PIG HEALTH TODAY®
NEW IDEAS FROM PIG RESEARCH
ISSUE 27

discoveries

15 seconds

- **Pharmacologic studies demonstrate that Draxxin® (tulathromycin injection) is rapidly released, rapidly distributed and persists in lung tissue.**
- **Draxxin also accumulates in phagocytic white blood cells that fight bacteria.**
- **Multiple clinical trials show that pigs infected with swine respiratory disease pathogens susceptible to Draxxin have better outcomes compared to controls.**

Pharmacology explains efficacy of Draxxin for SRD

Pharmacologic research demonstrating how Draxxin® (tulathromycin) injection behaves in the pig explains why this antimicrobial remains a valuable treatment for swine respiratory disease (SRD).

Developed by Zoetis scientists exclusively for veterinary use, Draxxin was the first antimicrobial in a macrolide class known as triamilides. A derivative of erythromycin, it is active against *Actinobacillus pleuropneumoniae* (APP), *Pasteurella multocida, Bordetella bronchiseptica, Haemophilus parasuis* and *Mycoplasma hyopneumoniae* (*M. hyo*) — all pathogens that can cause or contribute to SRD.[1]

"Even before its clinical efficacy was established, our scientists found Draxxin is rapidly released from an intramuscular injection site, that it's readily distributed throughout the body and that it persists in the lungs," said Ashley Johnson, DVM, Zoetis.

Johnson cited two key pharmacokinetic studies. In the first, Zoetis investigators administered the recommended dose of 2.5 mg/kg bodyweight either by intravenous injection (IV) into the ear or by intramuscular (IM) injection into the neck, then periodically obtained blood samples.[2]

Rapid release, extensive distribution

Plasma concentrations in the IV and IM groups were similar, but notable was the speed at which Draxxin was released from the IM injection site, the veterinarian said. The T_{max} value, which is the amount of time a drug is present in serum at the maximum concentration, was only 15 minutes, she said. That study also demonstrated that Draxxin is highly bioavailable.[3]

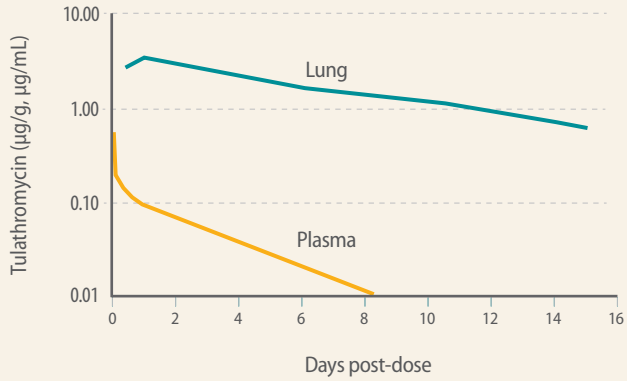
In a second pharmacokinetic study, Zoetis scientists evaluated drug concentrations in plasma and lungs after IM administration to healthy pigs. Lung concentrations were

continued

ASHLEY JOHNSON, DVM
ZOETIS

"The high distribution to lung and slow elimination following a single dose of [Draxxin] are desirable pharmacokinetic attributes for an antimicrobial drug indicated for the treatment of respiratory disease in swine."

Figure 1. Lung and plasma concentrations of Draxxin after IM administration



61.4 times the plasma AUC (Figure 1, Table 1). AUC stands for "area under the curve" and reflects the concentration of a drug and the length of time it's present in blood plasma, Johnson continued.

The elimination half-life of Draxxin in the lungs — the time it takes for the concentration of Draxxin to decline by 50% — was about 6 days. "That's an extremely long half-life," she commented.

At the time the studies were conducted, the investigators concluded that "The high distribution to lung and slow elimination following a single dose of [Draxxin] are desirable pharmacokinetic attributes for an antimicrobial drug indicated for the treatment of respiratory disease in swine."

Immune cell accumulation

One of the antimicrobial's most powerful attributes is its accumulation in immune cells, specifically alveolar macrophages and neutrophils, which are phagocytic white blood cells that fight off bacteria,[4] Johnson said.

When the uptake of Draxxin by neutrophils and alveolar macrophages was monitored for 4 hours after administration, the accumulation of Draxxin was significantly higher compared to accumulation of erythromycin ($p < 0.03$),[5,6] she said (Figure 2).

