Approval Date: March 31, 2006

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-250

AUREOMYCIN (Chlortetracycline) plus BOVATEC (Lasalocid sodium)

Indicated for the following combinations numbered indications of chlortetracycline and lasalocid sodium: 1 and 5, 1 and 6, 1 and 7, 1 and 8, 2 and 7 (with the exception of dairy replacement heifers), 3 and 5, 3 and 6, 3 and 7 (with the exception of dairy replacement heifers), 3 and 8 (with the exception of dairy cattle), 4 and 5, 4 and 6, 4 and 7 (with the exception of dairy replacement heifers), 4 and 8 (with the exception of dairy cattle).

Chlortetracycline

1) 500 to 4,000 g/ton hand feed continuously for not more than 5 days to provide 10 mg/lb per day – for the treatment of bacterial enteritis caused by *E. coli* and bacterial pneumonia caused by *P. multocida* organisms susceptible to chlortetracycline in calves, beef, and non-lactating dairy cattle.
2) 0.5 mg/lb bodyweight daily – for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline in beef cattle over 700 pounds.
3) 350 mg per head daily – for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline in beef cattle under 700 pounds.
4) 350 mg per head daily – for control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline in beef cattle.

Lasalocid sodium

5) 10 to 30 g/ton to provide 100 to 360 mg lasalocid per head per day – for improved feed efficiency in cattle fed in confinement for slaughter.
6) 25 to 30 g/ton to provide 250 to 360 mg lasalocid per head per day – for improved feed efficiency and rate of weight gain in cattle fed in confinement for slaughter.
7) 30 to 600 g/ton to provide 60 to 300 mg/head/day in at least one pound of feed – for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle, dairy and beef replacement heifers).
8) 30 to 181.8 g/ton to provide 1 mg/2.2 lb bodyweight per day – for the control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii* in cattle weighing up to 800 pounds with a maximum of 360 mg of lasalocid per head per day.

Sponsored By:

Alpharma Inc.

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FREEDOM OF INFORMATION SUMMARY

AUREOMYCIN plus BOVATEC for Beef Cattle

1. GENERAL INFORMATION:

a. File Number:	NADA 141-250
b. Sponsor:	Alpharma Inc. One Executive Drive Fort Lee, NJ 07024 Drug Labeler Code: 046573
c. Established Name:	Chlortetracycline plus lasalocid sodium
d. Proprietary Name:	1) AUREOMYCIN 50, AUREOMYCIN 70, AUREOMYCIN 90 or AUREOMYCIN 100 plus 2) BOVATEC-68, BOVATEC-91, or BOVATEC-20 Liquid
e. Dosage Form:	Type A medicated articles used in the manufacture of Type C medicated feeds
f. How Supplied:	Chlortetracycline: 50 lb. bag Lasalocid sodium: 50 lb. bag Lasalocid sodium liquid: 23.5 liter drum
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	Chlortetracycline: 50 to 100 g/lb (11 to 22%) Lasalocid: 68 g/lb (15%) or 91 g/lb (20%) Lasalocid liquid: 90.8 g/lb (20%)
i. Route of Administration:	Oral in feed
j. Species/Class:	Cattle, various classes
k. Recommended Dosage:	Dosages for the following combinations numbered indications of chlortetracycline and lasalocid sodium: 1 and 5, 1 and 6, 1 and 7, 1 and 8, 2 and 7 (with the exception of dairy replacement heifers), 3 and 5, 3 and 6, 3 and 7 (with the exception of dairy replacement heifers), 3 and 8 (with the exception of dairy cattle), 4 and 5, 4 and 6, 4 and 7 (with the

exception of dairy replacement heifers), 4 and 8 (with the exception of dairy cattle).

Chlortetracycline

1) 500 to 4,000 g/ton hand feed continuously for not more than 5 days to provide 10 mg/lb per day – for the treatment of bacterial enteritis caused by *E. coli* and bacterial pneumonia caused by *P. multocida* organisms susceptible to chlortetracycline in calves, beef, and non-lactating dairy cattle.
2) 0.5 mg/lb bodyweight daily – for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline in beef cattle over 700 pounds.
3) 350 mg per head daily – for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline in beef cattle under 700 pounds.
4) 350 mg per head daily – for control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline in beef cattle.

