

JUL 25 2003

Date of Approval: _____

FREEDOM OF INFORMATION SUMMARY

NADA 141-143

TETRADURE 300 (Oxytetracycline) INJECTION
OXYTETRACYCLINE INJECTION 300 mg/mL

"In cattle ... for the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp.; infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*; foot-rot and diphtheria caused by *Fusobacterium necrophorum*; bacterial enteritis (scours) caused by *Escherichia coli*; wooden tongue caused by *Actinobacillus lignieresii*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococcal and streptococcal organisms sensitive to oxytetracycline.

TETRADURE™ 300 (only) is also indicated for the control of respiratory disease in cattle at high risk of developing Bovine Respiratory Disease (BRD) associated with *Mannheimia (Pasteurella) haemolytica* and the dosage range for the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp. and infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*."

"In swine ... for the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli*; pneumonia caused by *Pasteurella multocida*; and leptospirosis caused by *Leptospira pomona*. In sows, oxytetracycline is indicated as an aid in the control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli*."

NEW ANIMAL DRUG APPLICATION

Sponsored by:

Norbrook Laboratories Limited
Station Works
Newry, BT35 6JP
Northern Ireland

NADA

141-143

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1. GENERAL INFORMATION

- a. File Number: NADA-141-143
- b. Sponsor: Norbrook Laboratories Limited
Station Works
Newry
BT35 6JP
Northern Ireland
Drug Labeler Code: 055529
- c. Established Name: Oxytetracycline injection
- d. Proprietary Name: TETRADURE 300 (Oxytetracycline) Injection (R_x product)
OXYTETRACYCLINE INJECTION 300 mg/mL (OTC product)
- e. Dosage Form: Injectable
- f. How Supplied: TETRADURE 300 and OXYTETRACYCLINE INJECTION 300 mg/mL are supplied in 100, 250 and 500 mL bottles.
- g. How Dispensed: R_x and OTC
- h. Amount of Active: Each mL contains 300 mg of oxytetracycline
Ingredients: base as amphoteric oxytetracycline.
- i. Route of Administration: The product is administered via intravenous, intramuscular or subcutaneous injection as described in the "Recommended Dosage" section below.
- j. Species/Class: Beef cattle, Non-lactating dairy cattle, calves, including pre-ruminating (veal) calves and swine.
- k. Recommended Dosage: CATTLE [beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves]:

A single intramuscular or subcutaneous dosage of 13.6 mg of oxytetracycline per pound of body weight, TETRADURE 300 is recommended for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*.

A single dosage of 9 to 13.6 milligrams TETRADURE 300 or 9 milligrams OXYTETRACYCLINE INJECTION 300 mg/mL per pound of body weight administered intramuscularly or subcutaneously is recommended in the treatment of the following conditions: 1) bacterial pneumonia caused by *Pasteurella* spp. (shipping fever) in

calves and yearlings, where retreatment is impractical due to husbandry conditions, such as cattle on range, or where repeated restraint is inadvisable;

2) infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*.

For other indications TETRADURE 300 and OXYTETRACYCLINE INJECTION 300 mg/mL are to be administered intramuscularly, subcutaneously, or intravenously at a level of 3 to 5 milligrams of oxytetracycline per pound of body weight per day. In the treatment of severe foot-rot and advanced cases of other indicated diseases, a dosage level of 5 milligrams per pound of body weight per day is recommended. Treatment should be continued 24 to 48 hours following remission of disease signs, however, not to exceed a total of four (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of the treatment, diagnosis and therapy should be re-evaluated by a veterinarian.

SWINE:

A single dosage of 9 milligrams oxytetracycline per pound of body weight administered intramuscularly is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine, where retreatment is impractical due to husbandry conditions or where repeated restraint is inadvisable.

TETRADURE 300 and OXYTETRACYCLINE INJECTION 300 mg/mL can also be administered by intramuscular injection at a level of 3 to 5 milligrams of oxytetracycline per pound of body weight per day. Treatment should be continued 24 to 48 hours following remission of disease signs, however, not to exceed a total of four (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of the treatment, diagnosis and therapy should be re-evaluated by a veterinarian.

For sows, administer once intramuscularly 3 milligrams of oxytetracycline per pound of body weight approximately eight (8) hours before farrowing or immediately after completion of farrowing as an aid in the control of infectious enteritis in baby pigs.

l. Pharmacological:
Category

Antimicrobial

m. Indications:

Beef and non-lactating dairy cattle, calves, including pre-ruminating (veal) calves: for the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp.; infectious bovine keratoconjunctivitis (pinkeye)

caused by *Moraxella bovis*; foot-rot and diphtheria caused by *Fusobacterium necrophorum*; bacterial enteritis (scours) caused by *Escherichia coli*; wooden tongue caused by *Actinobacillus lignieresii*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococcal and streptococcal organisms sensitive to oxytetracycline. Also, TETRADURE 300 is indicated (prescription use) for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*.

Swine: for the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli*; pneumonia caused by *Pasteurella multocida*; and leptospirosis caused by *Leptospira pomona*.

In sows, oxytetracycline is indicated as an aid in the control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli*.

2. EFFECTIVENESS:

This product is a "hybrid" NADA relying on approval of a listed (pioneer) animal drug to the extent it is allowed under 512 (n) of the Federal Food, Drug, and Cosmetic (FFD&C) Act and contains additional data needed to support changes in the generic product.

A. Dosage Characterization:

Dose Rationale:

The 3.0 to 5.0 mg/lb and 9 mg/lb doses and indications were established based on the pioneer product LIQUAMYCIN LA-200 approved under NADA 113-232.

The 13.6 mg/lb (30 mg/kg) dose for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica* was established based on label indications for similar European-approved products and studies conducted in Canada. The sponsor conducted field studies in the U.S. relying on the European approvals as dose establishment data.

The dosage range of 9 to 13.6 mg/lb for treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp. and infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis* was established based upon the pioneer product and additional safety studies conducted which demonstrated the safety of the upper end of the dose range (13.6 mg/lb) in cattle.

B. Substantial Evidence:

Dose Confirmation:

The requirements for establishing the effectiveness of the product at the dosages currently approved under NADA 113-232 were met by demonstrating comparable serum pharmacokinetics to LIQUAMYCIN LA-200 in both cattle and swine at a dose of 9 mg/lb.

CATTLE

1. Title: A Comparative Study of Plasma Level of Oxytetracycline in *Cattle* Following the Intramuscular Administration of Oxytetracycline 300 (Norbrook Laboratories Limited) and LIQUAMYCIN LA-200 (NADA 113-232, Pfizer)
2. Study Number: 039/94
3. Investigator: Mr. N. Orr
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

4. Study Design:

- a. Purpose: Effectiveness determination by comparison of plasma pharmacokinetics of the sponsor's oxytetracycline 300 mg/mL injection product to that of a pioneer product (oxytetracycline 200 mg/mL injection). Both products were administered intramuscularly at the recommended dosage in a cross-over design bioequivalence study.
- b. Test Animals: Twenty-four mixed breed, beef-type calves consisting of 12 males and 12 females weighing 910 to 1010 pounds were evaluated in the study.
- c. Control (reference): LIQUAMYCIN LA-200, NADA 113-232.
- d. Dosage form (test): 300 mg/mL injectable.
- e. Route of administration: intramuscular injection.
- f. Dose: Single treatment with 9 mg oxytetracycline per pound of body weight with a maximum of 10 mL administered in one site.
- g. Test duration: 49 days (42 day washout period).
- h. Pertinent parameters measured: Area Under the Curve (AUC) measured from time zero to the last quantifiable drug concentration (AUC_{0-last}), and Maximum Observed Drug Concentrations (C_{max}). Time to Maximum Concentration (T_{max}) values were used for qualitative comparisons.

5. Results:

Table 2.1. Pharmacokinetic variables of the test and the reference articles

Parameter	Mean Test	Mean Reference	Upper CL*	Lower CL*
AUC_{0-last} ($\mu\text{g} \cdot \text{hr/mL}$)	254.08	254.45	+3.4%	-3.7%
C_{max} ($\mu\text{g/mL}$)	8.20	8.34	+3.9%	-7.4%
T_{max} (hr)	5.5	4.5	-	-

* Confidence interval presented as % of reference article mean.

6. Conclusions: Norbrook's 300 mg/mL injectable oxytetracycline product and Pfizer's LIQUAMYCIN LA-200 are bioequivalent based on AUC and C_{max} values.

SWINE

1. Title: A Comparative Study of Plasma Levels of Oxytetracycline In Pigs Following the Intramuscular Administration of Oxytetracycline 300 (Norbrook Laboratories Limited) and LIQUAMYCIN LA-200 (NADA 113-232, Pfizer)
2. Study Number: 043/94
3. Investigator: Mr. N. Orr
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101 Killowen Road

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4. Study Design:

- a. Purpose: Effectiveness determination by comparison of plasma pharmacokinetics of the sponsor's oxytetracycline 300 mg/mL injection product to that of a pioneer product (oxytetracycline 200 mg/mL injection). Both products were administered intramuscularly at the recommended dosage in a parallel design bioequivalence study.
- b. Test Animals: Forty-eight Landrace/Large White crossbreed pigs consisting of 24 males and 24 females weighing 50 to 65 pounds were evaluated in the study.
- c. Control (reference): LIQUAMYCIN LA 200, NADA 113-232.
- d. Dosage form (test): 300 mg/mL injectable.
- e. Route of administration: intramuscular injection.
- f. Dose: Single treatment with 9 mg oxytetracycline per pound of body weight.
- g. Test duration: 7 days.
- h. Pertinent parameters measured: Area Under the Curve (AUC) measured from time zero to the last quantifiable drug concentration (AUC_{0-last}), and Maximum Observed Drug Concentrations (C_{max}). Time to Maximum Concentration (T_{max}) values were used for qualitative comparisons.

5. Results:

Table 2.2. Pharmacokinetic variables of the test and the reference articles

Parameter	Mean Test	Mean Reference	Upper CL*	Lower CL*
AUC_{0-last} ($\mu\text{g} \cdot \text{hr/mL}$)	114.8	107.5	+10.9%	+2.5%
C_{max} ($\mu\text{g/mL}$)	5.06	5.00	+7.4%	-5.0%
T_{max} (hr)	2.5	2.6	-	-

* Confidence interval presented as % of reference article mean.

6. Conclusions: Norbrook's 300 mg/mL injectable oxytetracycline product and Pfizer's LIQUAMYCIN LA-200 are bioequivalent based on AUC and C_{max} values.

Field Investigation:

A field investigation was undertaken to demonstrate the effectiveness of the 30 mg/kg (13.6 mg/lb) dose for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*. Two sites were included and the results from the trials combined statistically.

STUDY 1

1. Title: A Study to Evaluate the Prophylactic Effectiveness of Norbrook's OXYTET

30% Injectable Formulation in Reducing the Incidence and Severity of Bovine Respiratory Disease (BRD).

2. Study Number: KFL-4Q96-BRD-NB-K-02
3. Investigator: Alvin J. Edwards, D.V.M., Ph.D.
Knight Feedlot, Inc., Manhattan, KS
4. Study Design:
 - a. Purpose: To evaluate the effectiveness of the product in reducing the incidence and severity of naturally occurring bovine respiratory disease (BRD) in calves.
 - b. Test Animals: Approximately 1,200 mixed breed and crossbred beef-type steer and heifer calves weighing 330 to 714 pounds were obtained and randomly assigned to either the test or control group. All calves were treated within 96 hours of receipt at the feedlot.
 - c. Control: Saline solution 0.9%.
 - d. Diagnosis: Calves were observed daily for 30 days for signs, such as, poor general appearance, depressed attitude and reluctance to move. Rectal temperature was measured in animals displaying such signs and calves with temperatures greater than or equal to 104°F were treated with MICOTIL (single 10 mg/kg dose SQ) and returned to the pen. Calves were defined as "Healthy" that required no further treatment and had no evidence of BRD during the 30-day observation period. Calves were defined as "Failures" that required any supplemental treatment for BRD or died of respiratory disease.
 - e. Dosage form: 300 mg/mL injectable.
 - f. Route of administration: Intramuscular injection in the left side of the neck.
 - g. Dose: Single treatment with 13.6 mg oxytetracycline per pound of body weight.
 - h. Test duration: 30 days.
5. Results:

Table 2.3. Number of healthy and treatment failures administered the test or the control article

Treatment	n	Healthy	Failures
Test	601	426	175
Control	598	378	220
Total	1199	804	395

STUDY 2

1. Title: A Study to Evaluate the Prophylactic Efficacy of Norbrook's OXYTET 30% Injectable Formulation in Reducing the Incidence and Severity of Bovine Respiratory Disease (BRD).

