Approval Date: August 13, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-937

B. Sponsor

Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

C. Proprietary Name

COBAN®, BMD®

D. Established Name

monensin sodium, bacitracin methylene disalicylate

E. Dosage Form

Bacitracin methylene disalicylate is supplied as a Type A Medicated Article in concentrations of 25, 30, 40, 50, 60, or 75 grams of bacitracin activity per pound. Monensin sodium is supplied as a Type A Medicated Article in concentrations of 45 and 60 grams of monensin activity per pound.

F. Route of Adminsitration

OTC

G. Indication

For the prevention of coccidiosis caused by *Eimeria adenoeides*, *E. meleagrimitis*, and *E.gallopavonis* and as an aid in the control of transmissible enteritis complicated by organisms susceptible to bacitracin methylene disalicylate in growing turkeys.

H. Effect of Supplement

This supplemental application provides for a new combination including bacitracin methylene disalicylate, as an aid in the control of transmissible enteritis complicated by susceptible organisms at a new use level, when used in Type C medicated feeds in combination with monensin for the prevention of coccidiosis.

II. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amendedby 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, 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/drug intended only for the same use as

another active ingredient/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 thecombination contains more than one nontopical antibacterial active ingredient/animal drug, there is substantial evidence that each of the nontopical antibacterial activeingredients/animal drugs makes a contribution to the labeled effectiveness [Section512(d)(4)(D) of the FFDCA].

The approval of NADA 46-592 established the effectiveness of bacitracin methylene disalicylate (200 g/ton) as an aid in the control of transmissible enteritis complicated by susceptible organisms in growing turkeys when used for 5 to 7 days or as long as symptoms persist.

The approval of NADA 130-736 established the effectiveness of monensin sodium (54 to 90 g/ton) for the prevention of coccidiosis in growing turkeys due to *Eimeria adenoeides*, *E.meleagrimitis*, and *E. gallopavonis*.

The original approval of NADA 140-937 established the effectiveness of bacitracin methylene disalicylate (4 to 50 g/ton) for increased rate of weight gain in combination with monensin sodium (54 to 90 g/ton) for the prevention of coccidiosis caused by Eimeria adenoeides, E.meleagrimitis, and E. gallopavonis in growing turkeys. The data in this approval further demonstrates that the addition of bacitracin methylene disalicylate (220g/ton) to monensin sodium (60 g/ton) in complete turkey feed had no adverse effects on anticoccidial efficacy.

Based on the data in the approved single ingredient applications, the original approval of this NADA, and the provisions of the Animal Drug Availability Act of 1996, the burden to establish effectiveness of the combination use has been met.

III. TARGET 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 animal drugs/active ingredients 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 incombination, 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 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 animal drug is safe for the target animal.

The basic animal safety data for the individual drugs may be found in NADA 46-592 for BMD® and in NADA 130-736 for COBAN®. The effectiveness data in the original approval of this NADA demonstrate that no ill effects occurred when the drugs were combined, indicating that they are safe when fed in combination.

Additional safety studies were not required because: (1) the drugs have been approved singularly, and (2) adequate documentation has been provided to show that these compounds are compatible in combination when used in turkey feeds. Therefore, based on data in the original NADAs for the single ingredients, it is concluded that this combination of drugs may be safely fed to growing turkeys.

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 Tests

Basic toxicity data for bacitracin methylene disalicylate may be found in NADA 46- 592 (41 FR 10793; March 15, 1976 and 46 FR 41041; August14,1981), sponsored by ALPHARMA, Inc. Basic toxicity data for monensin may be found in NADA 38-878 (35FR 7734; May 20, 1970), sponsored by Elanco Animal Health. Specific data for monensin in turkeys is included in NADA 130-736 (52FR15718; April30,1987).

B. Tolerances and Safe Concentrations of Residues

The tolerance for residues of bacitracin methylene disalicylate (BMD®) in uncooked edible tissues is established at 21 CFR 556.70 at 0.5 ppm, negligible residue. A tolerance for marker residues of monensin (COBAN®) in turkeys is not needed (21 CFR 556.420).

C. Tissue Residue Depletion Studies

In a tissue residue study conducted to support the approval of the original NADA, five male and five female turkeys were medicated with monensin (90 g/ton) and bacitracin methylene disalicylate (200 g/ton) for 27 days and slaughtered at zero withdrawal (6hours). The tissues were assayed for monensin (skin fat) and bacitracin methylene disalicylate (muscle). All tissues sampled had less than 0.04 ppm of monensin and less than 0.3 ppm of bacitracin methylene disalicylate, which are the respective limits of detection for these assays. These results are comparable to those obtained when each drug is administered alone; therefore, these data support a zero withdrawal period for human consumption of edible tissues of turkeys treated with bacitracin methylene disalicylate plus monensin in the feed.

D. Assay Non-Interference Study

Data from tissue assays, which were included in the original approval of this NADA, demonstrated that there is no interference by monensin for bacitracin methylene disalicylate and no interference by bacitracin methylene disalicylate for monensin.

E. Regulatory Methods

Bacitracin: Antibiotic Residue 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 Tissue, Test Procedure Code9A. A.L. Laboratories Inc., One Executive Drive, P.O. Box 1399, FortLee,NJ 07024.

Monensin: Determination of Monensin in Tissues and Eggs. Method 5801654. Eli Lilly and Company, Box 708, Greenfield, IN 46140.

These methods are on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.

V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA comply with the requirements of Section 512 of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that monensin (54 to 90 g/ton) plus bacitracin methylene disalicylate (200 g/ton) are safe and effective for the prevention of coccidiosis caused by *Eimeria adenoeides*, *E. meleagrimitis*, and *E.gallopavonis* and as an aid in the control of transmissible enteritis complicated by organisms susceptible to bacitracin methylene disalicylate in growing turkeys.

In accordance with 21 CFR 514.106(b)(2)(iii) & (v), this supplemental approval is a Category II change which did not require a reevaluation of safety and efficacy data in the parent applications.

Residue data show that monensin is well within the established safe concentrations of 4.5ppm in liver, 3.0 ppm skin/fat, and 1.5 ppm muscle of the turkey at zero withdrawal. Residue data show bacitracin methylene disalicylate is well below tolerance of 0.5 ppm in edible turkey tissues at zero withdrawal.

In accordance with 21 CFR 25.33(a)(2), 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.

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.