Date of Approval:

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-008

OXY-TET™ 200; BIO-MYCIN® 200

(oxytetracycline injection)

"...for establishment of a 28-day withdrawal period for subcutaneous use in cattle and intramuscular use in swine, thereby establishing a 28-day withdrawal period for all approved routes of administration in cattle and swine."

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

I. GENERAL INFORMATION

ANADA Number:	200-008
Sponsor:	Boehringer Ingelheim Vetmedica, Inc. 2621 North Belt Highway St. Joseph, Missouri 64506
Established Name:	oxytetracycline injection
Proprietary Names:	OXY-TET™ 200 BIO-MYCIN® 200*
Marketing Status:	OTC
Supplemental Effect:	Establishes a 28-day withdrawal period for subcutaneous use of this product in cattle and intramuscular use of this product in swine, thereby establishing a 28-day withdrawal period for all approved routes of administration in cattle and swine.
References:	Freedom of Information Summaries dated November 16, 1994, for the original approval, and May 22, 1996, for the supplemental approval for subcutaneous use in cattle.

*OXY-TET™ 200 will hereafter denote both OXY-TET™ 200 and BIO-MYCIN® 200.

II. INDICATIONS FOR USE

OXY-TET™ 200 is intended for use in the treatment of the following diseases in beef cattle, nonlactating dairy cattle, and swine when due to oxytetracycline susceptible organisms:

BEEF CATTLE AND NONLACTATING DAIRY CATTLE

OXY-TET™ 200 is indicated in 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 staphylococci and streptococci organisms sensitive to oxytetracycline.

SWINE

In swine, OXY-TET™ 200 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, OXY-TET™ 200 is indicated as an aid in the control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli.*

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

A. Dosage Form

OXY-TET™ 200 is a sterile injectable solution available in 100-, 250-, and 500-mL bottles. Each milliliter contains 200 mg oxytetracycline.

B. Route(s) of Administration and Recommended Dosage

BEEF CATTLE AND NONLACTATING DAIRY CATTLE

OXY-TET™ 200 is to be administered by intramuscular, subcutaneous, or intravenous injection to beef cattle and nonlactating dairy cattle.

A single dose of 9 mg of OXY-TET™ 200 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*.

OXY-TET™ 200 can also be administered by intravenous, intramuscular, or subcutaneous injection at a level of 3 to 5 mg 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 mg per pound of body weight per day is recommended. Treatment should be continued 24 to 48 hours following remission of disease signs; however, treatment is not to exceed a total of four consecutive days. Consult your veterinarian if improvement is not noted within 24 to 48 hours of the beginning of treatment.

No more than 10 mL should be injected intramuscularly or subcutaneously at any one site in adult beef cattle and nonlactating dairy cattle; rotate injection sites for each succeeding treatment. The volume administered per injection site should be adjusted according to age and body size so that 1 to 2 mL per injection site is injected in small calves.

SWINE

A single dose of 9 mg of OXY-TET™ 200 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.

OXY-TET™ 200 can be administered by intramuscular injection at a level of 3 to 5 mg of oxytetracycline per pound of body weight per day. Treatment should be continued 24 to 48 hours following remission of disease signs; however, treatment is not to exceed a total of four consecutive days. Consult your veterinarian if improvement is not noted within 24 to 48 hours of the beginning of treatment.

For sows, administer once intramuscularly 3 mg of oxytetracycline per pound of body weight approximately 8 hours before farrowing or immediately after completion of farrowing.

For swine weighing 25 lb of body weight and under, OXY-TET™ 200 should be administered undiluted for treatment at 9 mg/lb but should be administered diluted for treatment at 3 or 5 mg/lb.

No more than 5 mL of OXY-TET™ 200 should be injected intramuscularly per site in adult swine; rotate injection sites for each succeeding treatment.

IV. EFFECTIVENESS

Since this supplemental application does not change the species, routes of administration, or dosages, no additional effectiveness studies were required. Studies conducted for the original ANADA approved November 16, 1994, and for the supplemental approval dated May 22, 1996, are summarized in the respective Freedom of Information Summaries.

