Approval Date: APR 2, 2002

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-194

Diclazuril (CLINACOX™) plus Bacitracin Methylene Disalicylate (BMD®)

For the prevention of coccidiosis caused by Eimeria adenoeides, E. gallopavonis, and E. meleagrimitis and for increased rate of weight gain and improved feed efficiency in growing turkeys.

Sponsored by:

Schering-Plough Animal Health Corporation
1095 Morris Avenue
Union, New Jersey 07083

FREEDOM OF INFORMATION SUMMARY

Combined use of CLINACOX™ and BMD® in Growing Turkey Feeds

I. GENERAL INFORMATION

NADA: 141-194

Sponsor: Schering-Plough Animal Health Corporation
1095 Morris Avenue
Union, New Jersey 07083

Generic Names: Diclazuril
Bacitracin methylene disalicylate

Trade Names: CLINACOX™
BMD®

Marketing Status: OTC

II. INDICATIONS FOR USE

Growing Turkeys: For the prevention of coccidiosis caused *by Eimeria adenoeides, E. gallopavonis*, and *E. meleagrimitis*, and for increased rate of weight gain and improved feed efficiency in growing turkeys.

III. DOSAGE

A. Dosage form: This original NADA provides for the combined use of these two Type A medicated articles as per 21 CFR 558.198 for diclazuril and 21 CFR 558.76 for bacitracin methylene disalicylate. Diclazuril is supplied as a Type A medicated article in a single concentration of 0.2% diclazuril. 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 methylene disalicylate activity per pound.

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

C. Recommended Dosage:

Diclazuril	Diclazuril is added to growing turkey feed at a concentration of 0.91 g/ton (1 ppm) for the prevention of coccidiosis caused by *Eimeria adenoeides, E. gallopavonis*, and *E. meleagrimitis.*

Bacitracin methylene disalicylate	Bacitracin methylene disalicylate is added to growing turkey feed at a concentration of 4 to 50 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 (FFDCA §512 (d)(4)(D)).

Diclazuril, as provided by Schering-Plough Animal Health, has previously been separately approved for use in growing turkey feed for the prevention of coccidiosis caused by *Eimeria adenoeides, E. gallopavonis*, and *E. meleagrimitis* (21 CFR 558.198(d)(2)).

Bacitracin methylene disalicylate as provided by Alpharma Inc. has previously been separately approved for increased rate of weight gain and improved feed efficiency in growing turkeys (21 CFR 558.76(d)(1)(i)). Effectiveness of each drug, diclazuril and bacitracin methylene disalicylate, 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 to which Schering-Plough Animal Health has right of reference.

Because diclazuril and bacitracin methylene disalicylate 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 provide appropriate concurrent use for the intended target population. The use of diclazuril plus bacitracin methylene disalicylate provides appropriate concurrent use because these drugs are intended to treat different conditions (diclazuril - coccidiosis; bacitracin methylene disalicylate - weight gain and feed efficiency) likely to occur simultaneously with sufficient frequency in growing turkeys. There is no more than one nontopical antibacterial (bacitracin methylene disalicylate) 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 growing turkeys for the purposes of §512 (d)(4) of the FFDCA, because diclazuril is approved only for prevention of a protozoal disease in growing turkeys.

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 growing turkeys for the prevention of coccidiosis caused by *Eimeria adenoeides, E. gallopavonis*, and *E. meleagrimitis* (21 CFR 558.198(d)(2)). Bacitracin methylene disalicylate as provided by Alpharma Inc. has previously been separately approved for increased rate of weight gain and improved feed efficiency in growing turkeys (21 CFR 558.76(d)(1)(i)). Target animal safety for each drug, diclazuril and bacitracin methylene disalicylate, 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 NADA 046-592 to which Schering-Plough has the right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of diclazuril and bacitracin methylene disalicylate 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 141-194.

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. The human food safety for the approved products has been established by data submitted to NADAs 140-951 (diclazuril) and 046-592 (bacitracin methylene disalicylate).

A. Toxicity Studies

Safety for this combination product has been established by data in NADA 140-951 for diclazuril and in NADA 046-592 for bacitracin methylene disalicylate. An ADI for diclazuril previously has been established at 0.025 mg/kg body weight/day. An ADI for bacitracin methylene disalicylate previously has been established at 0.05 mg/kg body weight/day.