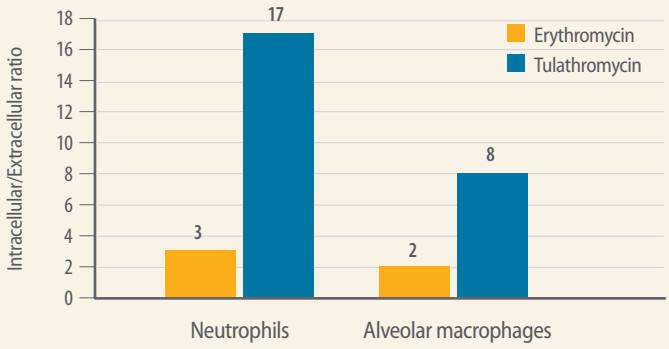
continued

Table 1. Plasma and lung pharmacokinetics of Draxxin in swine after IM administration at 2.5 mg/kg bodyweight

Pharmacokinetic assessment	Plasma	Lung
T_{max} (hours)	0.92	24
C_{max} (µg/mL)	0.581	3.47
$t_{1/2}$ (hours)	49-91	142
$AUC_{0\ inf\ h}$ (ng h/mL)	12,200	749,000
Volume of distribution at steady state (L/KG)	13.2	___
Bioavailability (%)	88	___
Lung AUC / Plasma AUC	___	61.4

T_{max} = time to maximum concentration • C_{max} = maximum concentration • $t_{1/2}$ = half life • AUC = area under concentration time curve

Figure 2. Accumulation of Draxxin in immune cells was significantly higher than for erythromycin.

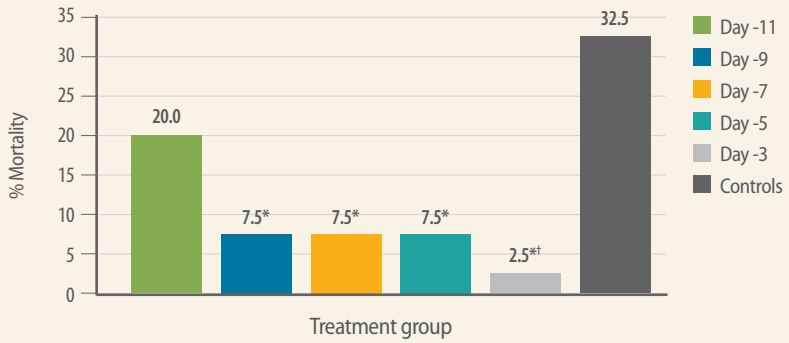


Note: Different superscript letters indicate statistical significance: [ab] $p < 0.03$

One of the antimicrobial's most powerful attributes is its accumulation in immune cells.

The clinical relevance of the early pharmacokinetic research is well established.

Figure 3. Mortality after intranasal challenge with APP serotype 5



* Significantly ($p \leq 0.05$) different from controls.
† Significantly ($p \leq 0.05$) different from day -11 results

Established clinical relevance

The clinical relevance of the early pharmacokinetic research is well established, Johnson continued.

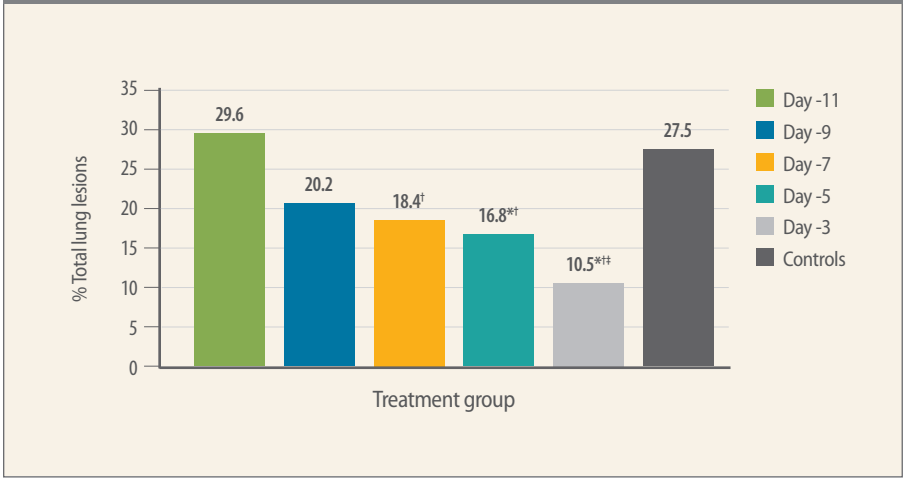
In one of the studies involving 240 healthy pigs about 6 weeks of age, animals were divided into one of six treatment groups.[7] Pigs in five of the groups received an IM injection of Draxxin at 2.5 mg/kg bodyweight, but each group received the injection a different number of days — at 3, 5, 7, 9 or 11 days — before pigs were challenged intranasally with APP serotype 5. To provide a control, the sixth group was not treated but was challenged.

