Approval Date:_____

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-146

Nicarbazin (NICARB®) plus Bacitracin zinc (BACIFERM®)

As an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix*, and *E. brunetti*) coccidiosis, and for increased rate of weight gain and improved feed efficiency in broiler chickens.

Sponsored by:

Koffolk, Inc.
P. O. Box 675935
14735 Las Quintas
Rancho Santa Fe, CA 92067

FREEDOM OF INFORMATION SUMMARY

Combined use of NICARB® and BACIFERM® in Broiler Chicken Feeds

I. GENERAL INFORMATION

NADA: 141-146

Sponsor: Koffolk, Inc.
P. O. Box 675935
14735 Las Quintas
Rancho Santa Fe, CA 92067

Generic Names: Nicarbazin
Bacitracin zinc

Trade Names: NICARB®
BACIFERM®

Marketing Status: OTC

II. INDICATIONS FOR USE

As an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina, E. maxima, E. necatrix,* and *E. brunetti*) coccidiosis, and for increased rate of weight gain and improved feed efficiency in broiler chickens.

III. DOSAGE

A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles: nicarbazin as per 21 CFR 558.366, and bacitracin zinc as per 21 CFR 558.78. Nicarbazin is supplied as a Type A medicated article in a concentration of 113.5 grams nicarbazin activity per pound. Bacitracin zinc is supplied as a Type A medicated article in a concentration of 50 grams bacitracin zinc activity per pound.

B. Route of Administration: Oral, via the feed.

C. Recommended Dosage:

Nicarbazin	Nicarbazin is added to broiler chicken feed at a concentration of 113.5 g/ton as an aid in preventing outbreaks of cecal

	(*Eimeria tenella*) and intestinal (*E. acervulina, E. maxima, E. necatrix,* and *E. brunetti*) coccidiosis.
Bacitracin zinc	Bacitracin zinc is added to chicken feed at concentrations from 4 to 50 g/ton for increased rate of weight gain and improved feed efficiency.

WARNING: Discontinue medication four (4) days before marketing the birds for human consumption to allow for elimination of the drug from the edible tissue.

CAUTION: Do not feed to laying hens in production. Do not use as a treatment for outbreaks of coccidiosis. Broiler chickens fed nicarbazin may show reduced heat tolerance when exposed to high temperature and high humidity to which they have not been accustomed and under severe conditions, fatalities may result. An ample supply of drinking water and adequate ventilation will improve the birds' tolerance of heat.

IV. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs 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 Agency finds that the NADA fails to demonstrate that 1) there is substantial evidence to demonstrate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the labeled effectiveness, 2) 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, or 3) where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness (21 USC 512 (d)(4)(D)).

Nicarbazin, as provided by Koffolk, Inc., has previously been separately approved for use in chicken feed as an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina, E. maxima, E. necatrix,* and *E. brunetti*) coccidiosis (21 CFR 558.366 (c)). Bacitracin zinc, as provided by Roche Vitamins Inc., has previously been separately approved for use in chicken feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.78 (d)(1)(i)). Effectiveness for each drug, nicarbazin and bacitracin zinc, when

administered alone in accordance with its approved uses and conditions of use, is demonstrated in Koffolk, Inc.'s approved NADA 9-476, and in Roche Vitamins Inc.'s NADA 46-920, to which Koffolk Inc. has a right of reference, respectively. Because nicarbazin and bacitracin zinc each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that nicarbazin plus bacitracin zinc provide appropriate concurrent use for the intended target population. The use of nicarbazin plus bacitracin zinc provides appropriate concurrent use because these drugs are intended to treat different conditions (nicarbazin, coccidiosis; bacitracin zinc, performance) likely to occur simultaneously with sufficient frequency in chickens. There is no more than one nontopical antibacterial (bacitracin zinc) contained in this combination animal drug intended for use in Type C medicated feed. Nicarbazin is not considered to be an antibacterial animal drug for use in chickens for the purposes of §512 (d)(4) of the FFDCA, because nicarbazin is approved only for prevention of a protozoal disease in chickens.

V. ANIMAL SAFETY

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients 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 target animal safety grounds unless there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination or a scientific issue is raised by target animal observations contained in studies submitted to the NADA for the combination and FDA finds that the application fails to establish that such combination active ingredient or animal drug is safe for the target animal.

Nicarbazin, as provided by Koffolk, Inc., has previously been separately approved for use in chicken feed as an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina, E. maxima, E. necatrix,* and *E. brunetti*) coccidiosis (21 CFR 558.366 (c)). Bacitracin zinc, as provided by Roche Vitamins Inc., has previously been separately approved for use in chicken feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.78 (d)(1)(i)). Target animal safety for each drug, nicarbazin and bacitracin zinc, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Koffolk, Inc. approved NADA 9-476, and in Roche Vitamins Inc.'s approved NADA 46-920, to which Koffolk, Inc. has a right of reference to, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of nicarbazin or bacitracin zinc 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 study (ies) is (are) required for approval of NADA 141-146.

VI. HUMAN SAFETY

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination 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 human safety grounds unless one or more of the active ingredients or animal drugs used in the combination at the longest withdrawal for the respective active ingredients or animal drugs in the combination exceeds the established tolerance, or one or more active ingredients or animal drugs in the combination interferes with the method of analysis for another active ingredient or drug in the combination.

A. Toxicity

Safety for this combination product has been established by data in NADA 98-378 for the combination use of bacitracin methylene disalicylate and nicarbazin, NADA 9-476 for nicarbazin, and NADA 46-920 for bacitracin zinc.

B. Tolerances

A tolerance for residues of bacitracin zinc or bacitracin methylene disalicylate has been previously established at 0.5 ppm (0.02 unit per gram) in uncooked edible tissues of chicken (21 CFR 556.70). A tolerance of 4 ppm has been previously established for residues of nicarbazin in uncooked chicken muscle, liver, skin, and kidney (21 CFR 556.445).

C. Residue Data

The available residue data support the assignment of a four day withdrawal period for chickens fed the combination of bacitracin zinc (50 g/ton) and nicarbazin (113.5 g/ton).

D. Regulatory Methods

A microbiological method entitled, "Modified Microbiological Method for Determination of Bacitracin in Tissues", is used to assay tissues for bacitracin residues. The determinative assay for measuring residues in liver from chickens treated with nicarbazin is by high performance liquid chromatography (HPLC) with UV detection. The regulatory method is provided in the AOAC reference: Lewis, J.L., Macy, T.D., & Gartiez, D.A. (1989) *J. Assoc. Off. Anal. Chem.* 72, 577-581. These methods are on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, MD 20855.

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of § 512 of the FFDCA and demonstrate that nicarbazin (113.5 g/ton) plus bacitracin zinc (4 to 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)(vi), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADAs. 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 tolerance for residues of bacitracin zinc or bacitracin methylene disalicylate has been previously established at 0.5 ppm (0.02 unit per gram) in uncooked edible tissues of chicken (21 CFR 556.70). A tolerance of 4 ppm has been previously established for residues of nicarbazin in uncooked chicken muscle, liver, skin, and kidney (21 CFR 556.445). The available residue data support the assignment of a four day withdrawal period for broiler chickens fed the combination of bacitracin zinc (50 g/ton) and nicarbazin (113.5 g/ton).

Attached labeling: Type C medicated feed (Blue Bird).