Date of Approval Letter:

FREEDOM OF INFORMATION SUMMARY

NEW ANIMAL DRUG APPLICATION

NADA 141-148

Combination of DECCOX® AND RUMENSIN® in Cattle Feed
(decoquinate and monensin)

"For the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*, and for increased feed efficiency in cattle being fed in confinement for slaughter"

Sponsored by**:**

Alpharma, Inc.

I. GENERAL INFORMATION

NADA Number:	141-148
Sponsor:	Alpharma, Inc. One Executive Drive, P.O. Box 1399 Fort Lee, New Jersey 07024
Established Names	decoquinate monensin
Trade Names:	DECCOX® RUMENSIN®
Marketing Status:	Over-The-Counter

II. INDICATIONS FOR USE

For the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*, and for increased feed efficiency in cattle being fed in confinement for slaughter.

III. DOSAGE

A. *Dosage Form:* This original NADA provides for the combined use of two Type A medicated articles, decoquinate as per 21 CFR 558.195(d) and monensin as per 21 CFR 558.355(f)(3)(i). Decoquinate is supplied as a Type A medicated article containing 27.2 grams of decoquinate per pound (6%). Monensin is supplied as Type A medicated article in concentrations of 20, 30, 45, 60, 80, or 90.7 grams of monensin per pound.

B. *Route of Administration:* Oral, in feed

C. *Recommended Dose:*
DECCOX®: 13.6 to 27.2 g/ton (22.7 mg/100 lb bodyweight/day)
RUMENSIN®: 5 to 30 g/ton (50 to 360 mg/head/day)

The resultant feed containing both drugs is then fed as the only feed for at least 28 days as specified in 21 CFR 558.195(d) and 21 CFR 558.355(f)(3)(i), which is the recommended duration for decoquinate.

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 or animal drugs makes a contribution to the labeled effectiveness (21 USC 360b(d)(4)(D)).

Decoquinate at 13.6 to 27.2 g/ton (22.7 mg/100 lb bodyweight), as provided by Alpharma Inc., has previously been separately approved for use in cattle feed for the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*, and is codified in 21 CFR 558.195(d).

Monensin at 5 to 30 g/ton (50 to 360 mg/head/day), as provided by Elanco Animal Health, has previously been separately approved for use in cattle feed for improved feed efficiency, and is codified in 21 CFR 558.355(f)(3)(i).

The effectiveness for the two drugs, decoquinate and monensin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in the approved NADAs 039-417 and 095-735, respectively.

Because decoquinate and monensin each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that decoquinate plus monensin provide appropriate concurrent use for the intended target population. The use of decoquinate and monensin provides appropriate concurrent use because these drugs are intended to treat different conditions (decoquinate, coccidiosis; monensin, increased feed efficiency) likely to occur simultaneously with sufficient frequency in cattle being fed in confinement for slaughter. There is no more than one nontopical antibacterial (none in this combination) contained in this combination animal drug intended for use in Type C medicated feed. Decoquinate is not considered to be an antibacterial animal drug for use in cattle for the purposes of 512(d)(4) of the FFDCA, because decoquinate is approved for the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii* in calves, beef and non-lactating dairy cattle. Monensin is not considered to be an antibacterial animal drug for use in cattle for the purposes of 512(d)(4) of the FFDCA, because monensin is approved for improved feed efficiency in cattle being fed in confinement for slaughter.

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 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.
Target animal safety for each drug, decoquinate and monensin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in

Alpharma's approved NADA 039-417 and Elanco Animal Health's approved NADA 095-735, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of decoquinate or monensin when used in combination in 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 the approval of NADA 141-148.

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 condition 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. Safety for the approved products, decoquinate and monensin, has been established by data submitted to NADAs 039-417 and 095-735, respectively.

A. *Toxicity Studies:* Data in the single ingredient applications demonstrate that the use of these drugs does not constitute a hazard to human health when used in accordance with approved labeling. Safety of this combination product has been established by data in NADA 095-735 for monensin and NADA 039-417 for decoquinate.

B. *Tolerance and Acceptable Daily Intake:* A tolerance of 0.05 ppm for residues of monensin in the edible tissue of cattle has been codified previously under 21 CFR 556.420. For decoquinate, a tolerance of 2 ppm in uncooked edible tissues other than skeletal muscle and 1 ppm in skeletal muscle in cattle has been codified previously under 21 CFR 556.170.

