I. GENERAL INFORMATION

A. File Number

NADA 039-417

B. Sponsor

Rhone Poulenc Inc.
500 Northridge Road
Suite 620
Atlanta, Georgia 30350

C. Proprietary Name

Deccox

D. Established Name

decoquinate

E. Dispensing Status

OTC

F. Effect of Supplement

This supplement adds a new species (young sheep) to the approved label.

II. EFFECTIVENESS

A. Pivotal Study No. 1.

1. Type of Study: Dose Titration

2. Name and Address of Investigator:

   Dr. William J. Foreyt
   Department of Veterinary
   Microbiology and Pathology
   Washington State University
   Pullman, Washington 99164

3. Purpose of the Study: To determine the effectiveness of decoquinate for the prevention of coccidiosis in naturally infected feedlot lambs and to determine the optimum dosage.

4. Test Animals: Twenty weaned lambs (average = 30.75 pounds) were randomly allocated for this study. The study consisted of 5 groups of 4 lambs each. The lambs were primarily Columbia cross. Each group consisted of castrated males and females. The animals were purchased from a herd at Deer Park, Washington. Lambs were weighed at days 3, 11, 22 and 31 of the experiment. Water was provided ad libitum.

5. Feed: Feed consisted of pelleted ration of alfalfa (62.5%) and barley (37.5%). Free choice pellets, hay, and mineralized salt were provided ad libitum.

6. Identification: Lambs were identified by colored tags according to group.

7. Location: The study was conducted at Washington State University, Animal Research Facilities, Pullman, WA.

8. Treatment: The treatments were infected non medicated (infected control), infected medicated with decoquinate* 0.5 mg/kg body weight. Medication was adjusted based on lamb weights on days 0, 7, 14, 21 and 28.

   *Decoquinate administered as Deccox Premix.

9. Test Duration: The medicated feed was fed for 31 days.

10. Diagnosis: Fecal samples were collected from the rectum of all lambs on experimental days 0, 4, 8, 11, 15, 22, 25 and 31. Species of oocysts were identified.

Parameters: Clinical Observation; Weight gain; Microscopic parasitic number; and Mortality.

Results: All lambs were passing oocysts when the titration study began. The coccidia species isolated in all the lambs were Eimeria ovinoidalis, E. ovina, E. crandallis, E. parva and E. intricata. No mortality reported in the study, and no weight differences were present among the groups (Refer to Table 1). Decoquinate at 0.5 mg/kg body weight suppressed oocyst production by post-treatment day 31. On day 31, the control group had an average of 8714 oocysts per gram of feces, and treated lambs had an average of 189 oocysts per gram of feces.

Decoquinate at 1.0 mg suppressed oocyst production on days 22, 25 and 31 of the experiment. Decoquinate at 4 mg/kg body weight suppressed oocyst production on days 15, 18, 22, 25 and 31 of the experiment. However, there were no numerical differences in oocyst suppression among the treated groups. No signs of toxicity or palatability problems were reported in this study.

The data showed that decoquinate premix at 0.5, 1.0 and 4.0 mg/kg body weight is efficacious against naturally occurring coccidia infections in lambs (Refer to Table 2).

Conclusion: The 0.5mg/Kg was selected to be the optimum dose because it was effective in the prevention of coccidiosis in young sheep and treated animals gained more weight on less feed, and they gained more weight than the sheep in the untreated control group. Additionally, the dose reflects the approved dose labeled for cattle, goats and poultry.