Compared to controls, mortality was significantly reduced in groups treated 5, 7 or 9 days before challenge (Figure 3). However, mortality was lowest in the group treated 3 days before challenge, and it was also significantly lower than mortality among those treated 11 days before challenge.

The mortality results indicate the duration of antimicrobial effectiveness for Draxxin against clinical disease caused by intranasal inoculation of the APP serotype 5 is up to 9 days, Johnson said.

Pigs treated with Draxxin 3 and 5 days before challenge also had significantly reduced weighted lung lesions compared to untreated controls. The weighted percentage of total lung lesions for pigs treated on 3, 5 or 7 days before challenge was significantly ($p = 0.0214$) less than those of pigs treated 9 days before challenge (Figure 4).

Figure 4. Percent of total lung with lesions by treatment group after APP challenge



* Significantly ($p \leq 0.05$) different from controls.
† Significantly ($p \leq 0.05$) different from day -11 results
‡ Significantly ($p \leq 0.05$) different from day -9 results

M. hyo efficacy

M. hyo, which remains a common and costly cause or contributor to SRD,[8] is highly susceptible to Draxxin, Johnson said. The minimum concentration inhibiting growth of 90% of the isolates (MIC_{90}) has been shown to be 0.05 µg/mL. Moreover, swine lung tissue concentrations of Draxxin well above the MIC_{90} level persist for at least 15 days after a single IM dose (Figure 5).[9]

Several studies have demonstrated the clinical efficacy of Draxxin against *M. hyo*.[10,11,12] In one of the studies, investigators evaluated the long-term performance and health of pigs treated with one IM dose of Draxxin after the animals were challenged once daily for 3 consecutive days with an *M. hyo* field isolate. Draxxin was administered between 11 and 23 days after the challenge.

Compared to saline-treated controls, pigs treated with Draxxin had a significantly improved average daily gain ($p \leq 0.0121$), they ate more and had a markedly improved overall feed-to-gain ratio. Mortality was also lower: 4.2% in treated pigs compared to 8.7% in controls.

Compilation of field trials

The efficacy of Draxxin was likewise demonstrated in large field trials with 3,600 weaned pigs infected with SRD pathogens.[13,14,15] Pigs in the studies were from three sources: a

M. hyo, which remains a common and costly cause or contributor to SRD, is highly susceptible to Draxxin.

Draxxin was also credited with a weight advantage in the nursery ranging from 1.54 pounds to 2.91 pounds...

commercial production system in the Midwest, a research facility with pigs obtained from sow farms and a second commercial Midwest production system with pigs that also had influenza A. Caregivers in the study did not know which of the pigs were or were not treated with Draxxin.

Compared to untreated controls, nursery mortality in pigs treated with Draxxin was from 33% to 54% lower. Numerically, fewer pigs had to be retreated, and in two of the studies where it was documented, fewer pigs had to be moved to hospital pens.

Figure 5. Lung drug concentrations in pigs following a single IM injection of Draxxin at 2.5 mg/kg bodyweight and the MIC_{90} level for *M. hyo*

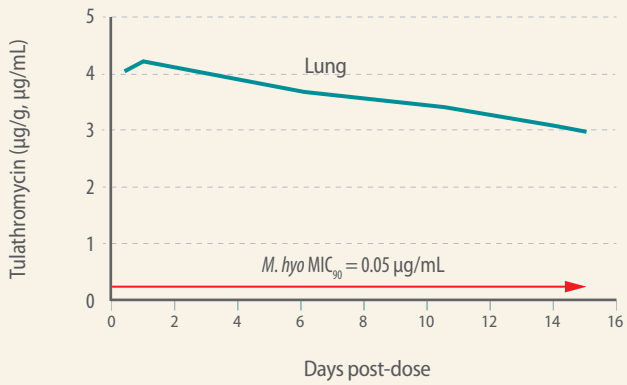
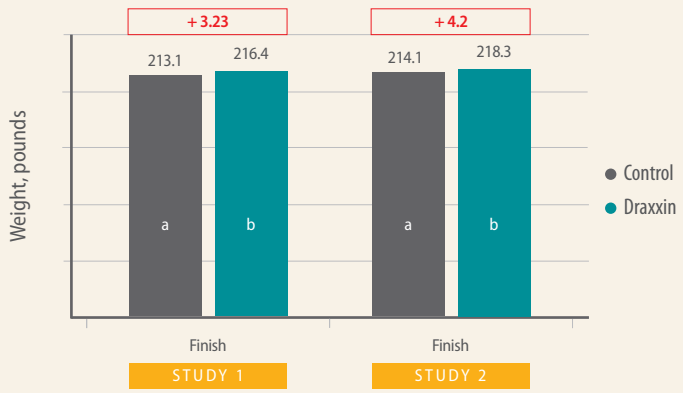