2. Study Number: MVS-4Q96-N-BRD-NB-01
3. Investigator: Kelly F. Lechtenberg, D.V.M., Ph.D. & Michael J. Hanna, D.V.M.
Midwest Veterinary Services, Inc.
Oakland, NE
4. Study Design:
 - a. Purpose: To evaluate the effectiveness of the product in reducing the incidence and severity of naturally occurring bovine respiratory disease (BRD) in calves.
 - b. Test Animals: 1,200 mixed breed and crossbred beef-type steer calves weighing 366 to 702 pounds were obtained and randomly assigned to either the test or control group. All calves were treated within 96 hours of receipt at the feedlot.
 - c. Control: Saline solution 0.9%.
 - d. Diagnosis: Calves were observed daily for 30 days for signs such as poor general appearance, depressed attitude and reluctance to move. Rectal temperature was measured in animals displaying such signs and calves with temperatures greater than or equal to 104°F were treated with Micotil (single 10 mg/kg dose SQ) and returned to the pen. Calves were defined as "Healthy" that required no further treatment and had no evidence of BRD during the 30-day observation period. Calves were defined as "Failures" that required any supplemental treatment for BRD or died of respiratory disease.
 - e. Dosage form: 300 mg/mL injectable.
 - f. Route of administration: Intramuscular injection in the left side of the neck.
 - g. Dose: Single treatment with 13.6 mg oxytetracycline per pound of body weight.
 - h. Test duration: 30 days.

5. Results:

Table 2.4. Number of healthy and treatment failures administered the test or the control article

Treatment	n	Healthy	Failures
Test	600	265	335
Control	600	245	355
Total	1200	510	690

6. Pooled Data Analysis from Field Studies:

Data from the two field studies described above were pooled and each case was designated to have resulted in a favorable or unfavorable response. Favorable responders are defined as animals that were treated with the test or control article and did not require further treatment, i.e., "healthy" (i.e., no evidence of BRD

during the 30-day observation period). Unfavorable responders are defined as animals that required additional medication even after being treated with the test or control article, i.e., “failures” (i.e., required any supplemental treatment for BRD or died of respiratory disease).

The resulting data were analyzed using an arcsine square root transformation on the proportion of healthy animals for each treatment for each pen adjusted for pen size. The model included terms for location (Kansas and Nebraska) and block within location (22 blocks; 15 at Nebraska and 7 at Kansas) as random effects. The model was also adjusted for the pen size variability. The analysis showed that the treatments were significantly different ($p=0.0065$, two-sided, $F=9.13$ with 1 and 21 degrees of freedom).

Table 2.5. Pooled data showing the number of healthy and treatment failures administered the test or the control article

Treatment/Location	n	Healthy	Failures
Oxytetracycline	1201	691	510
Control	1198	623	575
Total	2399	1314	1085

7. Conclusions: The results of these studies indicate that the product is effective in the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*.

Bioequivalence Study:

1. Title: A Comparative Study of Plasma Levels of Oxytetracycline in Cattle Following the Intramuscular and Subcutaneous Administration of OXYTET 30% (Norbrook Laboratories Limited).
2. Study Number: 058/97
3. Investigator: Mr. A. Carragher
Ballyedmond Castle Farms Limited
101 Killowen Road
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Co. Down, BT34 3AG
Northern Ireland
4. Study Design:
 - a. Purpose: Effectiveness determination by comparison of plasma pharmacokinetics of the sponsor's oxytetracycline 300 mg/mL injection product administered intramuscularly or subcutaneously at the recommended dosage in a cross-over design bioequivalence study.

- b. Test Animals: Twenty-four mixed breed, beef-type calves consisting of 12 males and 12 females weighing 910 to 1020 pounds were evaluated in the study.
- c. Control (reference): Norbrook oxytetracycline 300 mg/mL injectable.
- d. Dosage form: 300 mg/mL injectable.
- e. Route of administration: intramuscular or subcutaneous injection.
- f. Dose: Single treatment per period with 13.6 mg oxytetracycline per pound of body weight with a maximum of 10 mL administered in one site. Subcutaneous injections were made in the neck area and intramuscular injections were made in the muscles of the rump.
- g. Test duration: 53 days (42 day washout period).
- h. Pertinent parameters measured: Area Under the Curve (AUC) measured from time zero to the last quantifiable drug concentration (AUC_{0-last}), and Maximum Observed Drug Concentrations (C_{max}). Time to Maximum Concentration (T_{max}) values were used for qualitative comparisons.

5. Results:

Table 2.6. Pharmacokinetic variables of Oxytetracycline administered subcutaneously or intramuscularly

Parameter	Mean** Test (SC)	Mean** Reference (IM)	Upper CL*	Lower CL*
AUC_{0-last} ($\mu\text{g} \cdot \text{hr}/\text{mL}$)	301	287	1.10*	1.00*
C_{max} ($\mu\text{g}/\text{mL}$)	8.7	7.9	1.20*	1.02*
T_{max} (hr)	9.7	9.6	-	-

*Confidence intervals estimated about the ratio of means using Ln transformed parameters.

**Geometric means

- 6. Conclusions: The products were considered bioequivalent based on AUC and C_{max} confidence intervals lying within -20%, +25% of the mean of the reference product using log transformed concentration data.

3. TARGET ANIMAL SAFETY:

A. Drug Tolerance

The toxicological effects of oxytetracycline are well documented based on studies conducted with other oxytetracycline products. It can be concluded that the principal effects following administration of large doses of oxytetracycline are nephrotoxicosis and hepatotoxicosis. References include:

1. Griffin D.D. *et al.* 1979. Experimental Oxytetracycline Toxicity in Feedlot Heifers. *The Bovine Practitioner*. 14:37-41.
2. Lairmore M.D. *et al.* 1984. Oxytetracycline-associated nephrotoxicosis in feedlot calves. *JAVMA*, 185(7):793-795.
3. Rioud J-L. and Riviere J.E. 1989. Effects of Tetracyclines on the Kidney in Cattle and Dogs. *JAVMA*, 195(7):995-997.
4. TerHune T.N. and Upson D.W. 1989. Oxytetracycline pharmacokinetics, tissue depletion, and toxicity after administration of a long-acting preparation at double the label dosage. *JAVMA*, 194(7):911-917.
5. Vaala W.E. *et al.* 1987. Acute Renal Failure Associated with Administration of Excessive Amounts of Tetracycline in a Cow. *JAVMA*, 191(12):1601-1603.

B. Toxicity Test (IM Safety in Cattle)

1. Title: A Target Animal Safety Study in cattle Following Intramuscular Administration of OXYTET 30.
2. Study Number: 079/96
3. Investigator: Mr. N. Orr, B.V.M.S., M.R.C.V.S.
Ballyedmond Castle Farms Limited
101 Killowen Road
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4. General Design:
 - a. Purpose: To evaluate the safety of the test article in the target species (cattle). Treatment groups were administered the test article three times at rates 1, 2, and 4 times the recommended dose. Safety of the product was appraised via clinical examination, clinical pathology, and post mortem examination. The study was conducted in accordance with Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.
 - b. Animals: Twenty-four (12 steers and 12 heifers) cattle 6 to 9 months of age weighing 470 to 630 pounds.

- c. Control: Normal saline at a rate of 1 mL per 11 pound.
- d. Dosage form: 300 mg/mL injectable.
- e. Route of administration: Intramuscular injection
- f. Dose: 13.6, 27.2, and 54.4 mg/lb body weight at 0, 72, and 144 hours. A maximum volume of 10 mL was used per injection site.
- g. Test duration: Twenty-one (21) days from first administration.
- h. Pertinent measurements and observations: Physical and clinical examinations, clinical pathology (biochemistry, hematology and urinalysis), gross post mortem examination [one animal of each sex from each group and an extra calf in the high dose (4x) group which displayed signs of toxicity during the study], and histopathology.

5. Results:

a. Physical and Clinical Examinations:

With the exception of clinical signs related to the localized effects of product administration, the only animals demonstrating abnormality were in the high (4x) dose group. Anorexia was observed in the animals in this group for up to 8 days following the final injection. Localized injection site reaction was noted in all treatment groups and incidence tended to reflect the total dose administered. Incidence of hind limb lameness was noted in all treatment groups being most significant in the high dose (4x) group. A higher incidence of lameness was observed in the low dose (1x) group than the medium group, however, all lameness was resolved before 480 hours after the initial injections.

b. Clinical Pathology:

There were differences between the control and treated groups with transient increases in urea and creatinine (4x group), urine WBC count (4x) and transient decreases in total protein (2x, 4x), albumin (1x, 2x, 4x), sodium (2x, 4x) and potassium (4x) along with urine protein (4x) and urine pH (4x). These were attributed to renal dysfunction. The findings corroborate the known toxicity profile of oxytetracycline that is described as causing cortical epithelial necrosis at high dose rates. The high dose (4x) group was most severely affected. The clinical pathology findings supported the clinical observations made during the study.

c. Gross Post Mortem Examination and Histopathology:

Basophilic cortical and medullary tubules were detected in the high dose (4x) group corroborating the interpretation of renal dysfunction based on clinical pathology results. No findings of renal dysfunction were apparent in the control, 1x, or 2x groups based on post mortem examination. All other findings at gross examination were considered incidental. No hepatic pathology was noted.

6. Conclusion: TETRADURE 300 is safe when administered intramuscularly to cattle at a dose of 13.6 mg/lb body weight.

C. Toxicity Test (IV Safety in Cattle)

A pharmacokinetic study using the 13.6 mg/lb dose was provided in support of intravenous safety of the 300 mg/mL concentration product. The IV route of administration is applicable only to cattle.

1. Title: A Pharmacokinetic Study of Plasma Levels of Oxytetracycline in Cattle Following the Intramuscular and Intravenous Administration of OXYTET 30.
2. Study Number: 041/95
3. Investigator: Mr. A. Carragher, B.Sc.
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland
4. Study Design: The safety information was collected as part of a pharmacokinetic study conducted in a two-period cross-over design with a 42-day washout period. Animals were randomly assigned to treatment group. Safety of the product was appraised via clinical observation of the calves after treatment with the test article and at subsequent blood collections. The study was conducted in accordance with Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.
 - a. Purpose: The study was undertaken to determine the levels of oxytetracycline in plasma following the intramuscular and intravenous injection of the test article. Secondly, it demonstrates safety of the product after intravenous injection.
 - b. Test Animals: Twelve beef-type cattle (male and female) weighing between 900 to 970 pounds were tested.
 - c. Control: The animals served as their own controls in the crossover study design.
 - d. Dosage form: 300 mg/mL injectable.
 - e. Route of administration: Intramuscular and intravenous injection.
 - f. Dose: Single treatment with 30 mg oxytetracycline per kilogram (13.6 mg/lb) of body weight.
 - g. Test duration: 54 days with blood samples collected for up to 12 days after each administration of test article with a 42-day washout period.
 - h. Pertinent parameters measured: In regards to intravenous safety of the product, a general assessment of each calf was made at each blood sampling with particular attention paid to animals treated intravenously in each period of the

study. Additionally, injection sites were examined twice weekly after administration of the test article for signs of swelling, hardness/softness, heat, redness and pain indicative of adverse reaction to treatment.

5. Results: No evidence of collapse, neurological effects, changes in gait or states of consciousness were observed after administration of the test article. Various levels of hardness and swelling were observed after administration of the test article via both routes of administration with all reactions resolving by 28 days. No systemic reactions or any other significant adverse reactions were reported during the study.
6. Conclusions: Administration of the test article via the intravenous route was well tolerated by all calves at the dosage administered which was above the 3.0 to 5.0 mg/lb dose recommended for intravenous injection.

D. IM Irritation Study

1. Title: An Injection Site Evaluation Study of Oxytetracycline in Cattle Following Intramuscular Administration of OXYTET 30.
2. Study Number: 089/96
3. Investigator: Mr. A. Carragher, B.Sc.
Ballyedmond Castle Farms Limited
101 Killowen Road
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Co. Down, BT34 3AG
Northern Ireland
4. Study Design: The study was conducted parallel to a target animal safety study involving calves treated at 1, 2, and 4 times the recommended dose of 13.6 mg/lb. The results obtained from the 1x and 2x groups are included. Animals were randomly assigned to treatment group. Tissue irritation was appraised via clinical observation of the calves after treatment with the test article administered in the neck region. Additionally, a portion of the animals were sacrificed, and the injection site (in the neck area) was removed and examined for gross pathological changes. The study was conducted in accordance with the Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.
 - a. Purpose: To assess injection site irritation of the test article administered at the highest recommended volume in the neck region of calves.
 - b. Test Animals: Four (4) animals (2 male and 2 female) approximately 7.5 to 9 months of age and weighing 520 to 560 pounds.
 - c. Control: None applicable
 - d. Dosage form: 300 mg/mL injectable
 - e. Route of administration: Intramuscular injection in the neck, rump and leg

musculature

- f. Dose: 13.6 and 27.2 mg/lb with a maximum injection volume of 10 mL per site administered on three occasions 72 hours apart. Injections in the neck area were made at the first and third administrations.
 - g. Test duration: 21 days
 - h. Pertinent parameters measured: The injection sites were monitored throughout the study for gross signs of reaction and also immediately prior to sacrifice for swelling, hardness/softness, heat, redness and pain. Additionally, the animals were sacrificed 21 days after the initial injection (15 days after the final injection), and the injection sites were excised and examined for gross pathological changes.
5. Results: No injection site reactions were recorded at any of the neck sites. Post-mortem examination of the injection sites revealed lesions consisting of necrotic and fibrotic tissue, hemorrhage that appeared to be resolving with fewer lesions noted after 21 days than after 15 days.
 6. Conclusions: Intramuscular injection of the test article into the neck muscles of cattle at a volume of 10 mL per site results in some amount of localized tissue necrosis that resolves with time, but may still be present at 21 days post-injection.

