Approval Date: January 27, 2004

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-223

CLINACOX (Diclazuril) plus 3-NITRO (Roxarsone)

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*. For increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

Sponsored By:

Alpharma Inc.
One Executive Drive
P.O. Box 1399
Fort Lee, NJ 07024

TABLE OF CONTENTS

FREEDOM OF INFORMATION SUMMARY

CLINACOX plus 3-NITRO for Broiler Chickens

1. GENERAL INFORMATION:

a. File Number:	NADA 141-223
b. Sponsor:	Alpharma Inc. One Executive Drive P.O. Box 1399 Fort Lee, NJ 07024 Drug Labeler Code: 046573
c. Established Name:	Diclazuril plus Roxarsone
d. Proprietary Name:	CLINACOX plus 3-NITRO
e. Dosage Form:	Type A medicated articles used in the manufacture of a Type C medicated feed
f. How Supplied:	Diclazuril: 50 lb. bag Roxarsone: 50 lb. bag
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	Diclazuril: 0.2 percent activity Roxarsone: 10, 20, 50, and 80 percent activity
i. Route of Administration:	Oral in feed
j. Species/Class:	Broiler chickens
k. Recommended Dosage:	Diclazuril: 0.91 g diclazuril/ton feed Roxarsone: 22.7 to 45.4 g roxarsone/ton feed
l. Pharmacological Category:	Anticoccidial and arsenical
m. Indications:	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*. For increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

2. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the animal drugs/ active ingredients 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 FDA finds that the sponsor fails to demonstrate that:

- there is substantial evidence to indicate that any active ingredient/drug intended only for the same use as another active ingredient/animal drug in combination makes a contribution to the labeled effectiveness.

- 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.

- where the combination contains more than one nontopical antibacterial active ingredient/animal drug, there is a substantial evidence that each of the nontopical antibacterial active ingredients/animal drugs makes a contribution to the labeled effectiveness

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)(1)(i)). Because diclazuril is effective against *E. maxim*a 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*. Roxarsone as provided by Alpharma, has previously been separately approved for increased rate of weight gain, improved feed efficiency, and improved pigmentation in growing chickens (21 CFR 558.530(d)(1)(ii)). Effectiveness of each drug, diclazuril 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 to which Alpharma has right of reference, and in Alpharma's approved NADA 007-891 for roxarsone.

Because diclazuril 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 roxarsone provide appropriate concurrent use for the intended target population. The use of diclazuril plus roxarsone provides appropriate concurrent use because these drugs are intended to treat different conditions (diclazuril - coccidiosis; roxarsone – weight gain, feed efficiency, and pigmentation) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no nontopical antibacterial 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 section 512(d)(4) of the FFDCA, because diclazuril is approved only

for prevention of a protozoal disease in broiler chickens. Roxarsone is not considered to be an antibacterial animal drug for use in chickens for the purposes of section 512(d)(4) of the FFDCA, because roxarsone is not approved for use in chickens for the diagnosis, cure, mitigation, treatment, or prevention of bacterial disease and is not approved for any other use the Center for Veterinary Medicine deems attributable to its antibacterial properties.

3. TARGET ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in **animal feed** have previously been approved separately 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 that cannot adequately be evaluated based on the information contained in the application for the combination, and FDA finds that the application fails to show that the combination is safe, or

- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and FDA finds that the application fails to show that the combination is safe.

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)(1)(i)). 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*. Roxarsone as provided by Alpharma, has previously been separately approved for increased rate of weight gain, improved feed efficiency, and improved pigmentation in growing chickens (21 CFR 558.530(d)(l)(ii)). Target animal safety for each drug, diclazuril 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 for diclazuril to which Alpharma has a right of reference and Alpharma's NADA 007-891 for roxarsone. The Agency has found no substantiated scientific issue relating to the target animal safety of diclazuril 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 141-223.

4. HUMAN SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in animal feed have previously been approved separately 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 FDA finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or

- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or drug in the combination.

A. Toxicity:

Safety for this combination product has been established by data in NADA 140-951 for diclazuril and in NADA 007-891 for roxarsone. An acceptable daily intake (ADI) for diclazuril previously has been established at 25 micrograms per kilogram of body weight per day. An allowable daily intake value for roxarsone is not established at this time.

B. Tolerances for Residue:

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 tolerances 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 Data:

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 these 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 0.91 g diclazuril, 200 g bacitracin methylene disalicylate, 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.

Table 1: Tissue Residue Study 99450 Assay Results

(Liver Samples)

Group	Gender	Diclazuril, ppb	Arsenic, ppm		
			Day 0	Day 3	Day 5
			Withdrawal	**Withdrawal**	**Withdrawal**
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 withdrawal, the withdrawal period for roxarsone, were also well below the tolerance of 2 ppm. 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 the arsenic method involves ashing, assay noninterference testing for roxarsone is unnecessary.

D. Regulatory Methods for Residues:

A sponsor-validated gas chromatography/electron capture detection 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 roxarsone in edible tissues is on file at the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

E. User Safety Concerns:

There are no human warnings on the Type C Medicated Feed labeling.

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512(d)(4) of the FFDCA and 21 CFR Part 514 of the implementing regulations. Diclazuril plus roxarsone when administered at 0.91 g diclazuril/ton feed and 22.7 to 45.4 g roxarsone/ton feed is safe and effective for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E.*

acervulina, E. brunetti, E. mitis (mivati), and *E. maxima* and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens. 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*. A preslaughter withdrawal period of five days is required for the use of the combination of diclazuril plus roxarsone in broiler chickens.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act.

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 1 of the FOI Summary and the Blue Bird labeling that is attached to this document.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the lay person have been provided. Label directions provide detailed instruction in plain language. The drug product is not a controlled substance. Thus, the drug product is assigned OTC status, and the labeling is adequate for the intended use.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Type C Broiler Chicken Medicated Feed Blue Bird Label