FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 113-232

LIQUAMYCIN® LA-200®
(oxytetracycline amphoteric)

"...for changes to the product labeling to include use of the product in lactating dairy cows."

Sponsored by:

PFIZER ANIMAL HEALTH

Date of Approval: July 21, 1998

I. GENERAL INFORMATION

NADA Number:	113-232
Sponsor:	Pfizer Animal Health Exton, Pennsylvania 19341
Accepted Name:	oxytetracycline amphoteric
Trade Name:	LIQUAMYCIN® LA-200®
Marketing Status:	Over-the-counter (OTC)
Effect of Supplement:	This supplement provides for changes to the product labeling to include lactating dairy cows. Also, a tolerance for oxytetracycline in milk is established at 0.3 ppm.

II. INDICATIONS FOR USE

In beef cattle, dairy cattle, and calves, including pre-ruminating (veal calves), LIQUAMYCIN® LA-200® is indicated in the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp.; bovine keratoconjunctivitis caused by *Moraxella bovis*; foot-rot and diphtheria caused by *Fusobacterium necrophorum;* bacterial enteritis (scours) caused by *Escherichia coli*; wooden tongue caused by *Actinobacillus ligniersii*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococci and streptococci organisms sensitive to oxytetracycline.

III. PRODUCT INFORMATION

A. Dosage Form: LIQUAMYCIN® LA-200® is a sterile, ready-to-use broad spectrum antibiotic parenteral formulation. Each milliliter contains 200 milligrams of oxytetracycline base as oxytetracycline amphoteric in an aqueous vehicle containing 2-pyrrolidone and povidone.

B. Route of Administration: LIQUAMYCIN® LA-200® should be administered by intramuscular, subcutaneous, or intravenous injection to beef cattle, dairy cattle, and calves, including pre-ruminating (veal calves).

C. Recommended Dosage:

CATTLE: A single dose of 9 mg of LIQUAMYCIN® LA-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 their repeated restraint is inadvisable; 2) infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*.

LIQUAMYCIN® LA-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, 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.

IV. EFFECTIVENESS

Since the effectiveness of this product for the labeled indications has previously been established under this NADA for cattle, including beef cattle (lactating and non-lactating), non-lactating dairy cattle, and calves (including preruminating calves), and because the agency believes that lactation has negligible impact on the pharmacokinetics of oxytetracycline (based on the relatively small percentage of drug secreted into milk), additional effectiveness studies were not required for this supplemental application.

V. ANIMAL SAFETY

The safety of LIQUAMYCIN® LA-200® for the treatment of various diseases of cattle has been previously demonstrated in NADA 113-232. Approval of this supplemental application does not require re-evaluation of animal safety.

VI. HUMAN SAFETY

A. Safe Concentrations of Total Residues

1. 2-Pyrrolidone (excipient)

An Acceptable Daily Intake (ADI) of 1.2 mg/day was established for 2-pyrrolidone. The ADI was derived from a no-observed-effect-level of 20 mg/kg body weight per day in a 90-day oral toxicity study in the rat and a 1000-fold safety factor based on a reduction in body weight gain in females at the next highest dose of 100 mg/kg body weight per day.

ADI = 20 mg/kg/day ÷ 1000 safety factor
= 20 mcg/kg/day or 1.2 mg/day/60 kg person

The portion of the ADI set aside for milk is 20%. Consequently, the ADI for 2-pyrrolidone is allocated in the following manner:

ADI (milk) = 4 mcg/kg/day

ADI (tissues) = 16 mcg/kg/day

Using this ADI and the current daily consumption factor of 1.5L for milk, a safe concentration (SC) of 2-pyrrolidone in milk is calculated as follows:

SC (milk) = 4 mcg/kg x 60 kg /1.5 L
= 160 mcg/L = 160 ppb

2. Oxytetracycline

   Recently, the Center for Veterinary Medicine (CVM) conducted a re-evaluation of the toxicology and metabolism data that were used to support the original tolerance for oxytetracycline. The Center also reviewed studies performed after product approval.

   This information shows that adverse effect of oxytetracycline on the intestinal microflora is the appropriate endpoint for establishing the safe concentration for oxytetracycline. Since all tetracycline drugs have similar microbiological effects, changing the tolerance for oxytetracycline required an evaluation of the cumulative effect on the intestinal microflora of all tetracyclines approved for use as new animal drugs. Based on this evaluation, the safe concentration for total tetracycline microbiological activity was limited to 1 ppm in the total diet (1.5 mg/person/day).

