I. GENERAL INFORMATION

A. File Number

NADA 134-830

B. Sponsor

A. L. Laboratories, Inc.
One Executive Drive
PO Box 1399
Fort Lee, NJ 07024

C. Trade Name

Albac®, Coban®

D. Generic Name

bacitracin zinc, monensin sodium

E. Marketing Status

Over the Counter (OTC)

II. INDICATIONS FOR USE

As an aid in prevention of coccidiosis caused by Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. maxima and E. mivati; for increased rate of weight gain, and for improved feed efficiency in broiler chickens.

III. DOSAGE

A. DOSAGE FORM:
This NADA provides for the combined use of two approved Type A medicated articles, bacitracin zinc as per 21 CFR 558.78 and monensin as per 21 CFR 558.355, to make Type C medicated feed. Bacitracin zinc is marketed as a Type A medicated article containing 50 grams bacitracin activity/lb. Monensin is marketed as a Type A medicated article in concentrations of 45 and 60 grams monensin sodium/lb.

Bacitracin zinc is added to finished broiler Type C medicated feed at concentrations from 4-50 grams bacitracin/ton and monensin at concentrations of 90-110 grams monensin sodium/ton of feed.

B. ROUTE OF ADMINISTRATION: Orally in the feed.

C. RECOMMENDED DOSAGES:
Bacitracin zinc: 4-50 grams per ton
Monensin sodium: 90-110 grams per ton

IV. EFFECTIVENESS

Non-Interference Study

Two adequate and well-controlled battery experiments were conducted to evaluate the anticoccidial effectiveness of monensin when fed in combination with bacitracin zinc to broiler chickens. The studies (listed below) were conducted at the

experimental poultry farm of the University of Georgia, Department of Poultry Science, Athens, GA.

Experiment Nos. GA-B-118-85; GA-B-118-85/2

Investigator:

Larry R. McDougald, Ph.D.
Department of Poultry Science
University of Georgia
Athens, GA 30602

Monitor:

Ralph V. Fell, Ph.D.
Route 9, Box 42
Pine Bluff, AR 71603

Four hundred Arbor Acres x Peterson broiler chicks were caged in environmentally-controlled animal rooms. Each cage contained 10 wing-banded chicks (5 males and 5 females). Each of the five treatments (Table 1) were replicated four times in each of the two studies. The chicks were fed an unmedicated broiler starter feed until they were 12 days-of-age. At 12 days-of-age, chicks were weighed, stratified by body weight, randomly allocated to cages and provided medicated feed. At 14 days-of-age, the chicks were weighed and inoculated by oral gavage with mixed cultures of coccidia. The infective cultures were E. mitis, E. necatrix and E. brunetti in experiment GA-B-118-85 and E. acervulina, E. maxima and E. tenella in experiment GA-B-118-85/2. The coccidia species that were used were recent isolates obtained from commercial poultry farms in the United States.

Data, including death losses, intestinal lesion scores, dropping scores, weight gain and feed consumption were recorded over the 2 weeks following infection (Table 1). The infections reduced weight gains in the infected controls when compared with the uninfected controls. Treatment with monensin was effective in improving weight gain in all instances, whether it was used alone or in combination with bacitracin zinc. Lesion scores were recorded for the upper, mid and cecal areas of the gut. Monensin was effective in controlling coccidiosis caused by the six species of Eimeria in the broiler chickens. The use of bacitracin zinc with monensin did not interfere with the anticoccidial action of monensin.

Table 1 Anticoccidial activity of Monensin in combination with Bacitracin zinc against mixed *Eimeria spp.* infections in broiler chickens.