   An Acceptable Daily Intake (ADI) of 0.075 mg/kg bodyweight/day has been established for decoquinate. An ADI of 0.0125 mg/kg bodyweight/day has been established for monensin.

C. *Residue Non-Interference Study:* Residue data supporting the approved individual uses of decoquinate and monensin, each having zero withdrawal times, were submitted in their respective original applications (see Part A, above).

   The in-life portion of the following study (Study No. RC001-98CH5313) was conducted at Southwest Bio-Labs, Las Cruces, New Mexico with assays conducted at Analytical Development Corporation, Colorado Springs, Colorado and Colorado Animal Research Enterprises (CARE), Fort Collins, Colorado to establish that each

   drug in the presence of the other does not exceed its established tolerance at zero withdrawal and that the presence of the drugs in the same cattle tissue did not

interfere with the assay of either drug.

Crossbred control cattle (1 steer, 1 heifer) were fed unmedicated feed for 17 days. Test crossbred cattle (3 steers, 3 heifers) received feed containing 27.2 grams decoquinate and 30 and grams monensin for 14 days. All cattle were slaughtered within 12 hours after removing the feed. Liver tissue was collected and analyzed for residues. Decoquinate residues were measured using an HPLC method ("Analysis of Decoquinate Residues in Animal Tissues Using Zymate Robotic System", Analytical Chemistry Guidebook, USDA, FSIS, Winter, 1991). Monensin residues were measured by an HPLC method ("Determination of ionophores in the tissues of food animals by liquid chromatography", Food Additives and Contaminants, 1995. 12(6):731-737). The official microbiological method was used to detect tylosin in the tissue.

Mean Residues of Decoquinate, Monensin, and Tylosin in Liver Collected from Cattle Treated with Medicated Feed Containing 27.2 grams Decoquinate, 30 grams Monensin, and 10 grams Tylosin for 14 Days

Withdrawal Time in Hours	Decoquinate (ppm)	Monensin (ppm)	Tylosin (ppm)
0	<LOQ	0.014 ppm	<LOQ

LOQ: decoquinate = 0.15 ppm, monensin = 0.01 ppm, tylosin = 0.1 ppm

Samples of control liver were fortified with decoquinate, monensin, and tylosin. The data showed that the presence of decoquinate and monensin did not interfere with the assay of tylosin, the presence of decoquinate and tylosin did not interfere with the assay of monensin, and the presence of monensin and tylosin did not interfere with the assay of decoquinate.

Residues of decoquinate, monensin, and tylosin were below their respective tolerances at zero withdrawal, the established withdrawal periods for each of the drugs, thereby indicating an absence of interference.

D. *Analytical Methods for Residues (Regulatory Methods):* The regulatory method for the determination of decoquinate in tissues uses a fluorometric assay procedure and is found in *Official Methods of Analysis of AOAC International*, 16th edition. The regulatory method for monensin is a bioautography procedure. These methods are on file at the Center for Veterinary Medicine, Food and Drug Administration (HFV-199), 7500 Standish Place, Rockville, MD 20855.

VII. AGENCY CONCLUSIONS

The information submitted in support of this NADA comply with the requirements of Section 512 of the FFDCA and demonstrate that decoquinate (13.6 to 27.2 g/ton) and monensin (5 to 30 g/ton) are safe and effective for the claimed indications in section II of this FOI summary.

In accordance with Section 512 of 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 tolerance of 0.05 ppm for residues of monensin in the edible tissue of cattle has been codified previously under 21 CFR 556.420. For decoquinate, a tolerance of 2 ppm in tissues other than skeletal muscle and 1 ppm in skeletal muscle in cattle has been codified previously under 21 CFR 556.170. The data demonstrate that residues for decoquinate and monensin were below their respective tolerances at zero withdrawal, the established withdrawal periods for each of the drugs, thereby indicating an absence of interference.

The non-interference studies adequately demonstrated non-interference in the approved AOAC Type C medicated feed test methods for decoquinate and monensin for the proposed combined use.

There is reasonable certainty that the conditions of use, including directions on labeling, can and will be followed by cattle producers. Accordingly, the agency has concluded that this product shall retain 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 of preparing an environmental assessment in accordance with 21 CFR 25.33(a)(2).

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for food-producing animals does not qualify for marketing exclusivity because the application does not contain substantial evidence of the effectiveness of the drugs involved, any studies of animal safety, or, in the case of food-producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

VIII. APPROVED LABELING (attached)

Specimen (Blue Bird) label - Type B and Type C medicated feed.