

# ZOETIS INC.

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Draxxin® 25



Zoetis

(tulathromycin injection)

**Injectable Solution**

**Antibiotic**

25 mg of tulathromycin/mL

For use in suckling calves, dairy calves, veal calves, and swine. Not for use in ruminating cattle.

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

## DESCRIPTION

DRAXXIN 25 Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamylide. Each mL of DRAXXIN 25 contains 25 mg of tulathromycin as the free base in a 50% propylene glycol vehicle, monothioglycerol (5 mg/mL), citric acid (4.8 mg/mL) with hydrochloric acid and sodium hydroxide added to adjust pH. DRAXXIN 25 consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio.

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]- $\alpha$ -L-ribohexopyrano-syl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]- $\alpha$ -L-ribohexopyrano-syl]oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -D-xylohexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

## INDICATIONS

### Swine

DRAXXIN 25 Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica*, *Haemophilus parasuis*, and *Mycoplasma hyopneumoniae*; and for the control of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed.

### Suckling Calves, Dairy Calves, and Veal Calves

**BRD** - DRAXXIN 25 Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*.

## DOSAGE AND ADMINISTRATION

### Swine

Inject intramuscularly as a single dose in the neck at a dosage of 2.5 mg/kg (1 mL/22 lb) Body Weight (BW). Do not inject more than 4 mL per injection site.

Table 1. DRAXXIN 25 Swine Dosing Guide (25 mg/mL)

Animal Weight (Pounds) Dose Volume (mL)

4	0.2
10	0.5
15	0.7
20	0.9
22	1.0
25	1.1
30	1.4
50	2.3
70	3.2
90	4.0

### Calves

Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1 mL/22 lb) body weight (BW). Do not inject more than 11.5 mL per injection site.

Table 2. DRAXXIN 25 Calf Dosing Guide (25 mg/mL)

Animal Weight (Pounds) Dose Volume (mL)

50	2.3
75	3.4
100	4.5
150	7.0
200	9.0
250	11.5

## CONTRAINDICATIONS

The use of DRAXXIN 25 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

##### Swine

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

##### Calves

Calves intended for human consumption must not be slaughtered within 22 days from the last treatment with DRAXXIN 25 Injectable Solution. This drug is not for use in ruminating cattle.

#### PRECAUTIONS

##### Swine

The effects of DRAXXIN 25 Injectable Solution 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.

##### Cattle

The effects of Draxxin 25 Injectable Solution 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.

#### 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

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 extracellular pathogen activity typically associated with the macrolides.<sup>1</sup> Markedly higher tulathromycin concentrations are observed in the lung parenchyma as compared to the 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.<sup>2</sup> 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.<sup>3</sup> Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.

<sup>1</sup> Carbon, C. 1998. Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis., **27**:28-32.

<sup>2</sup> Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J., **16**:438-443.

<sup>3</sup> Andes D, Anon J, Jacobs MR, Craig WA. (2004). Application of pharmacokinetics and pharmacodynamics to antimicrobial therapy of respiratory tract infections. Clin Lab Med., **24**:477-502.

## 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 15 L/kg, which is consistent with extensive tissue binding. This large distribution volume results in a long terminal elimination half-life (60 to 90 hours) despite a rapid systemic free drug clearance (187 mL/kg/hr). 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 tulathromycin total systemic 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<sup>4</sup>, which is consistent with extensive tissue binding. This large distribution volume results in a long terminal elimination half-life of more than 100 hours, despite a rapid systemic free drug clearance (170 mL/kg/hr). 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.

<sup>4</sup> 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 CO<sub>2</sub>-enriched atmosphere. These values are represented in Table 3, below.

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

Indicated pathogen	Date isolated	No. of isolates	MIC <sub>50</sub> **	MIC <sub>90</sub> **	MIC range
			(µg/mL)	(µg/mL)	(µg/mL)
<i>Actinobacillus pleuropneumoniae</i>	2000-2002	135	16	32	16 to 32
	2007-2008	88	16	16	4 to 32
<i>Haemophilus parasuis</i>	2000-2002	31	1	2	0.25 to > 64
<i>Pasteurella multocida</i>	2000-2002	55	1	2	0.5 to > 64
	2007-2008	40	1	2	≤ 0.03 to 2
<i>Bordetella bronchiseptica</i>	2000-2002	42	4	8	2 to 8

\*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.

