HFA-305
Documents Management Branch

Approval Date: 1 4 2001

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-190

Diclazuril (CLINACOX™) plus Bacitracin Methylene Disalicylate (BMD®) plus Roxarsone (3-Nitro®)

1.) For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, 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.* As an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin. For increased rate of weight gain, improved feed efficiency and improved pigmentation in broiler chickens.

2) For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, 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.* As an aid in the control of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin. For increased rate of weight gain, improved feed efficiency and improved pigmentation in broiler chickens.

Sponsored by:

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

FOIS-1

FREEDOM OF INFORMATION SUMMARY

Combined use of CLINACOX™, BMD® and 3-NITRO® in Broiler Chicken Feeds

I. GENERAL INFORMATION

NADA: 141-190

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

Generic Names: Diclazuril
Bacitracin methylene disalicylate
Roxarsone

Trade Names: CLINACOX™
BMD®
3-NITRO®

Marketing Status: OTC

II. INDICATIONS FOR USE

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

III. DOSAGE

A. Dosage form: This original NADA provides for the combined use of these three Type A medicated articles as per 21 CFR 558.198 for diclazuril, 21 CFR 558.76 for bacitracin methylene disalicylate and 21 CFR 558.530 for roxarsone. Diclazuril is supplied as a Type A medicated article in a single concentration of 0.91 grams diclazuril activity per pound. Bacitracin methylene disalicylate is supplied as a Type A medicated article in concentrations of 10, 25, 30, 40, 50, 60, or 75 grams of bacitracin activity per pound. Roxarsone is supplied as a Type A medicated article in concentrations of 45.4, 90, 227, or 360 grams of roxarsone 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 tenella, E. necatrix, 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.*
Bacitracin methylene disalicylate	Bacitracin methylene disalicylate is added to broiler chicken feed at a concentration of 50 g/ton as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin or at 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.
Roxarsone	Roxarsone is added to broiler chicken feed at a concentration of 22.7 to 45.4 g/ton for increased rate of weight gain, improved feed efficiency and improved pigmentation.

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 tenella, E. necatrix, 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*. Bacitracin methylene disalicylate as provided by Alpharma, has previously been separately approved as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin (21 CFR 558.76 (d)(1)(vi)) as well as an aid in the control of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin (21 CFR 558.76 (d)(1)(ix)). Roxarsone as provided by Alpharma, has previously been separately approved for increased rate of weight gain, improved feed efficiency and improved pigmentation (21 CFR 558.530 (d)(1)(ii)). Effectiveness of each drug, diclazuril, bacitracin methylene disalicylate and roxarsone 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 for diclazuril, and in Alpharma's approved NADA 046-592 for bacitracin methylene disalicylate and Alpharma's NADA 007-891 for roxarsone to which Schering-Plough Animal Health has right of reference, respectively.

Because diclazuril and bacitracin methylene disalicylate and roxarsone 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 bacitracin methylene disalicylate and roxarsone provide appropriate concurrent use for the intended target population. The use of diclazuril plus bacitracin methylene disalicylate and roxarsone provides appropriate concurrent use because these drugs are intended to treat different conditions (diclazuril - coccidiosis; bacitracin methylene disalicylate - necrotic enteritis; and roxarsone - weight gain, feed efficiency and pigmentation) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial (BMD) 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 tenella, E. necatrix, 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)). Bacitracin methylene disalicylate as provided by Alpharma, has previously been separately approved as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin (21 CFR 558.76 (d)(1)(vi)) as well as an aid in the control of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin (21 CFR 558.76 (d)(1)(ix)). Roxarsone as provided by Alpharma, has previously been separately approved for increased rate of weight gain, improved feed efficiency and improved pigmentation (21 CFR 558.530 (d)(1)(ii)). Target animal safety for each drug, diclazuril, bacitracin methylene disalicylate and roxarsone, when administered alone in accordance with its approved uses and conditions of use was demonstrated in Schering-Plough Animal Health's approved NADA 140-951, and in Alpharma's approved NADAs 046-952 and 007-891 to which Schering-Plough has the right of reference, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of diclazuril, bacitracin methylene disalicylate and roxarsone 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 141-190.

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 140-951 for diclazuril, in NADA 046-592 for bacitracin methylene disalicylate and in NADA 007-891 for roxarsone. An ADI for diclazuril previously has been established at 0.025 mg/kg body weight/day. Allowable daily intake values for bacitracin methylene disalicylate and roxarsone are not established at this time.

B. Tolerances

Tolerances for parent diclazuril have been established as follows: 0.5 ppm in muscle, 1 ppm in skin/fat and 3 ppm in liver (21 CFR 556.185(b)(1)). The tolerance for residues of bacitracin methylene disalicylate is 0.5 ppm in uncooked edible tissues, milk and eggs (21 CFR 556.70). The tolerance for total residues of combined arsenic in chickens are established at 0.5 ppm in uncooked muscle tissue and eggs and 2 ppm in uncooked edible by-products (21 CFR 556.60(a)).

