HFV-305,
Division of
Dockets Management

Date of Approval:

SEP - 4 2007

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-244

DRAXXIN Injectable Solution

Tulathromycin
Cattle (Beef and Non-lactating Dairy)

To add *Mycoplasma bovis* to the list of target pathogens for the bovine respiratory disease control "at high risk" indication.

Sponsored by:

Pfizer, Inc.

2007-141-244

FOIS 3

## TABLE OF CONTENTS

I. GENERAL INFORMATION: ..... 1

II. EFFECTIVENESS: ..... 2

A. Dosage Characterization: ..... 2
B. Substantial Evidence: ..... 2

III. TARGET ANIMAL SAFETY: ..... 4

IV. HUMAN FOOD SAFETY: ..... 4

A. Toxicology: ..... 4
B. Residue Chemistry: ..... 4
C. Microbial Food Safety: ..... 4
D. Analytical Method for Residues: ..... 4

V. USER SAFETY: ..... 4

VI. AGENCY CONCLUSIONS: ..... 5

A. Marketing Status: ..... 5
B. Exclusivity: ..... 5
C. Supplemental Applications: ..... 5
D. Patent Information: ..... 5

VII. ATTACHMENTS: ..... 6

# I. GENERAL INFORMATION:

| | |
|---|---|
| **A. File Number:** | NADA 141-244 |
| **B. Sponsor:** | Pfizer, Inc.<br>235 East 42d St.<br>New York, NY 10017<br><br>Drug Labeler Code: 000069 |
| **C. Proprietary Name(s):** | DRAXXIN Injectable Solution |
| **D. Established Name(s):** | Tulathromycin |
| **E. Pharmacological Category:** | Antimicrobial |
| **F. Dosage Form(s):** | Sterile injectable solution |
| **G. Amount of Active Ingredient(s):** | 100 mg/mL |
| **H. How Supplied:** | 50 mL, 100 mL, 250 mL, and 500 mL glass vials |
| **I. How Dispensed:** | Rx |
| **J. Dosage(s):** | 2.5 mg/kg body weight (BW), administered once |
| **K. Route(s) of Administration:** | Subcutaneous (cattle) or intramuscular (swine) injection in the neck |
| **L. Species/Class(es):** | Beef and non-lactating dairy cattle, and swine |
| **M. Indication(s):** | Cattle: DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* (*Haemophilus somnus*), and *Mycoplasma bovis;* and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, ***and Mycoplasma bovis.***<br><br>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*.

**N. Effect(s) of Supplement:** This supplement provides for the addition of *Mycoplasma bovis* to the list of target pathogens for the BRD control "at high risk" indication.

## II. EFFECTIVENESS:

### A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains dosage characterization information for cattle.

### B. Substantial Evidence:

Effectiveness of tulathromycin 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* was previously demonstrated in the original approval, and is summarized in the FOI Summary for DRAXXIN Injectable Solution (NADA 141-244) dated May 24, 2005.

Effectiveness of tulathromycin for the treatment of BRD associated with *Mycoplasma bovis* was demonstrated using two experimentally-induced infection model studies and examining *M. bovis* data from cattle used in the BRD treatment studies conducted for the original approval of DRAXXIN Injectable Solution. These data are summarized in the FOI Summary for DRAXXIN Injectable Solution (NADA 141-244) dated August 18, 2006.

Effectiveness of tulathromycin for the control of respiratory disease in cattle at high risk of developing BRD associated with *M. bovis* was further demonstrated by examining *M. bovis* data from cattle used in the BRD control studies conducted for the original approval of DRAXXIN Injectable Solution.

#### 1. Identification of *Mycoplasma bovis* in Cattle Enrolled in BRD Control Studies

The presence of *M. bovis* in calves enrolled in the BRD control studies (1133C-60-99-310, 1133C-60-99-311, and 1133C-60-99-312) summarized in the FOI Summary for DRAXXIN Injectable Solution (NADA 141-244)

dated May 24, 2005, was examined. None of the isolates obtained from the Texas site (1131C-60-99-309) survived transport to the laboratory.

*M. bovis* was identified by fluorescent antibody (FA) test from samples which were cultured from nasopharyngeal swabs of saline-treated non-responders and from lung swabs or lung tissue of saline-treated calves that died during the studies. A total of 50 FA-positive isolates were identified, as shown in Table 1.

**Table 1. Number of isolates from cattle with naturally-occurring BRD which were positive for *M. bovis* by FA test.**

| Study Number and Location | No. of Isolates Positive for *M. bovis* by FA |
|---|---|
| 1133C-60-99-310 Idaho | 11 |
| 1133C-60-99-311 Nebraska | 4 |
| 1133C-60-99-312 California | 35 |
| **Total** | **50** |

## 2. Determination of Minimum Inhibitory Concentrations (MICs)

The MICs of tulathromycin were determined for *M. bovis* isolates obtained from calves enrolled in BRD treatment and control field studies in the U.S. in 1999. In the treatment studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves and from lung swabs or lung tissue of saline-treated calves that died. In the control studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders and from lung swabs or lung tissue of saline-treated calves that died. MICs were determined using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). The results are shown in Table 2.

**Table 2. Tulathromycin minimum inhibitory concentration (MIC) values* for *M. bovis* 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) |
|---|---|---|---|---|---|
| *Mycoplasma bovis* | 1999 | 43 | 0.125 | 1 | ≤ 0.063 to > 64 |

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The MIC to encompass 50% and 90% of the isolates, respectively.

## III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains a summary of target animal safety studies for cattle.

## IV. HUMAN FOOD SAFETY:

### A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains a summary of all toxicology studies.

### B. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains a summary of residue chemistry studies for cattle.

### C. Microbial Food Safety:

The impact of the proposed change in the control indication for tulathromycin in cattle from "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)*" to "For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*" on microbial food safety was carefully considered by the Agency. The Agency determined that this change should not significantly impact public health, and therefore an evaluation of microbial food safety regarding this change was not necessary at this time.

### D. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains the analytical method summaries for tulathromycin in cattle.

## V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to DRAXXIN Injectable Solution:

For use in animals only. Not for human use. Keep out of reach of children.

To request a material safety data sheet, call 1-800-733-5500.

## VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that DRAXXIN Injectable Solution, when used according to the label, is safe and effective for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mycoplasma bovis*. Additionally, data demonstrate that residues in food products derived from cattle treated with DRAXXIN Injectable Solution will not represent a public health concern when the product is used according to the label.

### A. Marketing Status:

Labeling restricts this drug to use by or on order of a licensed veterinarian. This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat BRD, and (b) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

### B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the control of respiratory disease in cattle at high risk of developing BRD associated with *Mycoplasma bovis* for which this supplement is approved.