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)(2)). The tolerance for residues of bacitracin methylene disalicylate is 0.5 ppm in uncooked edible tissues, milk and eggs (21 CFR 556.70).

C. Residue Non-interference Study

Residue data supporting the approved individual uses of diclazuril and bacitracin methylene disalicylate, each having zero withdrawal times, were submitted in their respective original applications (see Part A, above). The in-life portion of the following study (Study No. 98175) was conducted at Health Management Services, Tulare, California 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 turkey tissue does not interfere with the assay of either drug.

Schering-Plough Research Institute, Lafayette, New Jersey conducted Study No. 98176 (Study Directors: Chris Wrzesinski) to show that bacitracin methylene disalicylate would not adversely impact the depletion of diclazuril when both drugs were used at their maximum intended levels. A total of 93 newly hatched broiler turkeys (42 males and 51 females) was used in this study. The birds were assigned to three pens of each gender (14 males or 17 females), 6 pens total. One pen of each gender received an unmedicated basal diet, while the other two pens of each gender received a diet containing 0.9 g/ton (1ppm) diclazuril and 200 g/ton bacitracin methylene disalicylate. Turkeys were fed from day 1 to day 84, when they were sacrificed 6 hours (practical zero withdrawal) after removal of feed.

Livers from 9 birds, randomly pre-selected, from each pen were pooled in groups of three, homogenized, and assayed for the presence of diclazuril. The composite liver samples were shipped to Xenos Laboratories for measurement of diclazuril by a GC-ECD assay method. The results of the study are summarized in the table below.

TISSUE RESIDUE STUDY 98176 ASSAY RESULTS

Group	Gender	Diclazuril (ppm)
Controls	M	None detected[a]
	F	None detected[a]
Medicated	M	0.309[b] ± 0.023
	F	0.275 [b] ± 0.024

[a]Mean of 3 pooled liver samples; each pooled sample represents 3 birds; limit of quantification = 0.010 ppm.

[b]Mean of 6 pooled liver samples; each pooled sample represents 3 birds.

Liver diclazuril levels were approximately one order of magnitude below the applicable tolerance and were consistent with concentrations observed in livers of turkeys treated with diclazuril only. Therefore, bacitracin methylene disalicylate does not affect tissue residues of diclazuril at practical zero withdrawal when used in combination with diclazuril. It was concluded that concurrent treatment of turkeys with diclazuril and bacitracin methylene disalicylate does not affect the withdrawal time of diclazuril in the target tissue.

Substantial scientific evidence under NADA 46-952 demonstrates that the likelihood is extremely remote that other drugs used in combination of bacitracin methylene disalicylate would alter bacitracin residues in animal tissues. Furthermore, data collected over many years have shown that tissue residues of bacitracin methylene disalicylate are not detected, whether the drug is used alone or in combination. Consequently, studies to evaluate tissue residues and demonstrate assay noninterference for Alpharma's bacitracin methylene disalicylate are no longer required when each drug is included at appropriate levels. It can be concluded therefore that studies to evaluate the interference of bacitracin methylene disalicylate on the method(s) for the other components(s) of the combination are unnecessary.

D. Analytical Methods for Residues (Regulatory Methods)

A sponsor-validated GC/ECD method for diclazuril in edible tissues of turkeys is on file with the Center for Veterinary Medicine. The analytical method for the determination of bacitracin methylene disalicylate in edible tissues of turkeys is 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 diclazuril (0.91 g/ton, 1 ppm) plus bacitracin methylene disalicylate (4 to 50 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 plus bacitracin methylene disalicylate in growing turkeys.

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 effectiveness 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
Growing Turkey Ration
Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria adenoeides, E. gallopavonis*, and *E. meleagrimitis*, and for increased rate of weight gain and improved feed efficiency in growing turkeys.

ACTIVE DRUG INGREDIENTS

Diclazuril……..... 0.91 g/ton (1 ppm)
Bacitracin Methylene Disalicylate…….....…... 4 to 50 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.

(OVER)

FEEDING DIRECTIONS

Feed continuously as the sole ration.

CAUTION: Do not feed to breeding turkeys.

WARNING: Not for use in hens producing eggs for human consumption.

MANUFACTURED BY

BLUE BIRD FEED MILL
Robin, Indiana 46813

NET WEIGHT 50 LB (22.67 kg)