Medication	g/ton	Average Live Weight Gain (g)		Mortality		Total Lesion Scores/Bird		Total Dropping Scores/Bird	
		Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
None, unifnfected	0	461.4	454.9	0/40	0/40	0	0	0	0
None, Infected	0	357.1	127.0	1/40	27/40	4.74	12.00	7.25	15.50
Monensin	90	389.7	412.1	0/40	2/40	0.69	5.30	0.75	9.25
Bacitracin Zinc	100	256.9	100.8	2/40	27/40	5.88	12.00	5.00	15.75
Monensin+ Bacitracin Zinc	90 100	358.6	413.4	0/40	2/40	0.88	6.38	0.75	9.25

Study 1, infective cultures were from field isolates of *E. mitis, E. necatrix,* and *E. brunetti* (Study GA-B-118-85).
Study 2, infective cultures were from field isolates of *E. acervulina, E. maxima,* and *E. tenella* (Study GA-B-118-85/2).

Floor-Pen Study

Three floor-pen experiments were conducted using 2,720 broiler chickens. Bacitracin zinc was fed at 0 or 50 grams per ton of feed in combination with monensin at 110 grams per ton. The experiments were designed to evaluate the growth promoting effects of bacitracin zinc when fed in combination with monensin to broiler chickens.

Experiment No. TX-B-112-83

Investigator:

William F. Krueger, Ph.D.
Department of Poultry Science
Texas A&M University
College Station, TX 77843

Monitor:

Ralph V. Fell, Ph.D.
Route 9, Box 42
Pine Bluff, AR 71603

In this experiment, 1400 chicks were housed in a conventional, dirt-floor broiler house on the premises of Texas A&M University, College Station, TX. Each 8 x 10 ft pen was identically equipped with a 6 ft mechanical water trough and hanging tube-type feeders. Chicks were reared in a 22 hr photoperiod provided by a 40

watt incandescent light over each pen. Bedding was used litter, topped with a 1" layer of new pine shavings.

Fifty male and 50 female day-old, Cobb x Hubbard chicks were allocated randomly to 14 experimental pens. Treatments were assigned to pens in a randomized block design. Treatments were randomly assigned to blocks of contiguous pens. The 14 experimental pens allowed for 7 replications of the two treatments. The experiment consisted of two dietary treatments which were monensin at 110 grams/ton and monensin at 110 grams/ton plus bacitracin zinc at 50 grams/ton. The duration of the experiment was 47 days.

Results:

The addition of bacitracin zinc to the diet increased the rate of weight gain and improved feed efficiency over birds fed monensin alone (Table 2).

Experiment No. MO-B-114-84

Investigator:

Randall A. Primo
Ponderosa Research Company
French Village, MO 63036

Monitor:

Ralph V. Fell, Ph.D.
Route 9, Box 42
Pine Bluff, AR 71603

In this experiment, 600 birds were housed in a conventional, insulated, curtain-sided broiler house with wire partitions and a dirt floor. Each 5 x 8 pen was equipped with an automatic water fountain, a cylindrical hanging self feeder and a heat lamp brooder. Light to supplement natural daylight was supplied by an incandescent light over the center of each pen. Used litter was top-dressed with new wood shavings.

Day-old chicks were distributed randomly by sex into 12 pens so that each pen contained 25 male and 25 female chicks, with six replicates. For assignment of treatments to pens, the 12 pens were divided into blocks and dietary treatments assigned randomly within each block. The experiment entailed 2 dietary treatments, i.e., monensin at 110 grams per ton and monensin at 110 grams per ton + bacitracin zinc at 50 grams per ton. The duration of the experiment was 48 days.

Results:

The addition of bacitracin zinc to the diet increased the rate of weight gain and improved feed efficiency over birds fed monensin alone (Table 2).