E. Irritation Monitoring During Residue Study (Cattle)

1. Title: A Tissue Residue Study of Oxytetracycline in Cattle Following Intramuscular Administration of OXYTET 30.
2. Study Number: 011/96 (Injection site irritation was monitored as part of the residue depletion study supporting human food safety).
3. Investigator: Norbrook Laboratories, Research Division
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland
4. Study Design: Calves were randomly assigned to five groups sacrificed at various intervals to determine the residue depletion profile based on tissue concentrations of oxytetracycline. Injection site irritation was also assessed during the study. The study was conducted in accordance with Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.
 - a. Purpose: To assess injection site irritation of the test article administered at the highest recommended volume in the rump region of calves.
 - b. Test Animals: Twenty animals (10 male and 10 female) approximately 9

months to 2 years of age and weighing 620 to 795 pounds.

- c. Control: None applicable to injection site irritation assessment.
- d. Dosage form: 300 mg/mL injectable
- e. Route of administration: Intramuscular injection
- f. Dose: 5 mg/lb with a maximum injection volume of 10 mL per site administered for four consecutive days. Sites of administration included both sides of the rump and neck regions. The site of the final injection was the right rump musculature.
- g. Test duration: 28 days
- h. Parameters measured: The injection sites were monitored for up to 18 days after initial administration of the test article and also immediately prior to sacrifice. This involved assessment of swelling, hardness/softness, heat, redness and pain at the injection sites. Following sacrifice, injection sites at the final site of administration were excised, examined for gross lesions, and photographed.

5. Results:

- a. Clinical Observations: Transient reactions of swelling and/or hardness were noted at the rump injection sites of 14/20 animals. Two of these animals also exhibited swelling at the neck injection sites. The severity of swelling reactions ranged from mild (only notable on careful palpation) to severe (visible). No sloughing occurred, and all reactions resolved without need for veterinary intervention. The time to resolution of the clinical signs ranged from 2 to 16 days post-treatment. No systemic reactions, lameness, or other significant adverse reactions were recorded during the animal phase of the study.
- b. Gross Pathology Observations: Post mortem examination of the injection sites revealed lesions consisting of necrotic and fibrotic tissue, hemorrhage, and very small cystic areas. The severity of the lesions decreased with time. By Day 28 only very small areas of fibrotic and necrotic tissue were observed.

6. Conclusions: The amount of tissue irritation at the injection sites of TETRADURE 300, administered by intramuscular injection to cattle, is acceptable from an animal safety perspective. Intramuscular injection of TETRADURE 300 at volumes up to 10 mL per site results in transient swelling and tissue damage at the injection site. The lesions resolve quickly, but small amounts of abnormal muscle tissue may remain at the end of the 28-day withdrawal period.

F. Irritation Monitoring During Residue Study (Swine)

- 1. Title: A Tissue Residue Study of Oxytetracycline in Pigs Following Intramuscular Administration of OXYTET 30.
- 2. Study Number: 010/96 (Injection site irritation was monitored as part of the residue depletion study supporting human food safety).

3. Investigator: Norbrook Laboratories, Research Division
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland
4. Study Design: Pigs were randomly assigned to one of five groups sacrificed at various intervals to determine the residue depletion profile based on tissue concentrations of oxytetracycline. Injection site irritation was also assessed during the study. The study was conducted in accordance with Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.
 - a. Purpose: To assess injection site irritation of the test article administered at the highest recommended volume in the rump region of pigs.
 - b. Test Animals: Twenty animals (10 male and 10 female) approximately 14 to 18 weeks of age and weighing 114 to 157 pounds.
 - c. Control: None applicable to injection site irritation assessment.
 - d. Dosage form: 300 mg/mL injectable
 - e. Route of administration: Intramuscular injection
 - f. Dose: 5 mg/lb with a maximum injection volume of 5 mL per site administered for four consecutive days. Sites of administration included both sides of the rump and neck regions. The site of the final injection was the right rump musculature.
 - g. Test duration: 21 days
 - h. Parameters measured: The injection sites were monitored daily until the animals were sacrificed or until all reactions had resolved. Assessments included swelling, hardness/softness, heat, redness and pain at the injection sites. Following sacrifice, injection sites at the final site of administration were excised, examined for gross pathological changes, and photographed.
5. Results:
 - a. Clinical Observations: Transient reactions characterized by swelling and/or hardness were noted at the rump injection sites of 12/20 animals. Six animals exhibited swelling at the neck injection site. The severity of swelling reactions was characterized as mild (only notable on careful palpation). No sloughing occurred, and all reactions resolved without need for veterinary intervention. The time to resolution of the clinical signs was 2 or 3 days post-treatment. No systemic reactions, lameness, or other clinically significant adverse reactions were recorded during the animal phase of the study.
 - b. Gross Pathology Observations: Post mortem examination of the injection sites revealed lesions consisting of necrotic and fibrotic tissue and hemorrhage. The

severity of the lesions decreased with time and by Day 21 only a small area of fibrotic and necrotic tissue along with a small degree of hemorrhage was noted.

6. Conclusions: Intramuscular injection of this product results in transient swelling and tissue damage at the injection site. The lesions resolve quickly, but small amounts of abnormal muscle tissue may remain at the end of the 21 day withdrawal period. The product labeling will require a "trim out" statement.

G. Irritation Monitoring During PK Study (Cattle)

1. Title: A Comparative Study of Plasma Levels of Oxytetracycline in Cattle Following Intramuscular and Subcutaneous Administration of OXYTET 30 (Norbrook Laboratories Limited).
2. Study Number: 058/97
3. Investigator: Mr. A. Carragher
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland
4. Study Design:
 - a. Purpose: Effectiveness determination by comparison of plasma pharmacokinetics of the sponsor's oxytetracycline 300 mg/mL injection product administered intramuscularly or subcutaneously at the recommended dosage in a cross-over design bioequivalence study.
 - b. Test Animals: Twenty-four mixed breed, beef-type calves consisting of 12 males and 12 females weighing 910 to 1020 pounds were evaluated in the study.
 - c. Control (reference): Norbrook oxytetracycline 300 mg/mL injectable.
 - d. Dosage form: 300 mg/mL injectable.
 - e. Route of administration: Intramuscular or subcutaneous injection.
 - f. Dose: Single treatment per period with 13.6 mg oxytetracycline per pound of body weight with a maximum of 10 mL administered in one site. Subcutaneous injections were made in the neck area and intramuscular injections were made in the muscles of the rump.
 - g. Test duration: 53 days (42 day washout period).
 - h. Pertinent parameters measured: Swelling, hardness/softness, heat, redness and pain at injection sites were evaluated during the study.
5. Results: Injection site reactions of swelling and hardness were noted at all sites with mild or moderate pain associated with the subcutaneous sites only. Complete

resolution of the swelling and hardness associated with the intramuscular sites entailed 14 to 35 days. Complete resolution of the swelling and hardness associated with the subcutaneous injection sites required a minimum of 38 days and sometimes exceeded 101 days. No systemic reactions or any other significant adverse reactions related to either subcutaneous or intramuscular treatment were recorded.

6. **Conclusions:** Both intramuscular and subcutaneous administration of TETRADURE 300 produced varying degrees of swelling and transient pain in treated animals. Subcutaneous injection has the potential to cause a transient local tissue reaction that may result in trim-loss of edible tissue at slaughter. Consequently, product labeling will need to include statements regarding the potential occurrence of injection site swelling/discomfort in treated animals and the possibility of trim-loss of edible tissues at slaughter due to lesions/discoloration associated with injection sites(s).

H. Irritation Monitoring During Residue Study (Cattle)

1. **Title:** A Tissue Residue Study of Oxytetracycline and Injection Site Irritancy Evaluation in Cattle, Following the Subcutaneous Administration of OXYTET 30.
2. **Study Number:** 010/98
3. **Investigator:** Norbrook Laboratories, Research Division
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland
4. **General Design:**
 - a. **Test Animals:** Twenty-three beef-type steers and heifers approximately 7 months to 2 years of age weighing approximately 605 to 765 pounds were used. Three of the animals served as untreated controls to demonstrate lack of background oxytetracycline.
 - b. **Route, Time and Duration of Drug Administration:** A nominal dose of 5 mg oxytetracycline per pound of body weight once daily for 4 consecutive days was administered subcutaneously limiting the volume per injection site to 10 mL. This dose regimen represents the highest volume of product to be administered for all proposed indications. Additionally, one group of calves was administered a single subcutaneous injection at a nominal dose of 13.6 mg/lb limiting the volume per injection site to 10 mL.
 - c. **Pertinent Parameters Measured:** Gross observations of swelling, hardness/softness, heat, redness and pain at injection sites (in the area of the neck) were made during the study.

5. Results: Injection site reactions of swelling, hardness, and pain were noted at all injection sites, in absence of heat, softness, and redness. Most injection sites tended to decrease in size and magnitude with time. However, reactions at sites associated with the maximum dose volume tended to be more pronounced and persisted throughout the entire 28-day observation period. Complete resolution was only reported for some low volume administration sites.

Post-mortem examination of the injection sites revealed lesions consisting of fibrotic tissue with some necrosis and hemorrhage reducing in severity but persistent through the 28-day study period. No cystic lesions were noted.

Histopathology examinations revealed inflammatory changes at a majority of the injection sites with a reduction in severity evident by 28 days.

6. Conclusions: Subcutaneous administration of this 300 mg/mL oxytetracycline injectable product produced varying degrees of swelling and pain in treated animals. Fibrotic and necrotic tissues were evident through the 28-day period. This will require a "trim out" statement on the labeling.

4. HUMAN SAFETY:

A. Microbial Food Safety:

CVM evaluated microbial food safety information for oxytetracycline dihydrate (TETRADURE 300) at a dose rate of 13.6 mg/lb body weight for the control of bovine respiratory disease (BRD) in cattle at high risk of developing respiratory disease associated with *Pasteurella* spp. This risk assessment procedure involved conducting: 1) a release assessment to describe the probability that the antimicrobial new animal drug and its use in animals will result in the emergence of resistant bacteria or resistance determinants in the food animal under proposed conditions of use; 2) an exposure assessment to describe the likelihood of human exposure to the resistant bacteria or resistance determinants through consumption of edible products from treated animals, specifically, beef; and 3) a consequence assessment to describe the potential human health consequences of exposure to the defined resistant bacteria or resistance determinants by considering the human medical importance of tetracyclines in the treatment of human infectious disease.

It was determined that the risk associated with the use of this product is MEDIUM. An overall risk of MEDIUM is compatible with the proposed conditions of use for TETRADURE 300, *i.e.*, a dose rate of 13.6 mg/lb body weight for the control of bovine respiratory disease (BRD) in cattle at high risk of developing respiratory disease associated with *Pasteurella* spp.

B. Toxicity:

Oxytetracycline

It was concluded that this drug has low toxicity at therapeutic doses. The animal studies summarized in the submission, the summary paper on the human toxicity of oxytetracycline and the long history of use of this antibiotic were stated to be enough to alleviate concerns on the toxicity of oxytetracycline.

According to current requirements, CVM evaluated the safety of oxytetracycline residues present in the edible tissues of food animals on the intestinal flora of the consumer. This assessment was performed following a pathway approach proposed by CVM in the draft Guidance #52 *Assessment of the Effects of Antimicrobial Drug Residues from Food Animal Origin on the Human Intestinal Flora* published for comments in December of 2001. The pathway approach considered the microbiological activity of the drug on relevant bacteria of the human intestinal flora, the possibility of the drug residues reaching the human colon, the amount of residues remaining active in the colon environment, and the effects that the microbiological active residues could have on the intestinal flora.

It is concluded that oxytetracycline residues present in edible tissues of cattle treated with TETRADURE 300 at a dose level of 13.6 mg/lb would have no adverse impact on the intestinal flora of the consumer. The ADI calculated based on the amount of

residues present in edible cattle tissues, the concentration of microbiologically active residues reaching the human colon, human data on effect of tetracycline on human intestinal flora, and *in vitro* data from test systems containing human fecal flora, is similar to the codified ADI of 1.5 mg/person/day for all tetracyclines when 60% adsorption is applied. The amount of residues ingested in the total meal basket is lower than the codified ADI for all tetracyclines. The ADI is partitioned as follows: 40% for tissues and 60% for milk.

Glycerol Formal

Studies submitted to address the toxicity of glycerol formal were found adequate.

C. Safe Concentration of Residues:

Oxytetracycline

Safe concentrations of residues of oxytetracycline, following partitioning of the ADI, are: 2 ppm in muscle, 6 ppm in liver, and 12 ppm in kidney and fat (61 FR 67453).

Glycerol Formal

Residue and metabolism data for glycerol formal, plasma pharmacokinetic data for oxytetracycline and glycerol formal, and calculations estimating exposure to glycerol formal resulting from the consumption of meat derived from treated animals were presented. These data reference studies were originally submitted under NADA 128-409.