### C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

### D. Patent Information:

Tulathromycin is under the following U.S. patent numbers:

| U.S. Patent Number | Date of Expiration |
|---|---|
| 6,329,345 | November 18, 2019 |
| 6,420,536 | May 29, 2018 |
| 6,514,945 | January 24, 2021 |
| 6,583,274 | May 2, 2020 |
| 6,777,393 | May 29, 2018 |

## VII. ATTACHMENTS:

Facsimile Labeling:

a. DRAXXIN Injectable Solution – 50 mL vial label and insert
b. DRAXXIN Injectable Solution – 50 mL carton
c. DRAXXIN Injectable Solution – 50 mL shipper label
d. DRAXXIN Injectable Solution – 100 mL vial label and insert
e. DRAXXIN Injectable Solution – 100 mL carton
f. DRAXXIN Injectable Solution – 100 mL shipper label
g. DRAXXIN Injectable Solution – 250 mL vial label and insert
h. DRAXXIN Injectable Solution – 250 mL carton
i. DRAXXIN Injectable Solution – 250 mL shipper label
j. DRAXXIN Injectable Solution – 500 mL vial label and insert
k. DRAXXIN Injectable Solution – 500 mL carton
l. DRAXXIN Injectable Solution – 500 mL shipper label

# 50 mL Vial

COPY AREA
25.5" WIDE X 1.25" HIGH

linear pharmacokinetics are observed with subcutaneous doses ranging from 0.5 mg/kg to 5.0 mg/kg BW. No pharmacokinetic differences are observed in castrated male versus female calves.

*Clearance and volume estimates are based on intravascular comparators of tulathromycin administered either subcutaneous or intravenous injection.*

**Series**

Following intramuscular administration to healthy pigs at a dosage of 2.5 mg/kg, tulathromycin is rapidly and completely absorbed (Tmax ~0.25 hour). Subsequently, the drug rapidly distributes into body tissues, achieving a high tissue/serum concentration ratio (>15:1). The free drug is rapidly cleared from the systemic circulation (Clsystemic = 187 mL/hr/kg); however, it has a long terminal elimination half-life (t½ = 90 hours) owing to its extensive volume of distribution. Although concentrations are substantially higher in lung than in plasma, the clinical significance of these findings is undetermined. There are no gender differences in pharmacokinetics.

**MICROBIOLOGY**

**Cattle**

In vitro activity of tulathromycin has been demonstrated against *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, *Mycoplasma bovis*, four pathogens associated with BRD.

The minimum inhibitory concentrations (MICs) of tulathromycin against *Mycoplasma bovis* are recommended by the Clinical and Laboratory Standards Institute (M31-A2). All MIC values were determined using the 2:1 isomer ratio of this compound.

The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and control field studies in the U.S. in 1999. The respective results for U.S. isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves and from lung samples from all study calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders and from lung samples from all saline-treated calves that died. The results are shown in Table 3.

Table 3. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from U.S.

| Bacterial Species | Year | Number of Isolates | MIC50 (µg/mL) | MIC90 (µg/mL) | Range (µg/mL) |
|---|---|---|---|---|---|
| *Mannheimia haemolytica* | 1999 | 242 | 2 | 2 | 0.5 to 8 |
| *Pasteurella multocida* | 1999 | 231 | 0.5 | 1 | 0.25 to 8 |
| *Histophilus somni* | 1999 | 34 | 4 | 4 | 1 to 4 |
| *Mycoplasma bovis* | 1999 | 43 | 0.25 | 1 | <0.25 to 1 |

* The concentration between or at the concentration given that inhibits the growth of 50% and 90% of the isolates, respectively.

**Swine**

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

The MICs of tulathromycin against indicated SRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). All MIC values were determined using the 2:1 isomer ratio of this compound. The MICs of tulathromycin against lung isolates obtained from lung samples from saline-treated and non-treated sentinel pigs enrolled in SRD field studies in the U.S. and Canada between 2000 and 2002. The results are shown in Table 4.

Table 4. Tulathromycin MIC values* for indicated pathogens isolated from lungs of pigs with SRD in the U.S. and Canada

| Bacterial Species | Year | Number of Isolates | MIC50 (µg/mL) | MIC90 (µg/mL) | Range (µg/mL) |
|---|---|---|---|---|---|
| *Actinobacillus pleuropneumoniae* | 2000 | 55 | 16 | 32 | 8 to 32 |
| *Pasteurella multocida* | 2000 | 54 | 1 | 2 | 0.25 to 16 |
| *Bordetella bronchiseptica* | 2000 | 46 | 1 | 2 | 0.25 to 16 |
| *Haemophilus parasuis* | 2000 | 42 | 1 | 2 | 0.5 to 16 |

* The concentration between or at the concentration given that inhibits the growth of 50% and 90% of the isolates, respectively.

**Cattle**

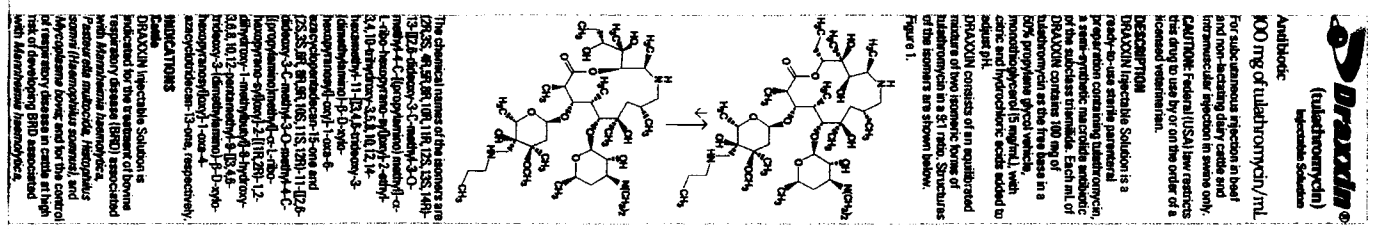
In a multi-location field study, 314 calves with naturally occurring BRD were treated with DRAXXIN.

Response to treatment were assessed by veterinarians blinded to treatment. A calf was defined as a calf with normal rectal temperature (< 104°F on Day 14, the cure rate was 90% for DRAXXIN-treated calves (282/314) versus 73% for saline-treated calves (74%). There were two BRD-related deaths in the DRAXXIN-treated calves versus four BRD-related deaths in the saline-treated calves. Efficacy was established in this study based on the DRAXXIN-treated calves.

In another multi-location field study with 388 calves at high risk of developing BRD, administration of DRAXXIN resulted in a statistically reduced incidence of BRD (11% versus 19%). Effectiveness evaluation was based on the DRAXXIN-treated calves compared to saline-treated calves.

Nasopharyngeal swabs were taken at normal rectal temperature, at the onset of BRD-related clinical signs, and at necropsy. Fifty-two DRAXXIN-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had culture results in pre-treatment nasopharyngeal swabs. Of the 52 DRAXXIN-treated calves, 37 (71.2%) were categorized as cures and 15 (28.8%) 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.

Two additional laboratory studies were conducted to confirm the effectiveness of DRAXXIN against *M. bovis*. A total of 166 calves were randomized and allocated to treatment groups. Of these, 4 calves were removed from the study because they became pyrexic and had abnormal respiration scores, they were treated with either DRAXXIN (2.5 mg/kg BW SQ) or an equipotent dose of saline.



