FREEDOM OF INFORMATION SUMMARY

Combined use of MAXIBAN® and BMD® in Chicken Feeds

I. GENERAL INFORMATION:

NADA: 140-926

Sponsor: Elanco Animal Health
A Division of Eli Lilly and Company
2001 West Main Street
Greenfield, IN 46140

Generic Names: Narasin/nicarbazin
Bacitracin methylene disalicylate

Trade names: Maxiban®
BMD®

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 and improved feed efficiency 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 Bacitracin methylene disalicylate as per 21 CFR §558.76. Maxiban® is supplied as a Type A medicated article in a single concentration of 36 grams each of narasin and nicarbazin activity per pound. Bacitracin methylene disalicylate is supplied as a Type A medicated article in concentrations of 10, 25, 30, 40, 50, 60, or 75 grams of bacitracin methylene disalicylate 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*.
Bacitracin methylene	Bacitracin methylene disalicylate is added to broiler chicken feed at concentrations from 4 to 50 g/ton for increased rate of weight gain and improved feed efficiency.

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.

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). Bacitracin methylene disalicylate, as provided by Alpharma 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 §558.76 (d)(1)(i)).

Effectiveness for each drug, Maxiban® and bacitracin methylene disalicylate, 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 46-592, to which Elanco Animal Health has a right of reference for purposes of this combination medicated feed approval.

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

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)). Bacitracin methylene disalicylate, as provided by Alpharma 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 §558.76 (d)(1)(i)). Target animal safety for each drug, Maxiban® and bacitracin methylene disalicylate, 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 46-592, to which Elanco Animal Health has a right of reference for purposes of this combination medicated feed approval**.** The Agency has found no substantiated scientific issue relating to the target animal safety of Maxiban® or bacitracin methylene disalicylate 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 140-926.

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. Toxicity Tests

Toxicology data are contained in NADA 46-592 for bacitracin methylene disalicylate and NADA 138-592 for Maxiban®.

B. Tolerances and Safe Concentrations

Tolerances for residues of bacitracin are established at 0.5 ppm in edible tissues of chickens (21 CFR 556.70).

A tolerance for residues of narasin residues in chickens is not needed. The safe concentrations for total narasin residues in uncooked edible tissues of chickens are: 0.6 ppm, muscle; 1.8 ppm, liver; and 1.2 ppm, fat and skin/fat (21 CFR 556.428).

A tolerance of 4 ppm is established for residues of nicarbazin in uncooked edible tissues of chickens (21 CFR 556. 445).

C. Tissue Residue Depletion Data

Tissue residue study AAC8721 was conducted at Lilly Research Laboratories, a Division of Eli Lilly and Company. Growing birds were kept for 49 days on a diet of bacitracin methylene disalicylate at 200 g/ton and Maxiban® at 90 g/ton until sacrifice at 6 hours (practical zero withdrawal) or at 1, 2, or 4 days following withdrawal of medicated feed.

The results of tissue residue analyses are given in Tables 1 - 3. Tissue residue study AAC8721 demonstrated that there is no change in the residue depletion pattern of each drug when bacitracin methylene disalicylate and Maxiban® were fed to broilers in combination. Assays on muscle conducted at Morris County Testing Laboratory, Morristown, NJ, showed

that bacitracin residues were below tolerance. Assays for nicarbazin and narasin in fat and liver, respectively, conducted by Eli Lilly and Company, also demonstrated that residues were below their permitted concentrations. The specific methods of analysis are noted in Sections E and F below.

TABLE 1 - NICARBAZIN RESIDUES IN LIVER TISSUE AT ZERO - TO FOUR-DAY WITHDRAWAL FROM BROILER CHICKENS MEDICATED WITH 50 PPM NARASIN, 50 PPM NICARBAZIN, AND 200 G/TON BACITRACIN METHYLENE DISALICYLATE[a]

				Nicarbazin Concentration (ppm)	
Bird Numbers	Sex	Withdrawal Time (Days)	X ± SD[b] Within Sex	X ± SD Overall	Log ppm
7678, 7680, 7681, 7685	M	0[c]	6.24 ± 1.94	8.50 ± 2.96	0.9292
7580, 7588, 7595, 7597	F	0	10.8 ± 1.77		
7679, 7684, 7686, 7688	M	1	4.55 ± 1.16	5.21 ± 1.13	0.7165
7578, 7579, 7596, 7598	F	1	5.87 ± 0.67		
7676, 7690, 7694, 7700	M	2	1.81 ± 0.65	2.19 ± 0.70	0.3399
7581, 7582, 7591, 7600	F	2	2.57 ± 0.57		
7677, 7682, 7696, 7697	M	4	0.26 ± 0.01	0.24 ± 0.05	-0.6266
7576, 7583, 7584, 7594	F	4	0.21 ± 0.07		
7659, 7662, 7663, 7669	M	Control	NDR[d]	NDR	NDR
7557, 7563, 7572, 7573	F	Control	NDR		

STATISTICAL RESULTS ON CONCENTRATION VS. WITHDRAWAL TIME

SLOPE = -2.02 ppm/day	INTERCEPT: 7.57 ppm	%RSD = 42.9	CORRELATION COEFFICIENT = -0.9564

STATISTICAL RESULTS ON LOG CONCENTRATION VS. WITHDRAWAL TIME

SLOPE = -0.399 log ppm/day (or -2.50 ppm/day)	INTERCEPT = 1.037 log ppm (or 10.9 ppm)
%RSD = 39.8	CORRELATION COEFFICIENT = -0.9885

[a] Notebook Reference: 7AT
[b] X = mean, SD = Standard Deviation
[c] Practical zero-day withdrawal (6 hours)
[d] NDR = no detectable residues at a test sensitivity of 0.10 ppm nicarbazin

