Date of Approval Letter: July 7, 2000

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 46-699

CHLORMAX™ 50, CHLORMAX™ 65, or CHLORMAX™ 70 (chlortetracycline)
Type A Medicated Article

"…for the control of porcine proliferative enteropathies (PPE)
associated with *Lawsonia intracellularis* susceptible to chlortetracycline."

Sponsored by:
Alpharma, Inc.

I. GENERAL INFORMATION

NADA Number:	46-699
Sponsor:	Alpharma Inc. One Executive Drive Fort Lee, New Jersey 07024
Accepted Name:	chlortetracycline
Trade Name:	CHLORMAX™ 50, CHLORMAX™ 65, or CHLORMAX™ 70 Type A Medicated Article
Marketing Status:	Over-the-counter (OTC)
Effect of Supplement:	This supplemental application adds the claim for the control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis* susceptible to chlortetracycline.

II. INDICATIONS FOR USE

Swine: For the control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis* susceptible to chlortetracycline.

For the treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* and bacterial pneumonia caused by *Pasteurella multocida* organisms susceptible to chlortetracycline.

For an increased rate of weight gain and improved feed efficiency.

..... Reducing the incidence of cervical lymphadenitis (jowl abscess) caused by Group E *Streptococci* susceptible to chlortetracycline.

Control of leptospirosis (reducing the incidence of abortion and shedding of *leptospirae*) caused by *Leptospira pomona*.

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

A. Dosage Form: This NADA provides for the use of a chlortetracycline Type A medicated article in Type B and Type C medicated swine feeds.

B. Route of Administration: Oral, by feed

C. Recommended Dosage: In Type C medicated feed, chlortetracycline to deliver a daily dose of 10 mg/lb body weight (approximately 400 grams per ton) for not more than 14 days.

IV. EFFECTIVENESS

A. Dose Justification

1. *Assay of Antimicrobial Effect of Bacitracin Methyl Disalicylate and Chlortetracycline in a Challenge Model of Porcine Proliferative Enteropathy.* S. McOrist, 4 June 1996

   A 1996 challenge model study evaluated various feed levels of chlortetracycline (CTC). The approved level of CTC was effective for the control of Porcine Proliferative Enteropathies (PPE) in pigs orally dosed with *Lawsonia intracellularis* (LI). Offering feed containing CTC at 100, 200, and 400 g/ton and BMD at 30 g/ton resulted in no clinical disease (morbidity) or histopathologic findings in the inoculated pigs. In contrast, the majority of unmedicated, infected pigs developed clinical disease associated with LI and exhibited gross and histopathologic lesions.

2. "*In vitro Assay of Antibiotics*." S. McOrist, 2 October 1995

   This 1995 *in vitro* study determined the minimum inhibitory concentration (MIC) of various agents against *Lawsonia intracellularis* (LI) in IEC-18 rat enterocyte cell cultures using both extracellularly and intracellularly active antibiotic assays. The intracellularly active antibiotic assay groups for CTC and bacitracin/CTC combination, with or without roxarzone, demonstrated significant inhibition of LI at concentrations of CTC between 1 and 4 µg/mL. This study supported the low MIC and likely sensitivity of LI to CTC and confirmed chlortetracycline's ability to act on an obligate intracellular bacterium.

B. Field Trial CS003-97BMCHxx

1. Investigator: Kelly F. Lechtenberg, D.V.M., Ph.D.
   Midwest Veterinary Services, Inc.
   RR#2, Box 49
   Oakland, Nebraska 68045

2. General Design

   a. *Purpose:* This study was conducted to confirm the efficacy of chlortetracycline (CTC), when fed to pigs at a daily dose of 10 mg/lb body weight (approximately 400 g/ton) for 14 days, for control of porcine proliferative enteropathies (ileitis) associated with *L. intracellularis*.

b. *Assignment of Experimental Animals to Pens:* The trial was conducted using 126 commercial-type pigs (33 to 66 lbs), naturally infected with ileitis. Pigs were randomly assigned to 8 pens (4 barrows and 4 gilts per pen) based on sex, clinical score, and body weight. Diagnosis of ileitis was based on clinical signs, gross lesions, and presence of *L. intracellularis* in fecal samples and at necropsy. Diseases attributable to *Brachyspira* (formerly *Serpulina*) *hyodysenteriae* (swine dysentery) and *Salmonella choleraesuis* were absent. Pigs were acclimated to their pens for five days prior to starting the treatment phase.