Copy Area
3.0625"Wide
X
1.25 High

110-300-07

**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.

**Net Contents: 50 mL**
NADA 141-244, Approved by FDA

Pfizer

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

Made in France

GLUE AREA
NO PRINTING

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

**DOSAGE AND ADMINISTRATION**
**Cattle**
Inject subcutaneously as a single dose at the rate of 2.5 mg/kg of 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 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 | 0.5 |
| 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 treated 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 calves to be processed for veal.
**Swine**
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

**CAUTIONS**
**Cattle**
In one field study, two calves treated with DRAXXIN at 2.5 mg/kg BW exhibited transient ataxia and recumbency. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.
**Swine**
In one field study, one out of 49 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

**CLINICAL PHARMACOLOGY**
Azithromycin (tulathromycin A) is a weak base (pKa approximately 9) and more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the physicochemical properties of the macrolides. Markedly higher tulathromycin concentrations are typically associated with the macrolides, which are lipophilic and weak bases (pKa 7.8–8.4). The lipophilicity of the macrolide allows it to penetrate into eukaryotic cells. In pH gradients, by increasing the macrolide pKa, PAE gains and the apparent volume of distribution (Vd) increase. The lipophilicity also increases the rate and extent of drug uptake by bacterial cells. Therefore, the tissue concentrations exceed those of the extracellular fluid. The tissue concentrations represent free (active) drug and pathogen dependent. In vitro, PAE depends on the exposure time, drug concentration and exposure time. Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been established in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

U.S. Patents: Not Applicable
US 5,250,519; US 5,606,040;
US 5,922,774; US 6,777,390

NADA 141-244, Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

Made in France

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

**HOW SUPPLIED**
DRAXXIN Injectable Solution is available in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

U.S. Patents: Not Applicable
US 5,250,519; US 5,606,040;
US 5,922,774; US 6,777,390

NADA 141-244, Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

Made in France

**ADVERSE REACTIONS**
**Cattle**
In one field study, two calves treated with DRAXXIN at 2.5 mg/kg BW exhibited transient ataxia and recumbency. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.
**Swine**
In one field study, one out of 49 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

**CLINICAL PHARMACOLOGY**
Azithromycin (tulathromycin A) is a weak base (pKa approximately 9) and more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the physicochemical properties of the macrolides. Markedly higher tulathromycin concentrations are typically associated with the macrolides, which are lipophilic and weak bases (pKa 7.8–8.4). The lipophilicity of the macrolide allows it to penetrate into eukaryotic cells. In pH gradients, by increasing the macrolide pKa, PAE gains and the apparent volume of distribution (Vd) increase. The lipophilicity also increases the rate and extent of drug uptake by bacterial cells. Therefore, the tissue concentrations exceed those of the extracellular fluid. The tissue concentrations represent free (active) drug and pathogen dependent. In vitro, PAE depends on the exposure time, drug concentration and exposure time. Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been established in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

U.S. Patents: Not Applicable
US 5,250,519; US 5,606,040;
US 5,922,774; US 6,777,390

NADA 141-244, Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

Made in France

*Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, and Haemophilus parasuis.*

**DOSAGE AND ADMINISTRATION**
**Cattle**
Inject subcutaneously as a single dose at the rate of 2.5 mg/kg of 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 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 | 0.5 |
| 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 treated 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 calves to be processed for veal.
**Swine**
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

**CAUTIONS**
**Cattle**
The effects of DRAXXIN on bovine 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.
**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 ataxia and recumbency. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.
**Swine**
In one field study, one out of 49 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

**CLINICAL PHARMACOLOGY**
Azithromycin (tulathromycin A) is a weak base (pKa approximately 9) and more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the physicochemical properties of the macrolides. Markedly higher tulathromycin concentrations are typically associated with the macrolides, which are lipophilic and weak bases (pKa 7.8–8.4). The lipophilicity of the macrolide allows it to penetrate into eukaryotic cells. In pH gradients, by increasing the macrolide pKa, PAE gains and the apparent volume of distribution (Vd) increase. The lipophilicity also increases the rate and extent of drug uptake by bacterial cells. Therefore, the tissue concentrations exceed those of the extracellular fluid. The tissue concentrations represent free (active) drug and pathogen dependent. In vitro, PAE depends on the exposure time, drug concentration and exposure time. Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been established in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

U.S. Patents: Not Applicable
US 5,250,519; US 5,606,040;
US 5,922,774; US 6,777,390

NADA 141-244, Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

Made in France

*Bordetella bronchiseptica, and Haemophilus parasuis.*

**DOSAGE AND ADMINISTRATION**
**Cattle**
Inject subcutaneously as a single dose at the rate of 2.5 mg/kg of 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 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 | 0.5 |
| 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 treated 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 calves to be processed for veal.
**Swine**
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

**CAUTIONS**
**Cattle**
The effects of DRAXXIN on bovine 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.
**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 ataxia and recumbency. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.
**Swine**
In one field study, one out of 49 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

**CLINICAL PHARMACOLOGY**
Azithromycin (tulathromycin A) is a weak base (pKa approximately 9) and more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the physicochemical properties of the macrolides. Markedly higher tulathromycin concentrations are typically associated with the macrolides, which are lipophilic and weak bases (pKa 7.8–8.4). The lipophilicity of the macrolide allows it to penetrate into eukaryotic cells. In pH gradients, by increasing the macrolide pKa, PAE gains and the apparent volume of distribution (Vd) increase. The lipophilicity also increases the rate and extent of drug uptake by bacterial cells. Therefore, the tissue concentrations exceed those of the extracellular fluid. The tissue concentrations represent free (active) drug and pathogen dependent. In vitro, PAE depends on the exposure time, drug concentration and exposure time. Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been established in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

U.S. Patents: Not Applicable
US 5,250,519; US 5,606,040;
US 5,922,774; US 6,777,390

NADA 141-244, Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

Made in France

*Haemophilus parasuis.*

**DOSAGE AND ADMINISTRATION**
**Cattle**
Inject subcutaneously as a single dose at the rate of 2.5 mg/kg of 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 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 | 0.5 |
| 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 treated 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 calves to be processed for veal.
**Swine**
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

**CAUTIONS**
**Cattle**
The effects of DRAXXIN on bovine 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.
**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 ataxia and recumbency. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.
**Swine**
In one field study, one out of 49 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

**CLINICAL PHARMACOLOGY**
Azithromycin (tulathromycin A) is a weak base (pKa approximately 9) and more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the physicochemical properties of the macrolides. Markedly higher tulathromycin concentrations are typically associated with the macrolides, which are lipophilic and weak bases (pKa 7.8–8.4). The lipophilicity of the macrolide allows it to penetrate into eukaryotic cells. In pH gradients, by increasing the macrolide pKa, PAE gains and the apparent volume of distribution (Vd) increase. The lipophilicity also increases the rate and extent of drug uptake by bacterial cells. Therefore, the tissue concentrations exceed those of the extracellular fluid. The tissue concentrations represent free (active) drug and pathogen dependent. In vitro, PAE depends on the exposure time, drug concentration and exposure time. Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been established in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

U.S. Patents: Not Applicable
US 5,250,519; US 5,606,040;
US 5,922,774; US 6,777,390

NADA 141-244, Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

Made in France

*parasuis.*

**DOSAGE AND ADMINISTRATION**
**Cattle**
Inject subcutaneously as a single dose at the rate of 2.5 mg/kg of 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 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 | 0.5 |
| 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 treated 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 calves to be processed for veal.
**Swine**
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

**CAUTIONS**
**Cattle**
The effects of DRAXXIN on bovine 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.
**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 ataxia and recumbency. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.
**Swine**
In one field study, one out of 49 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

