

Date of Approval: FEB 21 2008

# FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-279

NICARB plus BMD

(Nicarbazin and Bacitracin Methylene Disalicylate)

Type A Medicated Articles  
For Use in the Manufacture of Type C Medicated Feed  
Broiler Chickens

Nicarbazin (113.5 g/ton) and bacitracin methylene disalicylate (50 g/ton) - As an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix* and *E. brunetti*) coccidiosis and as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin in broiler chickens.

Nicarbazin (113.5 g/ton) and bacitracin methylene disalicylate (4 to 50 g/ton) - As an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix* and *E. brunetti*) coccidiosis and for increased rate of weight gain and improved feed efficiency in broiler chickens.

Sponsored by:

Alpharma Inc.

2008-141-279

FOIS

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**I. GENERAL INFORMATION:**

- A. File Number:** NADA 141-279
- B. Sponsor:** Alpharma Inc.  
440 Rte. 22  
Bridgewater, NJ 08807  
Drug Labeler Code: 046573
- C. Proprietary Names:** NICARB plus BMD
- D. Established Names:** Nicarbazin and bacitracin methylene disalicylate
- E. Pharmacological Categories:** Nicarbazin – Anticoccidial  
Bacitracin methylene disalicylate -  
Antimicrobial
- F. Dosage Forms:** Type A medicated articles to be used in the  
manufacture of Type C medicated feeds
- G. Amount of Active Ingredients:** Nicarbazin – 25 percent nicarbazin  
Bacitracin methylene disalicylate – 10, 25, 30,  
40, 50, 60 or 75 grams bacitracin per pound
- H. How Supplied:** Nicarbazin – 50 lb bag  
Bacitracin methylene disalicylate – 50 lb bag
- I. How Dispensed:** OTC
- J. Dosages:** Nicarbazin – 113.5 g/ton (0.0125%) as an aid in  
preventing outbreaks of cecal (*Eimeria tenella*)  
and intestinal (*E. acervulina*, *E. maxima*,  
*E. necatrix* and *E. brunetti*) coccidiosis in broiler  
chickens.
- Bacitracin methylene disalicylate – 50 g/ton as  
an aid in the prevention of necrotic enteritis  
caused or complicated by *Clostridium spp.* or  
other organisms susceptible to bacitracin in  
broiler chickens.
- Bacitracin methylene disalicylate – 4 to 50 g/ton  
for increased rate of weight gain and improved

feed efficiency in broiler chickens.

**K. Route of Administration:**

Oral, in feed

**L. Species/Class:**

Broiler chickens

**M. Indication:**

Nicarbazin (113.5 g/ton) and bacitracin methylene disalicylate (50 g/ton) - As an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix* and *E. brunetti*) coccidiosis and as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin in broiler chickens.

Nicarbazin (113.5 g/ton) and bacitracin methylene disalicylate (4 to 50 g/ton) - As an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix* and *E. brunetti*) coccidiosis and for increased 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 animal drugs/active ingredients 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, Center for Veterinary Medicine (CVM) will not refuse to approve an NADA for the combination on effectiveness grounds unless CVM finds that the sponsor fails to demonstrate that:

- there is substantial evidence to indicate that any active ingredient/drug intended only for the same use as another active ingredient/animal drug in combination makes a contribution to the labeled effectiveness.
- 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.
- where the combination contains more than one nontopical antibacterial active ingredient/animal drug, there is a substantial evidence that each of the nontopical

antibacterial active ingredients/animal drugs makes a contribution to the labeled effectiveness

Nicarbazin as provided by Phibro Animal Health has previously been separately approved at 113.5 g/ton for use in broiler chickens as an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix*, and *E. brunetti*) coccidiosis in broiler chickens (21 CFR 558.366(d)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved at 50 g/ton as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin in broiler chickens (21 CFR 558.76(d)(1)(vi)), and at 4 to 50 g/ton for increased rate of weight gain and improved feed efficiency in broiler chickens ((21 CFR 558.76(d)(1)(i)). Effectiveness of each drug, nicarbazin and bacitracin methylene disalicylate, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma Inc.'s approved NADA 046-592 for bacitracin methylene disalicylate, and Phibro Animal Health's approved NADA 009-476 for nicarbazin, to which Alpharma Inc. has right of reference.

