15	0.2
30	0.3
50	0.6
70	0.8
90	1.0
110	1.3
130	1.5
150	1.7
170	1.9
190	2.2
210	2.4
230	2.6
250	2.8
270	3.1
290	3.3

CONTRAINDICATIONS
The use of DRAXXIN Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS
FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.
NOT FOR USE IN CHICKENS OR TURKEYS.

RESIDUE WARNINGS
Cattle
Cattle intended for human consumption must not be slaughtered within 18 days from the last treatment. Do not use in female dairy cattle 20 months of age or older. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

Swine
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

PRECAUTIONS
Cattle
The effects of DRAXXIN on bovine reproductive performance, pregnancy and lactation have not been determined. Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

Swine
The effects of DRAXXIN on porcine reproductive performance, pregnancy and lactation have not been determined. Intramuscular injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

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

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

CLINICAL PHARMACOLOGY
At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the extracellular pathogen activity typically associated with the macrolides.[1] Markedly higher tulathromycin concentrations are observed in the lungs as compared to the plasma. The extent to which lung concentrations represent free (active) drug was not examined. Therefore, the clinical relevance of these elevated lung concentrations is undetermined.

Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens.[2] They also tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the 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. Of the two variables, concentration and exposure time, drug concentration tends to be the most powerful determinant of the duration of PAE.

Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.

Cattle
Following subcutaneous administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, tulathromycin is rapidly and nearly completely absorbed. Peak plasma concentrations generally occur within 15 minutes after dosing and product relative bioavailability exceeds 90%. Total systemic clearance is approximately 170 mL/hr/kg. Tulathromycin distributes extensively into body tissues, as evidenced by volume of distribution values of approximately 11 L/kg in healthy ruminating calves.[3] This extensive volume of distribution is largely responsible for the long elimination half-life of this compound [approximately 2.75 days in the plasma (based on quantifiable terminal plasma drug concentrations) versus 8.75 days for total lung concentrations (based on data from healthy animals)]. Linear pharmacokinetics are observed with subcutaneous doses ranging from 1.27 mg/kg BW to 5.0 mg/kg BW. No pharmacokinetic differences are observed in castrated male versus female calves.

Swine
Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed (T_{max} ~0.25 hour). Subsequently, the drug rapidly distributes into body tissues, achieving a volume of distribution exceeding 15 L/kg. The free drug is rapidly cleared from the systemic circulation ($CL_{systemic}$ =187 mL/hr/kg). However, it has a long terminal elimination half-life (60 to 90 hours) owing to its extensive volume of distribution. Although pulmonary tulathromycin concentrations are substantially higher than concentrations observed in the plasma, the clinical significance of these findings is undetermined. There are no gender differences in swine tulathromycin pharmacokinetics.

MICROBIOLOGY
Cattle
In vitro activity of tulathromycin has been demonstrated against *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni (Haemophilus somnus),* the three major pathogens associated with BRD.

All minimum inhibitory concentration (MIC) values were determined using the 9:1 isomer ratio of this compound. The MICs of tulathromycin were determined for isolates obtained from animals enrolled in field studies in the U.S. during 1999.

Table 3. Tulathromycin MIC values from field studies evaluating BRD in the U.S.

Organism	No. Isolates	MIC_{90}† (µg/mL)	MIC range (µg/mL)
*Mannheimia haemolytica**	642	2.0	0.5 to 64.0
*Pasteurella multocida**	221	1.0	0.25 to 64.0
*Histophilus somni (Haemophilus somnus)**	36	4.0	1.0 to 4.0
*Mycoplasma bovis***	35	1.0	≤0.063 to 2.0

†The minimum inhibitory concentration for 90% of the isolates.
*Clinical isolates supported by clinical data and indications for use.
**The correlation between *in vitro* susceptibility data and clinical response has not been confirmed.

Swine
In vitro activity of tulathromycin has been demonstrated against *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica,* and *Haemophilus parasuis,* commonly isolated pathogens associated with SRD.

All minimum inhibitory concentration (MIC) values were determined using the 9:1 isomer ratio of this compound. The MICs of tulathromycin were determined for isolates obtained from swine enrolled in SRD field studies in the U.S. and Canada during 2000 through 2002.

Table 4. Tulathromycin MIC values from field studies evaluating SRD in the U.S. and Canada.

Organism	No. Isolates	MIC_{90}* (µg/mL)	MIC range (µg/mL)
Actinobacillus pleuropneumoniae	135	32.0	16.0 to 32.0
Haemophilus parasuis	31	2.0	0.25 to >64.0
Pasteurella multocida	55	2.0	0.5 to >64.0
Bordetella bronchiseptica	42	8.0	2.0 to 8.0

*The minimum inhibitory concentration for 90% of the isolates.

EFFECTIVENESS
Cattle
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 attitude/activity, normal respiration, and a rectal temperature of ≤104°F on Day 14. The cure rate was significantly higher ($P \leq 0.05$) in DRAXXIN-treated calves (78%) compared to saline-treated calves (24%). There were two BRD-related deaths in the DRAXXIN-treated calves compared to nine BRD-related deaths in the saline-treated calves.

In another multi-location field study with 399 calves at high risk of developing BRD, administration of DRAXXIN resulted in a significantly reduced incidence of BRD (11%) compared to saline-treated calves (59%). Effectiveness evaluation was based on scored clinical signs of normal attitude/activity, normal respiration, and a rectal temperature of ≤104°F on Day 14. There were no BRD-related deaths in the DRAXXIN-treated calves compared to two BRD-related deaths in the saline-treated calves.

Swine
In a multi-location field study, 266 pigs with naturally occurring SRD were treated with DRAXXIN. Responses to treatment were compared to saline-treated controls. Success was defined as a pig with a normal attitude, normal respiration, and a rectal temperature of <104°F on Day 7. The treatment success rate was significantly greater ($P \leq 0.05$) in DRAXXIN-treated pigs (70.5%) compared to saline-treated pigs (46.1%).

ANIMAL SAFETY
Cattle
Safety studies were conducted in feeder calves receiving a single subcutaneous dose of 25 mg/kg BW, or 3 weekly treatments 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 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 once and two of six calves administered 15 mg/kg BW once.

A safety study was conducted in calves 13 to 27 days of age receiving 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.

Swine
Safety studies were conducted in pigs receiving a single intramuscular dose of 25 mg/kg BW, or 3 weekly intramuscular 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 occurred 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 at all dosages and resolved over time. No other drug-related lesions were observed macroscopically or microscopically.

STORAGE CONDITIONS
Store at or below 25°C (77°F).

HOW SUPPLIED
DRAXXIN Injectable Solution is available in the following package sizes:
100 mL vial
250 mL vial
500 mL vial

[1] Carbon C. Pharmacodynamics of macrolides, azalides, and streptogramins: effect on extracellular pathogens. *Clin Infect Dis* 1998;27:28-32.
[2] Nightingale CJ. Pharmacokinetics and pharmacodynamics of newer macrolides. *Pediatr Infect Dis J* 1997;16:438-443.
[3] Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.

U.S. Patents: See US 6,329,345; US 6,420,536; US 6,514,945; US 6,583,274; US 6,777,393

NADA 141-244, Approved by FDA

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Pfizer Animal Health
Division of Pfizer Inc, NY, NY 10017

To report a suspected adverse reaction call **1-800-366-5288.**
To request a material safety data sheet call **1-800-733-5500.**
For additional DRAXXIN product information call:
1-888-DRAXXIN or go to **www.DRAXXIN.com**

TAKE TIME OBSERVE LABEL DIRECTIONS

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