Date of Approval Letter: December 24, 1998

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 116-088

BMD® + COBAN® + 3-NITRO®
(bacitracin methylene disalicylate + monensin + roxarsone)

"...for use in broiler chickens for control of necrotic enteritis, improved feed efficiency and increased rate of weight gain, and for prevention of coccidiosis."

Sponsored by:
Alpharma, Inc

I. GENERAL INFORMATION

NADA Number:	116-088	
Sponsor:	Alpharma, Inc. One Executive Drive Fort Lee, New Jersey 07024	
Established Names and Pharmacologic Category:	bacitracin methylene disalicylate	(antibacterial)
	monensin sodium	(anticoccidial)
	roxarsone	(arsenical)
Trade Names:	BMD® COBAN® 3-NITRO®	
Marketing Status:	over-the-counter	
Effect of the Supplement:	This supplemental application adds the higher use level of bacitracin methylene disalicylate in broiler chicken feed (100 to 200 grams/ton) associated with the necrotic enteritis control claim which was approved under the single ingredient application (NADA 046-592).	

II. INDICATIONS FOR USE

As an aid in the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin methylene disalicylate; as an aid in the prevention of coccidiosis in broiler chickens caused *by Eimeria tenella*, *E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*; and for improved feed efficiency and increased rate of weight gain.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. *Dosage Form:* Type A medicated article to be mixed with feed to produce a Type C medicated feed.

B. *Route of Administration:* Oral, *via* a complete feed. Feed for 5 to 7 days or as long as signs of necrotic enteritis persist.

C. *Recommended Dosage:*

BMD®	100 to 200 g/ton
COBAN®	90 to 110 g/ton
3-NITRO®	22.7 to 34.0 g/ton, or 22.7 to 45.4 g/ton

IV. EFFECTIVENESS

Data supporting the effectiveness of bacitracin methylene disalicylate (100 to 200 g/ton) as an aid in the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin are in the FOI Summary for the approval of this claim under NADA 046-592.

Data supporting the effectiveness of monensin sodium (90 to 110 g/ton) as an aid for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* are in the FOI Summary for the approval of this claim under NADA 038-878.

Data supporting the effectiveness of roxarsone (22.7 to 45.4 g /ton) for increase in rate of weight gain and improved feed efficiency, and improved pigmentation are in the FOI Summaries for the approval of these claims under NADA 007-891.

The combination of these drugs is currently approved, and the additional claim for bacitracin methylene disalicylate does not overlap with those of the other two drugs present in the combination. Based on the data in the approved single ingredient applications, the burden to establish effectiveness of the combination use effected by this supplement has been met.

V. ANIMAL SAFETY

The animal safety for each ingredient drug in this combination, when administered in accordance with its approved uses and conditions of use, is demonstrated in the approved single ingredient application. The safety of these drugs in combination in broiler chickenfeed was also established by the original combination approval.

Additional safety studies were not required for increased BMD® levels (100 to 200 g/ton) in this combination because: (1) the ingredient drugs have been approved singularly, and (2) adequate information has been provided to show that these compounds are compatible in combination when used in broiler chicken feed.

VI. HUMAN SAFETY

A. *Toxicity Studies:* Data in the single ingredient applications demonstrate that the use of these drugs do not constitute a hazard to human health when used in accordance with approved labeling. The information related to Human Safety may be found in NADA 046-592 for bacitracin methylene disalicylate, NADA 038-878 for monensin sodium, and NADA 007-891 for roxarsone.

B. *Tolerance and Safe Concentrations:* Tolerances for bacitracin from bacitracin methylene disalicylate are established at 0.5 ppm (0.02 unit per gram), negligible residue in uncooked edible tissues of chickens and eggs (21 CFR 556.70). A tolerance for a marker residue for monensin in chickens is not needed. The safe concentrations for total residues of monensin in edible tissues of chickens are 1.5 ppm in muscle, 3.0 ppm in skin and adhering fat, and 4.5 ppm in liver (21 CFR.

556.420).

