BOEHRINGER INGELHEIM VETMEDICA, INC.
2621 North Belt Highway, St. Joseph, Missouri 64506-2002

NADA 200-008 (INAD 4798)
Oxy-tet™/ Bio-Mycin® Oxytetracycline 200 mg./mL Injection
Supplemental NADA To Allow Product Use For Lactating Dairy Cattle
(01db130c-6AUG01)

Draft Freedom Of Information Summary

Date of Approval:
September 3, 2002

FREEDOM OF INFORMATION SUMMARY

ANADA 200-008

OXY-TET™ 200 / Bio-Mycin® 200
(oxytetracycline injection)

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

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FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. ANADA Number:	200-008
B. Sponsor:	Boehringer Ingelheim Vetmedica, Inc. 2621 North Belt Highway St. Joseph, Missouri 64506
C. Established Name:	oxytetracycline injection
D. Tradename:	OXY-TET™ 200 Bio-Mycin® 200*
E. Marketing Status:	OTC
Effect of Supplement:	This supplement provides for changes to the product labeling to include lactating dairy cattle.
References:	Freedom of Information Summaries: November 16, 1994: Original approval May 22, 1996: Supplemental approval for subcutaneous use in cattle March 16, 1999: Supplemental approval of a 28-day withdrawal period for subcutaneous use 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.

* OXY-TET™ 200 will hereafter denote both OXY-TET™ 200 and Bio-Mycin® 200

II. INDICATION FOR USE:

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

BEEF CATTLE AND 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 DAIRY CATTLE

OXY-TET™ 200 is to be administered by intramuscular, subcutaneous, or intravenous injection to beef cattle and 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 re-treatment 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 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 I 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

1. Title: BioMycin® 200 Milk Residue Study in Dairy Cows .

A. **Type of Study:** Milk Residue

B. **Study Director:** Dan Ronning

Colorado Animal Research Enterprises, Inc.
6200 East County Road 56
Fort Collins, CO 80526

C. **General Design:**

i. Purpose: To extend the label claim for use in lactating dairy cows by measuring the oxytetracycline residue levels in milk after one treatment of BioMycin® 200.
ii. Dosage Form: BioMycin® 200 in 100 mL bottle.
iii. Route of Administration: Intramuscular
iv. Dosage Used: 20 mg/kg (9mg/lb) once.
v. Study Duration: Day -1 through Day 6
vi. Parameters Measured:
Body Weights: Once on Day -1.
Physical Examination: Once on Day -1.
Daily Observations: Clinical observations conducted daily by veterinarian for duration of study.
Milk Sample Collection: Samples were collected from each cow on day -1 (predose) and at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144 hours post-treatment.
vii. Analyses of Milk Samples: Assays of oxytetracycline levels were conducted by the cylinder-plate microbiology method.

D. **Results:**

Body Weights: Ranged from 633.0-815.5 kg (1396-1798 lb.).
Physical Examination: All animals were healthy throughout duration of trial.
Daily Observations: No abnormal clinical signs were noted and no adverse events.

Oxytetracycline Residues in Milk (See Table 1)

Table 1

Overall mean Oxytetracycline residue values* (µg/mL) ± SD in milk over time (hr)

Time post dosing (hour)	µg/mL oxytetracycline	Number of Animals
Predose	ND	20
12	2.458 + 0.616	20
24	2.647 + 0.504	20
36	2.199 + 0.595	20
48	1.188 + 0.350	20
60	0.924 + 0.355	20
72	<0.522 + 0.258	20
84	<0.363 + 0.228	20
96	<0.202 + 0.173	20
108	<0.160 + 0.179	20
120	<0.150 + 0.142	20
132	<0.150 + 0.109	20
144	<0.150 + 0.064	20

*ND = not detectable, considered 0.0 for computation of means and standard deviations. The limit of quantification for the assay of <0.150 was considered as 0.150 for computations of means and standard deviations. (Individual values for each animal not shown in this table).

