I. GENERAL INFORMATION

A. File Number

NADA 138-456

B. Sponsor

A. L. Laboratories, Inc.

C. Proprietary Name

BMD, Coban

D. Established Name

bacitracin methylene disalicylate and monensin sodium

E. Dosage Form

This NADA provides for the combined uses of these two approved Type A medicated articles, BMD as per 21 CFR 558.76 and Coban as per 21 CFR 558.355 into Type C medicated feed. BMD Type A medicated articles are marketed as a medicated premix containing 10, 25, 30, 40, 50, 60 and 75 grams/lb bacitracin. Coban Type A medicated articles are marketed as a medicated premix in concentrations of 45 and 60 grams/lb.
BMD is added to finished broiler Type C medicated feed at concentrations ranging from 4-50 g/ton and Coban at concentrations of 90-110 grams/ton of feed.

F. Dosage Regimen

Bacitracin methylene disalicylate: 4-50 grams per ton
Monensin sodium: 90-110 grams per ton

G. Route of Administration

Orally in the feed

H. Species/Class

Species and class (if applicable)

I. Indication

For improved feed efficiency and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. maxima* and *E. mivati*. Bacitracin methylene disalicylate 4-50 grams per ton in combination with 90-110 grams per ton monensin.
Bacitracin methylene disalicylate: 4-50 grams per ton
Monensin sodium: 90-110 grams per ton

J. Effect of Supplement

Monensin Sodium is presently approved for use in broiler chicken feed at 90-110 per ton as an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati* and *E. maxima* (21 CFR

558.355(f)(1)(i)). Monensin Sodium is presently approved for use in broiler chicken feed at 110 grams per ton in combination with bacitracin methylene disalicylate at 4-50 grams per ton for improved feed efficiency and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati* and *E. maxima* (21 CFR 558-355(f)(1)(xxiv)). This supplemental NADA provides data to support the request for Monensin Sodium to be used at a range of 90-110 grams per ton in combination with bacitracin methylene disalicylate at 4-50 grams per ton for improved feed efficiency and as an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati* and *E. maxima.*

II. EFFECTIVENESS

Six floor pen experiments were conducted using approved protocols and 23,676 broiler chickens. Bacitracin methylene disalicylate at 0, 10, 25 and 50 grams per ton of feed was used in five of the experiments, while 0, 5 and 50 grams per ton was used in one. Roxarsone at 0, 11.3, 22.7 and 45.4 grams per ton was used in five of the experiments, while 0 and 45.4 grams per ton was used in one. Monensin sodium at 110 grams per ton was included in all experimental feeds. The experiments were designed to test the effects of bacitracin methylene disalicylate in the presence of monensin on body weight gains and feed efficiency.

A description of the six experiments follows:

A. Experiment No: FV-B-29/30-74

Investigator:

Ralph V. Fell, Ph.D.
Box 488
Sheridan, AR 72150

The 56-day experiment was conducted at the S. B. Penick Animal Research Farm, French Village, MO from January 3, to February 28, 1974. The experiment consisted of 16 dietary treatments with three replicates of 70 one day old Vantress X Hubbard broiler chickens placed randomly, half male and half female in 48 pens. Each 9' x 6' pen was identically equipped with an infrared brooder, two tube type hanging feeders, and three Hart drinking cups. The floors were concrete and covered with wood shavings. The building was enclosed, continuously lighted and fan ventilated. The desired levels of drugs being studied were added to typical broiler starter/finisher rations and fed for the entire growing period except that monensin was withdrawn from the feed for the last five days.

B. Experiment No: FV-B-29/30-74

Investigator:

Ralph V. Fell, Ph.D.
Box 488
Sheridan, AR 72150

The second of the 56-day experiments was conducted concurrently with FV-B-29-74 in a second house at the S. B. Penick Animal Research Farm, French Village, MO from

January 3 to February 28, 1974. This experiment consisted of 16 dietary treatments with two replicates of 80 one-day old Vantress X Hubbard broiler chickens, placed randomly, half male and half female, in 32 pens. Each 6' x 10' pen was identically equipped with an infrared brooder, two tube type hanging feeders and three Hart drinking cups. Wood shavings were used as litter. The building was enclosed, continuously lighted and fan ventilated. The desired levels of drugs being studied were added to typical broiler starter/finisher rations and fed for the entire growing period, except that monensin was withdrawn from the feed for the last five days.