Lasalocid sodium

5) 10 to 30 g/ton to provide 100 to 360 mg lasalocid per head per day – for improved feed efficiency in cattle fed in confinement for slaughter.
6) 25 to 30 g/ton to provide 250 to 360 mg lasalocid per head per day – for improved feed efficiency and rate of weight gain in cattle fed in confinement for slaughter.
7) 30 to 600 g/ton to provide 60 to 300 mg/head/day in at least one pound of feed – for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle, dairy and beef replacement heifers).
8) 30 to 181.8 g/ton to provide 1 mg/2.2 lb bodyweight per day – for the control of coccidiosis caused by *Eimeria bovis*

and *Eimeria zuernii* in cattle weighing up to 800 pounds with a maximum of 360 mg of lasalocid per head per day.

l. Pharmacological Category: Antimicrobial and anticoccidial

m. Indications: Indicated for the following numbered indications of combinations of chlortetracycline and lasalocid sodium: 1 and 5, 1 and 6, 1 and 7, 1 and 8, 2 and 7 (with the exception of dairy replacement heifers), 3 and 5, 3 and 6, 3 and 7 (with the exception of dairy replacement heifers), 3 and 8 (with the exception of dairy cattle), 4 and 5, 4 and 6, 4 and 7 (with the exception of dairy replacement heifers), 4 and 8 (with the exception of dairy cattle).

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7) 30 to 600 g/ton to provide 60 to 300 mg/head/day in at least one pound of feed – for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle, dairy and beef replacement heifers).
8) 30 to 181.8 g/ton to provide 1 mg/2.2 lb bodyweight per day – for the control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii* in cattle weighing up to 800 pounds with a maximum of 360 mg of lasalocid per head per day.

2. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the animal drugs/ active ingredients intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on effectiveness grounds unless the FDA finds that the sponsor fails to demonstrate that:

- there is substantial evidence to indicate that any active ingredient/drug intended only for the same use as another active ingredient/animal drug in combination makes a contribution to the labeled effectiveness.

- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population.

- where the combination contains more than one nontopical antibacterial active ingredient/animal drug, there is a substantial evidence that each of the nontopical antibacterial active ingredients/animal drugs makes a contribution to the labeled effectiveness

Chlortetracycline, as provided by Alpharma Inc., has previously been separately approved for use in feed for calves, beef, and non-lactating dairy cattle for the treatment of bacterial enteritis caused by *E. coli* and bacterial pneumonia caused by *P. multocida* organisms susceptible to chlortetracycline (codified with this approval at 21 CFR 558.128(e)(4)(v)); for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline in beef

cattle over 700 pounds (21 CFR 558.128(e)(4)(ii)); for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline in beef cattle under 700 pounds (21 CFR 558.128(e)(4)(viii)(2)); and for control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline in beef cattle (21 CFR 558.128(e)(4)(viii)(1)). Lasalocid sodium as provided by Alpharma Inc., has previously been separately approved for improved feed efficiency in cattle fed in confinement for slaughter (21 CFR 558.311(e)(1)(vi)); for improved feed efficiency and rate of weight gain in cattle fed in confinement for slaughter (21 CFR 558.311(e)(1)(vii)); for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle, dairy and beef replacement heifers) (21 CFR 558.311(e)(1)(ix)); for the control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii* in cattle weighing up to 800 pounds (21 CFR 558.311(e)(1)(xiii)). Effectiveness of each drug, chlortetracycline and lasalocid sodium when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma's approved NADA 048-761 for chlortetracycline, and in Alpharma's approved NADA 096-298 for lasalocid sodium.

Because chlortetracycline and lasalocid sodium each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that chlortetracycline plus lasalocid sodium provide appropriate concurrent use for the intended target population. The use of chlortetracycline plus lasalocid sodium provides appropriate concurrent use because these drugs are intended to treat different conditions (chlortetracycline – bacterial enterititis, bacterial pneumonia, and anaplasmosis; lasalocid sodium – weight gain, feed efficiency, and coccidiosis) likely to occur simultaneously with sufficient frequency in cattle. There is no nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed. Lasalocid sodium is not considered to be an antibacterial animal drug for use in cattle for the purposes of section 512(d)(4) of the FFDCA, because lasalocid sodium is approved only for rate of weight gain, improved feed efficiency, and control of coccidiosis in beef cattle.

3. TARGET ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in animal feed have previously been approved separately for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on target animal safety grounds unless

- there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that cannot adequately be evaluated based on the information contained in the application for the combination, and FDA finds that the application fails to show that the combination is safe, or

- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and FDA finds that the application fails to show that the combination is safe.