C. Residue Non-interference Study

Schering-Plough Research Institute, Lafayette, NJ conducted Study No. 99450 (Study Director: Chris Wrzesinski) to show that diclazuril, bacitracin methylene disalicylate and roxarsone would not adversely impact the depletion of each other when the three drugs were used at their maximum intended levels. A total of 312 newly hatched chickens (154 male and 158 female) were divided into 2 treatment groups. Birds of Group 1 received a nonmedicated basal diet. Birds of Group 2 received a basal diet containing 0.91g diclazuril, 200 g of BMD and 45.4 g of roxarsone per ton of feed from 1 day until 37 days of age at which point they were switched over to nonmedicated feed. Randomly selected chickens were euthanized at 0, 3 and 5 days after the change over to nonmedicated feed. At each of the first 2 time points, the chickens to be euthanized were transferred to holding pens without access to feed and water 6 hours (practical zero withdrawal) prior to euthanization. For the last time point access to feed and water was removed 6 hours (practical zero withdrawal) prior to euthanization. Chickens were euthanized by CO_2 asphyxiation and exsanguinated.

Tissue Residue Study 99450 Assay Results
(Liver Samples)

Group	**Gender**	**Diclazuril**	**Arsenic**		
		ppb	Day-0	Day-3	Day-5
			Withdrawal	**Withdrawal**	**Withdrawal**
			ppm	ppm	ppm
Control	Male	None detected[a]	0		
	Female	None detected	0		
Medicated	Male	234 ± 52	1.50 ± 0.31	0.68 ± 0.20	0.40 ± 0.09
	Female	282 ± 59	1.59 ± 0.11	0.58 ± 0.20	0.43 ± 0.08

[a]One of the 6 control liver samples assayed 12.8 ppb which is slightly above the method LOQ of 10 ppb.

The composited livers were homogenized and portions of each composite liver sample were then shipped to analytical laboratories for determination of diclazuril and roxarsone residue levels (days 0, 3 and 5).

Liver concentrations of diclazuril in chickens in the medicated group were well below the applicable tolerance at zero withdrawal (i.e., 234 ppb and 282 ppb vs. 3 ppm). Concentrations

of arsenic in liver at day 5 of withdrawal, the withdrawal period for roxarsone, were also well below the tolerance of 2 ppm. Tissue residue concentrations of BMD were not determined as Alpharma has a waiver for this requirement under NADA 46-592. The results of this study demonstrate that residues of the drugs will be below their respective tolerances at the label withdrawal period of 5 days.

Assay noninterference was demonstrated by analyzing control liver samples that had been fortified with 600 ppb diclazuril or 600 ppb diclazuril plus 2000 ppb roxarsone with the method for diclazuril. Recovery from the sample containing diclazuril only was 112%, while that from the sample containing the two drugs was 123%. Because of the waiver mentioned above under NADA 46-592, similar assay noninterference work for BMD is not required. Also, because the arsenic method involves ashing, assay noninterference testing for roxarsone is unnecessary.

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 bacitracin methylene disalicylate and roxarsone in edible tissues 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 bacitracin methylene disalicylate (50 or 100 to 200 g/ton) plus roxarsone (22.7 to 45.4 g/ton) are safe and effective for the claims indicated in Section II of this FOI summary. A preslaughter withdrawal period of five days is required for the use of the combination of diclazuril plus bacitracin methylene disalicylate plus roxarsone 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).

Diclazuril/Bacitracin methylene disalicylate/Roxarsone
Broiler Chicken Ration #1
Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, 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.* As an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin. For increased rate of weight gain and improved feed efficiency and improved pigmentation in broiler chickens.

ACTIVE DRUG INGREDIENTS

Diclazuril..... 0.91 g/ton (1 ppm)
Bacitracin methylene disalicylate..... 50 g/ton
Roxarsone..... 22.7 to 45.4 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..... _____%

[1]If added.

INGREDIENTS

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

FEEDING DIRECTIONS

Feed continuously as the sole ration.

CAUTION: Use as sole source of organic arsenic; drug overdose or lack of water may result in leg weakness; feed continuously throughout growing period.

WARNING: Not for use in hens producing eggs for consumption. Withdraw 5 days before slaughter.

MANUFACTURED BY

BLUE BIRD FEED MILL
Robin, Indiana 46813

NET WT 50 LBS (22.67 kg)

Diclazuril/Bacitracin methylene disalicylate/Roxarsone
Broiler Chicken Ration #2
Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, 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.* As an aid in the control of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin. For increased rate of weight gain and improved feed efficiency and improved pigmentation in broiler chickens.

ACTIVE DRUG INGREDIENTS

Diclazuril..... 0.91 g/ton (1 ppm)
Bacitracin methylene disalicylate..... 100 to 200 g/ton
Roxarsone..... 22.7 to 45.4 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..... _____%

[1]If added.

INGREDIENTS

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

FEEDING DIRECTIONS

Feed continuously as the sole ration.

CAUTION: Use as sole source of organic arsenic; drug overdose or lack of water may result in leg weakness; feed continuously throughout growing period. Start at first clinical signs of disease, vary dosage based on severity of infection, administer continuously for 5 to 7 days or as long as clinical signs persist, then reduce medication to prevention levels (50 g/t).

WARNING: Not for use in hens producing eggs for consumption. Withdraw 5 days before slaughter.

MANUFACTURED BY

BLUE BIRD FEED MILL
Robin, Indiana 46813

NET WT 50 LBS (22.67 kg)