Figure 6. Finishing weights in controls and pigs treated with Draxxin



Note: Different superscripts mean statistically significant difference ($p < 0.05$) within rows

Draxxin was also credited with a weight advantage in the nursery ranging from 1.54 pounds to 2.91 pounds, and in two of the studies where pigs were weighed through finishing, treated pigs had a significant advantage ranging from 3.23 pounds to 4.2 pounds (Figure 6).

"The pharmacokinetic findings with Draxxin clearly explain its efficacy for SRD but even more important are the antimicrobial's practical benefits," Johnson said. "When only one dose is needed, compliance is likely to be better, there's less stress on animals when fewer injections are needed as well as lower labor costs."

Zoetis also has provided extra convenience by offering Draxxin 25 (tulathromycin injection), which has a lower concentration formulated for smaller pigs.

For more information, contact Dr. Johnson (ashley.johnson1@zoetis.com) or your Zoetis representative.

Important Safety Information: Withdraw Draxxin/Draxxin 25 five (5) days prior to slaughter in swine. Do not use in animals known to be hypersensitive to the product. See the full Prescribing Information attached.

[1] Overview of respiratory diseases of pigs. Merck Veterinary Manual. https://www.merckvetmanual.com/respiratory-system/respiratory-diseases-of-pigs/overview-of-respiratory-diseases-of-pigs

[2] Benchaoui HA, et al. Pharmacokinetics and lung tissue concentrations of tulathromycin in swine. J Vet Pharmacol Ther. 2004;27:203-210.

[3] Ibid.

[4] Fischer CD, et al. Direct and Indirect Anti-Inflammatory Effects of Tulathromycin in Bovine Macrophages: Inhibition of CXCL-8 Secretion, Induction of Apoptosis, and Promotion of Efferocytosis. Antimicrob Agents Chemother. 2013 March;57(3): 1385-1393.

[5] Siegel TW, et al. Cellular uptake of the triamilide tulathromycin by bovine and porcine phagocytic cells in vitro. J Anim Sci 2004;82(1):186.

[6] Fischer CD, et al. Direct and Indirect Anti-Inflammatory Effects of Tulathromycin in Bovine Macrophages

[7] McKelvie J, et al. Comparative efficacy of tulathromycin injectable solution (Draxxin) for the treatment of experimentally induced respiratory infections in swine. 2005 Am Assoc Swine Vet annual meeting, Toronto.

[8] Mycoplasmal pneumonia (enzootic pneumonia), Iowa State Unimversity. https://vetmed.iastate.edu/vdpam/FSVD/swine/index-diseases/mycoplasmal-pneumonia

[9] Benchaoui HA, et al. Pharmacokinetics and lung tissue concentrations

[10] Data on file. Study Report No. 1121R-60-07-292, Zoetis LLC.

[11] Data on file. Study Report No. 1121C-60-04-230, Zoetis LLC.

[12] Data on file. Study Report No. 1121C-60-03-209, Zoetis LLC.

[13] King D, et al. Effects of Draxxin at weaning in pigs on control of swine respiratory disease including "low" level of PRRS involvement and subsequent performance of pigs. 2013 Am Assoc Swine Vet annual meeting, San Diego.

[14] King D, et al. Effects of Draxxin at weaning for control of swine respiratory disease in pigs experiencing a natural outbreak. 2014 Am Assoc Swine Vet annual meeting, Dallas.

[15] Sievers C, et al. Effect of tulathromycin or ceftiofur free acid on post-weaning performance and economic return in porcine reproductive and respiratory syndrome virus infected pigs. 2014 Am Assoc Swine Vet annual meeting, Dallas.

discoveries

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To contact *Pig Health Today*:
editor@pighealthtoday.com
PIGHEALTHTODAY.COM

To contact Zoetis:
888.963.8471
ZOETISUS.COM/PORK

Draxxin® 25
(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 triamilide. 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]-α-L-ribohexopyrano-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 (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-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)-β-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.[1] 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.[2] 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.[3] Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.