   The limit of 1 ppm is equal to an ADI of 0.025 mg/kg of body weight (bw) per day. Sixty percent (60%) of the ADI is reserved for milk and 40% for edible tissues. The ADI for milk is calculated as follows:

   $$\text{ADI for milk} = 0.025 \times 0.60 = 0.015 \text{ mg/kg bw/day}$$

   Using the above ADI and the current consumption factors, the tolerance for total tetracyclines in milk is calculated as follows:

   $$\text{Tolerance for total tetracyclines in milk} = \frac{0.015 \text{ mg/kg bw/day} \times 60 \text{ kg}}{1.5\text{L}} = 0.6 \text{ ppm}$$

   If all of the unassigned ADI for oxytetracycline is used for milk, a tolerance of 0.6 ppm is calculated for oxytetracycline residues. However, to regulate oxytetracycline based on the active ingredient, oxytetracycline, rather than the vehicle, 2-pyrrolidone, a tolerance of 0.3 ppm is established for the sum of residues of the tetracyclines including chlortetracycline, oxytetracycline, and tetracycline, in milk. When residues of oxytetracycline are less than 0.3 ppm, residues of 2-pyrrolidone will be less than the safe concentration of 160 ppb.

B. Residue Depletion Studies

1. Oxytetracycline milk residue depletion study in cattle treated intramuscularly with LIQUAMYCIN® LA-200®

   Study HLA 6168-104 provided milk residue data for oxytetracycline.

   This study was conducted in accordance with GLP regulations and CVM guidelines by Hazleton Laboratories, Madison, Wisconsin, under the direction of Dr. R. A. Hiles. The objective was to determine the depletion profile of oxytetracycline residue in the milk of lactating dairy cattle following a single intramuscular administration of LIQUAMYCIN® LA-200® at 20 mg/kg.

At designated treatment intervals (24, 12, and 0 hours pre-treatment and 11, 24, 35, 48, 59, 72, 83, 96, 107, 120, 131, and 144 hours post-treatment), milk samples were collected from each of the twenty Holstein cows. All of the milk samples were assayed using a validated microbiological agar diffusion method. Mean milk residue values (± SD) are presented in Table 6.1. The statistical tolerance interval data are presented in Table 6.2.

Table 6.1 Mean residues (ppm ± SD) of oxytetracycline in milk following a single intramuscular injection of LIQUAMYCIN® LA-200® at a dose of 20 mg/kg body weight

Time (hours post-treatment)	Mean milk residues	Number of animals
0*	<0.15	NA
11	1.630 ± 0.525	20**
24	1.680 ± 0.353	20
35	1.220 ± 0.1542	20
48	0.824 ± 0.1728	20
59	0.572 ± 0.1462	20
72	0.354 ± 0.0975	20
83	0.234 ± 0.0712	20
96	0.216 ± 0.0541	13
107	0.198 ± 0.0330	4
120	0.155 ± 0.0071	2
131	<0.15	NA
144	<0.15	NA

* Sample collected immediately before dose administration

** No. of animals used in the calculation (*i.e.*, those animals with milk residues ≥0.15 ppm)

NA = not available

Table 6.2 Statistical tolerance interval (a 95% confidence interval on the 99th percentile) for residues of oxytetracycline in milk following a single intramuscular injection of LIQUAMYCIN® LA-200® at a dose of 20 mg/kg body weight

Time (hr)	Tolerance Value (ppb)
12	5130
24	3070
36	1870
48	1160
60	750
72	500
84	340
96	230
108	160
120	120

Oxytetracycline residues in milk will deplete to less than 600 ppb, the tolerance if all of the ADI is partitioned for milk, by 72 hours post-treatment.

2. 2-Pyrrolidone

Plasma pharmacokinetic data for 2-pyrrolidone administered at 40 mg/kg were provided to address the human food safety of 2-pyrrolidone in the edible tissues and in milk, an ultrafiltrate of plasma. A dose of 40 mg/kg was used because it provides the equivalent amount of 2-pyrrolidone that would result from administering the label dose of LIQUAMYCIN® LA-200® (i.e., LA-200® contains 400 mg 2-pyrrolidone/mL and is administered at the label dose of 1 mL/10 kg).

Radiolabeled total residue data for ^{14}C-2-pyrrolidone were used to evaluate the depletion of vehicle from tissues and plasma of three lactating dairy cattle. The results are shown in Tables 6.3 and 6.4.