Chlortetracycline, as provided by Alpharma Inc., has previously been separately approved for use in feed for calves, beef, and non-lactating dairy cattle for the treatment of bacterial enteritis caused by *E. coli* and bacterial pneumonia caused by *P. multocida* organisms susceptible to chlortetracycline (codified with this approval at 21 CFR 558.128(e)(4)(v)); for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline in beef

cattle over 700 pounds (21 CFR 558.128(e)(4)(ii)); for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline in beef cattle under 700 pounds (21 CFR 558.128(e)(4)(viii)(2)); and for control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline in beef cattle (21 CFR 558.128(e)(4)(viii)(1)). Lasalocid sodium as provided by Alpharma Inc., has previously been separately approved for improved feed efficiency in cattle fed in confinement for slaughter (21 CFR 558.311(e)(1)(vi)); for improved feed efficiency and rate of weight gain in cattle fed in confinement for slaughter (21 CFR 558.311(e)(1)(vii)); for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle, dairy and beef replacement heifers) (21 CFR 558.311(e)(1)(ix)); for the control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii* in cattle weighing up to 800 pounds (21 CFR 558.311(e)(1)(xiii)). Target animal safety of each drug, chlortetracycline and lasalocid sodium when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma's approved NADA 048-761 for chlortetracycline, and in Alpharma's approved NADA 096-298 for lasalocid sodium. The Agency has found no substantiated scientific issue relating to the target animal safety of chlortetracycline and lasalocid sodium when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety studies are required for approval of NADA 141-250.

4. HUMAN SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in animal feed have previously been approved separately for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on human safety grounds unless FDA finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or

- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or drug in the combination.

A. Toxicity:

Summaries of all toxicology studies supporting the human food safety of lasalocid sodium (BOVATEC) and chlortetracycline (AUREOMYCIN or CHLORMAX) are incorporated by reference to the original approvals (NADA 96-298, FOI summary dated July 25, 2001; NADA 141-185, FOI summary dated March 15, 2002; NADA 141-147, FOI summary dated September 29, 2000; NADA 048-761, FOI summary dated February 16, 1996). The Acceptable Daily Intake (ADI) for lasalocid is 10 micrograms per kilogram of body weight per day (21 CFR 556.347). An (ADI) of 25 µg/kg bodyweight/day has been established previously for total residues of tetracyclines including chlortetracycline, oxytetracycline, and tetracycline under 21 CFR 556.150.

For this combination product, an assessment of the effects of microbiologically active residues of neither lasalocid nor chlortetracycline on the human intestinal flora was required at this time.

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

Residue Non-Interference Study

Study No. CD-98-04

Investigator: Ross W. Miller, D.V.M.
Roche Vitamins Animal Health Research Station
Wrightstown, NJ

In-Life Facility: Roche Vitamins, Inc., Wrightstown, NJ

Analytical Facilities: Lasalocid in liver was analyzed by Analytical Development Corporation, Colorado Springs, CO. Chlortetracycline in kidney was analyzed by Colorado Animal Research Enterprises, Fort Collins, CO.

This study was conducted according to Good Laboratory Practices (21 CFR 58).

Ten calves (approximately 8 months old, 575 pounds body weight) were divided into 2 groups. The control group (2 steers and 2 heifers) received a diet without chlortetracycline and served to verify that methods were suitable for detection of tissue residues. The treated group (3 steers and 3 heifers) was dosed with 1 mg lasalocid per 2.2 pounds body weight and 10 mg chlortetracycline per pound of body weight for 14 days. Chlortetracycline as AUREOMYCIN-90 and lasalocid sodium as BOVATEC-68 was used. AUREOMYCIN and CHLORMAX have been determined to be equivalent as sources of chlortetracycline. Chlortetracycline was dosed by top-dressing a medicated supplement on the diet after the complete ration was delivered to the feed bunk. Kidneys and livers were collected from both treatment groups within 12 hours after consumption of their respective diets on the fourteenth day of feeding. The concentration of chlortetracycline in kidney was determined by the approved microbiological method. The concentration of lasalocid in liver was determined by an established HPLC method.

Mean Residues of Lasalocid in Liver and Chlortetracycline in Kidney Collected from Cattle Treated with Feed Containing 1 mg lasalocid per 2.2 pounds body weight (mixed into diet) and 10 mg chlortetracycline per pound body weight (provided as a top dressing) for 14 days.

Withdrawal Time in Hours	Lasalocid (ppm)	Chlortetracycline (ppm)
0	0.042 ± 0.025	1.730 ± 0.965

LOQ: lasalocid = 0.02 ppm, chlortetracycline = 0.025 ppm

Control kidney samples were fortified with lasalocid and control liver samples were fortified with chlortetracycline. The data showed that the presence of lasalocid did not interfere with the assay of chlortetracycline and the presence of chlortetracycline did not interfere with the assay of lasalocid.

Residues of lasalocid and chlortetracycline were below their respective tolerances at zero withdrawal, the established withdrawal periods for each of the drugs, thereby indicating an absence of interference.