Table 1. Summary of Mean Weights by Treatments

Decoquinate Group	Days After Treatment Initiation				Weight Gain
	3	11	22	31	
0 mg/kg	14.0	18.1	20.6	22.7	8.7
0.3m/kg	14.1	19.0	19.4	20.9	6.8
0.5 mg/kg	14.2	19.3	21.5	23.6	9.4
1.0 mg/kg	14.0	19.2	22.0	21.5	7.5
4.0 mg/kg	13.7	21.3	23.1	24.6	10.9

Table 2. Summary of mean oocyst counts by treatments

Decoquinate (mg/kg body weight)	Days After Treatment Initiation								
	0	4	8	11	15	18	22	25	31
0	1097	7680	1292	3221	2556	4562	10,715	8357	8714
0.3	2459	1958	1542	536	551	1092	321	2903	1922
0.5	2444	10,007	3860	426	980	1032	1905	425	189
1.0	1862	1793	2037	588	1472	344	276	56	246
4.0	2273	546	632	51	128	29	11	12	32

B. Pivotal Study No. 2.

1. Type of Study: Dose Confirmation

2. Name and Address of Investigator:

   Dwight D. Bowman, Ph.D.
   College of Veterinary Medicine
   Cornell University
   Ithaca, NY. 14853

3. Purpose of the study: To evaluate the effectiveness of decoquinate in feed at the rate of 0.5 mg/kg in coccidia free lambs infected by inoculation with known species of coccidia.

4. Test Animals: Eighteen lambs were acquired at birth and transferred to an isolation facility where they were hand-reared in a coccidia-free environment. There were 10 males and 8 females in the initial group.

5. Feed: Initially, lambs were fed bovine colostrum, Ultra Fresh® Lamb Milk Replacer and Entrolyte. When old enough to eat solid food, they were fed Hi-Energy Lamb Pellets.

6. Identification: Fourteen of the original 18 lambs were selected nine males and five females. Lambs were identified by ear tags bearing individual numbers. Six were assigned to non-medicated infected group and six assigned to medicated infected group. The remaining two were retained as monitors, non infected non-medicated.

7. Location: The study was conducted in the research facilities at the Veterinary

College, Cornell University, Ithaca, NY.

8. Treatment: The treatments were infected non-medicated (infected control) and infected medicated with decoquinate* at 0.5 mg/kg body weight. Medication was adjusted based on lamb weights on days 0, 7, 14, 21 and 28.

   *Decoquinate administered as Deccox Premix

9. Test duration: 31 days

10. Diagnosis: Necropsies of all dead animals, microscopic identification of asexual forms and gamonts of coccidia in tissues, and identification of oocysts in feces.

11. Parameters: Clinical observations (body condition, fecal scores and fecal staining around anus); weight; coccidia numbers by days and species; and mortality.

12. Results: None of the lambs were passing oocysts when the study began. The two animals, non medicated non infected remained negative for the entire period. Oocysts were present in the feces of all lambs that were inoculated. (See Table 2)

The number of oocysts shed by the infected controls was much higher than those found in the decoquinate treated group. Lambs in the infected control group began dying on Day 17 of the test and by Day 28 the mortality was 100 per cent. (See Table 1). Necropsies and microscopic examinations confirmed that all deaths were caused by coccidiosis. In contrast, there were no deaths in the decoquinate medicated group. General body condition, fecal scores and fecal staining around the anus were highly favorable to decoquinate medicated lambs over the infected control animals while the latter were alive.

Table 1. Average Weight and Mortality

Group	Treatment	Infection	Ave Day-17 Weight (kg)	Mortality Day 31	D/T
1	None	None	7.5	19.05	0/2
2	None	Yes	7.8	Dead	6/6
3	Decoquinate	Yes	8.06	16.08	0/6

Table 2. Oocysts Per Gram of Feces (Average per Group*)

Group	Species	Day Post Oocyst Inoculation				
		17	**21**	**24**	**28**	**31**
1	*E. ovinoidalis*	0	0	0	0	0
2	*E. ovinoidalis*	716,800	231,440	1,775,733	Dead	Dead
3	*E. ovinoidalis*	37,000	200	323	0	0
1	*E. baukuensis*	0	0	0	0	0
2	*E. baukuensis*	0	40,840	3,077,067	Dead	Dead
3	*E. baukuensis*	0	0	0	63,066	5,200
1	*E. Parva*	0	0	0	0	0
2	*E. Parva*	396,266	19,370	180,000	Dead	Dead
3	*E. Parva*	24,466	2,866	0	2,600	29,716
1	*E. crandalis*	0	0	0	0	0
2	*E. crandalis*	0	122,533	590,667	Dead	Dead
3	*E. crandalis*	0	0	533	9,466	13,266

*Based on the number animals alive on a given day.

