DATE OF APPROVAL LETTER: **JANUARY 14, 2002**

FREEDOM OF INFORMATION SUMMARY

NEW ANIMAL DRUG APPLICATION

NADA 141-124

MAXIBAN® + BMD®
(narasin and nicarbazin + bacitracin methylene disalicylate)

"For the prevention of coccidiosis caused *by Eimeria tenella, E. necatrix, E acervulina, E. maxima, E. brunetti,* and *E. mivati;* and as an aid in the control or prevention of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin."

Sponsored by:
Alpharma, Inc.

I. GENERAL INFORMATION

NADA: 141-124

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

Established Names: Narasin
Nicarbazin
Bacitracin methylene disalicylate

Proprietary Names: Maxiban®
BMD®

Marketing Status: OTC

Note: Narasin/nicarbazin will hereafter be referred to as Maxiban® , the Type A Medicated Article containing a fixed 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 as an aid in the control or prevention of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin.

III. DOSAGE

A. *Dosage form:* Type A medicated articles to be mixed with chicken feed to produce a Type C medicated feed for use as the sole ration.

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

C. *Recommended Dosage:*

For the prevention of coccidiosis and as an aid in the control of necrotic enteritis, narasin and nicarbazin at 27 to 45 grams/ton each and bacitracin methylene disalicylate at 100 to 200 g/ton for 5 to 7 days as long as clinical signs persist, then reduce the bacitracin to prevention level (50 g/ton). Feed continuously as the sole ration.

For the prevention of coccidiosis and as an aid in the prevention of necrotic enteritis, narasin and nicarbazin at 27 to 45 grams/ton each and bacitracin methylene disalicylate at 50 g/ton. Feed continuously as the sole ration.

IV. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act (ADAA) 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 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 or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients/animal drugs makes a contribution to the labeled effectiveness.

Narasin and nicarbazin (Maxiban®), as provided by Elanco Animal Health, a Division of Eli Lilly and Company, has previously been separately approved for use in broiler chickens for the prevention of coccidiosis (21 CFR 558.363(d)(1)(iii)). Bacitracin methylene disalicylate (BMD®) as provided by Alpharma Inc., has previously been separately approved for use in broiler chickens as an aid in the control or prevention of necrotic enteritis (21 CFR 558.76(d)(1)(vi)(ix)). Effectiveness for each drug, Maxiban® and BMD®, 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 Alpharma Inc.'s approved NADA 46-592, respectively. Because narasin and nicarbazin (Maxiban®) and bacitracin methylene disalicylate (BMD®) each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that narasin and nicarbazin (Maxiban®) plus bacitracin methylene disalicylate (BMD®) provide appropriate concurrent use for the intended target population. The use of narasin and nicarbazin (Maxiban®) plus bacitracin methylene disalicylate (BMD®) provides appropriate concurrent use because these drugs are intended to treat different conditions (narasin and nicarbazin, coccidiosis; bacitracin methylene disalicylate, necrotic enteritis) 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. Narasin and nicarbazin are not considered to be an antibacterial animal drug for use in broiler chickens for the purposes of 512(d)(4) of the FFDCA, as amended by the ADAA of 1996, because narasin and nicarbazin are approved only for prevention of a protozoal disease in broiler chickens. Thus, pursuant to FFDCA, as amended by the ADAA of 1996, no specific effectiveness studies are required for the approval of NADA 141-124.

V. ANIMAL SAFETY

In accordance with the FFDCA, as amended by the ADAA 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.

Narasin and nicarbazin (Maxiban®), as provided by Elanco Animal Health, a Division of Eli Lilly and Company, has been separately approved for use in broiler chickens for the prevention of coccidiosis (21 CFR 558.363(d)(1)(iii) and 21CFR 558.366(c)). Bacitracin methylene disalicylate (BMD®), as provided by Alpharma Inc., has previously been separately approved for use in broiler chickens as an aid in the prevention or control of necrotic enteritis (21 CFR 558.76(d)(1)(vi)(ix)). Target animal safety for each drug, Maxiban® and BMD®, 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 Alpharma Inc.'s approved NADA 46-592, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of Maxiban® or BMD® when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of this NADA for this combination. Thus, pursuant to FFDCA, as amended by the ADAA of 1996, no specific target animal safety study(ies) is (are) required for approval of NADA 141-124.

VI. HUMAN SAFETY

In accordance with the FFDCA, as amended by the ADAA 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 bacitracin methylene disalicylate (BMD®) have been submitted to NADA 138-952 and NADA 46-592, 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 in 21 CFR 556.445. The tolerance for residues of

bacitracin in uncooked edible tissues of chickens is established at 0.5 ppm in 21 CFR 556.70.

B. Residue Data

Tissue residue study AAC8721, performed by Elanco Animal Health, demonstrated that there were no changes in the residue depletion pattern of each drug when BMD® (bacitracin methylene disalicylate) and Maxiban® (narasin and nicarbazin) were fed to broilers in combination. Broiler chickens were fed *ad libitum* a ration medicated with Maxiban® (50 ppm narasin and 50 ppm nicarbazin) and BMD® (200 g/ton) for 49 days. Control birds were fed unmedicated feed. At practical zero-time (6 hour), one-, two-, and four-day withdrawal, the target tissues of abdominal fat, liver, and muscle were collected from sacrificed birds for the assay of narasin, nicarbazin, and bacitracin, respectively.

There were no detectable narasin residues at a test sensitivity of 0.02 ppm narasin in the two- and four-day withdrawal tissues. The residue level of nicarbazin in the four-day withdrawal tissues was 0.24 ± 0.05 ppm, which is well below the established tolerance level. The residue level of BMD® in medicated, practical zero-time withdrawal tissues was determined to be less than 0.30 ppm, which corresponds to the test sensitivity of the assay method.

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 grams/ton each of narasin and nicarbazin in finished feeds) and bacitracin methylene disalicylate (100 to 200 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 are 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 microbiological method is used to assay tissues for bacitracin residues. The method entitled; "Modified Microbiological Method for Determination of Bacitracin in Tissues" is available at: FDA, Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

VII. AGENCY CONCLUSIONS

The information submitted in support of this NADA satisfies the requirements of Section 512(d)(4) of the FFDCA and 21 CFR Part 514 of the implementing regulations. The data demonstrate that this combination Type C medicated feed is safe and effective in broiler chickens for the uses approved in this application.

Non-interference among the active ingredients (narasin, nicarbazin and bacitracin methylene disalicylate) in tissue residue depletion at the longest withdrawal time (5 days) or in the performance of the analytical methods for tissue residues was demonstrated.

Adequate directions for use have been written in labeling and there is reasonable certainty they will be followed in practice by poultry producers. Accordingly, the agency has concluded that this combination use shall have over-the-counter marketing status.

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.

This product does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the FFDCA.

VIII. ATTACHED PRODUCT LABELING

A. Bluebird Narasin/Nicarbazin/BMD PNE Type C Broiler Feed Medicated

B. Bluebird Narasin/Nicarbazin/BMD CNE Type C Broiler Feed Medicated