

Approval Date: January 13, 2000

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-153

**Diclazuril (CLINACOX™) plus
Bacitracin methylene disalicylate (BMD®)**

**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 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 BMD® in Broiler Chicken Feeds

I. GENERAL INFORMATION

NADA: 141-153

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

Generic Names: Diclazuril
Bacitracin methylene disalicylate

Trade Names: CLINACOX™
BMD®

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 bacitracin methylene disalicylate as per 21 CFR 558.76. Diclazuril is supplied as a Type A medicated article in a 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, 50, 60, or 75 grams of bacitracin 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*.

Bacitracin methylene disalicylate

Bacitracin methylene disalicylate is added to broiler chicken feed at concentrations from 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 (21 USC §512 (d)(4)(D)).

Freedom of Information Summary

NADA 141-153, Diclazuril + Bacitracin methylene disalicylate

Page 3

Diclazuril, as provided by Schering-Plough Animal Health, has previously been separately approved for use in broiler chicken 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* (21 CFR 558.198(d)(2)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved for use in broiler chicken feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.76 (d)(1)(i)). Effectiveness for 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, and in Alpharma Inc.'s previously approved NADA 46-592, to which Schering-Plough Animal Health has a 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, performance) likely to occur simultaneously with sufficient frequency in broiler chickens. 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 broiler chickens for the purposes of §512 (d)(4) of the FFDCFA, because diclazuril is approved only for prevention of a protozoal disease in broiler chickens.

V. ANIMAL SAFETY

In accordance with the FFDCFA, 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 chicken 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* (21 CFR

Freedom of Information Summary

NADA 141-153, Diclazuril + Bacitracin methylene disalicylate

Page 4

558.198(d)(2)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved for use in broiler chicken feed for increased rate of weight gain and improved feed efficiency (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, is demonstrated in Schering-Plough Animal Health's approved NADA 140-951, and in Alpharma Inc.'s approved NADA 46-592, 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 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 study (ies) is (are) required for approval of NADA 141-153.

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 Tests

Toxicity data for diclazuril and bacitracin methylene disalicylate are contained in NADAs 140-951 (diclazuril) and 46-592 (bacitracin methylene disalicylate).

B. Tolerances

Tolerances for parent diclazuril have been established as follows: 0.5 ppm in muscle, 1 ppm in fat and 3ppm in liver (21 CFR 556.175). For bacitracin methylene disalicylate, the tolerance in uncooked edible tissue has been set at 0.5 ppm (21 CFR 556.70).

C. Tissue Residue Depletion Study

Schering-Plough Research Institute, Lafayette, NJ conducted Study No. 97500 (Study Directors: Alice Bova and Chris Wrzesinski) to show that BMD would not adversely impact the depletion of diclazuril when both drugs were used at their maximum intended levels. A total of 240 newly hatched broiler chickens (120 M, 120 F) were used in this study. The birds were assigned to three groups of 80, equally mixed as to sex. The birds of Group 1 received an unmedicated basal

Freedom of Information Summary

NADA 141-153, Diclazuril + Bacitracin methylene disalicylate

Page 5

diet, those of Group 2 a basal diet containing 0.9 g/ton diclazuril and 50 g/ton BMD, and those of Group 3 a basal diet containing 0.9 g/ton diclazuril. Chickens were fed from day 1 to day 43, when they were sacrificed 6 hr (practical zero withdrawal) after removal of feed.

For each treatment group, livers from 18 males were pooled in 6 groups of 3 and homogenized. The same procedure was followed for livers from females. The composited liver samples were shipped to Janssen Pharmaceuticals for measurement of diclazuril with GC-ECD. The results of the study are summarized in the table below.

TISSUE RESIDUE STUDY 97500 ASSAY RESULTS

Group	Gender	Bacitracin (U/g) ^a	Diclazuril (ppm) ^b
Controls	M	na ^a	NQ ^c
	F	na ^a	NQ ^c
Diclazuril	M	na ^a	0.263
	F	na ^a	0.250
Diclazuril + Bacitracin	M	na ^a	0.249
	F	na ^a	0.237

^ana=Not assayed

^bMean of 6 pooled liver samples; each pooled sample represents 3 birds

^cNot quantifiable; limit of quantification = 0.010 ppm

Liver concentrations of diclazuril in diclazuril-treated chickens did not differ from those of chickens receiving the subject combination and were well below the applicable tolerance. Therefore, BMD does not affect tissue residues of diclazuril at practical zero withdrawal when used in combination with diclazuril.

Substantial scientific evidence under NADA 46-592 demonstrates that the likelihood is extremely remote that other drugs in combination with BMD would alter bacitracin residues in animal tissues. Furthermore, data collected over many years have shown that tissue residues of BMD are not detected, whether the drug is used alone or in combination. Consequently, studies to evaluate tissue residues and demonstrate assay noninterference for Alpharma Inc.'s BMD are no longer required when each drug is included at approved levels. It follows, too, that if no residues of BMD are detected in tissues, studies to evaluate the interference of BMD on the method(s) for other component(s) of the combination are unnecessary.

Freedom of Information Summary

NADA 141-153, Diclazuril + Bacitracin methylene disalicylate

Page 6

D. Regulatory Methods

A sponsor-validated GC/EC method for diclazuril in edible tissues of chickens is on file with the Center for Veterinary Medicine. The analytical method for the determination of bacitracin methylene disalicylate 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 (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.

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

cc: HFV-199 NADA 141-153, A0000 and M0001 Orig.
HFV-2 Special Mailing List
HFV-12 FOI Staff
HFV-102 GADQC Reserve Copy
HFV-153 Green Book (NTurner)
HFA-305 Dockets Management Branch
HFR-MA350 NWJ-DO
KPWeld/HFV-128:01/03/2000

cc: CVM Records\ONADE\N141153\A0000FOI.SUM

Net Weight lb (kg) on bag or bulk

Diclazuril/Bacitracin methylene disalicylate 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)
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.....	_____	%

¹If added.

²Shall 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

**SIGNATURE PAGE FOR THE
FREEDOM OF INFORMATION SUMMARY**

NADA OR ANADA # 141-153

FIRM Schering-Plough Animal Health

NAME OF DRUG Diclazuril + bacitracin methylene disalicylate

CONCURRENCES:
(Signature-date)

CONCURRENCES WITH
REVISIONS, IF REVISED

- | | | | |
|----|------------------------------|------|---------|
| 1. | Primary Reviewer
HFV-128 | Date | INITIAL |
| 2. | Team Leader
HFV-128 | Date | INITIAL |
| 3. | Division Director
HFV-120 | Date | INITIAL |
| 4. | QAST, HFV-102 | Date | INITIAL |
| 5. | Director, ONADE, HFV-100 | Date | INITIAL |
| 6. | Director, CVM, HFV-1 | Date | INITIAL |

Team/Reviewer: Attach this form to draft FOI Summary in Folder A of Approval Package
HFV-199: Attach this form to dated FOI Summary when filed in NADA.