Conclusion: The data collected in the dose titration study has been verified by the data generated in the dose confirmation study and together these pivotal studies have demonstrated that Decoquinate is effective in the prevention of coccidiosis caused by Eimeria bakuensis, E. crandallis, E. ovinoidalis and E. parva in young sheep.

III. TARGET ANIMAL SAFETY

A. Pivotal Target Animal Safety Study

1. Name and Address of Investigator:

   Dr. William J. Foreyi
   Microbiology and Pathology
   Washington State University
   Pullman, Washington 99164

2. Purpose of the Study: (This study is also the pivotal dose titration study). To determine the safety of decoquinate in lambs at doses up to 8x for 31 days.

3. Test Animals: Twenty weaned lambs (average = 30.75 pounds) were randomly allocated for this study. The study consisted of 5 groups of 4 lambs each. The lambs were primarily Columbia cross. Each group consisted of castrated males and females. The animals were purchased from a herd at Deer Park, Washington. Lambs were weighed at days 3, 11, 22 and 31 of the experiment. Water was provided ad *libitum.*

4. Feed: Feed consisted of pelleted ration of alfalfa (62.5%) and barley (37.5%). Free choice pellets, hay, and mineralized salt were provided *ad libitum.*

5. Identification: Lambs were identified by colored tags according to group.

6. Location: The study was conducted at Washington State University, Animal Research Facilities, Pullman, WA.

7. Treatment: The treatments were (a) infected nonmedicated(b) infected

medicated with decoquinate* 0.3 mg/kg body weight (c) infected medicated with decoquinate 0.5 mg/kg body weight (d) infected medicated with decoquinate 1.0 mg/kg body weight and (e) infected medicated with decoquinate 4.0 mg/kg body weight. The amount of medicated feed was adjusted on a weekly basis, based on weight of the lamb in each group.

8. Test Duration: The medicated feed was fed for 31 days.

9. Diagnosis: Fecal samples were collected from the rectum of all lambs on experimental days 0, 4, 8, 11, 15, 22, 25 and 31. Species of oocysts were identified.

10. Parameters: Clinical Observation (signs of toxicity); Microscopic parasitic number; and Mortality.

B. Conclusion: None of the lambs died or were clinically ill during the 31 day experimental period. No signs of toxicity or palatability problems were noted. All sheep were passing oocysts when the study began. Feeding decoquinate as high as 4.0 mg/kg body weight (8 times the recommended dose level) for 31 days was safe to the sheep.

IV. HUMAN FOOD SAFETY

A. Tolerances

The tolerances for residues of decoquinate in sheep are 1 ppm for muscle and 2 ppm for liver, kidney and fat.

B. Total Residue Depletion and Metabolism Studies

A study entitled "A Metabolism-Residue Study in Lambs with 14C-Decoquinate" was conducted by WIL Research Laboratories. Two wethers and two ewes, confined in metabolism cages and weighing about 40 to 50 kg, were treated with micronized 14C-3-decoquinate at 0.53 to 0.57 mg/kg per day (the intended dose) over a 4-day period. Dosing was done twice a day with gelatin capsules. One wether was used as a control. The drug had a specific activity of about 5.1 uCi/mg and a radiopurity of greater than 98%. The lambs were sacrificed at 8 to 12 hrs (practical zero withdrawal) after the last dose. Samples of edible tissue were collected and stored under freezer conditions.