Experiment No. ARK-B-120-84

Investigator:

Park W. Waldroup, Ph.D.
Department of Animal Sciences
University of Arkansas
Fayetteville, AR 72701

Monitor:

Ralph V. Fell, Ph.D.
Route 9, Box 42
Pine Bluff, AR 71603

In this experiment, 720 chicks were housed in a conventional steel-truss building with an insulated roof and sidewalls and a three-foot sidewall curtain. Pens were 7 x 8 ft and contained two hanging tube-type feeders, an automatic water fount and an infrared gas brooder. Used litter was top-dressed with new litter. Day-old, sexed chicks were randomly distributed by sex into the pens so that each pen contained 30 males and 30 females. The 12 pens allotted to this study permitted 6 replications of each of the 2 dietary treatments as follows: monensin at 110 per ton and monensin at 110 grams per ton + bacitracin zinc at 50 grams per ton. Treatments were assigned randomly to pens within each of the 6 blocks of pens. The duration of the experiment was 49 days.

Results:

The addition of bacitracin zinc to the diet increased the rate of weight gain and improved feed efficiency over birds fed monensin alone (Table 2).

Table 2 Performance Response Of Broiler Chickens To Bacitracin Zinc When Fed With Monensin

		Monensin, 110 g/ton		**Monensin, 110 g/ton + BZn, 50 g/ton**	
	No. Reps	**Mean Weight Gain (lb)**	**Feed/Gain**	**Mean Weight Gain (lb)**	**Feed/ Gain**
TX-B-112-83	7	3.59	2.25	3.77	2.11
MO-B-114-84	6	4.19	2.26	4.26	2.20
ARK-B-120-84	6	4.34	2.11	4.52	2.02
Grand Mean		4.04	2.21	4.18	2.11

Summary of Floor-Pen Study

The three floor-pen experiments, using 2,720 broiler chickens were conducted in different geographical locations to determine the growth promoting effects of bacitracin zinc in combination with monensin. The studies were designed and conducted to simulate varying conditions such as climate, geographical location,

weather, management practices, and degree of disease contamination of the premises.

Consistent with pen size 25 to 50 chicks of each sex were selected at random and assigned to pens. Six or 7 replicates were used per treatment group. Bacitracin zinc at 0 and 50 grams per ton of feed was used in combination with monensin at 110 grams per ton of feed in each study.

A pooled statistical analysis of the three experiments was conducted. The data demonstrate that the addition of bacitracin zinc to the diet at 50 grams per ton increased the rate of weight gain and improved feed efficiency significantly ($p < .05$) when compared to chicks fed monensin alone.

Summary of Effectiveness Studies

The results of the effectiveness studies qualify this application for range approval for the drug combination under CVM's Drug Combination Policy, revised October, 1983. The data demonstrate that both drugs contributed to the effectiveness of the combination drug.

These data support approval of this application for the use of monensin at 90 to 110 grams per ton and bacitracin zinc at 4 to 50 grams per ton as an aid in the prevention of coccidiosis caused by *Eimeria acervulina, E. brunetti, E. maxima, E. mivati, E. necatrix,* and *E. tenella* and for increased rate of weight gain and improved feed efficiency in broiler chickens.

V. ANIMAL SAFETY

The basic animal safety data for the individual drugs may be found in the parent NADAs (98-452 for bacitracin zinc and 38-878 for monensin). The effectiveness studies shown in Section IV demonstrate that no ill effects occurred when the drugs were combined indicating that they are as safe when fed in combination as when fed alone.

This application is in accord with the Center's Target Animal Safety Guidelines. Additional safety studies were not required because: (1) The drugs have been approved singly and (2) adequate documentation has been provided to show that these components are compatible in combination when used in broiler chicken feeds. Therefore, based on the data in the original NADAs, the non-interference study, the floor pen efficacy studies, and the drug residue elimination study, this combination of drugs may be safely fed to broiler chickens.

VI. HUMAN SAFETY

A. Toxicity Tests

The toxicology data that support the safety of residues of bacitracin zinc are filed in the parent NADA 98-452 sponsored by A. L. Laboratories, Inc. (approved April 5 1976, 41 FR 14367). The toxicology data for monensin are contained in the parent

NADA 38-878 sponsored by Elanco Products Co. (approved May 20, 1970, 35 FR 7734).

