Approval Date: JUL 3, 2000

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-157

Halofuginone hydrobromide (STENOROL®) plus Roxarsone (3-NITRO®)

1. For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati,* and *E. maxima*, and 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. maxima, E. mivati/E. mitis,* and *E. brunetti*, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in replacement caged laying chickens and replacement broiler breeder chickens.

Sponsored by:

Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024

FREEDOM OF INFORMATION SUMMARY

Combined use of STENOROL® and 3-NITRO® in Broiler and Replacement Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-157

Sponsor: Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024

Generic Names: Halofuginone hydrobromide
Roxarsone

Trade Names: STENOROL®
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. mivati,* and *E. maxima*, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. mivati/E. mitis,* and *E. brunetti*, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in replacement caged laying chickens and replacement broiler breeder chickens.

III. DOSAGE:

A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles, halofuginone hydrobromide as per 21 CFR 558.265(c)(1)(i) and (c)(3)(i), and roxarsone as per 21 CFR 558.530(d)(1)(i). Halofuginone hydrobromide is supplied as a Type A medicated article in a single concentration of 2.72 grams halofuginone 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:

Halofuginone hydrobromide	Halofuginone hydrobromide is added to broiler chicken feed at a concentration of 2.72 g/ton for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati* and *E. maxima*. Halofuginone hydrobromide is added to replacement caged laying chicken and replacement broiler breeder chicken feed at a concentration of 2.72 g/ton for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. mivati/E. mitis,* and *E. brunetti.*
Roxarsone	Roxarsone is added to growing chicken feed at concentrations from 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 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 Agency finds that the NADA fails to demonstrate that 1) there is substantial evidence to indicate 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/animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.

Halofuginone hydrobromide, as provided by Hoechst Roussel Vet, has previously been separately approved for use in broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati* and *E. maxima* (21 CFR

558.265(c)(1)(i)), and for use in replacement caged laying chickens and replacement broiler breeder chickens .for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. mivati/E. mitis,* and *E. brunetti* (21 CFR 558.265(c)(3)(i)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in growing chickens for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR 558.530(d)(l)). Effectiveness for each drug, halofuginone hydrobromide and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADA 130-951 (to which Alpharma Inc. has a right of reference), and in Alpharma's approved NADA 7-891, respectively.

Because halofuginone hydrobromide 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 halofuginone hydrobromide plus roxarsone provide appropriate concurrent use for the intended target population. The use of halofuginone hydrobromide plus roxarsone provide appropriate concurrent use because these drugs are intended to treat different conditions (halofuginone hydrobromide, coccidiosis; roxarsone, weight gain, feed efficiency and pigmentation problems) likely to occur simultaneously with sufficient frequency in broiler and replacement chickens. There is no nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed. Halofuginone hydrobromide is not considered to be an antibacterial animal drug for such use in chickens for the purposes of Section 512(d)(4) of the FFDCA, because halofuginone hydrobromide is approved only for prevention of a protozoal disease (coccidiosis) in broiler and replacement chickens. Roxarsone is not considered to be an antibacterial animal drug for such use in broiler 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.

V. ANIMAL 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 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 a combination active ingredient or animal drug is safe for the target animal.

Halofuginone hydrobromide, as provided by Hoescht Roussel Vet, has previously been separately approved for use in broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati* and *E. maxima* (21 CFR

558.265(c)(1)(i)), and for use in replacement caged laying chickens and replacement broiler breeder chickens for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. mivati/E. mitis,* and *E. brunetti* (21 CFR 558.265(c)(3)(i)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in growing chickens for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR 558.530(d)(l)). Target animal safety for each drug, halofuginone hydrobromide, and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADA 130-951 (to which Alpharma Inc. has a right of reference), and in Alpharma's approved NADAs 7-891, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of halofuginone hydrochloride or 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 141-157.

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. Tolerances

Data establishing the safety of halofuginone hydrobromide and roxarsone have been established by NADA 130-951 and 7-891, respectively. The marker residue selected to monitor for total residues of halofuginone hydrobromide in broilers is parent halofuginone hydrobromide and the target tissue selected is liver. A tolerance is established in broiler chickens of 0.16 ppm for parent halofuginone hydrobromide in liver. These marker residue concentrations in liver correspond to total residue concentrations of 0.3 ppm in liver. The safe concentrations for total residues of halofuginone hydrobromide in the uncooked edible tissues of broilers are 0.1 ppm in muscle, 0.3 ppm in liver, and 0.2 ppm in skin with adhering fat. As used in this section, "tolerance" refers to a concentration of a marker residue in the target tissue selected to monitor for total residues of the drug in the target animal, and "safe concentration" refers to the concentrations of total residues considered safe in edible tissues. Tolerances for residues of arsenic from roxarsone in chickens is established at 0.5 ppm in uncooked muscle tissue, 2 ppm in

uncooked edible by-products and 0.5 ppm in eggs (21 CFR 556.60). Liver is the target tissue for roxarsone.