**CLINICAL PHARMACOLOGY**
Azithromycin (tulathromycin A) is a weak base (pKa approximately 9) and more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the physicochemical properties of the macrolides. Markedly higher tulathromycin concentrations are typically associated with the macrolides, which are lipophilic and weak bases (pKa 7.8–8.4). The lipophilicity of the macrolide allows it to penetrate into eukaryotic cells. In pH gradients, by increasing the macrolide pKa, PAE gains and the apparent volume of distribution (Vd) increase. The lipophilicity also increases the rate and extent of drug uptake by bacterial cells. Therefore, the tissue concentrations exceed those of the extracellular fluid. The tissue concentrations represent free (active) drug and pathogen dependent. In vitro, PAE depends on the exposure time, drug concentration and exposure time. Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been established in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

U.S. Patents: Not Applicable
US 5,250,519; US 5,606,040;
US 5,922,774; US 6,777,390

NADA 141-244, Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

Made in France

**DOSAGE AND ADMINISTRATION**
**Cattle**
Inject subcutaneously as a single dose at the rate of 2.5 mg/kg of 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 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 | 0.5 |
| 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 treated 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 calves to be processed for veal.
**Swine**
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

**CAUTIONS**
**Cattle**
The effects of DRAXXIN on bovine 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.
**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 ataxia and recumbency. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.
**Swine**
In one field study, one out of 49 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

**CLINICAL PHARMACOLOGY**
Azithromycin (tulathromycin A) is a weak base (pKa approximately 9) and more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the physicochemical properties of the macrolides. Markedly higher tulathromycin concentrations are typically associated with the macrolides, which are lipophilic and weak bases (pKa 7.8–8.4). The lipophilicity of the macrolide allows it to penetrate into eukaryotic cells. In pH gradients, by increasing the macrolide pKa, PAE gains and the apparent volume of distribution (Vd) increase. The lipophilicity also increases the rate and extent of drug uptake by bacterial cells. Therefore, the tissue concentrations exceed those of the extracellular fluid. The tissue concentrations represent free (active) drug and pathogen dependent. In vitro, PAE depends on the exposure time, drug concentration and exposure time. Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been established in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

U.S. Patents: Not Applicable
US 5,250,519; US 5,606,040;
US 5,922,774; US 6,777,390

NADA 141-244, Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

Made in France

*Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, and Haemophilus parasuis.*

**DOSAGE AND ADMINISTRATION**
**Cattle**
Inject subcutaneously as a single dose at the rate of 2.5 mg/kg of 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 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 | 0.5 |
| 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 treated 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 calves to be processed for veal.
**Swine**
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

**CAUTIONS**
**Cattle**
The effects of DRAXXIN on bovine 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.
**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 ataxia and recumbency. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.
**Swine**
In one field study, one out of 49 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

**CLINICAL PHARMACOLOGY**
Azithromycin (tulathromycin A) is a weak base (pKa approximately 9) and more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the physicochemical properties of the macrolides. Markedly higher tulathromycin concentrations are typically associated with the macrolides, which are lipophilic and weak bases (pKa 7.8–8.4). The lipophilicity of the macrolide allows it to penetrate into eukaryotic cells. In pH gradients, by increasing the macrolide pKa, PAE gains and the apparent volume of distribution (Vd) increase. The lipophilicity also increases the rate and extent of drug uptake by bacterial cells. Therefore, the tissue concentrations exceed those of the extracellular fluid. The tissue concentrations represent free (active) drug and pathogen dependent. In vitro, PAE depends on the exposure time, drug concentration and exposure time. Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been established in the following package sizes:

50 mL vial
100 mL vial
250 mL vial
500 mL vial

U.S. Patents: Not Applicable
US 5,250,519; US 5,606,040;
US 5,922,774; US 6,777,390

NADA 141-244, Approved by FDA

Distributed by:

Pfizer Animal Health
Div. of Pfizer Inc., NY, NY 10017

To report a suspected adverse reaction call **1-888-398-2398**
For information on product safety data sheet call **1-800-733-0989**
For additional DRAXXIN product information call:
**1-800-DRAXXIN**
or go to **www.DRAXXIN.com**