B. Tolerances and Safe Concentrations of Residues

The tolerance for residues of bacitracin zinc in uncooked tissues of chickens is established at 0.5 ppm, negligible residue (21 CFR 556.70).

A tolerance for residues of monensin in chickens is not established because the total residues of the drug (parent + metabolites) are below the safe concentrations for the drug at zero withdrawal. The safe concentrations for monensin total residues in chicken tissues are: 1.5 ppm in muscle, 3.0 ppm in skin with adhering fat, and 4.5 ppm in liver (21 CFR 556.420).

C. Tissue Residue Non-Interference Studies

Data to demonstrate that the residue levels of bacitracin zinc and monensin are not adversely affected when the two drugs are fed in combination to broilers were generated in two residue studies. Both studies used overdosing levels of bacitracin zinc.

1. Non-interference on residues of monensin

The first non-interference study (CK-567) was conducted by Elanco Products Company, and it provided data to demonstrate that residue levels of monensin are not adversely affected by the presence of bacitracin zinc. The investigators were M.H. Gehle and J.E. Wachtstetter.

The study was a combined residue and efficacy trial, and it involved 600 broiler chickens which received one of the following treatments:

A. control diet

B. bacitracin zinc at 500 g/ton

C. monensin at 110 g/ton plus bacitracin zinc at 500 g/ton.

The birds were fed the respective diets until 56 days of age at which time groups were sacrificed at zero, 24 and 48 hours of withdrawal for the residue portion of the study. At each of those withdrawal intervals, liver, muscle, kidney and fat samples were collected from male and female birds. The samples were assayed for microbiologically active residues of monensin by Lilly Method No. 5801330 to give six values at each withdrawal interval.

Monensin residue levels in the range of 0.025 to 0.05 ppm or 0.05 to 0.10 ppm were found in five of the six zero withdrawal fat samples. The other fat samples and all muscle, liver and kidney samples showed no detectable residues of monensin.

Metabolism data generated under NADA 38-878 has shown that total residues of monensin in fat are well below the safe concentration in that tissue when microbiologically active residues of the drug in fat are in the range of 0.025 to 0.10 ppm. The monensin values reported above for monensin in fat tissue confirm that total residues of the drug are below the safe concentrations for the drug in birds fed rations containing the monensin plus bacitracin zinc combination.

2. Non-interference on residues of bacitracin zinc

The non-interference on monensin residues by the presence of bacitracin zinc in the combination was demonstrated in a second study conducted with the three-way combination of monensin, bacitracin zinc, and roxarsone. The dosing phase of the study (MO-B-TR-1) was conducted for A. L. Laboratories by the Ponderosa Research Company, French Village, Missouri, with Mr. Randall A. Primo as investigator. The assays for bacitracin zinc (CK-568) in tissues were conducted by Northvale Analytical Laboratory, Northvale, NJ.

The study involved two pens (12 birds each) of commercial broiler chicks. The birds in one pen were fed a non-medicated control diet and the birds in the other pen were fed a diet containing monensin (110 g/ton), bacitracin zinc (100 g/ton), and roxarsone (45.5 g/ton). At 48 days of age, three male and three female birds were withdrawn from the medicated feed for 24 hours and killed to provide tissue samples at one day of withdrawal. Six other birds received the medicated feed for 49 days and were killed at zero withdrawal. Breast muscle tissue was collected, frozen, and shipped to the analytical laboratory.

Assay of the medicated and unmedicated control muscle samples was conducted using Northvale Analytical Laboratory Test Procedure Code No. 9A, Modified Microbiological Method for Determination of Bacitracin in Tissues. The assays of all tissue samples were negative (< 0.1 ppm) for microbiologically active residues of bacitracin zinc.

The residue non-interference studies described above confirm that, for the two-way combination of monensin and bacitracin zinc, each drug in the presence of the other does not exceed its approved safe concentration or tolerance. These data support a zero withdrawal period for the use of this combination in broilers under CVM's combination drug policy.