An ADI of 0.01 mg/kg is calculated for glycerol formal. For a 60-kg person, this is equivalent to an acceptable daily intake of 0.6 mg/person/day. On the basis of muscle residues being below the LOD for the method at 5 days post-dosing, the sponsor calculates a maximum daily intake of 25 µg glycerol formal/person. For a 60-kg person, this represents an actual intake of 0.4 µg glycerol formal/kg body weight/day. A 24X safety margin between the ADI and actual daily intake (0.6 mg/person/day divided by 25 µg/person/day) on the basis of tissue residues 5 days post-dosing is calculated.

D. Residue Depletion Studies:

Oxytetracycline residue depletion studies were conducted (in cattle and swine) at the 5 mg/lb dose administered for 4 consecutive days on the premise that this is the highest labeled dose intended (total of 20 mg/lb). The studies were conducted administering product via the intramuscular and subcutaneous routes in cattle and the intramuscular route in swine.

Oxytetracycline

1. Title: A Tissue Residue Study of Oxytetracycline in Cattle Following the Intramuscular Administration of OXYTET 30

Conducted by: Norbrook Laboratories, Research Division

Ballyedmond Castle Farms Limited
 101 Killowen Road
 Rostrevor
 Co. Down, BT34 3AG
 Northern Ireland

Test Animals: Twenty-three (23) beef-type steers and heifers approximately 1 to 2 years of age weighing approximately 620 to 795 pounds were used. Three of the animals served as untreated controls to demonstrate lack of background for oxytetracycline.

Route, Time, and Duration of Drug Administration: A nominal dose rate of 5 mg oxytetracycline per pound of body weight once daily for four consecutive days was administered intramuscularly limiting the volume per injection site to a volume of 10 mL. This dose regimen represents the highest volume of product to be administered for all proposed indications.

Table 4.1. Oxytetracycline Residues in Tissues of Cattle Treated with OXYTET 30

Withdrawal Time (Days)	Oxytetracycline Residues ($\mu\text{g/g}$)			
	Muscle	Kidney	Liver	Fat
5	0.163 \pm 0.015*	1.020 \pm 0.064	0.482 \pm 0.082	<0.1
8	0.109 \pm 0.004	0.518 \pm 0.185	0.266 \pm 0.079	<0.1
11	<0.1	0.263 \pm 0.071	0.146 \pm 0.027	<0.1
21	<0.1	<0.1	<0.1	<0.1
28	<0.1	<0.1	<0.1	<0.1

*Mean \pm SEM

A statistical analysis of the depletion data using an upper 99th percentile tolerance limit with a 95% confidence interval resulted in calculated withdrawal times of 21 and 25 days in liver and kidney samples, respectively. Thus, the residue depletion data are consistent with the assignment of a 28-day pre-slaughter withdrawal period.

- Title: A Tissue Residue Study of Oxytetracycline in Swine Following Intramuscular Administration of OXYTET 30

Conducted By: Norbrook Laboratories, Research Division
 Ballyedmond Castle Farms Limited
 101 Killowen Road
 Rostrevor
 Co. Down, BT34 3AG
 Northern Ireland

Test Animals: Twenty-three (23) pigs, castrated males and females approximately

14 to 18 weeks of age weighing approximately 114 to 157 pounds were used. Three of the animals served as untreated controls to demonstrate lack of background for oxytetracycline.

Route, Time, and Duration of Drug Administration: A nominal dose rate of 5 mg oxytetracycline per pound of body weight once daily for four consecutive days was administered intramuscularly. This dose regimen represents the highest volume of product to be administered for all proposed indications.

Table 4.2. Oxytetracycline Residues in Tissues of Swine Treated with OXYTET 30

Withdrawal Time (Days)	Oxytetracycline Residues ($\mu\text{g/g}$)			
	Muscle	Kidney	Liver	Fat
2	0.421 \pm 0.096*	1.903 \pm 0.502	0.581 \pm 0.106	0.128 \pm 0.009
5	0.133 \pm 0.016	0.682 \pm 0.053	0.176 \pm 0.055	<0.1
8	<0.1	0.188 \pm 0.083	<0.1	<0.1
11	<0.1	0.138 \pm 0.062	<0.1	<0.1
21	<0.1	<0.1	<0.1	<0.1

*Mean \pm SEM

A statistical analysis of the depletion data, using an upper 99th percentile tolerance limit with a 95% confidence interval resulted in calculated withdrawal times of 18 days in kidney samples. These depletion data are consistent with the assignment of a 28-day preslaughter withdrawal period.

3. Title: A Tissue Residue Study of Oxytetracycline and Injection Site Irritancy Evaluation in Cattle Following Subcutaneous Administration of OXYTET 30

Conducted by: Norbrook Laboratories, Research Division
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

Test Animals: Twenty-three (23) beef-type steers and heifers approximately 7 months to 2 years of age weighing approximately 605 to 765 pounds, were used. Three of the animals served as untreated controls to demonstrate lack of background oxytetracycline.

Route, Time, and Duration of Drug Administration: A nominal dose rate of 5 mg oxytetracycline per pound of body weight once daily for four consecutive days was administered subcutaneously limiting the volume per injection site to 10 mL. This dose regimen represents the highest volume of product to be administered for all proposed indications. Additionally, one group of calves was administered a single subcutaneous injection at a nominal dose rate of 13.6 mg/lb limiting the volume per

injection site to 10 mL.

Design: The calves were euthanized at designated intervals (7, 10, 14, and 28 days) and muscle, kidney, liver, and fat samples were collected for oxytetracycline residue analysis using a validated microbiological agar diffusion method. Injection sites were evaluated during the study and at post mortem examination as described above in the Target Animal Safety section of this FOI Summary.

Table 4.3. Oxytetracycline Residues in Tissues of Cattle Treated with OXYTET 30 (Dose rate 5 mg/lb/day for 4 days)

Withdrawal Time (Days)	Oxytetracycline Residues ($\mu\text{g/g}$) Tissues				Oxytetracycline Residues ($\mu\text{g/g}$) Injection Sites			
	Muscle	Liver	Kidney	Fat	Site 1	Site 2	Site 3	Site 4
7	0.190 \pm 0.012*	0.574 \pm 0.137	0.873 \pm 0.094	<0.1	15.938 \pm 26.450	0.482 \pm 0.180	461.25 \pm 139.62	13.102 \pm 16.402
10	0.142 \pm 0.033	0.383 \pm 0.108	0.568 \pm 0.188	<0.1	1.267 \pm 1.143	0.494 \pm 0.221	436.000 \pm 142.75	8.002 \pm 7.286
14	0.123 \pm 0.018	0.332 \pm 0.184	0.509 \pm 0.207	<0.1	31.475 \pm 30.056	0.173 \pm 0.043	265.725 \pm 256.756	3.302 \pm 4.342
28	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.145 \pm 0.009	<0.1

*Mean \pm SEM

Table 4.4. Oxytetracycline (Dose Rate 13.6 mg/lb)

Withdrawal Time (Days)	Oxytetracycline Residues ($\mu\text{g/g}$) Tissues				Oxytetracycline Residues ($\mu\text{g/g}$) Injection Sites							
	Muscle	Liver	Kidney	Fat	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8
14	<0.1	0.168 \pm 0.01*	0.418 \pm 0.03	<0.1	177 \pm 33.54	1.37 \pm 0.16	268.7 \pm 45.15	3.56 \pm 0.97	170.6 \pm 73.38	1.99 \pm 0.74	246.3 \pm 85.06	1.95 \pm 0.33

*Mean \pm SEM

Withdrawal Period Calculation

The residue depletion data from the multidose residue study were analyzed using a statistical tolerance limit algorithm for the 99th percentile of the population with a 95% confidence limit. The residue depletion data are consistent with the pre-slaughter assignment of a 28-day withdrawal period.

Although not analyzed statistically, the 14-day residue data from the single dose residue study are comparable to the 14-day residue data from the multidose study. Thus, it is consistent with the public health to assign a 28-day withdrawal for the single dose treatment regime as well.

Glycerol Formal

Residue and metabolism data for glycerol formal originally provided under NADA 128-409, plasma pharmacokinetic data for oxytetracycline and glycerol formal, and calculations estimating exposure to glycerol formal resulting from the consumption of

meat derived from treated animals were presented.

Depletion characteristics of oxytetracycline and glycerol formal demonstrated that plasma residues of glycerol formal will deplete more rapidly than residues of oxytetracycline (a half-life of approximately 4 hours vs. a half-life of approximately 27 - 35 hours). It is concluded that residues of glycerol formal will not present human food safety concern at the withdrawal period anticipated for the active ingredient, oxytetracycline (i.e. 28 days).

E. Tolerance:

Tolerances of 2 ppm in muscle, 6 ppm in liver, 12 ppm in kidney, and 12 ppm in fat are codified for the uncooked edible tissues of beef cattle, non-lactating dairy cattle, and swine under 21 CFR 556.500.

F. Withdrawal Time:

A 28-day pre-slaughter withdrawal period is assigned for the use of oxytetracycline 300 mg/mL, via the intravenous, intramuscular, or subcutaneous routes of administration in beef cattle and non-lactating dairy cattle and via the intramuscular route of administration in swine.

G. Regulatory Method for Residues:

The regulatory analytical method for detection of residues of the drug is a cylinder plate diffusion microbiological assay using *Bacillus cereus* var. *mycoides* (ATCC 11778). The method is published by the Food and Drug Administration, "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, and Protocols", Revised October 1968, reprinted December 1974. The method is available from the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

5. AGENCY CONCLUSIONS:

The data submitted in support of this original NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that OXYTETRACYCLINE INJECTION 300 mg/mL and TETRADURE 300 INJECTION(Oxytetracycline) are safe and effective for use in cattle and swine for the approved indications, when administered as indicated in the product labeling at the approved dose.

Tolerances of 2 ppm in muscle, 6 ppm in liver, 12 ppm in kidney, and 12 ppm in fat are codified for the uncooked edible tissues of beef cattle, non-lactating dairy cattle, and swine under 21 CFR 556.500.

OXYTETRACYCLINE INJECTION 300 mg/mL is labeled for over-the-counter (OTC) use. Routine injection of cattle and swine is a widely accepted and recommended practice performed by the lay person for this product. Additionally, adequate directions for use have been written for the layman and the conditions for use prescribed on the label are likely to be followed in practice.

TETRADURE 300 INJECTION is restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is required to determine when cattle are at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*, and to monitor the animals for signs of adverse reactions when the drug is administered at higher doses than those recommended for other indications.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. This marketing exclusivity applies only to the increase in formulation concentration to 300 mg/mL; and to the veterinary prescription use of the product in cattle for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*, and for a dosage range of 9 to 13.6 mg/lb for the treatment of bacterial pneumonia caused by *Pasteurella* spp. (shipping fever) in calves and yearlings and infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*, for which new data were required.

Oxytetracycline is under U.S. patent number 6,110,905 and 6,310,053, which expire August 29, 2020 and October 30, 2021, respectively.

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

100, 250 and 500 mL vial labels for the Rx and OTC product
100, 250 and 500 mL carton labels for the Rx and OTC product
Package insert for the Rx and OTC product

Tetradure™ 300 (oxytetracycline injection) is a sterile preservative-free solution of the broad-spectrum antibiotic oxytetracycline. Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline, 2.7% w/v propylene glycol, 40% w/v glycerol formal, 10% w/v polyethylene glycol, and 0.4% w/v sodium formaldehyde sulfoxylate (as a preservative), mannitol, benzalkonium chloride hydrochloride and as required to adjust pH.

WARNING: Oculo-cervical treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration to swine may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS:
Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic resistance beyond the withdrawal period.

Use extreme care when administering this product by intravenous injection. Technicians, injection, or damage from an intravenous injection, may cause severe swelling at the injection site.

CAUTION:
Intramuscular or subcutaneous injection may result in local tissue reaction which persists beyond the slaughter withdrawal period. This may result in loss of edible tissue at slaughter.

TETRADURE™ 300

(OXYTETRACYCLINE) INJECTION
ANTIBIOTIC

Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline.

For the treatment of disease in beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves and swine.

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

Restricted Drug(s) (California). Use only as Directed

NADA 141-143, Approved By FDA U.S. Patent No. 6,110,905

Net Contents, 100 mL U.S. Patent No. 6,310,053



DISEASE - CATTLE: Tetradure™ 300 (oxytetracycline) injection is to be administered by intramuscular, subcutaneous or intravenous injection to beef cattle, calves, including pre-ruminating (veal) calves and non-lactating dairy cattle. At a single intramuscular or subcutaneous dose of 13.6 mg of oxytetracycline per pound of bodyweight, Tetradure™ 300 is recommended for the control of respiratory disease in cattle at high risk of developing BRD associated with Mannheimia (Pasteurella) haemolytica.

At a single intramuscular or subcutaneous dose range of 9 to 13.6 mg of oxytetracycline per pound of bodyweight, Tetradure™ 300 is recommended in the treatment of the following conditions:

1. Bacterial pneumonia caused by Pasteurella spp. (Shipping fever) in calves and yearlings, where treatment is impractical due to husbandry conditions, such as cattle on range or where repeated treatment is undesirable.