C. Experiment No: GA-B-53-77

Investigator:

Robert K. Page, D.V.M.
Department of Avian Medicine
College of Veterinary Medicine
University of Georgia
Athens, GA

Monitor:

Ralph V. Fell, Ph.D.
Box 488
Sheridan, AR 72150

This 56-day experiment was conducted at Winder, GA under the supervision of Dr. Robert K. Page from February 24, to April 20, 1976. The experiment consisted of 16 dietary treatments with three replicates of 60 one-day old Hubbard X Hubbard broiler chickens, half male and half female in each of 48 pens. Each 5' x 10' was identically equipped with thermostatically controlled brooders,self feeders and drinking fountains. New wood shavings were spread over built up litter.

The desired level of drugs being studied were added to a typical boiler starter/finisher ration and fed for the entire growing period except that monensin was withdrawn from the feed for the last five days.

D. Experiment No: 306-572-1-14

Investigators:

B. F. Schlegel, D.V.M.
Wheeler, AR

and

D. L. Gard, Ph.D.
Eli Lilly & Company
Greenfield, IN 46140
This 50-day experiment was conducted at facilities leased by Eli Lilly & Company, Wheeler, AR beginning on December 8, 1971. The experiment consisted of six dietary treatments with the negative controls being replicated six times and the other four treatments being replicated six times and the other four treatments being replicated

four times. One hundred one-day old male broiler chickens were placed randomly in each of 28 pens. Each 8' x 10' pen was equipped with area gas brooders, incandescent light, two 18' tube feeders and one 18' diameter automatic waterer. Reused litter was provided. The pens were in a building which had a concrete block foundation, wood frame walls, insulated ceiling, concrete floor and thermostatically controlled glass curtains. The desired levels of drugs being studied were added to a typical starter/finisher broiler ration and fed for the entire growing period except monensin was withdrawn from the feed for the last five days.

E. Experiment No: 306-572-2-2

Investigators:

B. F. Schlegel, D.V.M.
Wheeler, AR

and

D. L. Gard, Ph.D.
Eli Lilly & Company
Greenfield, IN 46140

This 61-day experiment was conducted at the same facilities as the previous experiment beginning February 28, 1972. The experiment consisted of 16 dietary treatments. Four treatments were replicated three times and the other 12 treatments were replicated four times. One hundred Vantress X Arbor Acre broiler chickens, half male and half female, were randomly distributed to each of the 60 pens. The desired level of drugs being studied were added to a typical starter/finisher broiler ration and fed for the entire growing period except monensin was withdrawn from the feed for the last five days.

F. Experiment No: 306-572-2-7

Investigators:

B. F. Schlegel, D.V.M.
Wheeler, AR

and

D. L. Gard, Ph.D.
Eli Lilly & Company
Greenfield, IN 46140

This 58-day experiment was conducted at the same facilities as the previous experiment beginning May 9, 1972. The experiment consisted of 16 dietary treatments. Four treatments were replicated three times and the other 12 treatments were replicated four times. One hundred Vantress X Arbor Acre Broiler chickens, half male and half female, were distributed randomly in each of the 60 pens. The desired levels of drugs being studied were added to typical broiler and starter/finisher rations fed for the entire growing period except monensin was withdrawn from the feed for the last five days.

G. Floor Pen Experiments Summary

Six adequate and well-controlled floor pen experiments, using approved protocols and 23,676 broiler chickens (in five experiments equal numbers of males and females, in one experiment all males) were conducted under conditions simulating actual field use to determine the growth promoting effects of bacitracin methylene disalicylate in the presence of monensin. Although these experiments were originally designed as titration studies, for purposes of this submission, only the highest levels of bacitracin methylene disalicylate (50 grams per ton) in the presence of monensin (110 grams per ton) are considered.