V. ANIMAL SAFETY

The supplemental approval does not change the approved dose(s) of oxytetracycline, the frequency, or routes of administration. Accordingly, no additional studies were required for animal safety. See the Freedom of Information (FOI) Summaries for the approval of the original and supplemental applications of OXY-TET™ 200 approved November 16, 1994**,** and May 22, 1996, respectively.

VI. HUMAN SAFETY

A. Tolerances for residues

The FDA has established tolerances for the sum of residues of tetracyclines, including chlortetracycline, oxytetracycline, and tetracycline, in tissues of beef cattle, non-lactating dairy cows, calves, swine, sheep, chickens, turkeys, and ducks (61 FR 67453, December 23, 1996). The tolerances established for oxytetracycline under 21 CFR 556.500 are as follows: 2 ppm in muscle; 6 ppm in liver; and 12 ppm in kidney and fat.

B. Residue depletion studies

1. Subcutaneous administration in cattle

a. Study number: 635-0144-91B-004

b. Investigator: Bill C. Clymer, Ph.D.
Clymer Research
Amarillo, Texas

c. General design:

(1) Purpose: This is a tissue residue depletion study for oxytetracycline injection, 200 mg/mL, conducted in beef calves. The study was conducted to comply with Good Laboratory Practices, 21CFR 58. Tissue analyses were conducted by Colorado Animal Research Enterprises (CARE), Fort Collins, Colorado 80524. The statistical analysis was conducted by Thomas J. Keefe, Ph.D., EnviroStat Associates, Fort Collins, Colorado 80526.

(2) Animals: 20 healthy beef calves.

(3) Dosage form: 200 mg/mL injectable solution

(4) Route of administration: subcutaneous injection

(5) Dose: a single treatment of 20 mg/kg, administered in the neck

(6) Test duration: 11 days

(7) Pertinent parameters measured: Approximately 500 g each of liver (cross-section of each lobe), 500 g each of injection site and noninjection site (semimembranosus) muscle, 200 g (or the maximum obtainable) abdominal fat, and both kidneys.

d. Results

Residue analyses were conducted at CARE, using an adapted validated microbiological assay. The data are presented in Table 6.1.

Table 6.1: Oxytetracycline residues (Mean ± SD) in bovine tissues following a single subcutaneous administration of OXY-TET™ 200, at a dose of 20 mg/kg

Days*	Oxytetracycline (ppm)				
	Liver	Kidney	Muscle	Fat	Injection site
2	3.96±1.54	8.27±2.41	1.32±0.45	0.20±0.10	603.32±358.73
5	0.43±0.07	1.08±0.27	0.19±0.02	<LOQ	153.46±135.94
8	0.19±0.16	0.31±0.19	0.21	<LOQ	30.59±42.17
11	0.16±0.09	0.34±0.18	0.20	<LOQ	105.75±208.01

*represents withdrawal time in days
LOQ = 0.1 ppm for kidney; 0.075 for liver, muscle, and fat

2. Intramuscular administration in swine

   a. Study number: 635-0144-91B-021

   b. Investigator: Diane Fagerberg, Ph.D.
   Colorado Animal Research Enterprises (CARE)
   Fort Collins, Colorado 80524

   c. General design:

      (1) Purpose: This is a tissue residue depletion study for oxytetracycline injection, 200 mg/mL, conducted in swine. The study was conducted to comply with Good Laboratory Practices, 21 CFR 58. Tissue analyses were conducted by CARE, Fort Collins, Colorado 80524. The statistical analysis was conducted by Thomas J. Keefe, Ph.D., EnviroStat Associates, Fort Collins, Colorado 80526.

      (2) Animals: 24 healthy swine.

      (3) Dosage form: 200 mg/mL injectable solution

      (4) Route of administration: intramuscular injection

      (5) Dose: a single treatment of 20 mg/kg, administered in the neck

      (6) Test duration: 28 days

      (7) Pertinent parameters measured: Approximately 500 g each of liver (cross-section of each lobe), 500 g each of injection site and noninjection site (semimembranosus) muscle, 200 g (or the maximum obtainable) abdominal fat, and both kidneys.

d. Results

Residue analyses were conducted at CARE, using an adapted validated microbiological assay. The data are presented in Table 6.2.