2. Infective bovine keratoconjunctivitis (pink eye) caused by Moraxella bovis.

NOTE: A single dose of 9 milligrams of oxytetracycline per pound of bodyweight (0.5 mL/100 lb) administered intramuscularly is recommended in the treatment of bacterial pneumonia caused by Pasteurella multocida in swine. Where re-treatment is impractical due to husbandry conditions or where repeated treatment is undesirable.

Keep in package insert for complete instructions, dosage, and usage.

Store at room temperature 15°-30°C (59°-86°F).

KEEP FROM FREEZING

Made in UK.

Manufactured by:

Merial Limited

Durham 20094-640 USA

TETRADURE is a trademark and Cattle Head Logo is a registered trademark of Merial.

Tetradure™ 300 (oxytetracycline injection) is a sterile preconstituted solution of the broad-spectrum antibiotic oxytetracycline. Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline, 2.7% w/v magnesium oxide, 40% w/v glycerol formal, 10% w/v polyethylene glycol, and 0.4% w/v sodium formaldehyde sulfoxylate (as a preservative) monohydrochloride and/or hydrochloric acid as required to adjust pH.

WARNING: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS:

Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period. Use extreme care when administering this product by intravenous injection. Paradoxical injection, or leakage from an intravenous injection, may cause severe swelling at the injection site.

CAUTION:

Intramuscular or subcutaneous injection may result in local tissue reaction which persists beyond the slaughter withdrawal period. This may result in loss of edible tissue at slaughter.

TETRADURE™ 300

(OXYTETRACYCLINE) INJECTION

ANTIBIOTIC

Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline.

For the treatment of disease in beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves and swine.

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

Restricted Drug(s) (California). Use only as Directed

NADA 141-143, Approved By FDA

U.S. Patent No. 6,110,905

Net Contents: 250 mL

U.S. Patent No. 6,310,053



006830L02

DOSAGE - CATTLE: Tetradure™ 300 (oxytetracycline) Injection is to be administered by intramuscular, intracutaneous or intravenous injection to beef cattle, calves, including pre-ruminating (veal) calves and non-lactating dairy cattle. At a single intramuscular or subcutaneous dose of 13.6 mg of oxytetracycline per pound of bodyweight, Tetradure™ 300 is recommended for the control of respiratory disease in cattle at high risk of developing BRD associated with *Moraxella (Pasteurella) haemolytica*.

At a single intramuscular or subcutaneous dose range of 9 to 13.6 mg of oxytetracycline per pound of bodyweight, Tetradure™ 300 is recommended in the treatment of the following conditions:

1 bacterial pneumonia caused by *Pasteurella* spp. (shipping fever) in calves and yearlings where re-treatment is impractical due to husbandry conditions such as cattle on range or where repeated restraint is inevitable.

2 infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella* spp.

SWINE: A single dose of 9 milligrams of oxytetracycline per pound of bodyweight (3.0 mL/100 lb) administered ~~intramuscularly~~ ^{subcutaneously} is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine where re-treatment is impractical due to husbandry conditions or where repeated restraint is inevitable.

Refer to package insert for complete indications, dosage, and usage. Store at room temperature 15° - 30°C (59° - 86°F).

KEEP FROM FREEZING

Made in UK.

Distributed by:

Merial Limited

Duluth, GA 30098-4640 USA

Batch No.

™TETRADURE is a trademark and

Cattle Head Logo is a registered

trademark of Merial. Eq.

Tetradure™ 300 (oxytetracycline injection) is a sterile preconstituted solution of the broad-spectrum antibiotic oxytetracycline. Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline; 2.7% w/v magnesium oxide; 40% v/v glycerol formal; 10% v/v polyethylene glycol; and 0.4% w/v sodium formaldehyde sulphoxylate (as a preservative), monoethanolamine and/or hydrochloric acid as required to adjust pH

WARNINGS: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS:

Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period. Use extreme care when administering this product by intravenous injection. Perivascular injection, or leakage from an intravenous injection, may cause severe swelling at the injection site.

CAUTION:

Intramuscular or subcutaneous injection may result in local tissue reaction which persists beyond the slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.

TETRADURE™ 300

(OXYTETRACYCLINE) INJECTION
ANTIBIOTIC

Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline.

For the treatment of disease in beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves and swine.

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

Restricted Drug(s) (California). Use only as Directed

NADA 141-143, Approved By FDA

U.S. Patent No. 6,110,905

Net Contents: 500 mL

U.S. Patent No. 6,310,053



007630L02

DOSAGE - CATTLE: Tetradure™ 300 (oxytetracycline) injection is to be administered by intramuscular, subcutaneous or intravenous injection to beef cattle, calves, including pre-ruminating (veal) calves and non-lactating dairy cattle. At a single intramuscular or subcutaneous dose of 13.6 mg of oxytetracycline per pound of bodyweight, Tetradure™ 300 is recommended for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*.

At a single intramuscular or subcutaneous dose range of 9 to 13.6 mg of oxytetracycline per pound of bodyweight, Tetradure™ 300 is recommended in the treatment of the following conditions:

1. bacterial pneumonia caused by *Pasteurella* spp. (shipping fever) in calves and yearlings, where re-treatment is impractical due to husbandry conditions, such as cattle on range, or where repeated restraint is inadvisable.
2. infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis*.

SWINE: A single dose of 9 milligrams of oxytetracycline per pound of bodyweight (3.0 mL/100 lb) administered intramuscularly is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine, where re-treatment is impractical due to husbandry conditions or where repeated restraint is inadvisable.

Refer to package insert for complete indications, dosage, and usage. Store at room temperature 15° - 30°C (59° - 86°F).

KEEP FROM FREEZING.

Made in UK.

Distributed by:

Merial Limited
Duluth, GA 30096-4640, USA

™TETRADURE is a trademark and Cattle Head Logo is a registered trademark of Merial.

Batch No

Exp

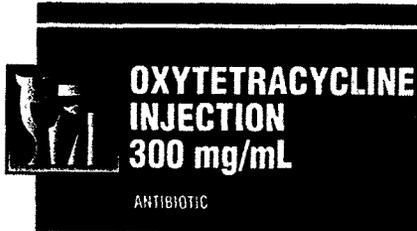
Oxytetracycline Injection 300 mg/mL is a sterile, preservative-free solution of the broad-spectrum antibiotic oxytetracycline. Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline, 2.7% w/v magnesium stibic acid, 40% w/v glycerol formal, 10% w/v polyethylene glycol, and 0.4% w/v sodium formalinolate solution (as a preservative), monochloroacetic acid and hydrochloric acid as required to adjust pH.

WARNING: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Fatal respiratory edema due to edema may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 6 minutes.

PRECAUTIONS:
Exceeding the highest recommended level of drug per pound of bodyweight per day administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period.

Use extreme care when administering this product by intravenous injection. Painful reactions, or leakage from an intravenous injection, may cause severe swelling at the injection site.

CAUTION: Intramuscular or subcutaneous injection may result in local tissue reaction which would impair the slaughter withdrawal period. This may result in loss of edible tissue at slaughter.



Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline.

For the treatment of disease in beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves and swine.

FOR USE IN ANIMALS ONLY

NADA 141-143, Approved By FDA

U.S. Patent No. 6,110,906

Net Contents: 100 mL

U.S. Patent No. 6,310,053

Restricted Drug(s) (California). Use only as Directed



DECADE:
Oxytetracycline Injection

CATTLE:
A single dosage of 8 milligrams of oxytetracycline per pound of bodyweight (3.6 mL/100 lb subcutaneous) is recommended in the treatment of the following conditions:

- (1) Bacterial pneumonia caused by Pasteurella spp. (shipping fever) in calves and yearlings, where re-treatment is impractical due to husbandry conditions, such as cattle on range or where treatment is impractical in individual.
- (2) Infectious bovine keratoconjunctivitis (pink eye) caused by Moraxella spp.

SWINE:
A single dose of 8 milligrams of oxytetracycline per pound of bodyweight (3.6 mL/100 lb subcutaneous) is recommended in the treatment of bacterial pneumonias caused by Pasteurella multocida in swine where re-treatment is impractical due to husbandry conditions or where treatment is impractical in individual.

Refer to package insert for complete instructions, dosage, and usage.

Store at room temperature (15° - 30°C (59° - 86°F)).

KEEP FROM FREEZING Batch No.

Distributed by Merial Limited, Durham, NC 27709-4040 USA

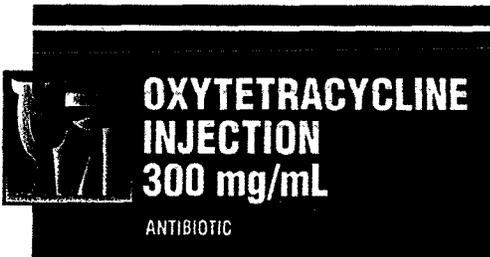
MADE IN THE UK

Oxytetracycline Injection 300 mg/mL is a sterile preconstituted solution of the broad-spectrum antibiotic oxytetracycline. Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline, 2.7% w/v magnesium oxide, 40% v/v glycerol formal, 10% v/v polyethylene glycol, and 0.4% w/v sodium formaldehyde sulfoxylate (as a preservative), monobenzoamine and/or hydrochloric acid as required to adjust pH.

WARNINGS: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS: Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period. Use extreme care when administering this product by intravenous injection. Paravascular injection, or leakage from an intravenous injection, may cause severe swelling at the injection site.

CAUTION: Intramuscular or subcutaneous injection may result in local tissue reaction which persists beyond the slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.



Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline. For the treatment of disease in beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves and swine.

FOR USE IN ANIMALS ONLY
NADA 141-143, Approved By FDA U.S. Patent No. 6,110,905
Net Contents: 250 mL U.S. Patent No. 6,310,053
Restricted Drug(s) (California). Use only as Directed



002630LD1

DOSEAGE:
Oxytetracycline Injection
CATTLE:
A single dosage of 9 milligrams of oxytetracycline per pound of bodyweight (3.0 mL/100 lb) administered intramuscularly or subcutaneously is recommended in the treatment of the following conditions:
(1) bacterial pneumonia caused by *Pasteurella* spp. (shipping fever) in calves and yearlings, where re-treatment is impractical due to husbandry conditions, such as cattle on range or where repeated restraint is inadvisable.
(2) infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis*.
SWINE: A single dose of 9 milligrams of oxytetracycline per pound of bodyweight (3.0 mL/100 lb) administered intramuscularly is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine, where re-treatment is impractical due to husbandry conditions or where repeated restraint is inadvisable.
Refer to package insert for complete indications, dosage, and usage.
Store at room temperature 15° - 30°C (59° - 86°F).
KEEP FROM FREEZING
Distributed by:
Merial Limited
Duluth, GA 30096-4640
USA
MADE IN THE UK

Oxytetracycline Injection 300 mg/mL is a sterile preconstituted solution of the broad-spectrum antibiotic oxytetracycline. Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline; 2.7% w/v magnesium oxide; 40% v/v glycerol formal; 10% v/v polyethylene glycol; and 0.4% w/v sodium formaldehyde sulfoxylate (as a preservative), monoethanolamine and/or hydrochloric acid as required to adjust pH.

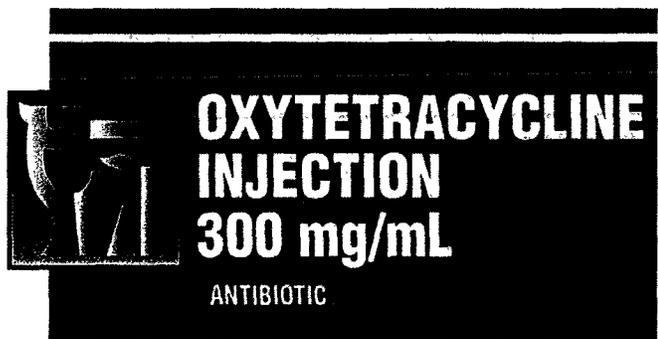
WARNINGS: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS:

Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period. Use extreme care when administering this product by intravenous injection. Perivascular injection, or leakage from an intravenous injection, may cause severe swelling at the injection site.

CAUTION:

Intramuscular or subcutaneous injection may result in local tissue reaction which persists beyond the slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.



Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline. For the treatment of disease in beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves and swine.

FOR USE IN ANIMALS ONLY

NADA 141-143, Approved By FDA U.S. Patent No. 6,110,905

Net Contents: 500 mL U.S. Patent No. 6,310,053

Restricted Drug(s) (California). Use only as Directed



DOSAGE:

Oxytetracycline Injection

CATTLE:

A single dosage of 9 milligrams of oxytetracycline per pound of bodyweight (3.0 mL/100 lb) administered *intramuscularly or subcutaneously* is recommended in the treatment of the following conditions

- (1) bacterial pneumonia caused by *Pasteurella* spp (shipping fever) in calves and yearlings, where re-treatment is impractical due to husbandry conditions, such as cattle on range, or where repeated restraint is inadvisable
- (2) infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis*.