The efficacy data were evaluated according to the combination drug guidelines revised October 1983: Drugs approved individually at a range and codified in the CFR are not required to be titrated in the combination. However, each drug's contribution to the combination must be demonstrated by data from studies conducted with the maximum approved drug level. For the NADA, data from two treatment groups from each of the six trials are adequate to satisfy these requirements. Treatment one (1) monensin at 110 g/ton: Treatment two (2) monensin 110 g/ton plus BMD at 50 g/ton.

The data for each of the above two treatments from the six trials were pooled for analysis for weight gain and feed efficiency. The analysis for weight gain showed no significant difference ($P = 0.10$) between the two treatments. The analysis of the feed to gain data showed a significant difference
($P < 0.01$) between the two treatments due to BMD.

The data from the non-interference studies and the six floor pen studies qualify the application for approval as an aid in the prevention of coccidiosis and for improved feed efficiency. The CVM policy outlined in the October 1983 revised guidelines permits the quantity of the range for BMD codified in 21 CFR 558.76(e)(i), which is 4 to 50 g/ton for use in combination with monensin at 90-110 g/ton.

SUMMARY OF RESPONSE OF BROILERS TO BACITRACIN-MD WHEN FED WITH MONENSIN

		Coban 110 g/ton			
		Coban 110 g/ton		**BMD 50 g/ton**	
	No. Reps.	**Average Weight (lb)**	**Feed/Gain**	**Average Weight (lb)**	**Feed/Gain**
FV-B-29-74	3	3.86	2.19	3.83	2.15
FV-B-30-74	2	3.89	2.20	4.01	2.15
GA-B-53-77	3	3.82	2.22	3.85	2.18
306-572-2-7	3	3.43	2.05	3.43	2.03
306-572-2-02	3	3.70	2.06	3.83	2.05
306-572-1-14	4-6	2.93	2.05	2.99	2.00
Average		3.60	2.13	3.66	2.09

H. Effectiveness - Non-Interference

This submission provides additional information to the existing Freedom of Information Summary and approval of BMD-4-50 grams/ton and Coban 110 grams/ton: 51 FR 12/17/86, 45105. These data report an additional non-interference

study to demonstrate that the presence of BMD at 200 grams/ton did not interfere with the anticoccidial properties of monensin at 90 grams/ton of feed. The experiment was conducted by Dr. K. W. Bafundo and Dr. D. J. Donovan, Lilly Research Laboratories, Greenfield, Indiana.

These data constitute a series of seven battery experiments conducted to determine the compatibility of monensin (99 ppm) and the therapeutic level of BMD (220 ppm) when fed in combination. Anticoccidial efficacy was assessed as an aid in the prevention of infections of Eimeria acervulina, E. maxima, E. mitis/E. mivati, E. brunetti, E. necatrix, E. tenella, and a mixed inoculum of the above coccidia as measured by growth performance (weight gain and feed/gain ratios) and reduction in mortality and lesion severity. The following seven tables (1-7) depict the efficacy profile of the combination.

Monensin, both alone and in combination with BMD, effectively reduced lesion scores and improved performance. The addition of BMD to feeds had no adverse effects on the efficacy of monensin as an aid in the prevention of coccidial infections. Thus, BMD was found to be compatible with monensin when the anticoccidial efficacy of the drug was assessed.

The data in Tables 1 through 7 show that 200 grams of BMD do not interfere with the anticoccidial activity of 90 grams/ton (99 ppm) of monensin, which supports the conclusion that BMD at 4-50 grams/ton will not interfere with the anticoccidial activity of monensin at 90 grams/ton (99 ppm).

Table 1 Experiment No. T1S8C8671 Percent Mortality, Weight Gain, Feed/Gain, and Intestinal Lesion Scores of broiler cockerels inoculated with *E. maxima*.