[1] Carbon, C. 1998. Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis., **27**:28-32.
[2] Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J., **16**:438-443.
[3] 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[4], 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.
[4] 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 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_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Actinobacillus pleuropneumoniae	2000-2002 2007-2008	135 88	16 16	32 16	16 to 32 4 to 32
Haemophilus parasuis	2000-2002	31	1	2	0.25 to > 64
Pasteurella multocida	2000-2002 2007-2008	55 40	1 1	2 2	0.5 to> 64 ≤ 0.03 to 2
Bordetella bronchiseptica	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.

Table 4. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating BRD in the U.S.

Indicated pathogen	Date isolated	No. of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	1999	642	2	2	0.5 to 64
Pasteurella multocida	1999	221	0.5	1	0.25 to 64
Histophilus somni	1999	36	4	4	1 to 4
Mycoplasma bovis	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 ≤ 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°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 ≤ 104°F on Day 14. The cure rate was significantly higher (P ≤ 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 pyrexic 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

Approved by FDA under # NADA 141-349

zoetis

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**

4019203A&P
Revised: March 2019

FULL PRESCRIBING INFORMATION FOR USE IN SWINE ONLY

Draxxin®

(tulathromycin injection)

Injectable Solution

Antibiotic

100 mg of tulathromycin/mL

For use in swine.

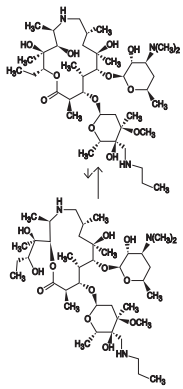
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

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, 500 mg propylene glycol, 19.2 mg citric acid and 5 mg monothioglycerol. Sodium hydroxide or hydrochloric acid may be 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 (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyrano-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)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS

Swine

DRAXXIN 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.

DOSAGE AND ADMINISTRATION

Swine

Inject intramuscularly as a single dose in the neck 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 21. 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

Swine

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

PRECAUTIONS

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

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.

POST APPROVAL EXPERIENCE

The following adverse events are based on post approval adverse drug experience 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 to product exposure using these data. For a complete listing of adverse reactions for DRAXXIN (tulathromycin injection) 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 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 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. 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.

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

*[2] Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J., **16**:438-443.*

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

Swine

In vitro activity of tulathromycin has been demonstrated against *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, Haemophilus parasuis,* and *Mycoplasma hyopneumoniae.*

The MICs of tulathromycin against indicated SRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A and M31-A3). MICs for *Haemophilus parasuis* were determined using Veterinary Fastidious Medium and were incubated up to 48 hours at 35 to 37°C in a CO2-enriched atmosphere. All MIC values were determined using the 9:1 isomer ratio of this compound. Isolates obtained in 2000 and 2002 were from lung samples from saline-treated pigs and non-treated sentinel pigs enrolled in Treatment of SRD field studies in the U.S. and Canada. Isolates obtained in 2007 and 2008 were from lung samples from saline-treated and DRAXXIN-treated pigs enrolled in the Control of SRD field study in the U.S. and Canada. The results are shown in Table 4.

Table 4. 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_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Actinobacillus pleuro-pneumoniae	2000-2002	135	16	32	16 to 32
	2007-2008	88	16	16	4 to 32
Haemophilus parasuis	2000-2002	31	1	2	0.25 to > 64
Pasteurella multocida	2000-2002	55	1	2	0.5 to > 64
	2007-2008	40	1	2	≤ 0.03 to 2
Bordetella bronchiseptica	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.

EFFECTIVENESS

Swine

In a multi-location field study to evaluate the treatment of naturally occurring SRD, 266 pigs were treated with DRAXXIN. 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 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 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°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%).

ANIMAL SAFETY

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 below 25°C (77°F), with excursions up to 40°C (104°F). Use this product within 45 days of the first puncture and puncture a maximum of 20 times. If more than 20 punctures are anticipated, the use of automatic injection equipment of a repeater syringe is recommended. When using a draw-off spike or needle with bore diameter larger than 16 gauge, discard any product remaining in the vial 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

zoetis

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 product information call: **1-888-DRAXXIN** or go to **www.DRAXXIN.com**

TAKE TIME OBSERVE LABEL DIRECTIONS

Made in Spain

Revised: June 2018
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