DATE OF APPROVAL LETTER: FEBRUARY 11, 2002

FREEDOM OF INFORMATION SUMMARY

NEW ANIMAL DRUG APPLICATION

NADA 141-154

ROBENZ® + BMD®
(robenidine hydrochloride + bacitracin methylene disalicylate)

"As an aid in 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:	141-154
Sponsor:	Alpharma Inc. One Executive Drive Fort Lee, NJ 07024
Established Names:	Robenidine hydrochloride Bacitracin methylene disalicylate
Proprietory Names:	ROBENZ® BMD®
Marketing Status:	OTC

II. INDICATIONS FOR USE

As an aid in 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:*

As an aid in the prevention of coccidiosis and as an aid in the control of necrotic enteritis: robenidine hydrochloride at 30 grams/ton and bacitracin methylene disalicylate at 100 to 200 g/ton for 5 to 7 days or as long as clinical signs persist, then reduce the bacitracin to prevention level (50 g/ton). Feed continuously as the sole ration.

As an aid in the prevention of coccidiosis and as an aid in the prevention of necrotic enteritis: robenidine hydrochloride at 30 g/ton 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.

Robenidine hydrochloride (ROBENZ®), as provided by Roche Vitamins Inc., has previously been separately approved for use in broiler/fryer chickens as an aid in the prevention of coccidiosis (21 CFR 558.515(d)). Bacitracin methylene disalicylate (BMD®), as provided by Alpharma Inc., has previously been separately approved for use in broiler chicken feed as an aid in the prevention or control of necrotic enteritis (21 CFR 558.76(d)(1)(vi) and (ix)). Effectiveness for each drug, ROBENZ® and BMD®, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Roche Vitamin Inc.'s approved NADA 48-486 and in Alpharma Inc.'s approved NADA 46-592, respectively. Because robenidine hydrochloride (ROBENZ®) 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 robenidine hydrochloride (ROBENZ®) plus bacitracin methylene disalicylate (BMD®) provide appropriate concurrent use for the intended target population. The use of robenidine hydrochloride (ROBENZ®) and bacitracin methylene disalicylate (BMD®) provides appropriate concurrent use because these drugs are intended to treat different conditions (robenidine hydrochloride, coccidiosis; bacitracin methylene disalicylate, necrotic enteritis) likely to occur simultaneously with sufficient frequency in broiler/fryer 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. Robenidine hydrochloride is not considered to be an antibacterial animal drug for use in broiler/fryer chickens for the purposes of 512(d)(4) of the FFDCA, as amended by the ADAA of 1996, because robenidine hydrochloride is approved only as an aid in the 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 141-154.

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.

Robenidine hydrochloride (ROBENZ®), as provided by Roche Vitamins Inc., has previously been separately approved for use in broiler/fryer chickens as an aid in the prevention of coccidiosis (21 CFR 558.515(d)). 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) and (ix)). Target animal safety for each drug, ROBENZ® and BMD®, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Roche Vitamin Inc.'s approved NADA 48-486 and Alpharma Inc.'s approved NADA 46-592, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of ROBENZ® 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 141-154.

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 robenidine hydrochloride (ROBENZ®) and bacitracin methylene disalicylate (BMD®) have been submitted to NADA 48-486 and NADA 46-592, respectively. Tolerances for residues of robenidine hydrochloride in chickens are established at 0.2 ppm in skin and fat and at 0.1 ppm (negligible residue) in edible tissues other than skin and fat (21 CFR 556.580). Tolerances for residues of bacitracin in uncooked edible tissues and eggs of chickens are established at 0.5 ppm (0.02 unit/g) in 21 CFR 556.70.

B. Residue Data

During experiment A-72-35-FT, male and female broiler chickens were fed medicated feed containing the combination of bacitracin methylene disalicylate at 200 g/ton, robenidine hydrochloride at 30 g/ton, and roxarsone at 45 g/ton for 8 weeks. Tissues were collected on 0 and 1 day withdrawal of medication for bacitracin assay, and at 0, 3, and 5 days withdrawal for robenidine and roxarsone analyses. There were no positive findings for bacitracin in any of the tissues (fat, kidney, liver, muscle, and skin) taken at 0 and 1 day withdrawal. Residues of robenidine at 0 day withdrawal of medication averaged <0.10, 0.32, 0.29, and 0.24 ppm for muscle, liver, kidney, and skin, respectively. Robenidine levels in liver and skin were below the sensitivity of the assay method (0.10 ppm) at 3 days withdrawal of medication. Residues in kidney ranged from <0.10 to 0.10 ppm at 3-day withdrawal. Levels of robenidine in fat at 0, 3, and 5 days withdrawal averaged 1.21, 0.20, and <0.10 to 0.12 ppm, respectively.

The available residue chemistry information supports the assignment of a five-day withdrawal period for broiler chickens fed the combination of robenidine hydrochloride (30 g/ton) and bacitracin methylene disalicylate (100 to 200 g/ton).

C. Regulatory Methods for Residues

The regulatory method for robenidine hydrochloride is the polarographic method on file at the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

A microbiological method is used to assay tissues for bacitracin residues. The method entitled; "Modified Microbiological Method for Determination of Bacitracin in Tissues" is on file at the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

VII. AGENCY CONCLUSION

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

Non-interference among the active ingredients (robenidine hydrochloride 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.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action qualifies for a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.33(a)(2).

VIII. ATTACHED PRODUCT LABELING

A. Bluebird Robenidine/BMD-P Type C Broiler/Fryer Feed Medicated
B. Bluebird Robenidine/BMD-CNE Type C Broiler/Fryer Feed Medicated