Treatment/ PPM	% Mortality (mean)	Weight Gain (grams)	Feed Gain (mean)	Intestinal Lesion Scores (mean)
NNC/ 0	0.0	257.9	1.473	0.00
IC/ 0	0.0	226.0	1.726	4.00
Monensin/ 99	0.0	272.3	1.444	0.00
BMD/ 220	0.0	215.9	1.731	4.00
Monensin +BMD/ 99+220	0.0	287.6	1.398	0.44

NNC = Non-Infected, Non-Medicated Controls
IC = Infected Controls

Table 2 Experiment No T1S8C8672 Percent Mortality, Weight Gain, Feed/Gain, and Intestinal Lesion Scores of broiler cockerels inoculated with *E. necatrix*.

Treatment/ PPM	% Mortality (mean)	Weight Gain (grams)	Feed Gain (mean)	Intestinal Lesion Scores (mean)
NNC/ 0	0.0	283.0	1.536	0.69
IC/ 0	0.0	208.3	1.743	3.75
Monensin/ 99	0.0	262.3	1.468	0.38
BMD/ 220	0.0	214.1	1.658	3.63
Monensin +BMD/ 99+220	0.0	263.0	1.494	0.35

NNC = Non-Infected, Non-Medicated Controls
IC = Infected Controls

Table 3 Experiment No. T1S8C8675 Percent Mortality, Weight Gain, Feed/Gain, and Intestinal Lesion Scores of broiler cockerels inoculated with *E. mivati/mitis*.

Treatment/ PPM	% Mortality (mean)	Weight Gain (grams)	Feed Gain (mean)	Intestinal Lesion Scores (mean)
NNC/ 0	0.0	301.3	1.487	0.00
IC/ 0	0.0	255.1	1.690	2.25
Monensin/ 99	0.0	270.1	1.581	0.00
BMD/ 220	0.0	214.9	1.740	3.25
Monensin +BMD/ 99+220	0.0	269.9	1.540	0.00

NNC = Non-Infected, Non-Medicated Controls
IC = Infected Controls

Table 4 Experiment No. T1S8C8719 Percent Mortality, Weight Gain, Feed/Gain, and Intestinal Lesion Scores of broiler cockerels inoculated with E. brunetti.

Treatment/ PPM	% Mortality (mean)	Weight Gain (grams)	Feed Gain (mean)	Intestinal Lesion Scores (mean)
NNC/ 0	0.0	304.8	1.587	0.63
IC/ 0	0.0	159.5	2.242	4.00
Monensin/ 99	0.0	290.3	1.630	1.88
BMD/ 220	0.0	137.5	2.428	3.94
Monensin +BMD/ 99+220	0.0	284.7	1.586	2.96

NNC = Non-Infected, Non-Medicated Controls
IC = Infected Controls

Table 5 Experiment No. T1S8C86D4 Percent Mortality, Weight Gain, Feed/Gain, and Intestinal Lesion Scores of broiler cockerels inoculated with E. tenella.

Treatment/ PPM	% Mortality (mean)	Weight Gain (grams)	Feed Gain (mean)	Intestinal Lesion Scores (mean)
NNC/ 0	0.0	296.4	1.540	0.00
IC/ 0	0.0	296.4	1.505	2.44
Monensin/ 99	0.0	283.5	1.541	0.56
BMD/ 220	0.0	287.4	1.606	3.56
Monensin +BMD/ 99+220	0.0	307.5	1.452	0.81

NNC = Non-Infected, Non-Medicated Controls
IC = Infected Controls

Table 6 Experiment No. T1S8C8718 Percent Mortality, Weight Gain, Feed/Gain, and Intestinal Lesion Scores of broiler cockerels inoculated with E. acervulina.

