Approval Date:_____

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 140-339

Nicarbazin (NICARB®) plus Bambermycins (FLAVOMYCIN®)

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:

Hoechst Roussel Vet
30 Independence Blvd.
P.O. Box 4915
Warren, New Jersey 07059

FREEDOM OF INFORMATION SUMMARY

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

I. GENERAL INFORMATION

NADA: 140-339

Sponsor: Hoechst Roussel Vet
30 Independence Blvd.
P.O. Box 4915
Warren, NJ 07059

Generic Names: Nicarbazin
Bambermycins

Trade Names: NICARB®
FLAVOMYCIN®

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 (c), and bambermycins as per 21 CFR 558.95 (d)(1)(i). Nicarbazin is supplied as a Type A medicated article in a single concentration of 113.5 grams nicarbazin activity per pound. Bambermycins is supplied as a Type A medicated article in concentrations of 2, 4, or 10 grams bambermycins activity per pound.

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

C. Recommended Dosage:

Nicarbazin	Nicarbazin is added to 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.
Bambermycins	Bambermycins is added to broiler chicken feed at concentrations from 1 to 2 g/ton for increased rate of weight gain and improved feed efficiency.

WARNING: Withdraw four (4) days prior to slaughter.

CAUTION: For broiler chickens only. Do not feed to laying hens in production. Broiler chickens fed feed medicated with nicarbazin may show reduced heat tolerance when exposed to high temperature and high ambient 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 360b (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)). Bambermycins, as provided by Hoechst Roussel Vet, has previously been separately approved for use in broiler chicken feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.95 (d)(1)(i)). Effectiveness for each drug, nicarbazin and bambermycins, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Koffolk, Inc.'s approved NADA 9-476, to which Hoechst Roussel Vet has a right of reference, and in Hoechst Roussel Vet's approved NADA 44-759, respectively. Because nicarbazin and bambermycins 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 bambermycins provide appropriate concurrent use for the intended target population. The use of nicarbazin plus bambermycins provides appropriate concurrent use because these drugs are intended to treat different conditions (nicarbazin, coccidiosis; bambermycins, performance)

likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial (bambermycins) 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 broiler chickens for the purposes of §512 (d)(4) of the FFDCA, because nicarbazin is approved only for prevention of a protozoal disease in broiler 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)). Bambermycins, as provided by Hoechst Roussel Vet, has previously been separately approved for use in broiler chicken feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.95 (d)(1)(i)). Target animal safety for each drug, nicarbazin and bambermycins, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Koffolk, Inc. approved NADA 9-476, to which Hoechst Roussel Vet has a right of reference, and in Hoechst Roussel Vet's approved NADA 44-759, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of nicarbazin or bambermycins 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 is required for approval of NADA 140-339.

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. Tolerances

Data establishing the safety of nicarbazin and bambermycins have been submitted to NADA 9-476 and NADA 44-759 respectively. A tolerance for nicarbazin in chicken tissues has been established at 4.0 ppm (21 CFR 556.445). In accordance with 21 CFR 556.1(a)(4), a tolerance is not required for the use of bambermycins in broiler chicken feed.

B. Tissue Residue and Assay Noninterference Data

The residue data supporting the approved individual uses of nicarbazin and bambermycins and their withdrawal times of 4 and 0 days, respectively, have been submitted in their original applications. The data in Table I is a summary of the tissue residue study in which it was demonstrated that each drug (in the presence of the other drug) does not exceed its established safe concentration at 4 days for nicarbazin and 0 day for bambermycins. The data demonstrate that neither drug interfere in the other drugs' tissue residue assay. The data summarized in Table I are from a study in which 100 broilers were fed from one day of age to 49 days of age the combination of bambermycins at 20 g/t, nicarbazin at 113 g/t and roxarsone at 0.005%. This tissue residue study was conducted by:

Drs. P. Griminger and H. Fisher
Department of Nutrition
Cook College / Rutgers, The State University
New Brunswick, NJ 08903

A noninterference study for nicarbazin was conducted by spiking control tissue samples with 2.0 & 4.0 ppm of nicarbazin plus 0.1 ppm bambermycins and then assaying for nicarbazin content. The results demonstrated no interference of bambermycins on the tissue assay for nicarbazin.

A noninterference study for bambermycins was conducted by spiking control tissue samples with 0.05 ppm bambermycins plus 25.0 ppm nicarbazin and then assaying for bambermycins content. The results demonstrated no interference of nicarbazin on the tissue assay for bambermycins.

These data support a 4-day withdrawal for the nicarbazin/bambermycins combination.

Table 1. Residue depletion study assay results (PPM).

		Tissue [1]		
Drug	Withdrawal Day	Liver	Skin/Fat	Muscle
Bambermycins	0	ND[2]	ND	ND
Nicarbazin[3]	0	32.9 (6.87)	6.2 (1.55)	4.7 (1.86)
"	3	3.3 (1.26)	0.5 (0.14)	0.2 (0.11)
"	4	1.4 (0.77)	0.3 (0.12)	0.1 (0.00)
"	5	1.1 (0.47)	0.3 (0.13)	0.1 (0.00)

1. Average of 6 to 8 birds. Standard Deviation in parentheses.
2. ND = None Detected – Method sensitivity: 0.0125 ppm.
3. Method sensitivity: 1.0 ppm.

C. Regulatory Methods for Residues

A regulatory tissue method for bambermycins is not required because of the establishment of a zero (0) withdrawal period in broiler chickens (21 CFR 558.95).

The regulatory tissue assay method titled "Determination of Nicarbazin in Chicken Tissues by High-Performance Liquid Chromatography" is on file at the Food and Drug Administration, Freedom of Information Publication Room, 5600 Fishers Lane, Rockville, MD 20857.

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the FFDCA and demonstrate that nicarbazin (113.5 g/ton) plus bambermycins (1 to 2 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.

Residue data show that residues of nicarbazin are within the established tolerance of 4 ppm in uncooked edible tissues of chickens. Residue data supports a 4 (four) day withdrawal for this combination medicated broiler chicken feed.

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