TABLE 2 - NARASIN RESIDUES IN ABDOMINAL FAT TISSUE AT ZERO - TO FOUR-DAY WITHDRAWAL FROM BROILER CHICKENS MEDICATED WITH NARASIN (50 PPM), NICARBAZIN (50 PPM), AND BACITRACIN METHYLENE DISALICYLATE (200 G/TON)[a]

			Narasin Concentration (ppm)		
Bird Number	Sex	Withdrawal Time (Days)	Individual X	Within Sex X + SD[b]	Overall X + SD
7678	M	0[c]	0.027	0.022 ± 0.004	
7680	M	0	<0.020[d]		
7685	M	0	<0.020		
7580	F	0	0.036	0.037 ± 0.004	
7588	F	0	0.041		
7595	F	0	0.033		0.030 ± 0.009
7684	M	1	NDR[e]	NDR	
7686	M	1	NDR		
7688	M	1	NDR		
7578	F	1	<0.020[f]	<0.020	
7579	F	1	<0.020[f]		
7596	F	1	0.021		<0.020
7700	M	2	NDR	NDR	
7690	M	2	NDR		
7694	M	2	NDR		
7582	F	2	NDR	NDR	
7591	F	2	NDR		
7600	F	2	<0.020		NDR
7677	M	4	NDR	NDR	
7696	M	4	NDR		
7697	M	4	NDR		
7583	F	4	NDR	NDR	
7584	F	4	NDR		
7594	F	4	NDR		NDR
7662	M	Control	0.039	<0.020	
7663	M	Control	NDR		
7669	M	Control	NDR		
7557	F	Control	NDR	NDR	
7563	F	Control	NDR		
7572	F	Control	NDR		NDR

[a] Notebook Reference: 8AV
[b] X = mean, SD = standard deviation
[c] Practical zero-day withdrawal (6 hours)
[d] Narasin residue detected below 0.020 ppm
[e] NDR = No detectable residues at a test sensitivity of 0.020 ppm narasin
[f] Although no response was measurable, a visual response was observed for these samples.

TABLE 3 - BACITRACIN METHYLENE DISALICYLATE RESIDUES IN MUSCLE TISSUE AT ZERO - TO FOUR-DAY WITHDRAWAL FROM BROILER POULTRY MEDICATED WITH NARASIN (50 PPM), NICARBAZIN (50 PPM), AND BACITRACIN METHYLENE DISALICYLATE (200 G/TON)[a]

			Bacitracin Methylene Disalicylate Concentration (ppm)		
Bird Number	Sex	Withdrawal Time (Days)	Individual X	Within Sex X + SD[b]	Overall X + SD
7678	M	0[c]	<0.3[d]	<0.3	
7680	M	0	<0.3		
7685	M	0	<0.3		
7687	M	0	<0.3		
7580	F	0	<0.3		
7588	F	0	<0.3		
7595	F	0	NDR[e]		
7597	F	0	NDR		<0.3
7679	M	1	NDR	NDR	
7684	M	1	NDR		
7686	M	1	NDR		
7688	M	1	NDR		
7578	F	1	NDR	NDR	
7579	F	1	NDR		
7596	F	1	NDR		
7598	F	1	NDR		NDR
7676	M	2	NDR	NDR	
7690	M	2	NDR		
7694	M	2	NDR		
7700	M	2	NDR		
7581	F	2	NDR	NDR	
7582	F	2	NDR		
7591	F	2	NDR		
7600	F	2	NDR		NDR

TABLE 3 (Continued) -

			Bacitracin Methylene Disalicylate Concentration (ppm)		
Bird Number	Sex	Withdrawal Time (Days)	Individual X	Within Sex X + SD[b]	Overall X + SD
7677	M	4	NDR	NDR	
7682	M	4	NDR		
7696	M	4	NDR		
7697	M	4	NDR		
7576	F	4	NDR	NDR	
7583	F	4	NDR		
7584	F	4	NDR		
7594	F	4	NDR		NDR
7659	M	Control	NDR	NDR	
7662	M	Control	NDR		
7663	M	Control	NDR		
7669	M	Control	NDR		
7573	F	Control	NDR	NDR	
7563	F	Control	NDR		
7572	F	Control	NDR		
7557	F	Control	NDR		NDR

[a] Summary of data from Appendix F
[b] X = mean, SD = standard deviation
[c] Practical zero-day withdrawal (6 hours)
[d] Bacitracin methylene disalicylate (BMD) residue detected below 0.3 ppm
[e] NDR = No detectable residues at a test sensitivity of 0.3 ppm BMD

D. Tissue Residue Noninterference Study

Study AAC8721 demonstrates noninterference in tissue residue assays. Control, or nonmedicated, tissues were used for negative control, recovery, interference, and stability assays. The assay noninterference was determined by fortifying control tissue at 0.2 ppm narasin, 4 ppm nicarbazin and 0.5 ppm bacitracin methylene disalicylate. 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 bacitracin methylene disalicylate. No interference was observed with the assay of bacitracin methylene disalicylate in the presence of 0.2 ppm narasin and 4.0 ppm nicarbazin.

E. Regulatory Methods

Bacitracin - Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, Protocols. National Center for Antibiotic and Insulin Analyses. Dept. HEW, Washington DC 20204, Rev. October 1968. Modified Method for Determination of Bacitracin in Tissues, Test Procedure Code 9A, A.L. Laboratories, Inc., One Executive Drive, P.O. Box 1399, Fort Lee, NJ 07024.

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.

F. 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.

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 bacitracin methylene disalicylate (4 to 50 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 bacitracin are within the established tolerance of 0.5 ppm in edible tissues of chickens; 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. Residue data supports a 5 (five) day withdrawal for this combination medicated broiler chicken feed.

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