Treatment/ PPM	% Mortality (mean)	Weight Gain (grams)	Feed Gain (mean)	Intestinal Lesion Scores (mean)
NNC/ 0	0.0	300.8	1.614	0.00
IC/ 0	0.0	245.8	1.814	3.56
Monensin/ 99	0.0	300.1	1.539	0.06
BMD/ 220	0.0	261.0	1.680	3.38
Monensin +BMD/ 99+220	0.0	304.4	1.555	0.00

NNC = Non-Infected, Non-Medicated Controls
IC = Infected Controls

Table 7 Experiment No. T1S8C8678 Percent Mortality, Weight Gain, Feed/Gain, and Intestinal Lesion Scores of broiler cockerels inoculated with E. tenella, E. acervulina, E. maxima, E. necatrix, E. brunetti and E. mivati/mitis.

Treatment/ PPM	% Mortality (mean)	Weight Gain (grams)	Feed Gain (mean)	Lesion Scores	
				Intestinal (mean)	Cecal (mean)
NNC/ 0	0.0	296.6	1.562	0.00	0.06
IC/ 0	0.0	211.6	1.866	6.75	3.44
Monensin/ 99	0.0	288.8	1.564	0.25	0.00
BMD/ 220	0.0	204.9	2.005	8.00	3.50
Monensin +BMD/ 99+220	0.0	287.1	1.559	0.00	0.25

NNC = Non-Infected, Non-Medicated Controls
IC = Infected Controls

III. TARGET ANIMAL SAFETY

The basic animal safety data for the individual drugs may be found in the original NADA 46-592 for bacitracin methylene disalicylate, NADA 38-878, for monensin and its referenced INADs and MFs, including NADA 49-463. Safety for the combination of bacitracin methylene disalicylate and monensin was demonstrated by the results of the non-interference study conducted by Elanco Products Co. and the results of six floor pen studies described in Section IV.

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

IV. HUMAN SAFETY

It has been established in the original NADAs (46-592 for bacitracin methylene disalicylate and 38-878 for monensin) that these products are not a hazard to human health when used according to approved labeling. Tolerances for residues of bacitracin methylene disalicylate are established at 0.5 ppm negligible residue in uncooked chicken tissue (21 CFR 556.70). Safe concentrations for total residues of monensin in chickens are 1.5 ppm in muscle, 3.0 ppm in skin with adhering fat and 4.5 ppm in liver (21 CFR 556.70). The tissue residue data supporting uses of bacitracin methylene disalicylate and monensin have been presented in the original applications for each.

The drug residue depletion study as presented was conducted by Elanco Products Co. Sexed, day-old Penobscot broiler chicks were used in a 56-day study. Chicks were allotted to pens by grab sample from each compartment of the shipping boxes so that each pen received 50 males or 50 females. The floor pens provided 0.9 square feet per bird.

Each pen was bedded with clean, ground corn cobs. Feed and water was provided ad libitum . Feed was provided to each pen in two hanging feeders. The chicks were fed typical broiler starter and finisher rations. At 56 days the medicated feeds were replaced with non-medicated feeds.

Room temperature was maintained at 70° ± 5° F. Supplemental heat was provided by thermostatically controlled infrared heat lamps. Continuous light was provided. Ventilation was provided by 2 attic and 4 window fans.

At termination and up to 120 hours following treatment, birds of each sex were randomly selected and sacrificed for each drug to be assayed at each sampling interval. Feathers were mechanically removed. Samples of muscle, liver, kidney and skin/fat were collected from each bird, individually bagged and submitted for assay.

The summary of the tissue residue depletion study in Table 8 establishes that each drug in the presence of the other does not exceed its established safe concentration or tolerances. In addition, one drug does not interfere in the other's tissue residue

assay. In this study broiler chickens were fed a combination of bacitracin methylene disalicylate (50 g/ton) and monensin (110 g/ton) for 56 days. Edible tissues as required for each drug or combination of drugs were assayed for presence of drug residue.

Tissue assay non-interference and method validation studies for bacitracin assay were conducted by spiking control chicken tissues with bacitracin zinc standard and monensin and then assaying for bacitracin residue. The results demonstrated no interference by monensin for bacitracin (MO-B-TR-1-85). The recovery of bacitracin from the spiked tissues was 84 percent.