## Calves

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 (M31-A2). These values are represented in Table 4, below.

Indicated pathogen	Date isolated	No. of isolates	MIC <sub>50</sub> **	MIC <sub>90</sub> **	MIC range
			(µg/mL)	(µg/mL)	(µg/mL)
<i>Mannheimia haemolytica</i>	1999	642	2	2	0.5 to 64
<i>Pasteurella multocida</i>	1999	22131	0.5	1	0.25 to 64
<i>Histophilus somni</i>	1999	36	4	4	1 to 4
<i>Mycoplasma bovis</i>	1999	43	0.125	1	≤ 0.063 to > 64

\*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 were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore effectiveness studies conducted with DRAXXIN 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 attitude, normal respiration, and 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%). *M. hyopneumoniae* was isolated from 106 saline-treated and non-treated sentinel pigs in this study.

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 intranasally and intratracheally 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 ( $P < 0.0001$ ) for DRAXXIN-treated pigs than for saline-treated pigs in both studies (8.52% vs. 23.62% 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 attitude, normal respiration, and rectal temperature of  $< 104^{\circ}\text{F}$ . The treatment success rate was significantly greater ( $P < 0.05$ ) in DRAXXIN-treated pigs compared to saline-treated pigs (59.2% vs. 41.2%).

## 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 (100 mg/mL) support the effectiveness for DRAXXIN 25 Injectable Solution.

**BRD** - In a multi-location field study, 314 calves with naturally occurring BRD were treated with DRAXXIN Injectable Solution (100 mg/mL). 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  $\leq 104^{\circ}\text{F}$  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.

Fifty-two DRAXXIN Injectable Solution (100 mg/mL)-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *Mycoplasma bovis* identified in cultures from pre-treatment nasopharyngeal swabs. Of the 52 DRAXXIN-treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were treatment failures.

A Bayesian meta-analysis was conducted to compare the BRD treatment success rate in young calves (calves weighing 250 lbs or less and fed primarily a milk-based diet) treated with DRAXXIN Injectable Solution (100 mg/mL) to the success rate in older 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 for the approval of DRAXXIN Injectable Solution (100 mg/mL) in the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate in young calves was at least as good as the BRD treatment success rate in older calves. As a result, DRAXXIN Injectable Solution (100 mg/mL) was considered effective for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* in suckling calves, dairy calves, and veal calves.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN Injectable Solution (100 mg/mL) against *Mycoplasma bovis*. A total of 166 calves were inoculated intratracheally with field strains of *Mycoplasma bovis*. When calves became pyrexemic and had abnormal respiration scores, they were treated with either DRAXXIN (2.5 mg/kg BW) subcutaneously or an equivalent volume of saline. Calves were observed for signs of BRD for 14 days post-treatment, then were euthanized and necropsied. In both studies, mean lung lesion percentages were statistically significantly lower in the DRAXXIN-treated calves compared with saline-treated calves (11.3% vs. 28.9%,  $P = 0.0001$  and 15.0% vs. 30.7%,  $P < 0.0001$ ).

## 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 systemic target animal safety studies conducted with DRAXXIN Injectable Solution support the systemic safety for DRAXXIN 25 Injectable Solution.

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 (both studies utilized DRAXXIN Injectable Solution (100 mg/mL)). 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.

Sixteen growing pigs were injected with either saline or DRAXXIN 25 Injectable Solution as a single injection of 4 mL. Injection site observations included two instances of erythema in the DRAXXIN 25-treated group on Day 1 post-injection. No heat, sensitivity, firmness, necrosis, drainage, or swelling was observed at any injection sites in either treatment group. The gross and microscopic findings in the DRAXXIN 25-treated group were consistent with inflammatory changes induced by injections and were considered to be mild or moderate with progression to macroscopic resolution by Day 28 post-injection 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 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 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 subcutaneously. 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/AnimalVeterinary/SafetyHealth>.

For additional DRAXXIN 25 product information call:

**1-888-DRAXXIN** or go to **[www.DRAXXIN.com](http://www.DRAXXIN.com)**

Made in Brazil

Revised: September 2014

Net Contents:

50 mL        060003AA

100 mL      060001AA

250 mL      060005AA

**CPN: 3690375.1**