SWINE: A single dose of 9 milligrams of oxytetracycline per pound of bodyweight (3.0 mL/100 lb) administered *intramuscularly* is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine, where re-treatment is impractical due to husbandry conditions or where repeated restraint is inadvisable

Refer to package insert for complete indications, dosage, and usage.

Store at room temperature
15° - 30°C (59° - 86°F).

KEEP FROM FREEZING

Distributed by:
Merial Limited
Duluth, GA 30096-4640
USA

Batch No

Exp

MADE IN THE UK

250 mL
 300 mg/mL
 INJECTION
 OXYTETRACYCLINE

284054C01

**OXYTETRACYCLINE
 INJECTION
 300 mg/mL**
 ANTIBIOTIC

**OXYTETRACYCLINE
 INJECTION
 300 mg/mL**
 CATTLE DOSAGE GUIDE

OXYTETRACYCLINE INJECTION 300 mg/mL is a sterile, preconstituted solution of the broad-spectrum antibiotic oxytetracycline.

CAUTION: Intramuscular injection may result in local tissue reaction which persists beyond the slaughter withdrawal period. This may result in trim loss of edible tissues at slaughter.

WARNINGS: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in cerebral collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS: Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 ml intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle, and 5 ml intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period.

Use extreme care when administering this product by intravenous injection. Paravascular injection or leakage from intravenous injection may cause swelling at injection site.

**STORE AT ROOM TEMPERATURE
 15 C - 30 C (59 - 86 F)
 KEEP FROM FREEZING**

REFER TO PACKAGE INSERT FOR COMPLETE DIRECTIONS

Restricted Drug(s) (California)

Not for Human Use.
 Use Only as Directed.

DISTRIBUTED BY:
 Merck Animal Health
 Kenilworth, NJ 07033
 USA

MADE IN THE UK

**OXYTETRACYCLINE
 INJECTION
 300 mg/mL**
 SWINE DOSAGE GUIDE

At the first signs of pneumonia* administer a single dose of Oxytetracycline Injection 300 mg/mL by deep intramuscular injection according to the following weight categories**

Animal weight (lb)	Number of ml or cc
10	0.3
25	0.8
50	1.5
75	2.3
100	3.0
125	3.8
150	4.5
175	5.3
200	6.0
225	6.8
250	7.5
275	8.3
300	9.0
325	9.8

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 5 ml at any one injection site.

Discontinue treatment 28 days prior to slaughter.

At the first signs of pneumonia or pink eye* administer a single dose of Oxytetracycline Injection 300 mg/mL by deep intramuscular or subcutaneous injection according to the following weight categories**

Animal weight (lb)	Number of ml or cc
100	3.0
200	6.0
300	9.0
400	12.0
500	15.0
600	18.0
700	21.0
800	24.0
900	27.0
1000	30.0
1100	33.0
1200	36.0

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 10 ml at any one injection site (1 to 2 ml per site in small calves).

Discontinue treatment 28 days prior to slaughter.



U.S. Patent No. 6,110,305
 U.S. Patent No. 6,310,053

Net Contents
 250 mL



Net Contents
500 mL

**OXYTETRACYCLINE
INJECTION
300 mg/mL**

**OXYTETRACYCLINE
INJECTION
300 mg/mL**

ANTIBIOTIC



U.S. Patent No. 6,110,925
U.S. Patent No. 6,310,053

Net
Contents
500 mL



**OXYTETRACYCLINE
INJECTION
300 mg/mL**

CATTLE DOSAGE GUIDE

At the first signs of pneumonia or pasteurellosis* administer a single dose of Oxytetracycline Injection 300 mg/mL by deep intramuscular or subcutaneous injection according to the following weight categories**

Animal weight (lb)	Number of mL or cc
100	3.0
200	6.0
300	9.0
400	12.0
500	15.0
600	18.0
750	21.0
900	24.0
1000	27.0
1200	33.0
1500	39.0

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 10 mL at any one injection site (5 to 2 mL per site in small calves).

Discontinue treatment 28 days prior to slaughter.

OXYTETRACYCLINE INJECTION 300 mg/mL is a sterile, preservative-free solution of the broad-spectrum antibiotic oxytetracycline.

CAUTION: Intramuscular injection may result in tissue reaction which persists beyond the slaughter withdrawal period. This may result in the loss of edible tissues at slaughter.

WARNINGS: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Do not use in lactating dairy animals. Feed withdrawal administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS: Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle and 5 mL intramuscularly per injection site in adult swine may result in antibiotic residues beyond the withdrawal period.

Use extreme care when administering this product by intravenous injection. Perivascular necrosis or exsude from intravenous injection may cause swelling at injection site.

STORE AT ROOM TEMPERATURE
15 to 30 C (59 to 86 F)

KEEP FROM FREEZING

REFER TO PACKAGE INSERT FOR COMPLETE DIRECTIONS

Restricted Drugs (California).

Not for Human Use.

Use Only as Directed.

DISTRIBUTED BY:
Merial Limited
Duluth, GA 30030-4040
USA

MADE IN THE UK

**OXYTETRACYCLINE
INJECTION
300 mg/mL**

SWINE DOSAGE GUIDE

At the first signs of pneumonia* administer a single dose of Oxytetracycline Injection 300 mg/mL by deep intramuscular injection according to the following weight categories**

Animal weight (lb)	Number of mL or cc
10	0.3
25	0.8
50	1.5
75	2.3
100	3.0
125	3.8
150	4.5
175	5.3
200	6.0
225	6.8
250	7.5
275	8.3
300	9.0
325	9.8

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 5 mL at any one injection site.

Discontinue treatment 28 days prior to slaughter.

Exp. _____
 Batch No. _____

Net Contents
 100 mL

**OXYTETRACYCLINE
 INJECTION
 300 mg/mL**

204053C01

**OXYTETRACYCLINE
 INJECTION
 300 mg/mL**

ANTIBIOTIC



MADE IN THE U.K.
 U.S. Patent No. 6,110,805
 U.S. Patent No. 6,310,053

Net Contents
 100 mL



**OXYTETRACYCLINE
 INJECTION
 300 mg/mL**

CATTLE DOSAGE GUIDE

At the first signs of pneumonia or pink eye* administer a single dose of Oxytetracycline Injection 300 mg/mL by deep intramuscular or subcutaneous injection according to the following weight categories.**

Animal weight (lb)	Number of mL or cc
100	3.0
200	6.0
300	9.0
400	12.0
500	15.0
600	18.0
700	21.0
800	24.0
900	27.0
1000	30.0
1100	33.0
1200	36.0

*See package insert for dosing instructions for other indicated diseases and for product information.

**Do not administer more than 10 mL of any one injection site (1 to 2 mL per site in small calves).

Discontinue treatment 28 days prior to slaughter.

OXYTETRACYCLINE INJECTION 300 mg/mL is a sterile preconstituted solution of the broad spectrum antibiotic oxytetracycline.

CAUTION: Intramuscular injections may result in local tissue reaction which persists to post the slaughter withdrawal period. This may result in the loss of edible tissues at slaughter.

WARNINGS: Discontinue treatment at least 28 days prior to slaughter of all cattle and swine. **Do not use in sickle cell thalassemia.** Rapid intravenous administration may also result in an allergic response. Oxytetracycline should be administered intravenously slowly over a period of at least 30 minutes.

PRECAUTIONS: Exceeding the highest recommended level of drug per pound of live weight per day, accumulating more than the recommended number of treatments, and/or exceeding 10 mL intramuscular or subcutaneous per one hundred pounds of live weight may, in calves, dairy cattle, and hogs, produce milk rejection when milk samples are tested for antibiotic residues beyond the withdrawal period.

Use extreme care when administering this product to patients with renal insufficiency. Patients with renal insufficiency may have increased toxicity.

STORE AT ROOM TEMPERATURE 15 C - 30 C (59 - 86 F). KEEP FROM FREEZING.

RESTRICTED DRUGS (California)
Refer to Package Insert for Complete Directions.

Not for Human Use. Use Only as Directed.

DISTRIBUTED BY:
 Merial Limited
 Dulais, GA 30116-1630
 USA

MADE IN THE U.K.

**OXYTETRACYCLINE
 INJECTION
 300 mg/mL**

SWINE DOSAGE GUIDE

At the first signs of pneumonia* administer a single dose of Oxytetracycline Injection 300 mg/mL by deep intramuscular injection according to the following weight categories.**

Animal weight (lb)	Number of mL or cc
10	0.3
25	0.6
50	1.2
75	1.8
100	2.4
125	3.0
150	3.6
175	4.2
200	4.8
225	5.4
250	6.0
275	6.6
300	7.2
325	7.8
350	8.4
375	9.0

*See package insert for dosing instructions for other indicated diseases and for product information.

**Do not administer more than 5 mL at any one injection site.

Discontinue treatment 28 days prior to slaughter.



Net Contents:
500 mL

(OXYTETRACYCLINE) INJECTION

TETRADURE™
300

0204061C01

TETRADURE™
300

(OXYTETRACYCLINE) INJECTION

ANTIBIOTIC

Each mL contains 300 mg of Oxytetracycline base as amphoteric oxytetracycline.

For the treatment of diseases in beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves and swine.

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA 141-143, Approved By FDA

U.S. Patent No. 6,110,905
U.S. Patent No. 6,310,053

Net Contents:
500 mL

TETRADURE™
300

(OXYTETRACYCLINE) INJECTION

CATTLE DOSAGE GUIDE

At the first signs of pneumonia or pink eye* or for the control of respiratory disease in cattle at a high risk of developing BRD administer a single dose of Tetradure™ 300 by deep intramuscular or subcutaneous injection (dose rate 13.6 mg/lb) according to the following weight categories**

Animal weight (lb)	Number of mL or cc	Animal weight (lb)	Number of mL or cc
100	3.0 - 4.5	700	21.0 - 31.7
200	6.0 - 9.0	800	24.0 - 36.3
300	9.0 - 13.6	900	27.0 - 40.8
400	12.0 - 18.1	1000	30.0 - 45.3
500	15.0 - 22.6	1100	33.0 - 49.8
600	18.0 - 27.2	1200	36.0 - 54.4

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 10 mL at any one injection site (1 to 2 mL per site in small calves).

Discontinue treatment 28 days prior to slaughter.

TETRADURE™ 300 (Oxytetracycline) Injection is a sterile, preconstituted solution of the broad-spectrum antibiotic oxytetracycline.

CAUTION: Intramuscular injection may result in local tissue reaction which persists beyond the slaughter withdrawal period. This may result in trim loss of edible tissues at slaughter.

WARNINGS: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS: Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period.

Use extreme care when administering this product by intravenous injection. Perivascular injection or leakage from intravenous injection may cause swelling at injection site.

STORE AT ROOM TEMPERATURE 15°-30°C (59°-86°F)
KEEP FROM FREEZING

REFER TO PACKAGE INSERT FOR COMPLETE DIRECTIONS.

Restricted Drug(s) (California). Use Only as Directed.

Not for Human Use.

DISTRIBUTED BY:
Merial Limited
Duluth, GA 30096-4640, USA

TETRADURE is a trademark and Cattle Head Logo is a registered trademark of Merial.

MADE IN THE UK

TETRADURE™
300

(OXYTETRACYCLINE) INJECTION

SWINE DOSAGE GUIDE

At the first signs of pneumonia* administer a single dose of Tetradure™ 300 by deep intramuscular injection according to the following weight categories**

Animal weight (lb)	Number of mL or cc	Animal weight (lb)	Number of mL or cc
10	0.3	175	5.3
25	0.8	200	6.0
50	1.5	225	6.8
75	2.3	250	7.5
100	3.0	275	8.3
125	3.8	300	9.0
150	4.5	325	9.8

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 5 mL at any one injection site.

Discontinue treatment 28 days prior to slaughter.





Net Contents
250 mL

(OXYTETRACYCLINE) INJECTION

TETRADURE™
300

TETRADURE™
300

(OXYTETRACYCLINE) INJECTION

ANTIBIOTIC

TETRADURE™
300

(OXYTETRACYCLINE) INJECTION

CATTLE DOSAGE GUIDE

At the first signs of pneumonia or pink eye* or for the control of respiratory disease in cattle at a high risk of developing BRD administer a single dose of Tetradure™ 300 by deep intramuscular or subcutaneous injection (see site, 13 p. 10) according to the following weight categories**

Animal weight (lb)	Number of mL or cc	Animal weight (lb)	Number of mL or cc
100	3.0 - 4.5	700	21.0 - 31.7
200	6.0 - 9.0	800	24.0 - 36.3
300	9.0 - 13.5	900	27.0 - 40.8
400	12.0 - 18.1	1000	30.0 - 45.3
500	15.0 - 22.6	1100	33.0 - 49.8
600	18.0 - 27.2	1200	36.0 - 54.2

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 10 mL at any one injection site (1 to 2 mL per site in small calves).

Discontinue treatment 28 days prior to slaughter.

TETRADURE™ 300 (Oxytetracycline) Injection is a sterile, preservatives solution of the broad spectrum antibiotic oxytetracycline.

CAUTION: Intramuscular injection may result in local tissue reaction which persists beyond the slaughter withdrawal period. This may result in firm loss of edible tissues at slaughter.