Nicarbazin and bacitracin methylene disalicylate are each intended for a different use; therefore, the NADA need not demonstrate by substantial evidence, that either drug, nicarbazin and bacitracin methylene disalicylate, contributes to the labeled effectiveness of the combination. Nicarbazin and bacitracin methylene disalicylate provide appropriate concurrent use because these drugs are intended to treat different conditions likely to occur simultaneously in broiler chickens. Nicarbazin is approved as an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix*, and *E. brunetti*) coccidiosis in chickens. Bacitracin methylene disalicylate is approved as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin in broiler chickens and for increased rate of weight gain and improved feed efficiency in chickens.

### III. TARGET ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in animal feed have previously been approved separately for the particular uses and conditions of use for which they are intended for use in combination, CVM 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 that cannot adequately be evaluated based on the information contained in the application for the combination, and FDA finds that the application fails to show that the combination is safe, or

- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and FDA finds that the application fails to show that the combination is safe.

Nicarbazin as provided by Phibro Animal Health has previously been separately approved at 113 g/ton for use in chickens as an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix*, and *E. brunetti*) coccidiosis in broiler chickens (21 CFR 558.366(d)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved at 50 g/ton as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin in broiler chickens (21 CFR 558.76(d)(1)(vi)), and at 4 to 50 g/ton for increased rate of weight gain and improved feed efficiency in chickens ((21 CFR 558.76(d)(1)(i))).

Under the provisions of ADAA, this original approval allows for the combination of nicarbazin (as provided by Phibro Animal Health) and bacitracin methylene disalicylate (as provided by Alpharma Inc.). Target animal safety of each drug, nicarbazin and bacitracin methylene disalicylate when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma Inc.'s approved NADA 046-592, and Phibro Animal Health's NADA 009-476, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of nicarbazin and 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 studies are required for approval of NADA 141-279.

#### IV. HUMAN FOOD SAFETY:

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have already been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on human food safety grounds unless CVM finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or
- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or animal drug in the combination.

**A. Toxicology:**

Safety of the individual drugs in this combination product has been established by data submitted to NADA 9-476 for nicarbazin (NICARB) and to NADA 46-592 for bacitracin methylene disalicylate (BMD, FOI Summary for the approval effective April 30, 1982, 47 FR 18591). Safety of the combination product has been established by data in NADA 98-378.

**B. Residue Chemistry:**

**1. Summary of Residue Chemistry Studies**

Data demonstrating residue depletion and assay noninterference for the drugs of this combination have been provided to NADA 98-378.

**2. Target Tissue and Marker Residue Assignment**

No marker residue and target tissue is specified for either nicarbazin or bacitracin methylene disalicylate.

**3. Tolerance Assignments**

The tolerance for residues of nicarbazin in uncooked muscle, liver, skin, and kidney of chickens is 4 ppm (21 CFR 556.445). The tolerance for residues of bacitracin from bacitracin methylene disalicylate in uncooked edible tissues of chickens is 0.5 ppm (21 CFR 556.70).

**4. Withdrawal Time(s)**

The available data support a withdrawal period of 4 days for the combination use of nicarbazin (113.5 g/ton) and bacitracin methylene disalicylate (4 to 50 g/ton or 50 g/ton).

**C. Microbial Food Safety:**

The Agency determined that an assessment of the microbial food safety associated with this application for the combination of nicarbazin and bacitracin methylene disalicylate for use in chickens, approvable pursuant to the provisions of the Animal Drug Availability Act (1996), was not necessary at this time.

**D. Analytical Method for Residues:**

A microbiological method, "Modified Microbiological Method for Determination of Bacitracin in Tissues," is used to assay tissues for bacitracin residues. The determinative assay for measuring residues in liver from chickens treated with nicarbazin is by high performance liquid chromatography (HPLC) with UV detection. The regulatory method is provided in the AOAC reference: Lewis, J.L., Macy, T.D.,

& Gartiez, D.A., (1989) J. Assoc. Off. Anal. Chem. 72, 577-581. The methods are available from the Center for Veterinary Medicine, FDA, 7500 Standish Place, Rockville, MD 20855.