Table 6.3 Concentration of total radioactivity (μg/g)* and unchanged 2-pyrrolidone (μg/g) in edible tissues of cattle treated IM with 40 mg/kg ^{14}C-2-pyrrolidone

Tissue	Day 1		Day 7		Day 21	
	Total	2-pyrrolidone	Total	2-pyrrolidone	Total	2-pyrrolidone
Plasma	13.3	2.74	N/A	N/A	0.26	<0.05
Liver	23.7	3.04	4.84	<0.05	0.84	<0.05
Muscle	12.1	3.31	1.12	<0.05	0.59	<0.05
Kidney	23.9	3.49	2.95	<0.05	0.72	<0.05
Fat	17.2	1.39	1.03	<0.05	4.22	<0.05
Injection site**	12.2	3.52	1.14	<0.05	0.71	<0.05

* μg 2-pyrrolidone equivalents/g

** mean right and left rear limb injection site values

N/A = Not available

Table 6.4 Plasma concentrations of total radioactivity (μg/mL)* and unchanged 2-pyrrolidone in cattle treated IM with 40 mg/kg ^{14}C-2-pyrrolidone

Hours after dosing	1	2	4	6	8	10	12	24
Total radioactivity	46.0	56.0	52.5	43.9	42.8	34.8	32.0	12.2
2-pyrrolidone	51.4	55.5	56.6	43.3	40.3	25.5	26.8	6.7

* μg 2-pyrrolidone equivalents/g

Using the plasma pharmacokinetic data from 4 to 24 hours, a half-life of 6.6 hours (r^2= -0.9919) is calculated for unchanged 2-pyrrolidone in plasma. For purposes of modeling, it was assumed that concentrations of unchanged 2-pyrrolidone in milk would be comparable to concentrations in the other edible tissues. Plasma concentrations were used to estimate residues of unchanged 2-pyrrolidone in milk beyond 24 hours post-dosing, Table 6.5.

Table 6.5 Estimated milk concentrations of unchanged 2-pyrrolidone (μg/mL) at various times beyond 24 hours post-treatment in cattle receiving 40 mg/kg 2-pyrrolidone IM

Time (hr.)	2	12	24	48	72	120	168
Concentration (ppm)†	55.5	26.8	6.7	0.54	0.04*	<0.05*	<0.05*
Concentration (ppm)‡	55.5	26.8	6.7	0.84	0.11	<0.05*	<0.05*

* LOQ = 0.05 μg/mL
† = half-life =6.6 hours
‡ = half-life = 8 hours

Applying a half-life estimate of 8 hours to the pharmacokinetic data for 2-pyrrolidone residues in plasma, calculated residues of 2-pyrrolidone in milk will deplete to less than 160 ppb by 72 hours post-dosing. Assigning a milk discard in excess of 72 hours will ensure the safety of the entire LIQUAMYCIN® LA-200® product and permits the regulatory monitoring of residues using the active ingredient, oxytetracycline, rather than the vehicle, 2-pyrrolidone.

C. Milk Discard Time Calculation

On the basis of data from the residue and pharmacokinetic studies, a milk discard period of 96 hours is assigned for the use of oxytetracycline in lactating dairy cattle. A tolerance of 300 ppb is established for residues of oxytetracycline in milk. Using a statistical tolerance algorithm, it is calculated that residues of the active ingredient, oxytetracycline, will deplete to less than 300 ppb by 96 hours post-dosing. Assigning a 96-hour milk discard period will simultaneously ensure that residues of oxytetracycline are less than the assigned tolerance of 300 ppb and that residues of 2-pyrrolidone in milk have depleted to less than 160 ppb at the time milk from treated dairy cattle is presented for human consumption.

The milk residue depletion study was conducted in cattle treated intramuscularly. Comparative plasma pharmacokinetic data indicate that the depletion following subcutaneous administration is somewhat slower than that associated with intramuscular administration as shown in Table 6.6. This slower depletion results in higher terminal oxytetracycline concentrations following subcutaneous administration but the differences were not statistically significant.