c. *Test Article Administration:* CHLORMAX™ Type A Medicated Article was mixed in complete swine feed to create a Type C medicated feed containing 400 g/ton CTC to deliver a daily dose of 10 mg/lb body weight based on voluntary feed intake for pigs of this weight. Feed was offered *ad libitum*. The same basal (non-medicated) feed was offered following arrival at the test site during the 5-day acclimation phase. Based on actual feed intake, the average dose of CTC was 8.7-mg/lb body weight.

d. *Pertinent Variables Measured:* Primary variables were Mortality and Treatment Success, based on clinical scores. Average Daily Gain (ADG), Average Daily Feed (ADF) intake, and Feed to Gain (F/G) Ratio were secondary variables.

The investigator, who was blinded to treatment assignments, assessed attitude, abdominal appearance, and fecal score (diarrhea and/or blood) daily during the acclimation and treatment phases and assigned a score to each. Attitude was scored as 0, 1, or 2; abdominal appearance was scored as 0, 1, or 2; and fecal consistency was scored as 0, 1, 2, 3, or 4. The sum of these variables, the daily total score, determined whether an animal was a treatment success or failure. If a pig's daily total score did not meet the criteria for treatment success (<3) on any of 14 days of the treatment phase, that pig was designated a treatment failure.

e. *Result of Clinical Observations:* No pigs died or were removed during the treatment phase. The average success rate for CTC-treated pens was significantly greater than for unmedicated pens ($p<0.05$). Trial results, as reported on an individual pig basis, are summarized in Table 4.1.

Table 4.1. Proportion of treatment successes and success rate for 126 pigs with naturally-occurring porcine proliferative enteropathies (ileitis)

Treatment	Proportion of treatment success	Success rate (percent)
Unmedicated controls	30/63	47.6
CTC in complete feed at 400 g/ton for 14 days	59/63	93.6

f. *Statistical Analysis:* The experimental unit was the pen. Clinical variables were analyzed using non-parametric procedures. An initial test for homogeneity was conducted to determine if the odds ratios across all blocks differed (homogeneity of odds ratio). A second test computed an exact confidence interval for the common odds ratio and tested whether the common odds ratio was unity (odds ratio estimation).

h. *Adverse Reactions:* The investigator reported no adverse reactions during or upon completion of this study.

i. *Conclusion:* Feeding 400 g/ton chlortetracycline for 14 days is effective for the control of proliferative enteropathies (ileitis) associated with *L. intracellularis* in pigs.

V. ANIMAL SAFETY

The target animal information is contained in the FOI Summary for the original approval of NADA 46-699. No new data were generated for this supplement because the dosage of CTC for this indication remains within the approved dose range for swine.

VI. HUMAN FOOD SAFETY

The current tolerance established for the sum of residues of the tetracyclines, including chlortetracycline, in tissues of swine is 2 parts per million (ppm) in muscle, 6 ppm in liver, and 12 ppm in fat and kidney, as described in 21 CFR 556.150. Chlortetracycline has a zero-day pre-slaughter withdrawal period in swine, as described in 21 CFR 558.128.

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR Part 514 of the implementing regulations. The data demonstrate that CHLORMAX™ 50 Type A Medicated Article is effective for the control of porcine proliferative enteropathies (PPE, ileitis) caused by *Lawsonia intracellularis* when administered in swine feed for 14 days at a dosage of 10 mg/lb body weight, which is generally equivalent to CTC at a level of 400 g/ton of feed.

Under the Center's supplemental approval policy, 21 CFR 514.106(b)(2)(v), this is a Category II change. The approval of this change is based on new safety and effectiveness data provided with the application.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action is categorically excluded under 21 CFR 25.33(a)(1) from the requirement to prepare an environmental assessment (EA).

Under Section 512(c)(2)(F)(iii) of the Act, this approval for food-producing animals qualifies for THREE (3) years of marketing exclusivity beginning on the date of approval

because the application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or in the case of food-producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new claim for which the supplemental application was approved.

VIII. APPROVED PRODUCT LABELING

Copies of facsimile Type A medicated article labeling and specimen (Blue Bird) Type B and Type C medicated feed labels are attached to this document.

A. CHLORMAX™ 50 Type A Medicated Article

B. Blue Bird CTC40 Type B Swine Feed

C. Blue Bird CTC Type C Swine Feed

Copies of applicable labels may be obtained by writing to the following:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, Maryland 20855