FREEDOM OF INFORMATION SUMMARY

Combined use of MAXIBAN® and 3-NITRO® in Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-113

Sponsor: Elanco Animal Health
2001 W. Main St.
P. O. Box 708
Greenfield, IN 46140

Generic Names: Narasin/nicarbazin
Roxarsone

Trade names: MAXIBAN®
3-NITRO®

Marketing status: OTC

(**Note:** Narasin/nicarbazin will hereafter be referred to as Maxiban®, the Type A medicated article containing a fixed 1:1 ratio of narasin and nicarbazin)

II. INDICATIONS FOR USE:

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

III. DOSAGE:

A. Form: This NADA provided for the combined use of these two Type A medicated articles, Maxiban® as per 21 CFR §558.363 and §558.366, and roxarsone as per 21 CFR §558.530. Maxiban® is supplied as a Type A medicated article in a single concentration of 36 grams each of narasin and nicarbazin activity per pound. Roxarsone is supplied as a Type A medicated article in concentrations of 45.4, 90, or 227 grams of roxarsone activity per pound.

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

C. Recommended Dosage:

Maxiban®	Maxiban® is added to broiler chicken feed at concentrations from 27 to 45 g/ton for

	the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina*, *E. maxima*, *E. brunetti,* and *E. mivati*.
Roxarsone	Roxarsone is added to broiler chicken feed at concentrations from 22.7 to 45.4 g/ton for increased rate of weight gain, improved feed efficiency, and improved pigmentation.

WARNING: Withdraw 5 days before slaughter.

CAUTION: For broiler chickens only. Do not feed to laying hens. Do not allow adult turkeys, horses or other equines access to formulations containing narasin. Ingestion of narasin by these species has been fatal. Nicarbazin medicated broilers may show reduced heat tolerance if exposed to high temperature and high humidity. Provide adequate drinking water and ventilation during these periods. 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.

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)).

Maxiban®, as provided by Elanco Animal Health, has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* (21 CFR §558.363 (c)(1)(iii) and §558.366 (c)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in broiler chicken feed for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR §558.530 (d)(1)(i)). Effectiveness for each drug, Maxiban® and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal

Health's NADA 138-952, and in Alpharma Inc.'s approved NADA 7-891, to which Elanco Animal Health has a right of reference, respectively.

Because roxarsone is intended for a different use from Maxiban®, the NADA need not demonstrate, by substantial evidence, that roxarsone contributes to the labeled effectiveness of the combination. Because Maxiban® and roxarsone each has at least one use that is different from all other animal drugs used in the combination, the NADA must demonstrate that Maxiban® plus roxarsone provide appropriate concurrent use for the intended target population. The use of Maxiban® plus roxarsone provides appropriate concurrent use because these drugs are intended to treat different conditions (Maxiban®, coccidiosis; roxarsone, performance) likely to occur simultaneously with sufficient frequency in broiler chickens. Maxiban® 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 Maxiban® 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 broiler chickens for the purposes of §512(d)(4) of the FFDCA, because roxarsone is not approved for use in broiler 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 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 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.

Maxiban®, as provided by Elanco Animal Health, has previously been separately approved for use in broiler chicken feed for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* (21 CFR §558.363 (c)(1)(iii) and §558.366 (c)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in broiler chicken feed for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR §558.530 (d)(1)(i)). Target animal safety for each drug, Maxiban® and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's NADA 138-952, and in Alpharma Inc.'s approved NADA 7-891, to which Elanco Animal Health has a right of reference, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of Maxiban® 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.

VI. HUMAN SAFETY:

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 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 narasin and nicarbazin (Maxiban®) and roxarsone have been submitted to NADAs 138-952 and NADA 7-891, respectively. A tolerance for narasin residues in chickens is not needed. A tolerance of 4 ppm is established for residues of nicarbazin in uncooked chicken muscle, liver, skin, and kidney (21 CFR §556.445) Tolerances for residues of arsenic from roxarsone in chickens are 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).