WARNINGS: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS: Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle, and non lactating dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period.

Use extreme care when administering this product by intravenous injection. Penicillinase injection or leakage from intravenous injection may cause swelling at injection site.

STORE AT ROOM TEMPERATURE 15°-30° C (59°-85° F)

KEEP FROM FREEZING

REFER TO PACKAGE INSERT FOR COMPLETE DIRECTIONS.

Restricted Drug(s) (California). Use Only as Directed.

Not for Human Use.

DISTRIBUTED BY:
Merial Limited
Duluth, GA 30096-4640, USA

*TETRADURE is a badmark and Cattle Head Logo is a registered badmark of Merial.

MADE IN THE UK

TETRADURE™
300

(OXYTETRACYCLINE) INJECTION

SWINE DOSAGE GUIDE

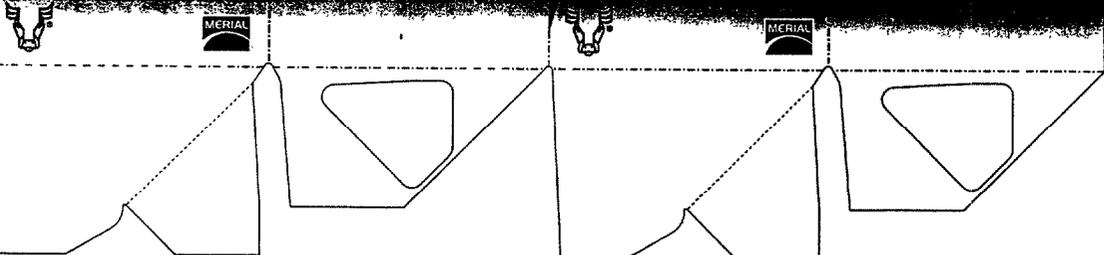
At the first signs of pneumonia* administer a single dose of Tetradure™ 300 by deep intramuscular injection according to the following weight categories**

Animal weight (lb)	Number of mL or cc	Animal weight (lb)	Number of mL or cc
10	0.3	175	5.3
25	0.8	200	6.0
50	1.5	225	6.8
75	2.3	250	7.5
100	3.0	275	8.3
125	3.8	300	9.0
150	4.5	325	9.8

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 5 mL at any one injection site.

Discontinue treatment 28 days prior to slaughter.



100 mL
Net Contents
(OXYTETRACYCLINE) INJECTION
**TETRADURE™
300**

**TETRADURE™
300**

(OXYTETRACYCLINE) INJECTION
ANTIBIOTIC

Each mL contains 300 mg of Oxytetracycline base as anhydrous oxytetracycline.

For the treatment of diseases in beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (weal) calves and swine.

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA 141-143, Approved By FDA
U.S. Patent No. 6,110,905
U.S. Patent No. 6,310,063

Net Contents:
100 mL

**TETRADURE™
300**

(OXYTETRACYCLINE) INJECTION

CATTLE DOSAGE GUIDE

At the first signs of pneumonia or pink eye* or for the control of respiratory disease in cattle at a high risk of developing BRD administer a single dose of Tetradure™ 300 by deep intramuscular or subcutaneous injection (dose rate 13.6 mg/lb) according to the following weight categories**

Animal weight (lb)	Number of mL or cc	Animal weight (lb)	Number of mL or cc
100	3.0 - 4.5	700	21.0 - 31.7
200	6.0 - 9.0	800	24.0 - 36.3
300	9.0 - 13.6	900	27.0 - 40.8
400	12.0 - 18.1	1000	30.0 - 45.3
500	15.0 - 22.6	1100	33.0 - 49.8
600	18.0 - 27.2	1200	36.0 - 54.4

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 10 mL at any one injection site (1 to 2 mL per site in small calves).

Discontinue treatment 28 days prior to slaughter.

TETRADURE™ 300 (Oxytetracycline) Injection is a sterile, preconstituted solution of the broad-spectrum antibiotic oxytetracycline.

CAUTION: Intramuscular injection may result in local tissue reaction which persists beyond the slaughter withdrawal period. This may result in trim loss of edible tissues at slaughter.

WARNINGS: Discontinue treatment at least 28 days prior to slaughter of cows and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

PRECAUTIONS: Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non lactating dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period.

Use extreme care when administering this product by intravenous injection. Paravascular injection or leakage from intravenous injection may cause swelling at injection site.

STORE AT ROOM TEMPERATURE 15°-30° C (59°-86° F)
KEEP FROM FREEZING

REFER TO PACKAGE INSERT FOR COMPLETE DIRECTIONS.

Restricted Drug(s) (California). Use Only as Directed.

Not for Human Use.

DISTRIBUTED BY:
Merial Limited
Duluth, GA 30099-1640, USA

*TETRADURE is a trademark and Cattle Head Logo is a registered trademark of Merial.

MADE IN THE UK

**TETRADURE™
300**

(OXYTETRACYCLINE) INJECTION

SWINE DOSAGE GUIDE

At the first signs of pneumonia* administer a single dose of Tetradure™ 300 by deep intramuscular injection according to the following weight categories**

Animal weight (lb)	Number of mL or cc	Animal weight (lb)	Number of mL or cc
10	0.3	175	5.0
25	0.8	200	6.0
50	1.5	225	6.8
75	2.3	250	7.5
100	3.0	275	8.3
125	3.8	300	9.0
150	4.5	325	9.8

*See package insert for dosing instructions for other indicated diseases and full product information.

**Do not administer more than 5 mL at any one injection site.

Discontinue treatment 28 days prior to slaughter.



TETRADURE™

300

(OXYTETRACYCLINE) INJECTION

ANTIBIOTIC

Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline.

For Use in Beef Cattle, Non-lactating Dairy Cattle, Calves, Including Pre-ruminating (Veal) Calves and Swine.

READ ENTIRE BROCHURE CAREFULLY BEFORE USING THIS PRODUCT.

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

INTRODUCTION:

TETRADURE™ 300 (oxytetracycline) Injection is a sterile, ready to use solution of the broad-spectrum antibiotic oxytetracycline dihydrate. Oxytetracycline is an antimicrobial agent that is effective in treatment of a wide range of diseases caused by susceptible gram-positive and gram-negative bacteria.

TETRADURE™ 300 should be stored at room temperature 59°-86°F (15°-30°C). The antibiotic activity of oxytetracycline is not appreciably diminished in the presence of body fluids, serum or exudates.

INGREDIENTS:

TETRADURE™ 300 (oxytetracycline) Injection is a sterile, pre-constituted solution of the broad-spectrum antibiotic oxytetracycline dihydrate. Each mL contains 300 mg oxytetracycline as base, 40% (v/v) glycerol formal, 10% (v/v) polyethylene glycol 200, 2.7% (w/v) magnesium oxide, 0.4% (w/v) sodium formaldehyde sulphoxylate (as a preservative) and monoethanolamine (as required to adjust pH).

INDICATIONS:

TETRADURE™ 300 is intended for use in treatment for the following diseases when due to oxytetracycline-susceptible organisms:

Beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves:

TETRADURE™ 300 is indicated in the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp., and *Hemophilus* spp. TETRADURE™ 300 is indicated for the treatment of infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis*, foot-rot and diphtheria caused by *Fusobacterium necrophorum*; bacterial enteritis (scours) caused by *Escherichia coli*; wooden tongue caused by *Actinobacillus lignieresii*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococcal and streptococcal organisms sensitive to oxytetracycline. Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*.

Swine:

TETRADURE™ 300 is indicated in the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli*; pneumonia caused by *Pasteurella multocida*; and leptospirosis caused by *Leptospira pomona*.

In sows TETRADURE™ 300 is indicated as an aid in control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli*.

PHARMACOLOGY:

Oxytetracycline is derived from the metabolic activity of the actinomycete, *Streptomyces rimosus*. Oxytetracycline is an antimicrobial agent that is effective in the treatment of a wide range of diseases caused by susceptible gram-positive and gram-negative bacteria.

The antibiotic activity of oxytetracycline is not appreciably diminished in the presence of body fluids, serum or exudates.

Studies have shown that the half-life of oxytetracycline in blood following intramuscular treatment with TETRADURE™ 300 at 5 mg per pound of bodyweight is approximately 23 hours in cattle and 18 hours in swine.

Studies have shown when TETRADURE™ 300 is administered once intramuscularly to cattle or swine at 9 mg per pound of bodyweight, blood oxytetracycline concentration of greater than 0.2 mcg/mL have been observed for 3 to 4 days.

Studies have shown when TETRADURE™ 300 is administered once intramuscularly or subcutaneously to cattle at 13.6 mg per pound of bodyweight, blood oxytetracycline concentration of greater than 0.2 mcg/mL have been observed for at least 7 to 8 days.

DOSAGE AND ADMINISTRATION:

Beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves:

A single intramuscular or subcutaneous dosage of 13.6 mg of oxytetracycline per pound of bodyweight, TETRADURE™ 300 is recommended for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*.

At a single intramuscular or subcutaneous dose range of 9 to 13.6 mg of oxytetracycline per pound of bodyweight, TETRADURE™ 300 is recommended in the treatment of the following conditions:

- (1) Bacterial pneumonia caused by *Pasteurella* spp (shipping fever) in calves and yearlings where retreatment is impractical due to husbandry conditions, such as cattle on range, or where their repeated restraint is inadvisable.
- (2) Infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis*.

For other indications TETRADURE™ 300 is to be administered intramuscularly, subcutaneously or intravenously at a level of 3 to 5 mg of oxytetracycline per pound of bodyweight per day. In treatment of foot-rot and advanced cases of other indicated diseases, a dosage level of 5 mg per pound of bodyweight per day is recommended. Treatment should be continued 24 to 48 hours following remission of disease signs, however, not to exceed a total of four (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of treatment, diagnosis and therapy should be re-evaluated.

Do not administer intramuscularly in the neck of small calves due to lack of sufficient muscle mass.

Use extreme care when administering this product by intravenous injection. Perivascular injection or leakage from an intravenous injection may cause severe swelling at the injection site.

Swine:

A single dosage of 9 mg of oxytetracycline per pound of bodyweight administered intramuscularly is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine, where retreatment is impractical due to husbandry conditions or where repeated restraint is inadvisable.

TETRADURE™ 300 can also be administered by intramuscular injection at a level of 3 to 5 mg of oxytetracycline per pound of bodyweight per day. Treatment should be continued 24 to 48 hours following remission of disease signs; however, not to exceed a total of four (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of treatment, diagnosis and therapy should be re-evaluated.

For sows, administer once intramuscularly 3 mg of oxytetracycline per pound of bodyweight approximately eight (8) hours before farrowing or immediately after completion of farrowing as an aid in the control of infectious enteritis in baby pigs.

For swine weighing 25 lbs of bodyweight and under, TETRADURE™ 300 should be administered undiluted for treatment of 9 mg/lb but should be administered diluted for treatment at 3 or 5 mg/lb.

Bodyweight	9 mg dosage of undiluted TETRADURE™ 300		3 or 5 mg/lb dosage volume of diluted TETRADURE™ 300	
	9 mg/lb	3 mg/lb	Dilution*	5 mg/lb
5 lb	0.15 mL	0.4 mL	37.5 mg/mL	0.7 mL
10 lb	0.30 mL	0.6 mL	50 mg/mL	1.0 mL
25 lb	0.75 mL	1.0 mL	75 mg/mL	1.7 mL

* To prepare dilutions, add one part of TETRADURE™ 300 to three (3), five (5) or seven (7) parts of the sterile water, or 5% dextrose solution as indicated; the diluted product should be used immediately.

PRECAUTIONS:

Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal time.

At the first sign of any adverse reaction, discontinue use of the product. Some of the reactions may be attributable either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause.

Shortly after injection treated animals may have transient hemoglobinuria resulting in darkened urine.

As with all antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. The absence of a favourable response following treatment, or the development of new signs or symptoms may suggest an overgrowth of non-susceptible organisms. If superinfections occur, the use of this product should be discontinued and appropriate specific therapy should be instituted.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving TETRADURE™ 300 in conjunction with penicillin.

STORAGE:

Store at room temperature, 59°-86°F (15°-30°C). Keep from freezing.

WARNINGS:

WARNINGS: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

CAUTION:

Intramuscular or subcutaneous injection may result in local tissue reactions which persists beyond the slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.

Intramuscular injection in the rump area may cause mild temporary lameness associated with swelling at the injection site. Subcutaneous injection in the neck area may cause swelling at the injection site.

ADVERSE REACTIONS:

Reports of adverse reactions associated with oxytetracycline administration include injection site swelling, restlessness, ataxia, trembling, swelling of eyelids, ears, muzzle, anus and vulva (or scrotum and sheath in males), respiratory abnormalities (labored breathing), frothing at the mouth, collapse and possibly death. Some of these reactions may be attributed either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause.

PRESENTATION:

TETRADURE™ 300 is available in 100 mL, 250 mL and 500 mL vials.