The non-interference of bacitracin on the determination of monensin was examined by the analysis of negative control chicken tissues fortified with the equivalent of 5.0 and 0, and 5.0 and 0.05 ppm bacitracin zinc standard and monensin, respectively (S-AAC-83-03). No interference of bacitracin on the recovery of monensin was observed. Prepared extracts of tissue fortified with the equivalent of 5.0 ppm bacitracin gave no zone of inhibition on the bioautographic plate. The recovery of monensin from tissue fortified with 5.0 ppm bacitracin and 0.05 ppm monensin was about 86 percent (0.043/0.005) which is on the order of the expected experimental variation.

Based upon the established no withdrawal times for monensin and bacitracin methylene disalicylate, no residues were above tolerances in any tissues from these broiler chickens. The data support no withdrawal for the bacitracin methylene disalicylate/monensin combination.

TABLE 8 RESIDUE DEPLETION ASSAY RESULTS

	Day	**Liver**	**Kidney**	**Skin/Fat**	**Muscle**
Monensin					
Estab. Safe Conc.		4.5	-	3.0	1.5
Monensin alone	0	none	none	negligible	negligable
+ Bacitracin-MD	0	none	none	negligible	negligible
Bacitracin-MD					
Establish Tolerance					0.5
Bacitracin-MD alone	0				none
+ Monensin	0				none

Monensin Assay Procedure
No. 5801645 for chicken tissues and eggs. Eli Lilly and Co.,
Greenfield Laboratories, Greenfield, IN.

Antibiotics Residues in Milk, Dairy Products and Animal Tissues:
Methods, Reports, Protocols. National Center for Antibiotic and Insulin Analyses.
Dept. HEW, Washington, DC 20204, Rev. October 1968. Modified Method for Determination
of Bacitracin in Tissues, Test Procedure Code 9A, A. L. Laboratories, Inc.,
Englewood Cliffs, NJ 07632.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the ACT and demonstrate that monensin (90-110 g/ton) plus bacitracin MD (4-50 g/ton) are safe and effective for the claims indicated in Section II of this FOI summary.

This supplemental NADA is regarded as a Category II application under CVM's supplemental approval policy (21 CFR § 514.106 (b)(2)) which did not require reevaluation of safety and efficacy data in the parent NADAs. The supplement provides for a change in the approved dose for one of the ingredients in the combination. Monensin at a level of 110 g/ton is approved for use in combination with bacitracin methylene disalicylate at a level of 4 to 50 g/ton. The supplement provides for the use of monensin at a level of 90 to 110 g/ton.

Residue data show monensin is well within the established safe concentration of 4.5 ppm in liver, 3.0 ppm skin/fat and 1/5 ppm muscle of the chicken at zero withdrawal. Residue data show bacitracin MD is well below tolerance of 0.5 ppm in edible chicken tissues at zero withdrawal.

Non-interference studies demonstrated that monensin alone prevented an outbreak of coccidiosis and in the presence of bacitracin MD when the birds were exposed to the six major species of Eimeria. The data from six well controlled floor pen studies demonstrate the effectiveness of bacitracin (50 g/ton) in the presence of monensin (110 g/ton). These data qualify the application for approval under CVM's policy outlined in the combination drug guidelines revised October 1983. This policy permits the granting of range approval for bacitracin MD (4-50 g/ton) plus monensin (90-110 g/ton) as an aid in the prevention of coccidiosis and for improved feed efficiency in broiler chickens, as shown in Section II of this FOI summary.

Under section 512(c)(2)(F)(iii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, this supplement does not qualify for an exclusivity period. The reports supporting the supplemental approval do not qualify as "new clinical or field investigations" under that section because there is an earlier approval under section 512(b)(1) of the Federal Food, Drug, and Cosmetic Act for the combined use of monensin sodium and bacitracin methylene disalicylate in broiler chickens based on similar investigations.

VI. ATTACHMENTS

Type C Medicated Feed package label
Copies of this label 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.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.