B. Residue Data

This study was directed by J. M. Rodewald of Elanco Animal Health, a division of Eli Lilly and Company in cooperation with Alpharma Inc. Broiler chickens were fed a basal unmedicated ration until three weeks of age and then fed a ration medicated with Maxiban® (90 g/ton), bacitracin methylene disalicylate (50 g/ton) and roxarsone (45.4 g/ton) for three weeks (to approximately 6 weeks of age). Control birds were kept on unmedicated basal ration for the duration of the study (until approximately 6 weeks of age). At practical zero-time withdrawal (six hours after withdrawn of medicated ration) birds were euthanized and the skin with adhering fat and the abdominal fat were collected for determination of narasin residue. At practical zero-time withdrawal, all control group birds were euthanized and samples of breast and thigh muscle, abdominal fat, skin with adhering fat, and the liver minus the gall bladder were collected from each bird. Samples of the liver were collected from euthanized birds at practical zero-time, 24 hours, 48 hours, and 96 hours post withdrawal of the medicated ration for the determination of nicarbazin residue. Samples of the liver were collected from euthanized birds at practical zero-time, 24 hours, 72 hours, and 120 hours post withdrawal of the medicated ration for the determination of total arsenic.

Mean narasin residues in abdominal fat and skin with adhering fat of treated birds at practical zero withdrawal were determined to be less than 0.6 ppm. The data for narasin were reported to be less than 0.6 ppm because, in this particular study, it was the lowest concentration used in preparing the standard curve. In previous instances, the method, run in the same manner

as in this study, has been shown to be sensitive to at least 0.02 ppm, and inasmuch as no zones of inhibition were observed for any fat sample, narasin, in fact, can be taken to be less than 0.02 ppm. Mean nicarbazin residues in the liver at practical zero-time, 24 hours, 48 hours, and 96 hours post withdrawal were 10.4 (range 16.5 to 2.0), 8.0 (range 10.0 to 6.1), 4.1 (range 6.1 to 0.7) and 0.5 ppm (range 0.9 to 0.2), respectively. Mean arsenic residues in the liver at practical zero-time, 24 hours, 72 hours, and 120 hours post withdrawal were 1.8 (range 2.98 to 0.49), 0.8 (range 1.15 to 0.44), 0.5 (range 0.64 to 0.30), and 0.6 ppm (range 1.18 to 0.34), respectively.

Assay noninterference among the drugs of the combination was demonstrated by the following data obtained from analyses of control tissues fortified with 1.2 ppm narasin, 0.5 ppm bacitracin methylene disalicylate, 2 ppm roxarsone and/or 4 ppm nicarbazin. In abdominal fat, narasin was determined to be 1.07 ± 0.14 ppm in tissue spiked with narasin only and 1.09 ± 0.12 ppm in tissue spiked with all four drugs. In skin/fat, narasin was determined to be 1.06 ± 0.12 ppm in tissue spiked with narasin only and 0.94 ± 0.07 ppm in tissue spiked with all four drugs. In liver, nicarbazin was determined to be 3.46 ± 0.04 ppm in tissue spiked with nicarbazin only and 3.46 ± 0.11 ppm in tissue spiked with all four drugs.

Because the method for arsenic involves ashing, similar work showing noninterference of the other drugs on the method for roxarsone is unnecessary.

The available residue chemistry information supports the assignment of a five day withdrawal period for broiler chickens fed the combination of narasin and nicarbazin (equivalent to 27 to 45 g/ton each of narasin and nicarbazin in finished feeds) and roxarsone (22.7 to 45.4 g/ton).

C. Regulatory Methods for Residues

A regulatory method is not required for the assay of narasin in tissues. Tissues were assayed for narasin residues using Method AM-AA-CA-R108-AB-755, entitled “Determination and Confirmation of Narasin Residues in Chicken Target Tissue, Abdominal Fat,” Elanco Animal Health, A Division of Eli Lilly and Company, P.O. Box 708, Greenfield, Indiana 46140.

A high performance liquid chromatography method is used to assay tissues for nicarbazin. Tissues were assayed using Method AM-AA-CA-R110-AF-755 entitled “Determination of Nicarbazin in Chicken Tissues by High Performance Liquid Chromatography,” Elanco Animal Health, A Division of Eli Lilly and Company, P.O. Box 708, Greenfield, Indiana 46140.

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 Maxiban® (fixed 1:1 ratio of 27 to 45 g/ton each of narasin and nicarbazin) plus roxarsone (22.7 to 45.4 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.

Residue data show that residues of narasin are within the established tolerances of 0.6 ppm (muscle), 1.8 ppm (liver), and 1.2 ppm (fat and skin/fat); residues of nicarbazin are within the established tolerance of 4 ppm in uncooked edible tissues of chickens.

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