**Livestock Drug - Not for Human Use.
Restricted Drug(s) California. Use Only as Directed.**

DISTRIBUTED BY:

Merial Limited
Duluth, GA 30096-4640, USA

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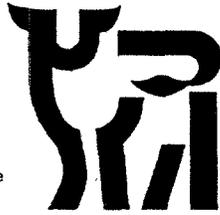
MADE IN THE UK

U.S. Patent No. 6,110,905

U.S. Patent No. 6,310,053



OXYTETRACYCLINE INJECTION 300 mg/mL



ANTIBIOTIC

Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline.

For Use in Beef Cattle, Non-lactating Dairy Cattle, Calves, Including Pre-ruminating (Veal) Calves and Swine.

READ ENTIRE BROCHURE CAREFULLY BEFORE USING THIS PRODUCT.

INTRODUCTION:

OXYTETRACYCLINE INJECTION 300 mg/mL is a sterile, ready to use solution of the broad-spectrum antibiotic oxytetracycline dihydrate. Oxytetracycline is an antimicrobial agent that is effective in treatment of a wide range of diseases caused by susceptible gram-positive and gram-negative bacteria.

OXYTETRACYCLINE INJECTION 300 mg/mL should be stored at room temperature 59°-86°F (15°-30°C). The antibiotic activity of oxytetracycline is not appreciably diminished in the presence of body fluids, serum or exudates.

INDICATIONS:

OXYTETRACYCLINE INJECTION 300 mg/mL is intended for use in treatment for the following diseases when due to oxytetracycline-susceptible organisms:

Beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves:

OXYTETRACYCLINE INJECTION 300 mg/mL is indicated in the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp., and *Hemophilus* spp. OXYTETRACYCLINE INJECTION 300 mg/mL is indicated for the treatment of infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis*, foot-rot and diphtheria caused by *Fusobacterium necrophorum*; bacterial enteritis (scours) caused by *Escherichia coli*; wooden tongue caused by *Actinobacillus lignieresii*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococcal and streptococcal organisms sensitive to oxytetracycline.

Swine:

OXYTETRACYCLINE INJECTION 300 mg/mL is indicated in the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli*; pneumonia caused by *Pasteurella multocida*; and leptospirosis caused by *Leptospira pomona*.

In sows OXYTETRACYCLINE INJECTION 300 mg/mL is indicated as an aid in control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli*.

DOSAGE AND ADMINISTRATION:

Beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves:

A single dosage of 9 mg of oxytetracycline per pound of bodyweight administered intramuscularly or subcutaneously is recommended in the treatment of the following conditions:

- (1) Bacterial pneumonia caused by *Pasteurella* spp (shipping fever) in calves and yearlings where retreatment is impractical due to husbandry conditions, such as cattle on range, or where their repeated restraint is inadvisable.
- (2) Infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis*.

For other indications OXYTETRACYCLINE INJECTION 300 mg/mL is to be administered intramuscularly, subcutaneously or intravenously at a level of 3 to 5 mg of oxytetracycline per pound of bodyweight per day. In treatment of foot-rot and advanced cases of other indicated diseases, a dosage level of 5 mg per pound of bodyweight per day is recommended. Treatment should be continued 24 to 48 hours following remission of disease signs, however, not to exceed a total of four (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of treatment, diagnosis and therapy should be re-evaluated by a veterinarian.

Do not administer intramuscularly in the neck of small calves due to lack of sufficient muscle mass.

Use extreme care when administering this product by intravenous injection. Perivascular injection or leakage from an intravenous injection may cause severe swelling at the injection site.

Swine:

A single dosage of 9 mg of oxytetracycline per pound of bodyweight

administered intramuscularly is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine, where retreatment is impractical due to husbandry conditions or where repeated restraint is inadvisable.

OXYTETRACYCLINE INJECTION 300 mg/mL can also be administered by intramuscular injection at a level of 3 to 5 mg of oxytetracycline per pound of bodyweight per day. Treatment should be continued 24 to 48 hours following remission of disease signs; however, not to exceed a total of four (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of treatment, diagnosis and therapy should be re-evaluated by a veterinarian.

For sows, administer once intramuscularly 3 mg of oxytetracycline per pound of bodyweight approximately eight (8) hours before farrowing or immediately after completion of farrowing as an aid in the control of infectious enteritis in baby pigs.

For swine weighing 25 lbs of bodyweight and under, OXYTETRACYCLINE INJECTION 300 mg/mL should be administered undiluted for treatment of 9 mg/lb but should be administered diluted for treatment at 3 or 5 mg/lb.

Bodyweight	9 mg dosage of undiluted Oxytetracycline Injection	3 or 5 mg/lb dosage volume of diluted Oxytetracycline Injection		
	9 mg/lb	3 mg/lb	Dilution*	5 mg/lb
5 lb	0.15 mL	0.4 mL	37.5 mg/mL	0.7 mL
10 lb	0.30 mL	0.6 mL	50 mg/mL	1.0 mL
25 lb	0.75 mL	1.0 mL	75 mg/mL	1.7 mL

* To prepare dilutions, add one part of OXYTETRACYCLINE INJECTION 300 mg/mL to three (3), five (5) or seven (7) parts of the sterile water, or 5% dextrose solution as indicated; the diluted product should be used immediately.

DIRECTIONS FOR USE:

OXYTETRACYCLINE INJECTION 300 mg/mL is intended for use in the treatment of disease due to oxytetracycline-susceptible organisms in beef cattle, non-lactating dairy cattle and swine. A thoroughly cleaned, sterile needle and syringe should be used for each injection (needles and syringes may be sterilized by boiling in water for 15 minutes). In cold weather OXYTETRACYCLINE INJECTION 300 mg/mL should be warmed to room temperature before administration to animals. Before withdrawing the solution from the bottle, disinfect the rubber cap on the bottle with suitable disinfectant, such as 70 percent alcohol. The injection site should be similarly cleaned with the disinfectant. Needles of 16 to 18 gauge and 1 to 1½ inches long are adequate for intramuscular or subcutaneous injections. Needles of 2 to 3 inches in length are recommended for intravenous use.

INTRAMUSCULAR ADMINISTRATION:

Intramuscular injections should be made by directing the needle of suitable gauge and length into the fleshy part of a thick muscle such as in the neck, rump, hip, or thigh regions; avoid blood vessels and major nerves. Before injecting the solution, pull back gently on the plunger. If blood appears in the syringe, a blood vessel has been entered; withdraw the needle and select a different site.

No more than 10 mL should be injected intramuscularly at any one site in adult beef cattle and non-lactating dairy cattle, and not more than 5 mL per site in adult swine; rotate injection sites for each succeeding treatment. The volume administered per injection site should be reduced according to age and body size so that 1 to 2 mL per site is injected in small calves.

SUBCUTANEOUS ADMINISTRATION:

Subcutaneous injections should be made by directing the needle of suitable gauge and length through the loose folds of the neck skin in front of the shoulder. Care should be taken to ensure that the tip of the needle has penetrated the skin but is not lodged in the muscle. Before injecting the solution, pull back gently on the plunger. If blood appears in the syringe, a blood vessel has been entered; withdraw the needle and select a different site. The solution should be injected slowly into the area between the skin and muscles. No more than 10 mL should be injected subcutaneously at any one site in adult beef cattle and non-lactating dairy cattle; rotate injection sites for each succeeding treatment. The volume administered per injection site should be reduced according to age and body size so that 1 to 2 mL per site is injected in small calves.

INTRAVENOUS ADMINISTRATION

OXYTETRACYCLINE INJECTION 300 mg/mL may be administered intravenously to beef cattle and non-lactating dairy cattle. As with all highly concentrated materials, OXYTETRACYCLINE INJECTION 300 mg/mL should be administered slowly by the intravenous route.

Preparation of the Animal for Injection:

1. Approximate location of vein. The jugular vein runs in the jugular groove on each side of the neck from the angle of the jaw to just above the brisket and slightly above and to the side of the windpipe. (See Fig 1).
2. Restraint. A stanchion or chute is ideal for restraining the animal. With a halter, rope, or cattle leader (nose tongs), pull the animal's head around the side of the stanchion, cattle chute, or post in such a manner to form a bow in the neck (See Fig. 2), then snub the head securely to prevent movement. By forming the bow in the neck, the outside curvature of the bow tends to

expose the jugular vein and make it easily accessible. Caution. Avoid restraining the animal with a tight rope or halter around the throat or upper neck which might impede blood flow. Animals that are down present no problem so far as restraint is concerned.

3. Clip hair in area where injection is to be made (over the vein in the upper third of the neck). Clean and disinfect the skin with alcohol or other suitable antiseptic.

Figure 1



Figure 2



JUGULAR GROOVE

Entering the Vein and Making the Injection:

1. Raise the vein. This is accomplished by tying the choke rope tightly around the neck close to the shoulder. The rope should be tied in such a way that it will not come loose and so that it can be untied quickly by pulling the loose end (See Fig. 2). In thick-necked animals, a block of wood placed in the jugular groove between the rope and the hide will help considerably in applying the desired pressure at the right point. The vein is a soft flexible tube through which blood flows back to the heart. Under ordinary conditions it cannot be seen or felt with the fingers. When the flow of blood is blocked at the base of the neck by the choke rope, the vein becomes enlarged and rigid because of the back pressure. If the choke rope is sufficiently tight, the vein stands out and can be easily seen and felt in thin-necked animals. As a further check in identifying the vein, tap it with the fingers in front of the choke rope. Pulsations that can be seen or felt with the fingers in front of the point being tapped will confirm the fact that the vein is properly distended. It is impossible to put the needle into the vein unless it is distended. Experienced operators are able to raise the vein simply by hand pressure, but the use of a choke rope is more certain.
2. Inserting the needle. This involves three distinct steps. First, insert the needle through the hide. Second, insert the needle into the vein. This may require two or three attempts before the vein is entered. The vein has a tendency to roll away from the point of the needle, especially if the needle is not sharp. The vein can be steadied with the thumb and finger of one hand. With the other hand the needle point is placed directly over the vein, slanting it so that its direction is along the length of the vein, either toward the head or toward the heart. Properly positioned this way, a quick thrust of the needle will be followed by a spurt of blood through the needle, which indicates that the vein has been entered. Third, once in the vein, the needle should be inserted along the length of the vein all the way to the hub, exercising caution to see that the needle does not penetrate the opposite side of the vein. Continuous steady flow of blood through the needle indicates that the needle is still in the vein. If blood does not flow continuously, the needle is out of the vein (or clogged) and another attempt must be made. If difficulty is encountered, it may be advisable to use the vein on the other side of the neck.
3. While the needle is being placed in proper position in the vein, an assistant should get the medication ready so that the injection can be started without delay after the vein has been entered.
4. Making the injection. With the needle in position as indicated by continuous flow of blood, release the choke rope by a quick pull on the free end. This is essential - the medication cannot flow into the vein while it is blocked. Immediately connect the syringe containing OXYTETRACYCLINE to the needle and slowly depress the plunger. If there is resistance to depression of the plunger, this indicates that the needle has slipped out of the vein (or is clogged) and the procedure will have to be repeated. Watch for any swelling under the skin near the needle, which would indicate that the medication is not going into the vein. Should this occur, it is best to try the vein on the opposite side of the neck.
5. Removing the needle. When injection is complete, remove needle with straight pull. Then apply pressure over area of injection momentarily to control any bleeding through needle puncture, using cotton soaked in alcohol or other suitable antiseptic.

PRECAUTIONS:

Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal time.

Consult with your veterinarian prior to administering this product in order to determine the proper treatment required in the event of adverse reaction. At the first sign of any adverse reaction, discontinue use of the product and seek the advice of your veterinarian. Some of the reactions may be attributable either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause.

Shortly after injection treated animals may have transient hemoglobinuria resulting in darkened urine.

As with all antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. The absence of a favourable response following treatment, or the development of new signs or symptoms may suggest an overgrowth of non-susceptible organisms. If superinfections occur, the use of this product should be discontinued and appropriate specific therapy should be instituted.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving OXYTETRACYCLINE INJECTION 300 mg/mL in conjunction with penicillin.

STORAGE:

Store at room temperature, 59-86°F (15-30°C). Keep from freezing.

WARNINGS:

Warnings: Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration in cattle may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

CAUTION:

Intramuscular or subcutaneous injection may result in local tissue reactions which persists beyond the slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.

Intramuscular injection in the rump area may cause mild temporary lameness associated with swelling at the injection site. Subcutaneous injection in the neck area may cause swelling at the injection site.

ADVERSE REACTIONS:

Reports of adverse reactions associated with oxytetracycline administration include injection site swelling, restlessness, ataxia, trembling, swelling of eyelids, ears, muzzle, anus and vulva (or scrotum and sheath in males), respiratory abnormalities (labored breathing), frothing at the mouth, collapse and possibly death. Some of these reactions may be attributed either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause.

PRESENTATION:

OXYTETRACYCLINE INJECTION 300 mg/mL is available in 100 mL, 250 mL and 500 mL vials.

Livestock Drug - Not for Human Use.
Restricted Drug(s) California. Use Only as Directed.

DISTRIBUTED BY:

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MADE IN THE UK

U.S. Patent No. 6,110,905
U.S. Patent No. 6,310,053