79-1106-00-X1
July 2007
MOCK12045

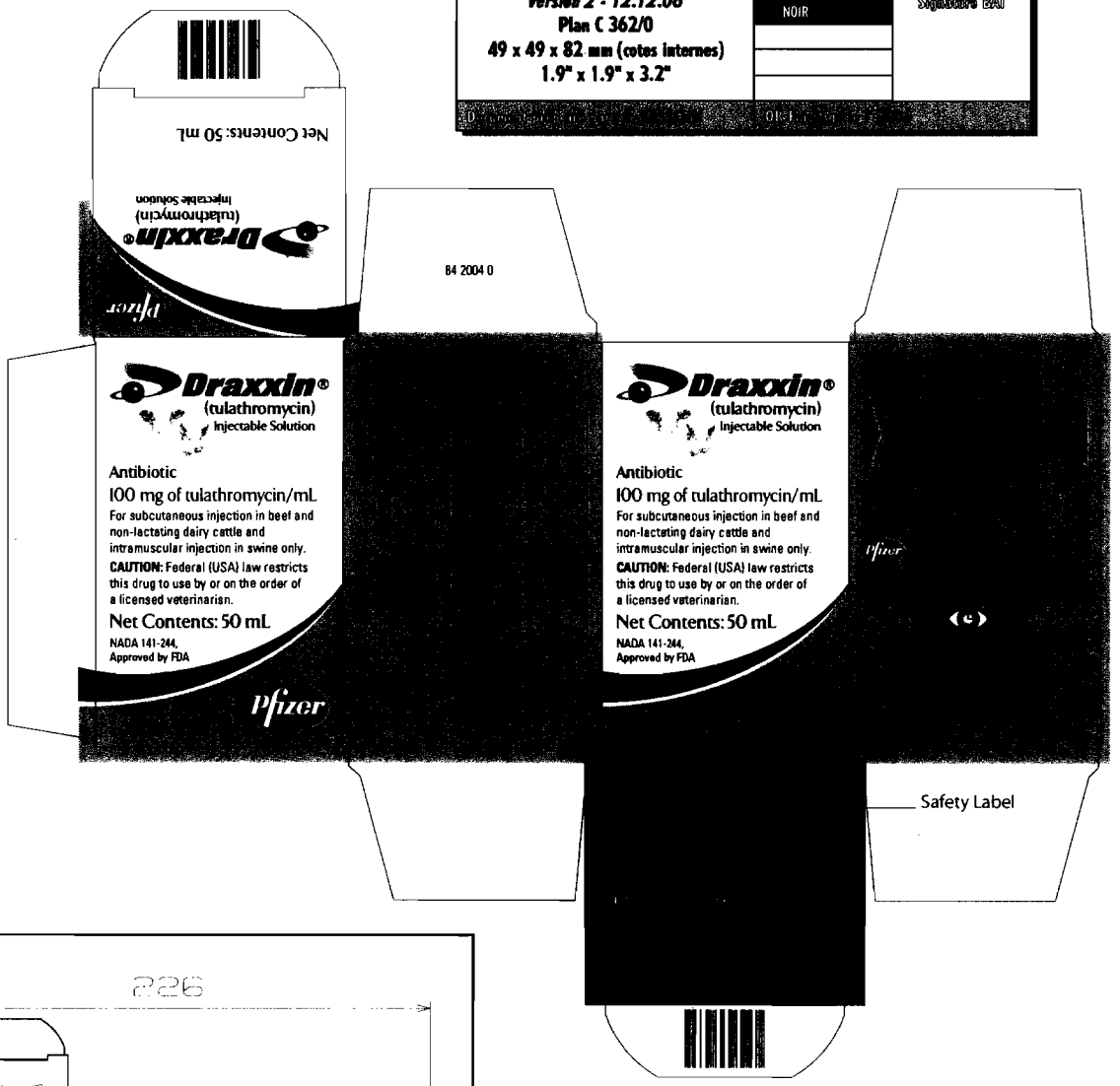
Made in France

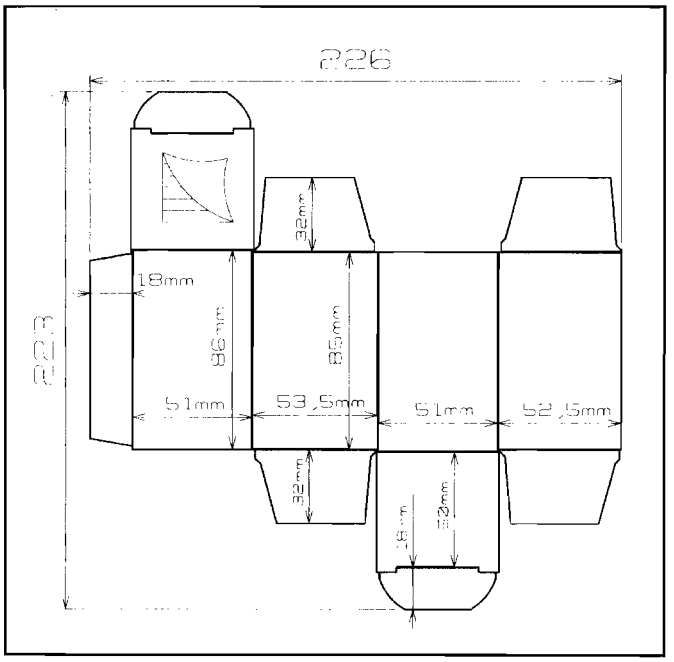
COPY AREA
25.5"WIDE X 1.25"HIGH

**DRAXXIN 50ml US**
**8420040 - Création**
***Version 2 - 12.12.06***
**Plan C 362/0**
**49 x 49 x 82 mm (cotes internes)**
**1.9" x 1.9" x 3.2"**

Couleur: PMS 541 C, PMS 116 C, PMS 471 C, NOIR

Approval Signature BAT



QUANTITY : 40

# DRAXXIN® (TULATHROMYCIN) 50mL

INJECTABLE SOLUTION

STORE AT OR BELOW 25°C (77°F)

EXP : 02/2009 LOT : 7010001

(17)090201(10)7010001

(01)10087219094454(30)40

8189000

03-1106-00-0

MKP10690

DISTRIBUTED BY:
PFIZER ANIMAL HEALTH
DIV. OF PFIZER INC
NY, NY 10017

Pfizer

MADE IN FRANCE

7010001
19-02-07
11:01

7010001

# 100 mL Vial

COPY AREA
1.5" WIDE
X
27.5" HIGH

1.27 mg/kg BW to 5.0 mg/kg BW. No pharmacokinetic differences are observed in castrated male versus female calves.

[3] *Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.*

**Swine**

Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed (Tmax ~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, Histophilus somni*, and *Mycoplasma bovis*, four pathogens associated with BRD.

The minimum inhibitory concentrations (MICs) of tulathromycin against indicated BRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). All MIC values were determined using the 9:1 isomer ratio of this compound.

The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and at-risk field studies in the U.S. in 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves and from lung swabs or lung tissue of saline-treated calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders and from lung swabs or lung tissue of saline-treated calves that died. The results are shown in Table 3.

**Table 3.** 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 | 842 | 2 | 2 | 0.5 to 64 |
| *Pasteurella multocida* | 1999 | 721 | 0.5 | 1 | 0.25 to 64 |
| *Histophilus somni* | 1999 | 36 | 4 | 4 | 1 to 4 |
| *Mycoplasma bovis* | 1999 | 40 | 0.125 | 1 | ≤0.063 to >64 |

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The MIC to encompass 50% and 90% of the isolates, respectively.

**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.

The MICs of tulathromycin against indicated SRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). All MIC values were determined using the 9:1 isomer ratio of this compound. Isolates were obtained from lung samples from saline-treated pigs and non-treated sentinel pigs enrolled in SRD field studies in the U.S. and Canada between 2000 and 2002. 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 |
| *Haemophilus parasuis* | 2000-2002 | 31 | 1 | 2 | 0.25 to >64 |
| *Pasteurella multocida* | 2000-2002 | 55 | 1 | 2 | 0.5 to >64 |
| *Bordetella bronchiseptica* | 2000-2002 | 42 | 4 | 8 | 2 to 8 |

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The MIC to encompass 50% and 90% of the isolates, respectively.

**EFFECTIVENESS**

**Cattle**

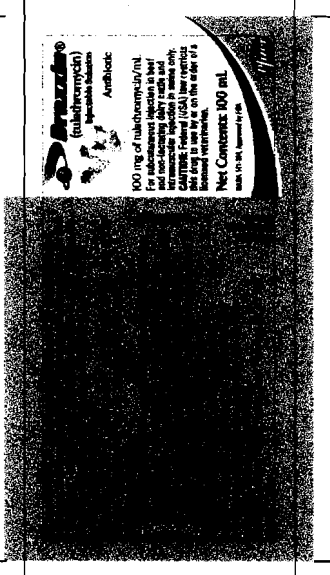
In a multi-location field study, 314 calves with naturally occurring BRD were treated with DRAXXIN. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude/activity, normal respiration, and a rectal temperature of ≤ 104°F on Day 14. The cure 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. Fifty saline-treated calves classified as non-responders in this study had *M. bovis* identified in cultures of post-treatment nasopharyngeal swabs or lung tissue.

Fifty-two DRAXXIN-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *M. 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.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN against *M. bovis*. A total of 166 calves were inoculated intratracheally with field strains of *M. bovis*. When calves became pyrexic and had abnormal respiration scores, they were treated with either DRAXXIN (2.5 mg/kg BW SC) 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

COPY AREA
3.3125" WIDE
X
1.5" HIGH




BASE LABEL
COPY AREA
3.2813" WIDE
X
1.5" HIGH

COPY AREA
1.5" WIDE
X
27.5" HIGH

**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.

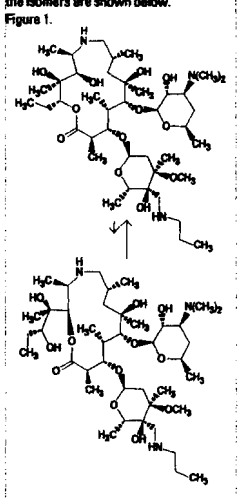
**CAUTION:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

**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-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**

**Cattle**

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

treated calves compared with saline-treated calves (11.3% vs. 28.9%, P=0.0001 and 15.0% vs. 30.7%, P<0.0001).