D. Assay Non-Interference Studies

1. Bacitracin zinc assay

The non-interference on the assay for bacitracin zinc by the presence of residues of monensin was demonstrated by the assay of control samples of chicken muscle that were spiked with bacitracin zinc (0.5 ppm) with and without monensin (0.5 ppm) and roxarsone (0.5 ppm). The recovery values for both sets of samples were both about 85%, indicating no interference in the assay.

2. Monensin assay

A non-interference study on the bioautographic method for monensin was conducted by spiking control tissue samples with monensin and bacitracin zinc and then assaying these tissues for monensin content. The results demonstrated no interference by bacitracin zinc for monensin.

E. Regulatory Methods

1. Bacitracin zinc

An analytical method for microbiologically active residues of bacitracin zinc in tissues is described in the following reports: 1) "Antibiotic Residue in Milk, Dairy Products and Animal Tissues: Methods, Reports, Protocols," National Center for Antibiotic Analyses, Dept. HEW Washington DC 20204, Rev. October 1968; and 2) "Modified Method for Determination of Bacitracin in Tissues," Test Procedure Code 9A, A. L. Laboratories, Inc., One Executive Drive, PO Box 1399, Fort Lee, NJ 07024.

2. The use of monensin in chickens is approved under NADA 38-878 without the need for a tolerance or an official regulatory method. However, analytical methods for the drug are available such as the bioautographic methods that are used in non-interference studies with monensin. A current bioautographic method is described in Part 5.044 of the *Chemistry Laboratory Guidebook* published by the United States Department of Agriculture.

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Sections 512 of the Act and demonstrate that monensin (90-110 g/ton) plus bacitracin zinc (4-50 g/ton) are safe and effective for the claims indicated in Section II of this FOI Summary.

Pursuant to 21 CFR 514.106 (b)(2), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of the safety and effectiveness data in the parent applications. The drugs are to be fed in Type C Medicated feeds, in accordance with Section II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

A residue study referenced in this application demonstrates that microbiologically active residues of monensin at 0-day withdrawal will be 0.1 ppm or less in fat tissue and generally nondetectable in other tissues when chickens are medicated with the combination of bacitracin zinc and monensin. These levels correspond to total residue levels (parent monensin plus its metabolites) much less than the monensin safe concentrations of 1.5 ppm in muscle, 3.0 ppm in skin with adhering fat, and 4.5 ppm in liver.

A second residue study, which was contained in the application, demonstrates that microbiologically active residues of bacitracin zinc at 0-day withdrawal will be less

than the 0.5 ppm bacitracin tolerance when chickens are fed the combination of bacitracin zinc and monensin.

Adequate information was submitted to demonstrate non-interference between the assays for each drug. The approval of this application will not significantly increase human exposure to drug residues.

Non-interference studies demonstrate that monensin in the presence of bacitracin zinc prevented an outbreak of coccidiosis when the birds were exposed to the six major species of Eimeria. The data from three well-controlled floor-pen studies demonstrate the effectiveness of bacitracin zinc for increased rate of weight gain and improved feed efficiency in broiler chickens in the presence of monensin. The policy outlined in CVM's guideline for drug combinations for use in animals provides for the granting of range approval for monensin (90-110 g/ton) as an aid in the prevention of coccidiosis caused by *Eimeria acervulina, E. brunetti, E. maxima, E. mivati, E. necatrix,* and *E. tenella;* for bacitracin zinc (4-50 g/ton) for increased rate of weight gain and improved feed efficiency in broiler chickens.

Section 512(c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act, provides a three-year period of exclusivity to NADAs for previously approved active ingredients that require reports of new clinical or field investigations (other than bioequivalence or residue studies) and, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) essential to the approval of the application and conducted or sponsored by the applicant. This new animal drug application qualifies for such an exclusivity period which will expire three years from the date of the approval letter.

VIII. ATTACHMENTS

Bag label

Copies of these labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.