#### V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to NICARB:

**Keep this and all drugs out of the reach of children.**

The representative (blue bird) labeling for the Type C medicated feeds contains no information regarding safety to humans handling, administering, or exposed to NICARB or BMD. This is based upon review of the MSDS sheets for NICARB and BMD, and the individually approved blue bird labeling.

#### VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512(d)(4) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that NICARB (113.5 g/ton) plus BMD (50 or 4 to 50 g/ton), when used according to the label, is safe and effective as an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix* and *E. brunetti*) coccidiosis, as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin, and for increased rate of weight gain and improved feed efficiency in broiler chickens. Additionally, data demonstrate that residues in food products derived from broiler chickens treated with NICARB plus BMD will not represent a public health concern when the product is used according to the label.

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.

##### A. Marketing Status:

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the lay person have been provided. Label directions provide detailed instruction in plain language. The drug product is not a controlled substance. Thus, the drug product is assigned OTC status, and the labeling is adequate for the intended use.

##### B. Exclusivity:

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act.

**C. Patent Information:**

No patent information was supplied by the sponsor.

**VII. ATTACHMENTS:**

Final Printed Labeling:

Nicarbazin and Bacitracin Methylene Disalicylate - NE Broiler Chicken Ration Type  
C Medicated Feed

Nicarbazin and Bacitracin Methylene Disalicylate Broiler Chicken Ration Type C  
Medicated Feed

**Nicarbazin and Bacitracin Methylene Disalicylate – NE  
Broiler Chicken Ration  
Type C Medicated Feed**

As an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix* and *E. brunetti*) coccidiosis and as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin in broiler chickens.

**ACTIVE DRUG INGREDIENTS**

Nicarbazin\* ..... 113.5 g/ton (0.0125%)  
Bacitracin methylene disalicylate\* ..... 50 g/ton

**GUARANTEED ANALYSIS**

Crude protein, not less than .....	_____	%
Lysine, not less than .....	_____	%
Methionine, not less than .....	_____	%
Crude fat, not less than .....	_____	%
Crude fiber, not more than .....	_____	%
Calcium, not less than .....	_____	%
Calcium, not more than .....	_____	%
Phosphorus, not less than .....	_____	%
Salt <sup>1</sup> , not less than .....	_____	%
Salt <sup>1</sup> , not more than .....	_____	%

<sup>1</sup>If added.

**INGREDIENTS**

Each ingredient must be named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

**FEEDING DIRECTIONS**

Feed continuously as sole ration from time chicks are placed on litter until past the time when coccidiosis is ordinarily a hazard.

**CAUTION:** Do not feed to laying hens. Do not use as a treatment for outbreaks of coccidiosis. Do not use in flushing mashers.

**WARNING:** Withdraw 4 days before slaughter.

**MANUFACTURED BY**

BLUE BIRD FEED MILL  
Robin, IN 12345  
NET WT 50 LBS (22.67 kg)

\* BMD® is a registered trademark of Alpharma Inc. Nicarb® is a registered trademark of KOFFOLK Inc.

**Nicarbazin and Bacitracin Methylene Disalicylate  
Broiler Chicken Ration  
Type C Medicated Feed**

As an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina*, *E. maxima*, *E. necatrix* and *E. brunetti*) coccidiosis and for increased rate of weight gain and improved feed efficiency in broiler chickens.

**ACTIVE DRUG INGREDIENTS**

Nicarbazin\* ..... 113.5 g/ton (0.0125%)  
Bacitracin methylene disalicylate\* ..... 4 to 50 g/ton\*\*

**GUARANTEED ANALYSIS**

Crude protein, not less than ..... %  
Lysine, not less than ..... %  
Methionine, not less than ..... %  
Crude fat, not less than ..... %  
Crude fiber, not more than ..... %  
Calcium, not less than ..... %  
Calcium, not more than ..... %  
Phosphorus, not less than ..... %  
Salt<sup>1</sup>, not less than ..... %  
Salt<sup>1</sup>, not more than ..... %

<sup>1</sup>If added.

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**BLUE BIRD FEED MILL**  
Robin, IN 12345  
NET WT 50 LBS (22.67 kg)

\* BMD® is a registered trademark of Alpharma Inc. Nicarb® is a registered trademark of KOFFOLK Inc.  
\*\* The final printed label on the formulated Type C Medicated Feed must bear a single concentration of each drug.