**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 and two of six calves administered 15 mg/kg BW.

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:
- 50 mL vial
- 100 mL vial
- 250 mL vial
- 500 mL vial

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

*Distributed by:*
Pfizer Animal Health
Div. of Pfizer Inc. NY, NY 10017

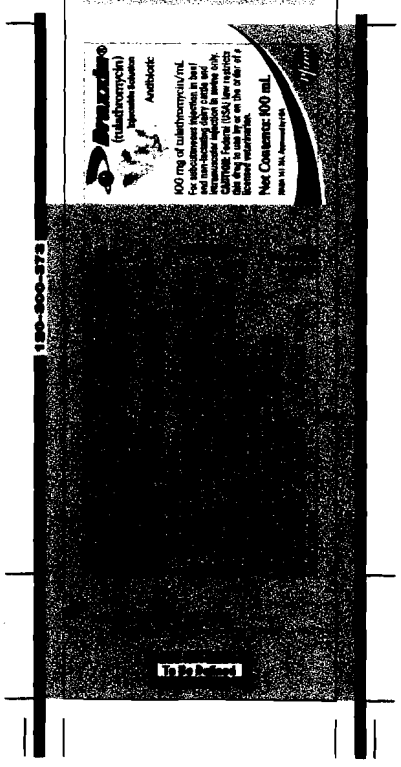
To report a suspected adverse reaction call 1-800-366-5288
To request a material safety data sheet call 1-800-733-5580

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

79-9947-00-X2
July 2007
Made in France MOCK1205

GLUE AREA
NO COPY

FRONT COVER
COPY AREA
3.4375"WIDE
X
1.5"HIGH




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 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 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.

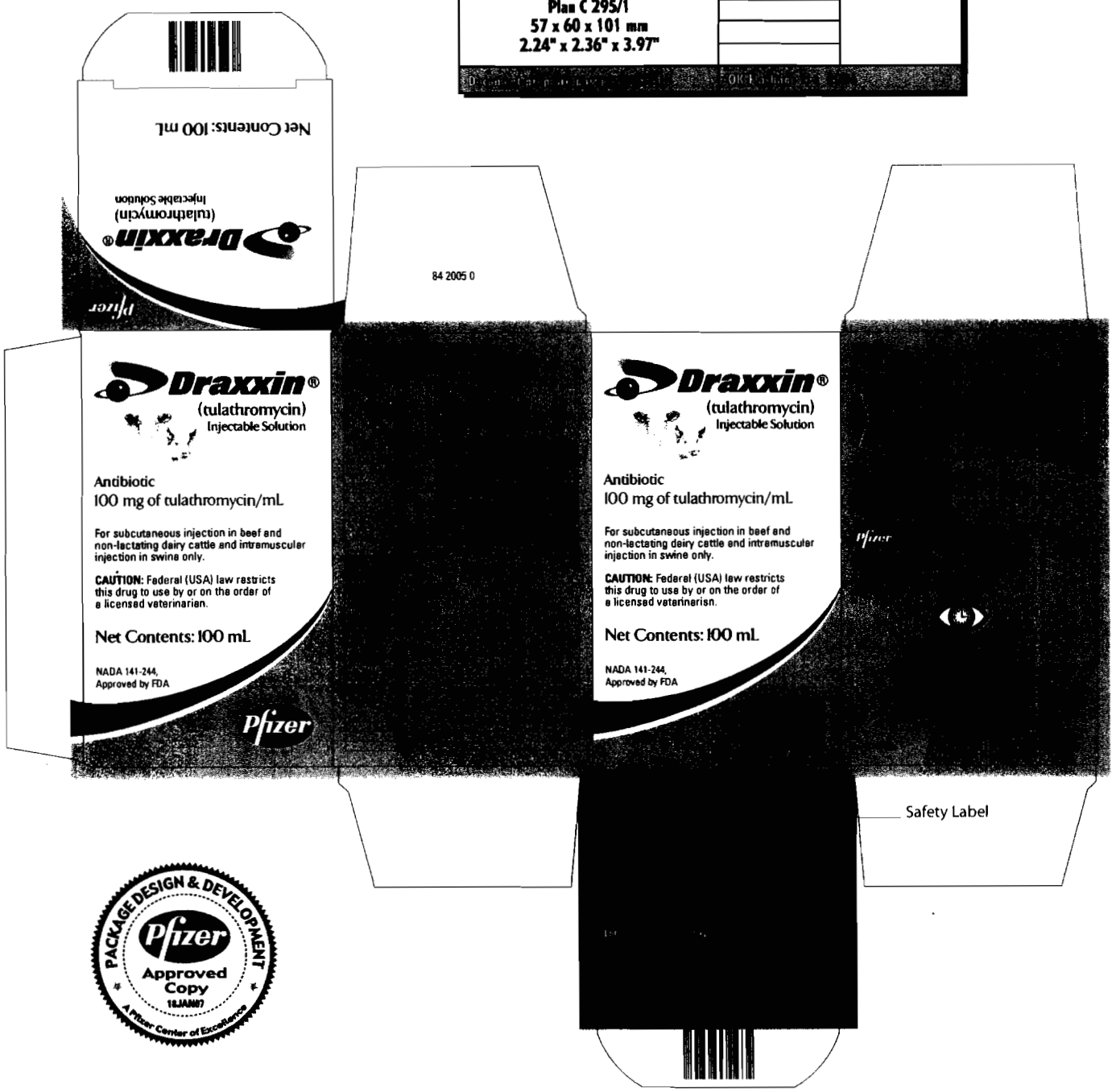
Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens.[2] They also tend to exhibit concentration independent killing; 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.


[1] *Carbon, C. 1998. Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis., 27:29-32.*
[2] *Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J., 16:438-443.*


**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

| Service Développement Pfizer Amboise | Couleurs | Autres |
|---|---|---|
| **DRAXXIN 100ml US**<br>**8420050 - Création**<br>***Version 2 - 11/01/07***<br>**Plan C 295/1**<br>**57 x 60 x 101 mm**<br>**2.24" x 2.36" x 3.97"** | PMS 541 C<br>PMS 116 C<br>PMS 471 C<br>NOIR | Approval Signature BAT |
| Document Composition | OK Fashion | |




PACKAGE DESIGN & DEVELOPMENT
Pfizer
Approved Copy
18JAN07
A Pfizer Center of Excellence

QUANTITY : 12

# DRAXXIN® (TULATHROMYCIN) 100mL

INJECTABLE SOLUTION

STORE AT OR BELOW 25°C (77°F)

EXP : 02/2009 LOT : 7010101

(17)090201(10)7010101

(01)10087219080365(30)12

8174000

03-9950-00-2

MKPT0700

DISTRIBUTED BY:
PFIZER ANIMAL HEALTH
DIV. OF PFIZER INC
NY, NY 10017

Pfizer

MADE IN FRANCE

7010101
19-02-07
11:31

7010101

# 250 mL Vial

COPY AREA
2.625" WIDE
X
16.687" HIGH

[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.

*[3] Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.*

**Swine**

Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed (Tmax ~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 (CLsystemic = 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, Histophilus somni,* and *Mycoplasma bovis,* four pathogens associated with BRD.

The minimum inhibitory concentrations (MICs) of tulathromycin against indicated BRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). All MIC values were determined using the 9:1 isomer ratio of this compound.

