Approval Date: January 13, 2000

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-090

Diclazuril (CLINACOX™) plus Virginiamycin (STAFAC®)

1) 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.

2) 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 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 STAFAC® in Broiler Chicken Feeds

I. GENERAL INFORMATION

NADA: 141-090

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

Generic Names: Diclazuril
Virginiamycin

Trade Names: CLINACOX™
STAFAC®

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 virginiamycin as per 21 CFR 558.635. Diclazuril is supplied as a Type A medicated article in a concentration of 0.91 grams diclazuril activity per pound. Virginiamycin is supplied as a Type A medicated article in concentrations of 5, 10, 20, 50, or 227 grams of virginiamycin 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*.
Virginiamycin	Virginiamycin is added to broiler chicken feed at 5 g/ton for increased rate of weight gain and improved feed efficiency, or at 5 to 15 g/ton for increased rate of weight gain.

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)(1)). 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*. Virginiamycin, as provided by Pfizer Animal Health, has previously been separately approved for use in broiler chicken feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.635(d)(2)(ii)). Virginiamycin, as provided by Pfizer Animal Health, has previously been separately approved for use in broiler chicken feed for increased rate of weight gain (21 CFR 558.635(d)(2)(i)). Effectiveness for each drug, diclazuril and virginiamycin, 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 Pfizer Animal Health's previously approved NADA 91-467, to which Schering-Plough Animal Health has a right of reference. Because diclazuril and virginiamycin 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 virginiamycin provide appropriate concurrent use for the intended target population. The use of diclazuril plus virginiamycin provides appropriate concurrent use because these drugs are intended to treat different conditions (diclazuril, coccidiosis; virginiamycin, performance) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial (virginiamycin) 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)(1)). Virginiamycin, as provided by Pfizer Animal Health,

has previously been separately approved for use in broiler chicken feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.635(d)(2)(ii)). Virginiamycin, as provided by Pfizer Animal Health, has previously been separately approved for use in broiler chicken feed for increased rate of weight gain (21 CFR 558.635(d)(2)(i)). Target animal safety for each drug, diclazuril and virginiamycin, 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 Pfizer Animal Health's approved NADA 91-467, 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 virginiamycin 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 141-090.

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 virginiamycin are contained in NADA 140-951 (diclazuril) and NADA 91-467 (virginiamycin).

B. Tolerances

The acceptable daily intake (ADI) for total residues of diclazuril is 25 micrograms per kilogram of body weight per day. Tolerances for parent diclazuril have been established as follows: 0.5 ppm in muscle, 1 ppm in fat and skin with adhering fat, 3 ppm in liver, and 0.5 ppm for kidney (21 CFR 556.175). For virginiamycin, the tolerances in uncooked edible tissues of poultry have been set at 0.1 ppm for muscle, 0.2 ppm for skin and fat and 0.3 ppm for liver (21 CFR 556.750).

C. Tissue Residue Depletion Studies

Two tissue residue studies were conducted to determine whether the combined feeding of diclazuril and virginiamycin alters the concentration of either drug in edible tissues.

Study V-M-4052-92 Study Director: John W. Byrd, Ph.D.
Southwest Bio-Labs, Inc.
401 N. 17th St., Suite 11
Las Cruces, NM 88005

In the first study, twelve 2-day-old broiler chicks, equally mixed as to sex, were fed a medicated diet containing 1 ppm diclazuril and 45.4 g/ton roxarsone. On study day 20, 20 g/ton ^{14}C-virginiamycin was added to the medicated feed. Birds were fed the 3-way combination until day 48, when the birds were sacrificed at six hours (practical zero withdrawal) after feed removal.

The tissues of birds were assayed for total residues by combustion and liquid scintillation counting. The results of the assays are given in the table below.

TISSUE RESIDUE STUDY ASSAY RESULTS:
ZERO DAYS WITHDRAWAL

Group	Gender	Virginiamycin(ppm)[a]
Liver	M	0.130
	F	0.134
Muscle	M	0.013
	F	<0.007
Skin/fat	M	<0.013
	F	<0.013

[a]Sample size = 6 birds; minimal detectable ppm: liver, muscle – 0.007, skin/fat – 0.013

Study 97499 Study Directors: Alice Bova, BS, Chris Wrzesinski, MS
Schering-Plough Research Institute
144 Route 94
P.O. Box 32
Lafayette, NJ 07848

In the second experiment, birds were reared in floor pens from day of age to day 43 of the study. Treatments were randomly assigned to pens. Pens contained 20 birds each. Two pens of each gender were fed the blank control feed, diclazuril at 1 ppm, or the drug combination (1 ppm diclazuril and 20 g/ton of virginiamycin) continuously. Tissue samples were collected on day 43. Three pooled liver samples, each of which represented three birds, from each pen were assayed. For this study, the GC-EC method was used to assay for the presence of diclazuril. No samples were collected for virginiamycin assay. The results are presented in the table below.

TISSUE RESIDUE STUDY 97499 ASSAY RESULTS

Group	Gender	Diclazuril (ppm)[a]
Controls	M	NQ[b]
	F	NQ[c]
Diclazuril	M	0.275
	F	0.216
Diclazuril + Virginiamycin	M	0.274
	F	0.290

[a]Mean of 6 pooled liver samples: each pooled sample represents 3 birds
[b]The average of one pen was not quantifiable; the average of the other pen was 0.016 ppm; limit of quantification = 0.010 ppm
[c]Not quantifiable; limit of quantification = 0.010 ppm

Study V-M-4052-92 showed that total residues of virginiamycin in all edible tissues of chickens were well below the respective tolerances at practical zero withdrawal. Study 97499 demonstrated that residues of parent diclazuril in liver were at least one order of magnitude below the applicable tolerance. The results of these studies support the use of the two-way combination of diclazuril and virginiamycin in broiler chicken feeds with no requirement of a withdrawal period.

D. Assay Noninterference

In conjunction with the second tissue residue study (Study 97499), a liver sample from a control bird was spiked with diclazuril plus virginiamycin and assayed by GC-ECD for diclazuril. The results indicated that the presence of virginiamycin does not interfere with the diclazuril assay. A demonstration of diclazuril with the virginiamycin assay was not necessary since the virginiamycin assay involved combustion of tissues and liquid scintillation detection of radiolabeled material.

E. Regulatory Methods

A sponsor-validated GC-ECD method for diclazuril in edible tissues of chickens is on file with the Center for Veterinary Medicine. The requirement of a regulatory method to monitor tissue residues of virginiamycin in edible tissues was waived under NADA 91-467.

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 virginiamycin (5 g/ton and 5 to 15 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).

Net weight lb (kg) on bag or bulk

Diclazuril/Virginiamycin 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)
Virginiamycin…….……..……. 5 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

Net weight lb (kg) on bag or bulk

Diclazuril/Virginiamycin 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 in broiler chickens.

ACTIVE DRUG INGREDIENT

Diclazuril……..... 0.91 g/ton (1 ppm)
Virginiamycin…….…….....……... 5 to 15 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