Table 6.6 Least Square Means and Confidence Intervals comparing LIQUAMYCIN® LA-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)	4.74	3.68	0.78	65%	91%
AUC_{LAST} (μg*hr/mL)	119.5	118.3	0.99	87%	111%
T_{MAX}* (hr)	2.5	5.0	N/A	N/A	N/A
T_{LAST} (hr)	116	96	N/A	N/A	N/A
$C_{0.5}$* (μg/mL)	3.029	1.23	0.4	N/A	N/A
C_{24} (μg/mL)	1.763	1.99	1.13	N/A	N/A
C_{48} (μg/mL)	0.54	0.67	1.25	N/A	N/A
C_{96} (μg/mL)	0.10	0.14	1.34	N/A	N/A

* statistically significantly different ($p<0.05$)

**90% confidence intervals about the difference in treatment means using IM doses of LA-200® as the reference treatment. Equivalence is based upon a test and reference means differing by not more than ±20% (untransformed data).

N/A = Not applicable

The 96-hour oxytetracycline concentration ratio would indicate that milk residues of oxytetracycline following subcutaneous administration could be as much as 134% higher than those seen with intramuscular administration (*i.e.*, as high as 308 ppb 96 hours post-dosing). While this implies that milk residues would exceed the tolerance of 300 ppb, it assumes that 100% of the animals in the herd have been treated with oxytetracycline at its maximum dose and that milk from all of the treated animals will be consumed by humans. Since oxytetracycline injection will be used therapeutically, it is assumed that no more than one-third of the herd will be treated at any given time and, as such, oxytetracycline residues in bulk milk are expected to be less than 105 ppb.

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 supplemental NADA comply with the requirements of Section 512 of the Act and demonstrate that use of LIQUAMYCIN® LA-200® in lactating dairy cows is safe and effective for the indications stated on the product labeling. Under the Center's supplemental approval policy 21 CFR 514.106(b)(2), this is a Category II supplement which did not require re-evaluation of the safety and effectiveness data in the parent application.

Adequate directions for use of the product to treat lactating dairy cows 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 toxicology of both the active ingredient, oxytetracycline, and the vehicle, 2-pyrrolidone, was evaluated for this approval. Based on a battery of toxicology tests evaluating the 2-pyrrolidone vehicle, an acceptable daily intake (ADI) of 20 µg/kg body weight/day was calculated. The ADI was partitioned for tissues and milk providing an ADI of 4 µg/kg body weight/day for milk. This yielded a safe concentration for total 2-pyrrolidone residues of 160 ppb in milk. The ADI for residues of oxytetracycline has recently been revised (61 FR 67453). If all of the unassigned ADI for oxytetracycline is used for milk, a tolerance of 600 ppb is calculated for oxytetracycline residues. However, to regulate oxytetracycline based on the active ingredient, oxytetracycline, rather than the vehicle, 2-pyrrolidone, a tolerance of 300 ppb is established for the sum of residues of the tetracyclines including chlortetracycline, oxytetracycline, and tetracycline, in milk. Any residues of the tetracyclines present in milk at a level of 300 ppb or less are considered safe.

A milk discard period of 96 hours is assigned for the use of oxytetracycline in lactating dairy cattle. The discard period is based on a statistical analysis of the depletion data, using an upper tolerance limit containing 99 percent of the population with a 95 percent confidence limit. Assigning a 96-hour milk discard period will simultaneously ensure that residues of oxytetracycline are less than the assigned tolerance of 300 ppb and that residues of 2-pyrrolidone in milk have depleted to less than 160 ppb at the time milk from treated dairy cattle is presented for human consumption.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact (FONSI) and the evidence supporting that finding are contained in an environmental assessment, which may be seen in the Dockets Management Branch (HFA-305), Room 1061, 5630 Fishers Lane, Rockville, Maryland 20852.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food-producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval, because the application contains substantial evidence of effectiveness of the drug involved, studies of animal safety or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for approval of the supplement and conducted or sponsored by the applicant. Exclusivity applies only to use of this drug in lactating dairy cattle for the labeled indications for which the supplemental application was approved. A notice of this supplemental approval is being forwarded for publication in the FEDERAL REGISTER.

LIQUAMYCIN® LA-200® patent number US 4,018,889 expired April 19, 1994.

VIII. Approved Product Labeling

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

A. LIQUAMYCIN® LA-200® – Vial Label (100 mL)

B. LIQUAMYCIN® LA-200® – Vial Label (250 mL)

C. LIQUAMYCIN® LA-200® – Vial Label (500 mL)

D. LIQUAMYCIN® LA-200® – Vial Carton (100 mL)

E. LIQUAMYCIN® LA-200® – Vial Carton (250 mL)

F. LIQUAMYCIN® LA-200® – Vial Carton (500 mL)

G. LIQUAMYCIN® LA-200® – Package Insert