The tolerances for roxarsone (as residue of arsenic in edible tissues of chickens) are established at 0.5 ppm in uncooked muscle, 2.0 ppm in edible byproducts, and 0.5 ppm in eggs (21 CFR 556.60).

C. *Tissue Residue Depletion Studies and Assay Non-Interference:* Data supporting the approved individual uses of bacitracin methylene disalicylate, monensin, and roxarsone, and their respective withdrawal times of 0, 0, and 5 days have been submitted in the respective single ingredient applications.

Non-interference among the active ingredients (bacitracin methylene disalicylate at 50 g/ton, monensin at 110 g/ton, and roxarsone at 45.4 g/ton) when fed in a tissue residue depletion study demonstrated that the withdrawal times for the individual compounds were not altered. Additionally, the lack of interference in the performance of the analytical methods for tissue residues of the individual drugs was demonstrated in the original approval of this combination (NADA 116-088). Residue data submitted to the sponsor's approved application for a bacitracin zinc product (NADA 138-703) support the approval of this supplemental application for the combination use of 100 to 200 g/ton bacitracin methylene disalicylate, 90 to 110 g/ton monensin, and either 22.7 to 34.0 g/ton or 22.7 to 45.4 g/ton roxarsone in broiler chickens.

The 5-day withdrawal period for this combination was confirmed in Study AEF-1-83, conducted by Thomas Kennedy, AEF Research, Waunakee, Wisconsin. An equal number of male and female broiler chickens were fed a diet containing 200 g/ton bacitracin zinc, 110 g/ton monensin, and 45 g/ton roxarsone for 48 days. The data showed that each drug depleted to levels used in the approval of the drugs initially within the same time frames. These results support the proposed 5-day withdrawal period for the combination product. Because the sponsor has demonstrated that the depletion characteristics are very similar, the use of data from a study using the zinc salt rather than the methylene disalicylate salt of bacitracin is acceptable.

D. *Analytical Methods for Residues (Regulatory Methods):*

1. Bacitracin methylene disalicylate: Antibiotic Residue in Milk, Dairy Products and Animal Tissues: Methods, Reports, Protocols. National Center for Antibiotics and Insulin Analysis. Dept. HEW, Washington, DC 20204, Revised October, 1968.

   Modified Method for Determination of Bacitracin in Tissue, Test Procedure Code 9A, A.L. Laboratories Inc., One Executive Drive, P.O. Box 1399, Fort Lee, NJ 07024

2. Monensin: Determination of Monensin in Tissues and Eggs. Method 5801654. Eli Lilly and Company, Box 708, Greenfield, IN 46140.

3. Roxarsone: Arsenic (Total) Residues in Animal Tissues. Spectrophotometric Method. 41.009 In: Official Method of Analysis, 14th Edition, (Sidney William, ed.), AOAC, page 777, Virginia, USA, 1984.

VII. AGENCY CONCLUSIONS

The information submitted in support of this supplemental NADA satisfies the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act, as amended by the Animal Drug Availability Act (ADAA) of 1996, and implementing regulations. The data demonstrate that the combination Type C medicated feed is safe and effective for the use in the broiler chickens approved in this supplemental application.

The human food safety of this combination has been previously demonstrated under the original NADA 116-088 and NADA 138-703 as codified at 21 CFR 558.355(f)(1)(xviii) and 21 CFR 558.355(f)(1)(xix). The increased level of BMD® in this combination does not impose an increased risk of unsafe residues. Data show that tissue residues of bacitracin, monensin, and roxarsone are unchanged from those found in the approvals for the individual drugs and support a 5-day withdrawal period.

Adequate directions for use have been written in labeling and there is reasonable certainty they will be followed in practice by poultry producers. Accordingly, the agency has concluded that this product shall retain over-the-counter marketing status.

In accordance with 21 CFR 514.106(b)(2)(iii) & (v), this supplemental approval is a Category II change which did not require a reevaluation of safety and efficacy data in the parent application.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action qualifies for a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.33(a)(2).

VIII. APPROVED LABELING (attached)

Specimen (Blue Bird) label - Type C medicated feed.