Table 6.2: Oxytetracycline residues (Mean ± SD) in swine tissues following a single intramuscular administration of OXY-TET™ 200, at a dose of 20 mg/kg

Days*	Oxytetracycline (ppm)				
	Liver	Kidney	Muscle	Fat	Injection site
2	1.78±0.48	7.39±3.26	1.47±0.54	0.11±0.06	566.68±528.04
5	0.41±0.17	1.79±0.80	0.42±0.14	<LOQ	67.93±56.94
8	0.13±0.09	0.58±0.21	0.12±0.09	<LOQ	26.23±53.56
11	<LOQ	0.28±0.04	<LOQ	<LOQ	1.24
21	<LOQ	0.24±0.03	<LOQ	<LOQ	<LOQ
28	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

*represents withdrawal time in days
LOQ = 0.1 ppm for kidney; liver, muscle, and fat

C. Withdrawal calculations

Withdrawal periods for the intramuscular, intravenous, and subcutaneous use of OXY-TET™ 200 in cattle, and for the intramuscular use of this drug in swine have previously been established in the original ANADA dated November 16, 1994, or in the supplemental application dated May 22, 1996. A withdrawal period of 28 days was assigned for the use of OXY-TET™ 200 in cattle *via* the intramuscular and intravenous routes of administration based on the blood level bioequivalence study conducted in support of the original ANADA. Because the study, conducted under CVM's 1990 Bioequivalence Guidance, demonstrated blood level bioequivalence, a tissue residue depletion study was not required to support the approval. A withdrawal period of 42 days was assigned for the intramuscular use of OXY-TET™ 200 in swine based on a tissue residue depletion study conducted in support of the original ANADA approval. A withdrawal period of 36 days was assigned for the subcutaneous use of OXY-TET™ 200 in cattle based on a tissue residue study conducted in support of the supplemental ANADA dated May 22, 1996. See the FOI Summaries for ANADA 200008 dated November 16, 1994, and May 22, 1996, for additional information.

For this supplemental application, the withdrawal periods for the intramuscular use of OXY-TET™ 200 in swine and for the subcutaneous use of OXY-TET™ 200 in cattle have been recalculated. The recalculations were performed using the revised tetracycline tolerances (61 FR 67453), and a statistical tolerance limit algorithm for the 99th percentile with 95% confidence. As a result of these recalculations, a 28-day withdrawal period is assigned for the intramuscular

administration of OXY-TET™ 200 in swine, and for the subcutaneous use of OXY-TET™ 200 in cattle. The 28-day withdrawal period for the intravenous and intramuscular administration of OXY-TET™ 200 in cattle, assigned as part of the original approval, remains unchanged.

D. Regulatory Analytical Method for Residues

The regulatory analytical method for detection of residues of the drug is a microbiological test using *Bacillus cereus* var. *mycoides* (ATCC 11778). The method is found in *Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports and Protocols*, Revised October 1968, Reprinted December 1974, National Center for Antibiotic and Insulin Analysis, FDA, Washington, DC 20204.

VII. AGENCY CONCLUSIONS

The data submitted in support of this ANADA supplement satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. As a result of recalculations using the revised tetracycline tolerances (61 FR 67453), a 28-day withdrawal period is assigned for the intramuscular administration of OXY-TET™ 200 in swine, and for the subcutaneous use of OXY-TET™ 200 in cattle. The 28-day withdrawal period for the intravenous and intramuscular administration of OXY-TET™ 200 in cattle, assigned as part of the original approval, remains unchanged.

Adequate directions for use of the product to treat cattle and swine have been written for the layman, and the conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall continue to have over-the-counter marketing status.

The agency has determined under 21 CFR 25.33(a)(1) that this action is of the type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)(x)), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug and, therefore, did not require a reevaluation of the human food or target animal safety data in the parent application.

OXY-TET™ 200 Injectable Solution is under U.S. patent number 5,075,295, which expires December 12, 2009.

VIII. APPROVED LABELING

A copy of the draft facsimile labeling is attached to this document.

A. BIO-MYCIN® 200 - Vial Labels

B. BIO-MYCIN® 200 - Package Inserts