Approval Date: July 3, 2000

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-158

Diclazuril (CLINACOX™) plus Bambermycins (FLAVOMYCIN®)

For the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mitis (mivati)* and *E. maxima.* Because diclazuril is effective against *E. maxima* later in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Diclazuril was shown in studies to reduce lesion scores and improve performance and health of birds challenged with *E. maxima.* For increased rate of weight gain and improved feed efficiency in broiler chickens.

Sponsored by:

Schering-Plough Animal Health Corporation
1095 Morris Avenue
P. O. Box 3182
Union, New Jersey 07083

FREEDOM OF INFORMATION SUMMARY

Combined use of CLINACOX™ and FLAVOMYCIN® in Broiler Chicken Feeds

I. GENERAL INFORMATION

NADA: 141-158

Sponsor: Schering-Plough Animal Health Corporation
1095 Morris Avenue
P. O. Box 3182
Union, New Jersey 07083

Generic Names: Diclazuril
Bambermycins

Trade Names: CLINACOX™
FLAVOMYCIN®

Marketing Status: OTC

II. INDICATIONS FOR USE

For the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mitis (mivati),* and *E. maxima.* Because diclazuril is effective against *E. maxima* later in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Diclazuril was shown in studies to reduce lesion scores and improve performance and health of birds challenged with *E. maxima*. 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: diclazuril as per 21 CFR 558.198, and bambermycins as per 21 CFR 558.95. Diclazuril is supplied as a Type A medicated article in a concentration of 0.91 grams diclazuril activity per pound. Bambermycins is supplied as a Type A medicated article in concentrations of 2, 4, or 10 grams of bambermycins activity per pound.

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

C. Recommended Dosage:

Diclazuril	Diclazuril is added to broiler chicken feed at a concentration of 0.91 g/ton for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mitis (mivati),* and *E. maxima.* Because diclazuril is effective against *E. maxima* later in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Diclazuril was shown in studies to reduce lesion scores and improve performance and health of birds challenged with *E. maxima*.
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.

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)).

Diclazuril, as provided by Schering-Plough Animal Health, has previously been separately approved for use in feed for chickens for the prevention of coccidiosis caused by

Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mitis (mivati), and *E. maxima* (21 CFR 558.198(d)(2)). Because diclazuril is effective against *E. maxima* later in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Diclazuril was shown in studies to reduce lesion scores and improve performance and health of birds challenged with *E. maxima*. Bambermycins, as provided by Hoescht-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, diclazuril and bambermycins, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Schering-Plough Animal Health's approved NADA 140-951, and in Hoescht-Roussel Vet's previously approved NADA 44-759, to which Schering-Plough Animal Health has a right of reference. Because diclazuril 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 diclazuril plus bambermycins provide appropriate concurrent use for the intended target population. The use of diclazuril plus bambermycins provides appropriate concurrent use because these drugs are intended to treat different conditions (diclazuril, 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. Diclazuril 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 diclazuril 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.

Diclazuril, as provided by Schering-Plough Animal Health, has previously been separately approved for use in broiler chickens for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mitis (mivati),* and *E. maxima* (21 CFR 558.198(d)(2)). Because diclazuril is effective against *E. maxima* later in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Diclazuril was shown in studies to reduce lesion scores and improve performance and health of birds challenged with *E. maxima* (21 CFR 558.198(d)(2)). Bambermycins, as provided by Hoescht-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, diclazuril and bambermycins, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Schering-Plough Animal Health's approved NADA 140-951, and in Hoescht-Roussel Vet's approved NADA 44-759, to which Schering-Plough Animal Health has a right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of diclazuril 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 studies are required for approval of NADA 141-158.

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 Studies

Safety for this combination product has been established by data in NADA 44-759 for bambermycins and NADA 140-951 for diclazuril. An ADI for diclazuril previously has been established at 0.025 mg/kg body weight/day. An ADI for bambermycins is not established at this time.