Total residue concentrations in muscle, liver and kidney were measured by combustion and scintillation counting. Abdominal fat was macerated and extracted to give two fractions. Aliquots of the extracts were analyzed directly for radioactivity after evaporation of the solvent. The insoluble fraction was analyzed by combustion and scintillation counting. The total residue for fat was given as the sum of the two fractions. The results of radioanalyses on the edible tissues are given in Table 1. The total residue in each tissue is less than one-half of the tolerances of 1 ppm for muscle and 2 ppm for the other edible tissues.

Table 1. Average Total Residue Concentrations in Edible Tissues of Sheep Treated at 0.5 mg/kg/day for 4 Days and Sacrificed at Zero Withdrawal

Animal	Average Total Residue in ppm			
	Liver	**Kidney**	**Muscle**	**Fat**
2 (male)	0.177	0.111	0.009	0.022
3 (male)	0.271	0.130	0.024	0.031
4 (female)	0.200	0.111	0.010	0.022
5 (female)	0.222	0.108	0.010	0.003
average all	0.218	0.115	0.013	0.020

Isolates from the lambs were analyzed with TLC to give residue profiles. In this profiling work, four lanes were used: Lanes A and D were spotted with 14C-decoquinate, while Lanes B and C were spotted with liver or kidney isolates. Decoquinate represented from 20.6% to 59.3% of the radioactivity in liver and from 13% to 36.6% of the radioactivity in kidney. While there was some variability of the percentage for decoquinate in the individual animals, the profiles were similar.

As noted above, the profiling data from sheep show that decoquinate makes up from 20.6% to 59.3% of the radioactivity in liver and from 13% to 36.6% of the radioactivity in kidney. Moreover, there appeared to be at least two other fractions. These results compare favorably with those in rats as presented in J. Ag. Food Chem., 19, 1234 (1971), which was submitted to this NADA several years ago and which is referenced in the final report of the study. In that article, it was reported that decoquinate was 42% of the radioactivity in rat liver and about 38% of the radioactivity in rat kidney. In addition, three other components were found on TLC. These data from rat and sheep demonstrate comparative metabolism in the two species.

C. Withdrawal Period

The results of the residue study show that at 8 to 12 hours post dosing (practical zero withdrawal), the total residue of decoquinate is less than one-half of the tolerances of 1 ppm for muscle and 2 ppm for the other edible tissues. Therefore, a withdrawal period is not required for the use of decoquinate at 0.5 mg/kg/day for the prevention of coccidiosis in sheep.

D. Regulatory Method

Neither a withdrawal period nor a regulatory method is required for this use of decoquinate in sheep.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR Part 514 of the implementing regulations. The data demonstrate that decoquinate Type A medicated article is safe and effective for the prevention of coccidiosis in young sheep caused by Eimeria ovinoidalis, E. crandallis, E. parva, and E. bakuensis.

The tolerances for residues of decoquinate in sheep are 1 ppm for muscle and 2 ppm for liver, kidney and fat.

The results of the residue study show that at 8 to 12 hours post dosing (practical zero withdrawal), the total residue of decoquinate is less than one-half of the tolerances of 1 ppm for muscle and 2 pp. for the other edible tissues. Therefore, a withdrawal period is not required for the use of decoquinate at 0.5 mg/kg/day for the prevention of coccidiosis in young sheep.

Decoquinate for food producing animals is generally over-the-counter. Accurate diagnosis can be made with reasonable degree of certainty by the layman. Adequate directions for use have been written for the layman, and the conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall have over-the-counter marketing status.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)(vii)), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Under Section 512(c)(2)(F)(iii) of the Act, this approval for food-producing animals qualifies for THREE (3) years of marketing exclusivity beginning on the date of approval because the supplemental application contains reports of new clinical or field investigations (other than bioequivalence or residue studies) essential to the approval of the application and conducted or sponsored by the applicant. The THREE years of marketing exclusivity applies only to the claim for the prevention of coccidiosis in sheep for which the supplemental application was approved.

VI. ATTACHMENTS

#1-Blue Bird Labeling (Type A medicated article) #2-Bag Labeling (Type B medicated feed)

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.