B. Residue Data

The residue data supporting this approval are found in Hoescht Roussel Vet's NADA 140-533 (bacitracin MD and roxarsone in combination with halofuginone for broilers) to which Alpharma Inc. has a right of reference. The following table summarizes data obtained from a study in which broilers were fed the combination of halofuginone hydrobromide (2.72 g/ton0, bacitracin MD (100 g/ton) and roxarsone (45.4 g/ton) for 29 days prior to withdrawal period.

RESIDUE DEPLETION STUDY ASSAY RESULTS (PPM)

Drug	Tissue	Withdrawal Day*			
[redacted]		0	1	4	5
Halofuginone	Liver	0.48(±0.22)	0.60 (±0.15)	0.03(±0.02)	0.018(±0.01)
Roxarsone	Liver	0.87(±0.09)	1.46(±0.25)	0.32(±0.16)	0.13(±0.11)

*Average of 6 birds, except for halofuginone at withdrawal day 4 the average is from 3 birds; standard deviation is in parenthesis.

The available residue chemistry information supports the assignment of a five day withdrawal period for broiler chickens, replacement caged laying chickens, and replacement broiler breeder chickens fed the combination of halofuginone hydrobromide (2.72 g/ton) and roxarsone (22.7 – 45.4 g/ton).

C. Regulatory Methods for Residues

An HPLC method is used to assay tissues for halofuginone residues. The method entitled "Analysis of an Anti-Coccidial Drug, Halofuginone, in Poultry Tissue" is on file at the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, Maryland 20855.

A spectrophotometric method is used to assay tissues for roxarsone residues. The method entitled "Arsenic (Total) Residues in Animal Tissues, Spectrophotometric Method" is published in the AOAC, 15th Edition 973.78, page 626.

VII. AGENCY CONCLUSIONS:

The data submitted in support of this NADA comply with the requirements of Section 512 of the FFDCA and demonstrate that use of halofuginone hydrobromide (2.72 g/ton) plus roxarsone

(22.7 to 45.4 g/ton) with a 5 day withdrawal period is 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.

The available residue chemistry information supports the assignment of a five day withdrawal period for broiler chickens, replacement cage laying chickens, and replacement broiler breeder chickens fed the combination of halofuginone hydrobromide (2.72 g/ton) and roxarsone (22.7 to 45.4 g/ton). The combination of halofuginone, bacitracin methylene disalicylate, and roxarsone has been previously approved, thus approval of this application will not be inconsistent with public health.

Attached labeling: Type C Medicated Feed (Blue Bird) - Broiler and replacement chickens

Net weight lb (kg) on bag or bulk

Halofuginone hydrobromide/Roxarsone Broiler Chicken Ration
Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati,* and *E. maxima*, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

ACTIVE DRUG INGREDIENT

Halofuginone hydrobromide……2.72 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…….....……_____%
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: Withdraw 5 days prior to slaughter. Halofuginone hydrobromide has been found to be an eye and skin irritant. Avoid contact with skin, eyes, and clothing. Avoid inhalation of dust. Halofuginone hydrobromide is toxic to fish and other aquatic life. Keep out of lakes, ponds, and streams.

CAUTION: Do not feed to laying chickens or waterfowl. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Halofuginone hydrobromide/Roxarsone Replacement Caged Laying Chicken Ration

Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. mivati/E. mitis,* and *E. brunetti*, and for increased rate of weight gain, improved feed efficiency, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in replacement caged laying chickens.

ACTIVE DRUG INGREDIENT

Halofuginone hydrobromide……2.72 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……_____%
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 sole ration to replacement cage laying chickens until 20 weeks of age.

WARNING: Withdraw 5 days prior to slaughter. Halofuginone hydrobromide has been found to be an eye and skin irritant. Avoid contact with skin, eyes, and clothing. Avoid inhalation of dust. Halofuginone hydrobromide is toxic to fish and other aquatic life. Keep out of lakes, ponds, and streams.

CAUTION: Do not feed beyond sexual maturity. Do not feed to laying chickens or waterfowl. Halofuginone hydrobromide at the use level in replacement caged laying chickens in the absence of coccidiosis may adversely affect weight gains. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Halofuginone hydrobromide/Roxarsone Replacement Broiler Breeder Ration

Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. mivati/E. mitis,* and *E. brunetti*, and for increased rate of weight gain, improved feed efficiency, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in replacement broiler breeder chickens.

ACTIVE DRUG INGREDIENT

Halofuginone hydrobromide……2.72 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……_____%
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 sole ration to replacement broiler breeder chickens until 16 weeks of age.

WARNING: Withdraw 5 days prior to slaughter. Halofuginone hydrobromide has been found to be an eye and skin irritant. Avoid contact with skin, eyes, and clothing. Avoid inhalation of dust. Halofuginone hydrobromide is toxic to fish and other aquatic life. Keep out of lakes, ponds, and streams.

CAUTION: Do not feed beyond sexual maturity. Do not feed to laying chickens or waterfowl. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345