Approval Date: September 3, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-947

B. Sponsor

Elanco Animal Health

C. Proprietary Name

Mexiban®, Lincomix®

D. Established Name

Narasin/nicarbazin

E. Dosage 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 lincomycin as per 21 CFR §558.325. Maxiban® is supplied as a Type A medicated article in a single concentration of 36 grams each of narasin and nicarbazin activity per pound. Lincomycin is supplied as a Type A medicated article in concentrations of 4, 10, 20, and 50 grams of lincomycin activity per pound.

F. ROUTE OF ADMINISTRATION:

Oral, via the feed.

G. RECOMMENDED DOSAGES:

- **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*.

- **Lincomycin:** Lincomycin is added to broiler chicken feed at concentrations from 2 to 4 g/ton for increase in rate of weight gain and improved feed efficiency.

WARNING: Withdraw 5 days before slaughter.

CAUTION: For broiler chickens only. Not for use in layers, breeders, or turkeys. 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. Do not allow rabbits, hamsters, guinea pigs, horses, or ruminants access to feeds containing lincomycin. Ingestion by these species may result in severe gastrointestinal effects.

H. Dispensing Status

OTC

I. Indication

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

II. 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). Lincomycin, as provided by Pharmacia & Upjohn Inc., has previously been separately approved for use in feed for broiler chickens for increased rate of weight gain and improved feed efficiency (21 CFR §558.325 (c)(1)(a)). Effectiveness for each drug, Maxiban® and lincomycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 138-952, and in approved NADA 97-505, to which Elanco Animal Health has a right of reference.

Because lincomycin is intended for a different use from Maxiban®, the NADA need not demonstrate, by substantial evidence, that lincomycin contributes to the labeled effectiveness of the combination. Because Maxiban® and lincomycin 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 lincomycin provide appropriate concurrent use for the intended target population. The use of Maxiban® plus lincomycin provides appropriate concurrent use because these drugs are intended to treat different conditions (Maxiban®, coccidiosis; lincomycin, performance) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial (lincomycin) contained in this combination animal drug intended for use in Type C medicated feed. 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.

III. 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)). Lincomycin, as provided by Pharmacia & Upjohn Inc., has previously been separately approved for use in broiler chicken feed for increase in rate of weight gain and improved feed efficiency (21 CFR §558.325 (c)(1)(i)). Target animal safety for each drug, Maxiban® and lincomycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 138-952, and in approved NADA 97-505, to which Elanco Animal Health has a right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of Maxiban® or lincomycin 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) are required for the approval of NADA 140-947.

IV. HUMAN FOOD 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 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 and Safe Concentration of Residues

The basic safety data for lincomycin may be found in the parent NADA 97-505, and VMF 5249; for narasin in the parent NADA 118-980; for nicarbazin in the parent NADA 135-468. The tolerance for lincomycin residues are established at 0.1 ppm negligible residues in uncooked edible tissues of chickens (21 CFR 556.360). The safe concentration for total narasin residues in uncooked, edible chicken tissues are: 0.6 ppm in muscle; 1.8 ppm in liver; 1.2 ppm in skin with adhering fat and fat (21

CFR 556.428). A tolerance of 4 ppm is established for residues of nicarbazin in uncooked chicken muscle, liver, skin, and kidney (21 CFR §556.445).

B. Tissue Residue Depletion Studies

Tissue residue depletion studies were conducted at Lilly Research Laboratories, A Division of Eli Lilly and Company, Experiment No. AAC8814, with the growing birds on a diet of lincomycin at 4 grams per ton and Maxiban® at 90 grams per ton until slaughter at 6 hours (practical zero) or 1, 2 or 4 days following medicated feed withdrawal. The results of this study demonstrated that there was no change in the residue depletion pattern of each drug when lincomycin and Maxiban® were fed to broilers in combination. Mean narasin concentrations were 0.095 + 0.033 ppm in abdominal fat at practical zero withdrawal (6 hr). A ratio of 3:1 for total narasin residues in skin with adhering fat and fat to parent narasin in skin with adhering fat was established under NADA 118-980. The mean residue level of nicarbazin in the 4 day withdrawal tissue was 0.23 + 0.04 ppm in liver; for lincomycin, mean residue levels were below the limit of detection for muscle, liver and skin/fat tissues sampled at 0,1, 2, or 4 day withdrawal (test sensitivity of 0.067 ppm). The data produced in this study are consistent with a 5 day withdrawal period for lincomycin in combination with Maxiban®.

Tissue residue values[1] for nicarbazin, narasin, and lincomycin at 0, 1, 2, and 4 day withdrawal.

	Nicarbazin	**Narasin**	**Lincomycin**
Day Withdrawal	X(average)+ SD Overall	X(average)+ SD Overall	X(average)+ SD Overall
0	8.27 ± 1.75	0.095 ± 0.033	NDR
1	4.47 ± 1.04	<0.022	NDR
2	1.56 ± 0.68	NDR	NDR
4	0.23 ± 0.04	NDR	NDR

1Values given are residues detected in the target tissue for each compound (nicarbazin and lincomycin – liver; narasin – abdominal fat)

C. Tissue Residue Non-interference Study

Study AAC8814 demonstrates non-interference in tissue residue assays. Control or nonmedicated, tissues were used for negative control, recovery, interference, and stability assays. The assay non-interference was determined by fortifying control tissue at 0.2 ppm narasin, 4 ppm nicarbazin and 0.5 ppm lincomycin. The stability of the residues was confirmed by assaying fortified control tissues at the beginning and end of the time period approximating the storage period of the last set of dosed tissues that were assayed. No interference was observed with the assay of narasin or nicarbazin residues in their respective target tissues in the presence of 0.5 ppm lincomycin. No interference was observed with the assay of lincomycin in the presence of 0.2 ppm narasin and 4.0 ppm nicarbazin.

D. Regulatory Methods

Lincomycin - SOP No. 9760/209/519/041; Standard Operating Procedures for a Tissue Residue Study in Broiler Chickens Treated with Lincomycin: The Upjohn Company, Kalamazoo, MI 49001.

Nicarbazin - Determination of Nicarbazin in Chicken Tissues by High-Performance Liquid Chromatography. Method AM-AA-CA-R110-AF-755. Eli Lilly and Company, Box 708, Greenfield, IN 46140.

E. Tissue Residue Method

Narasin - Determination and confirmation of Narasin Residues in Chicken Target Tissue, Abdominal Fat. Method AM-AA-CA-R108-AB-755, Eli Lilly and Company, Box 708, Greenfield, IN 46140.

V. 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 lincomycin (2 to 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 narasin is within the established safe concentrations in edible chicken tissues (0.6 ppm in muscle; 1.8 ppm in liver; 1.2 ppm in skin and fat). Residue data show that nicarbazin is within the established safe concentrations in edible chicken tissues (4.0 ppm in uncooked chicken muscle, liver, skin, and kidney). A tolerance for residues of lincomycin in chickens is not required.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.