The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and at-risk field studies in the U.S. in 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves and from lung swabs or lung tissue of saline-treated calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders and from lung swabs or lung tissue of saline-treated calves that died. The results are shown in Table 3.

**Table 3.** 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 MIC to encompass 50% and 90% of the isolates, respectively.

**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.

The MICs of tulathromycin against indicated SRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). All MIC values were determined using the 9:1 isomer ratio of this compound. Isolates were obtained from lung samples from saline-treated pigs and non-treated sentinel pigs enrolled in SRD field studies in the U.S. and Canada between 2000 and 2002. 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 pleuropneumoniae* | 2000-2002 | 135 | 16 | 32 | 16 to 32 |
| *Haemophilus parasuis* | 2000-2002 | 31 | 1 | 2 | 0.25 to > 64 |
| *Pasteurella multocida* | 2000-2002 | 55 | 1 | 2 | 0.5 to > 64 |
| *Bordetella bronchiseptica* | 2000-2002 | 42 | 4 | 8 | 2 to 8 |

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The MIC to encompass 50% and 90% of the isolates, respectively.

## 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. Fifty saline-treated calves classified as non-responders in this study had *M. bovis* identified in cultures of post-treatment nasopharyngeal swabs or lung tissue.

Fifty-two DRAXXIN-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *M. 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.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN against *M. bovis.* A total of 186 calves were inoculated intratracheally with field strains of *M. bovis.* When calves became pyrexic and had abnormal respiration scores, they were treated with either DRAXXIN (2.5 mg/kg BW SC) 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).

**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 and two of six calves administered 15 mg/kg BW.

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

COPY AREA
4.0625" WIDE
X
2.625" HIGH

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.

Net Contents: 250 mL

NADA 141-244, Approved by FDA

Pfizer

Pfizer

BASE LABEL
COPY AREA
4.03125" WIDE

COPY AR
2.625" WI
X
16.687" H

# 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.

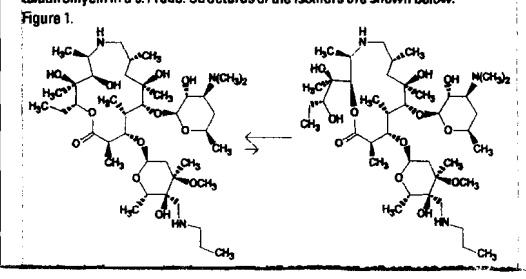
**CAUTION:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

## 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.



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

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

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

*Distributed by:*
**Pfizer Animal Health**
Div. 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

79-9948-00-X2
July 2007
MDCK1206

Made in France

GLUE AREA
NO COPY

FRONT COVER
COPY AREA
4.0625" WIDE
X
2.625" HIGH

**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.

Net Contents: 250 mL

NADA 141-244, Approved by FDA

Pfizer

8179000
79-9948-00-X2
MDCK1206

Distributed by:
Pfizer Animal Health
Div. of Pfizer Inc, NY, NY 10017

Made in France

PULL SLOWLY TO OPEN

To Be Defined

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


[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.*


**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

DRAXXIN 250ml US
8420060 - Création
Version 2 - 11/01/07
Plan C 296/1
71 x 71 x 145 mm
2.79" x 2.79" x 5.7"

PMS 54 C
PMS 116 C
PMS 471 C
NOIR

Approved
Signature BAT

84 2006 0

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.

Net Contents: 250 mL

NADA 141-244, Approved by FDA

Pfizer

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.

Net Contents: 250 mL

NADA 141-244, Approved by FDA

Pfizer

Safety Label

PACKAGE DESIGN & DEVELOPMENT
Pfizer
Approved
Copy
A Pfizer Center of Excellence

QUANTITY : 6

# DRAXXIN® (TULATHROMYCIN) 250mL

INJECTABLE SOLUTION

STORE AT OR BELOW 25°C (77°F)