By the last sampling at 144 hours, the milk from 18 cows did not have detectable residues. At the time one cow had detectable but nonquantifiable oxytetracycline residue levels and one cow had residue levels of 262-269 ppb, which approached the 300 ppb tolerance limit. The milk oxytetracycline levels of that cow were comparable to the other test cows through the 36 hour time point. Thereafter, the milk oxytetracycline residues markedly exceeded those from any other cow. There were no unusual circumstances associated with the test article administration to her or atypical clinical to explain the divergent residue depletion profile.

E. **Statistical Results:**

The data on assayed oxytetracycline (OTC) concentrations were statistically evaluated according to FDA/CVM's "Guideline for Establishing a Withdrawal Period." Adherence to the Guideline's recommended use of both simple averages (unweighted means) and the "pure error" mean square (the intra-assay variance) in all calculations yielded an estimated 95% upper tolerance of the 99th percentile of OTC residues in cow's milk at 96 hours post-treatment equal to 0.451ppm. Application of either the more statistically appropriate use of weighted means or the more biologically relevant use of the residual mean-square error yielded estimates of the 95% upper tolerance for the 99th percentile of OTC residues in cow's milk at 96 hours post-treatment that were between 0.529 ppm and 0.736 ppm.

F. **Conclusions:**

The animal testing aspect of the study was conducted to GLP standards. Study procedures were conducted as per protocol and no circumstances occurred that might have adversely affected the outcome or integrity of the study.

Statistically, because each method of estimation found that the 95% upper tolerance limit for the 99th percentile of OTC residues in cow's milk at 96 hours post-treatment was less than 0.900 ppm, which is 3 times the accepted tolerance limit for oxytetracycline in cow's milk of 0.300 ppm (300 ppb) as required by the Guideline, 96 hours is seen to be the valid withdrawal time for cow's milk following one treatment of BioMycin® 200 administered intramuscularly at 9 mg/lb (20 mg/kg) bodyweight.

2. Pharmacokinetic comparison of IM and SC routes of administration

The milk residue depletion study was conducted in cattle treated intramuscularly (see above). Comparative plasma pharmacokinetic data indicate that the depletion following subcutaneous administration is more rapid than that associated with intramuscular administration as shown in Table 2. This more rapid depletion results therefore in lower terminal oxytetracycline concentrations following subcutaneous administration.

Table 2

Least square means and confidence intervals comparing Bio-Mycin® 200 when administered by the intramuscular (IM) and subcutaneous (SC) routes

Parameter	Mean (IM Dosing)	Mean (SC Dosing)	Ratio (SC/IM)	Lower CI*	Upper CI*
C_{max} (µg/mL)	5.57	9.27	1.66	50%	83%
AUC_{108} (µg*hr/mL)	178.6	198.3	1.11	7%	15%
T_{max} (hr)	3.19	2.16	N/A	N/A	N/A
T_{108} (hr)	114.01	92.42	N/A	N/A	N/A
$C_{0.5}$ (µg/mL)	3.553	6.275	1.77	N/A	N/A
C_{24} (µg/mL)	3.079	3.148	1.02	N/A	N/A
C_{48} (µg/mL)	1.239	0.816	0.66	N/A	N/A
C_{96} (µg/mL)	0.177	0.107	0.60	N/A	N/A

* L = lower bound on the 90% confidence interval and U= upper bound on the 90% confidence interval for the difference between the IM and SC formulation product means

The 96 hour Oxytetracycline concentration ratio would indicate that milk residues of Oxytetracycline following subcutaneous administration could be as much as 60% lower than those with intramuscular administration.

3. Milk Discard Withdrawal Conclusion

On the basis of the data from the residue and pharmacokinetic studies, it was concluded that a 96 hour withdrawal time (milk discard) was valid after one injection of BioMycin® 200 administered either intramuscularly or subcutaneously at the dosage rate of 20 mg/kg (9 mg/lb) bodyweight.

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.

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.

Data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for five years of marketing exclusivity beginning on the date of approval because no active ingredient, including any ester or salt of the active ingredient, of the drug has been approved in any other application.

VIII. APPROVED LABELING

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

A. Bio-Mycin® 200 Vial (expanded content) Labels