B. Tolerances

Tolerances for parent diclazuril previously have been established as follows: 0.5 ppm in muscle, 1 ppm in skin/fat, and 3 ppm in liver (21 CFR 556.175). Tolerances for bambermycins are not established at this time.

C. Residue Non-interference Study

Residue data supporting the approved individual uses of diclazuril and bambermycins, each having zero day withdrawal times, were submitted in their respective original applications (see Part A, above). The in–life portion of the following study (Study No. 98506) was conducted at Schering-Plough Animal Health Center, Terre Haute, IN with assays conducted at Xenos Laboratories, Inc., Ottawa, Canada and Springborn Laboratories, Inc., Wareham, Massachusetts

to establish that each drug in the presence of the other does not adversely impact the depletion of each drug and that the presence of the drugs in the same broiler chicken tissue does not interfere with the assay of either drug.

A total of 95 newly hatched broiler chickens (45 males, 50 females) were divided into two treatment groups. Group 1 birds received an unmedicated basal diet. Group two birds received a basal diet containing 0.9 g/ton diclazuril and 2 g/ton bambermycins. Broiler chickens were fed from one day of age until day 42 and were sacrificed after a 6-hour withdrawal period. Diclazuril was measured in liver by a sponsor-validated GC/ECD method. Bambermycins were measured in liver by a microbiological method.

Mean Diclazuril Residues and Mean Bambermycins Residues in Liver Collected from Broiler Chickens Treated with Medicated Feed Containing 0.9 g/ton Diclazuril and 2 g/ton Bambermycins		
Withdrawal Time in Hours	Diclazuril (ppm)	Bambermycins (ppm)
0	0.322 $\pm$ 0.030 ppm	< 0.2 ppm (detection limit)

Diclazuril residues were well below the liver tolerance and bambermycins residues were not detected at zero withdrawal, the established withdrawal periods for both drugs, thereby indicating an absence of interference.

D. Regulatory Methods

A sponsor-validated GC-ECD method for diclazuril in edible tissues of broiler chickens is on file with the Center for Veterinary Medicine. The analytical method for the determination of bambermycins in edible tissues of broiler chickens is on file at the Center for Veterinary Medicine, Food and Drug Administration, 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 diclazuril (0.91 g/ton) plus bambermycins (1 to 2 g/ton) are safe and effective for the claims indicated in Section II of this FOI summary. A preslaughter withdrawal period of zero days is required for the use of the combination of diclazuril and bambermycins in broiler chickens.

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.

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

Net weight lb (kg) on bag or bulk

Diclazuril/Bambermycins Broiler Chicken Ration
Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mitis (mivati),* and *E. maxima.* Because diclazuril is effective against *E. maxima* later in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Diclazuril was shown in studies to reduce lesion scores and improve performance and health of birds challenged with *E. maxima*. For increased rate of weight gain and improved feed efficiency in broiler chickens.

ACTIVE DRUG INGREDIENT

Diclazuril……..... 0.91 g/ton (1 ppm)
Bambermycins…….…….....…….... 1 to 2 g/ton

GUARANTEED ANALYSIS

Crude Protein, not less than……..……_____%
Lysine, not less than…….....……_____%
Methionine, not less than……...……_____%
Crude Fat, not less than……..……...……_____%
Crude Fiber, not more than…….……...……_____%
Calcium, not less than…….....……_____%
Calcium, not more than……..…….....….._____%
Phosphorus, not less than……..……_____%
Salt[1], not less than…….....…._____%
Salt[1], not more than…….....……_____%
Sodium[2], not less than…….....……_____%
Sodium[2], not more than…….....……_____%

[1]If added.
[2]Shall be guaranteed only when total sodium exceeds that furnished by the maximum salt guarantee.

INGREDIENTS

Each ingredient must be named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

DIRECTIONS FOR USE

Feed continuously as the sole ration.

WARNING: Do not use in hens producing eggs for human food.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345