EXP: 02/2009 LOT: 7010201

(17)090201(10)7010201

(01)10087219080419(30)6

8175000

03-9951-00-2

MKPT0710

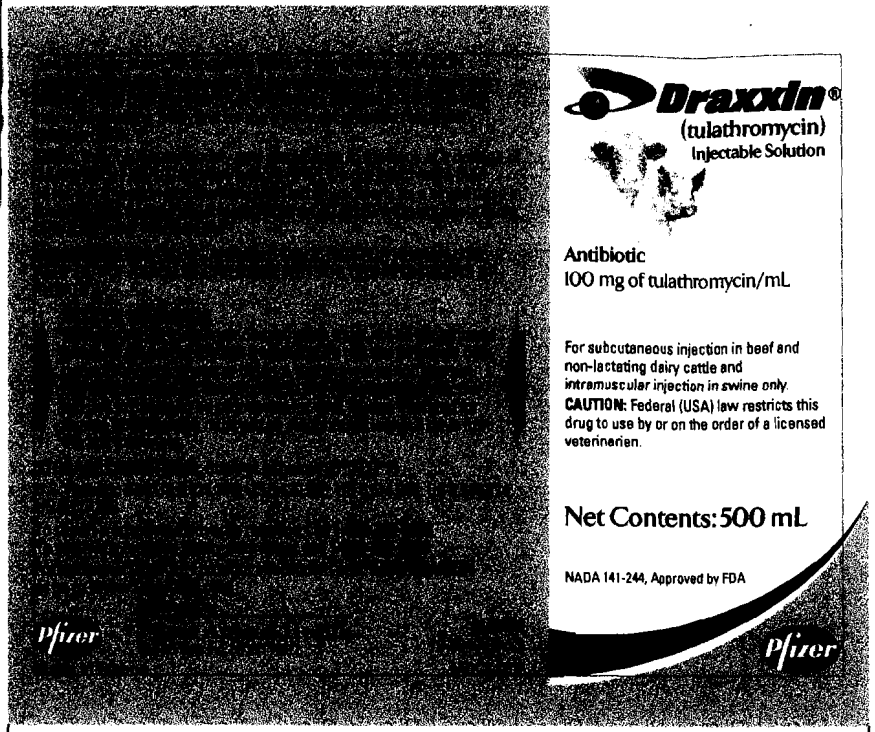
DISTRIBUTED BY:
PFIZER ANIMAL HEALTH
DIV. OF PFIZER INC
NY, NY 10017

MADE IN FRANCE

7010201
19-02-07
11:33

7010201

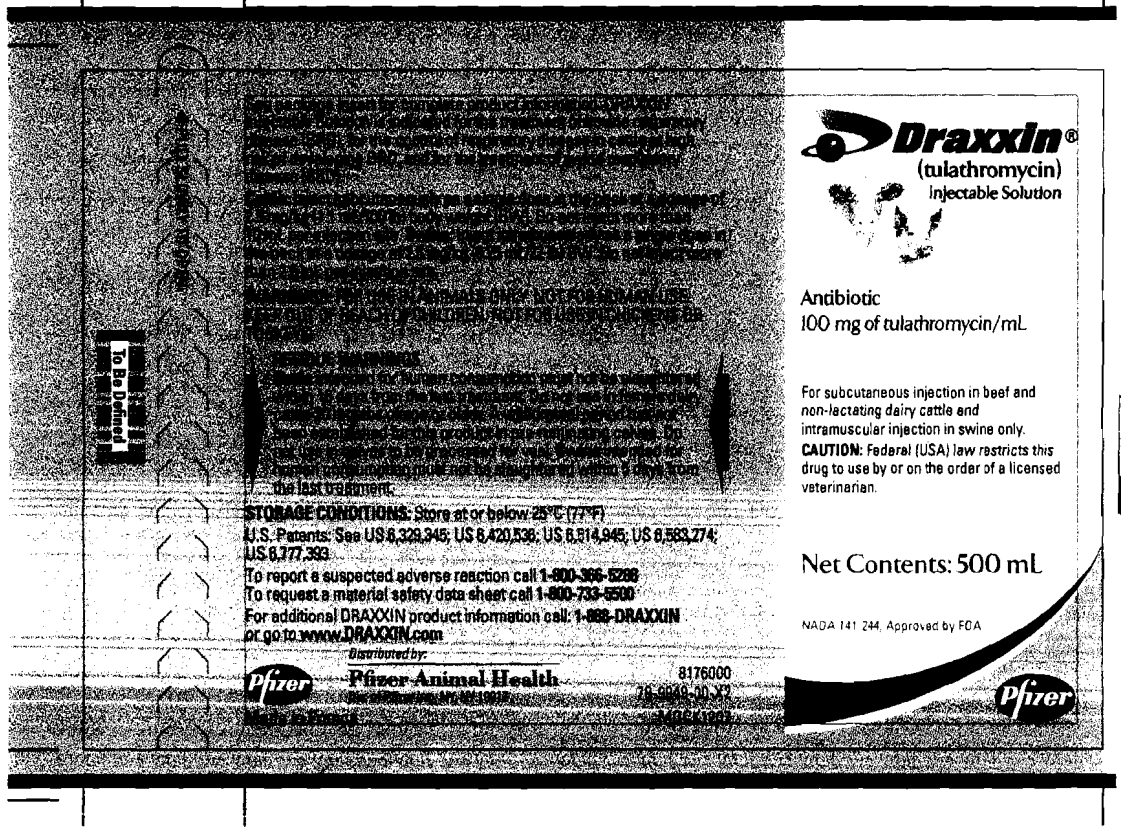
# 500 mL Vial




BASE LABEL
COPY AREA
3.125" HEIGHT x 4.03125" WIDTH

**Die# 120-300-22**

LEAFLET COPY AREA




FRONT COVER
COPY AREA
3.125" HEIGHT x 4.1875" WIDTH

LEAFLET COPY AREA
STARTS HERE
3.125" X 12.406"

OVERALL LEAFLET SIZE
22.062" X 3.5"

# 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.

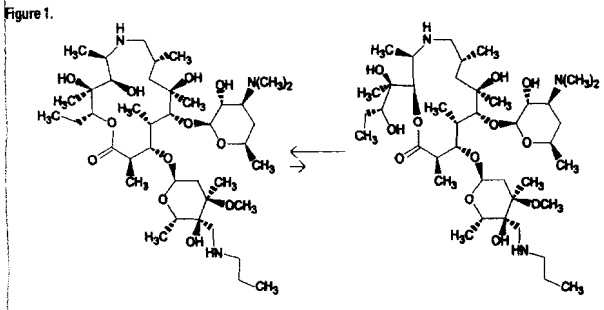
**CAUTION:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

**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-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**

**Cattle**

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

**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 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 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.

[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., 16:436-443.*

**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.

[3] *Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.*

**Swine**
Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed (Tmax ~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, Histophilus somni,* and *Mycoplasma bovis,* four pathogens associated with BRD.

The minimum inhibitory concentrations (MICs) of tulathromycin against indicated BRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). All MIC values were determined using the 9:1 isomer ratio of this compound.

The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and at-risk field studies in the U.S. in 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves and from lung swabs or lung tissue of saline-treated calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders and from lung swabs or lung tissue of saline-treated calves that died. The results are shown in Table 3.

**Table 3.** 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 MIC to encompass 50% and 90% of the isolates, respectively.

**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.

The MICs of tulathromycin against indicated SRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). All MIC values were determined using the 9:1 isomer ratio of this compound. Isolates were obtained from lung samples from saline-treated pigs and non-treated sentinel pigs enrolled in SRD field studies in the U.S. and Canada between 2000 and 2002. 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 pleuropneumoniae* | 2000-2002 | 135 | 16 | 32 | 16 to 32 |
| *Haemophilus parasuis* | 2000-2002 | 31 | 1 | 2 | 0.25 to > 64 |
| *Pasteurella multocida* | 2000-2002 | 55 | 1 | 2 | 0.5 to > 64 |
| *Bordetella bronchiseptica* | 2000-2002 | 42 | 4 | 8 | 2 to 8 |

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The MIC to encompass 50% and 90% of the isolates, respectively.

**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≤ 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. Fifty saline-treated calves classified as non-responders in this study had *M. bovis* identified in cultures of post-treatment nasopharyngeal swabs or lung tissue.

Fifty-two DRAXXIN-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *M. 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.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN against *M. bovis.* A total of 166 calves were inoculated intratracheally with field strains of *M. bovis.* When calves became pyrexic and had abnormal respiration scores, they were treated with either DRAXXIN (2.5 mg/kg BW SC) 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).

**Swine**
In a multi-location field study, 286 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≤ 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 and two of six calves administered 15 mg/kg BW.

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:
- 50 mL vial
- 100 mL vial
- 250 mL vial
- 500 mL vial

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

*Distributed by:*
**Pfizer Animal Health**
Div. 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 1-800-733-5300

For additional DRAXXIN product information call:
1-800-DRAXXIN or go to www.DRAXXIN.com

TAKE TIME — OBSERVE LABEL DIRECTIONS

79-9949-00-X2
July 2007
MOCK1207

Made in France

LEAFLET COPY AREA
CONTINUES HERE
3.125" x 12.312"

OVERALL LEAFLET SIZE
22.062" X 3.5"

Die# 120-300-22

DRAXXIN 500ml US
8420070 - Création
Version 2 - 11/01/07
Plan C 375/0
81 x 82 x 187 mm
3.18" x 3.22" x 7.36"

NOIR
PMS 541 C
PMS 471 C
PMS 116 C

Approval Signature BAT

64 2007 0

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.

Net Contents: 500 mL

NADA 141-244, Approved by FDA

Pfizer

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.

Net Contents: 500 mL

NADA 141-244, Approved by FDA

Pfizer

Draxxin®
(tulathromycin)
Injectable Solution

Net Contents: 500 mL

Pfizer

Safety Label

PACKAGE DESIGN & DEVELOPMENT
Pfizer
Approved Copy
16JAN07
A Pfizer Center of Excellence

QUANTITY : 6

# DRAXXIN® (TULATHROMYCIN) 500mL

INJECTABLE SOLUTION

STORE AT OR BELOW 25°C (77°F)

EXP: 02/2009 LOT: 7010301

(17)090201(10)7010301

(01)10087219080433(30)6

8176000

03-9952-00-2

NKPT0720

DISTRIBUTED BY:
PFIZER ANIMAL HEALTH
DIV. OF PFIZER INC
NY, NY 10017

MADE IN FRANCE

7010301
19-02-07
11:38

7010301