2. Target Tissue and Marker Residue Assignment

The target tissue for lasalocid is liver. The marker residue for lasalocid is parent lasalocid. Although a target tissue is not designated for chlortetracycline, residues deplete most slowly from kidney. Therefore, kidney was used to monitor the depletion of chlortetracycline in cattle in this study. Microbiologically active residues (parent drug plus metabolites) are measured with the method noted below.

3. Tolerance Assignment

The tolerance for lasalocid in bovine liver is 0.7 ppm (21 CFR 556.347). Tolerances for chlortetracycline in edible tissue of cattle are established as 2 ppm in muscle, 6 ppm in liver, and 12 ppm in fat and kidney (21 CFR 556.150).

4. Withdrawal Times

Zero-day withdrawal time is supported by data in Study No. CD-98-04. Residues of lasalocid and chlortetracycline were below their respective tolerances at zero withdrawal.

B. Microbial Food Safety:

For this combination product, there were no microbial food safety requirements to be addressed at this time.

D. Analytical Method for Residues:

1. Determinative Method

The regulatory method for detection of chlortetracycline residues is a microbiological assay using *Bacillus cereus* var. *mycoides* (ATCC 11778) as the test organism (Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports, and Protocols, Food and Drug Administration, Washington, D.C., 1968). Lasalocid residues are measured by a validated HPLC method.

2. Availability of Method

The validated regulatory methods for detection of residues of chlortetracycline and lasalocid are available from the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

E. User Safety Concerns:

There are no human warnings on the Type C Medicated Feed labeling.

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512(d)(4) of the FFDCA and 21 CFR Part 514 of the implementing regulations. Chlortetracycline when administered at 500 to 4,000 g/ton, 0.5 mg/lb bodyweight daily or 350 mg per head daily plus lasalocid sodium when administered at 10 to 30 g/ton, 25 to 30 g/ton, 30 to 600 g/ton or 30 to 181.8 g/ton are safe and effective for the claims indicated in section 1 of this FOI Summary

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act.

Pursuant to 21 CFR 514.106 (b)(2)(vi), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and effectiveness data in the parent NADAs.

The drugs are to be fed in Type C medicated feeds, in accordance with section 1 of the FOI Summary and the Blue Bird labeling that is attached to this document.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the lay person have been provided. Label directions provide detailed instruction in plain language. The drug product is not a controlled substance. Thus, the drug product is assigned OTC status, and the labeling is adequate for the intended use.

No patents were submitted by the sponsor with this application.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

BLUE BIRD AUREO/BOV FE TYPE B Confined Cattle Feed
BLUE BIRD AUREO/BOV FE/ROG TYPE B Confined Cattle Feed
BLUE BIRD AUREO/BOV ROG TYPE B Pasture Cattle Feed
BLUE BIRD AUREO/BOV COCCI TYPE B Cattle Feed
BLUE BIRD AUREO/BOV FE TYPE C Confined Cattle Feed
BLUE BIRD AUREO/BOV FE/ROG TYPE C Confined Cattle Feed
BLUE BIRD AUREO/BOV ROG TYPE C Pasture Cattle Feed
BLUE BIRD AUREO/BOV COCCI TYPE C Cattle Complete Feed
BLUE BIRD AUREO 0.5/BOV ROG TYPE B Pasture Cattle Feed
BLUE BIRD AUREO 0.5/BOV ROG TYPE C Pasture Cattle Feed
BLUE BIRD AUREO 350 ANA/BOV FE TYPE B Confined Cattle Feed
BLUE BIRD AUREO 350 ANA/BOV FE/ROG TYPE B Confined Cattle Feed

BLUE BIRD AUREO 350 ANA/BOV ROG TYPE B Pasture Cattle Feed
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BLUE BIRD AUREO 350 ANA/BOV FE TYPE C Confined Cattle Feed
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BLUE BIRD AUREO 350 ANA/BOV ROG TYPE C Pasture Cattle Feed
BLUE BIRD AUREO 350 ANA/BOV COCCI TYPE C Cattle Complete Feed
BLUE BIRD AUREO 350 RESP/BOV FE TYPE B Confined Cattle Feed
BLUE BIRD AUREO 350 RESP/BOV FE/ROG TYPE B Confined Cattle Feed
BLUE BIRD AUREO 350 RESP/BOV ROG TYPE B Pasture Cattle Feed
BLUE BIRD AUREO 350 RESP/BOV COCCI TYPE B Cattle Feed
BLUE BIRD AUREO 350 RESP/BOV FE TYPE C Confined Cattle Feed
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BLUE BIRD AUREO 350 RESP/BOV COCCI TYPE C Cattle Complete Feed