I. GENERAL INFORMATION

A. File Number

NADA 140-934

B. Sponsor

SmithKline Beecham Animal Health
1600 Paoli Pike
West Chester, PA 19380

C. Proprietary Name

VALBAZEN®

D. Established Name

Albendazole

E. Dosage Form

Suspension 4.55% (45.5 mg/mL)

F. Dosage Regimen

Seven and one-half (7.5) mg of albendazole per kg of body weight (3.4 mg/lb) administered orally with a suitable syringe or dosing gun.

G. Route of Administration

Oral

H. Indication

For the removal and control of the following endoparasites infecting sheep:

1. Liver flukes:

Fasciola hepatica, Fascioloides magna(adults)

2. Tapeworms:

Common tapeworms: *Moniezia expansa*

Fringed tapeworms: *Thysanosoma actinioides*(heads and segments)

3. Lungworms:

Dictyocaulus filaria(adults and 4th stage larvae)

4. Stomach worms:

Barberpole worms: *Haemonchus contortus* (adults and 4th stage larvae)

Brown stomach worms: *Ostertagia circumcincta, Marshallagia marshalli*(adults and 4th stage larvae)

Small stomach worms: *Trichostrongylus axei*(adults and 4th stage larvae)

5. Intestinal worms:

Thread-necked intestinal worms: *Nematodirus spathiger, N. filicollis*(adults and 4th stage larvae)

Cooper's worms: *Cooperia oncophora* (adults and 4th stage larvae)

Bankrupt worms: *T. colubriformis* (adults and 4th stage larvae)

Nodular worms: *Oesophagostomum columbianum*(adults and 4th stage larvae)

Large-Mouth Bowel Worms: *Chabertia ovina*(adults and 4th stage larvae)

II. EFFECTIVENESS

This NADA relies on adequate well-controlled studies demonstrating the anthelmintic effectiveness of albendazole in cattle included in approved NADA 110-048 (Albendazole Suspension, 54 FR 25114, June 13, 1989) and NADA 128-070 (Albendazole Paste, 54 FR 51385, November 17, 1989).

In these studies, the cattle were either experimentally or naturally infected with one or more species of nematodes, cestodes and/or trematodes. The claim for each major parasitic species is supported by adequate and well-controlled studies.

Arithmetic means were calculated to determine efficacy and efficacy was expressed in percent removal of worms as compared to controls. The percent reduction was calculated as follows:

Percentage Reduction of Parasites = [(Arithmetic mean no. parasites in control animals – Artithmetic mean no. parasites in treated animals)/Arithmetic mean no. parasites in control animals] x 100

As a product for use in sheep, albendazole qualifies for review under the "Minor Use Drug Program." NADA 110-048 (oral suspension) and NADA 128-070 (oral paste) serve as representative formulations approved for use in a major species (cattle). Since there were no drugs approved for treatment of liver fluke infections, albendazole was made available for treatment of cattle and sheep from 1980 to 1985 on an emergency investigational new animal drug basis in the states where liver fluke disease prevailed.

Developmental research in sheep was conducted in nine pivotal studies consisting of six dose-titration and three dose-confirmation efficacy trials in four different geographic locations in the United States as well as internationally. Doses ranging from 2.5 to 15 mg albendazole per kg body weight, were given orally. The results from these studies were used to determine the most effective dose. A dose of 7.5 mg/kg was effective against the greatest number of parasite species infecting sheep.

Albendazole, in a suspension formulation, was administered orally as a drench, and was evaluated for efficacy using the controlled test, as recommended by the Center for Veterinary Medicine in its "Guidelines for Evaluation of Bovine Anthelmintics," which serves as a guide for all ruminant species. Briefly stated, a certain number of infected sheep remain untreated; the remainder receive medication. After a suitable period of time post-treatment (usually 5 to 7 days, but longer in some circumstances), treated and untreated (control) animals are killed and necropsied. Remaining parasites are identified and counted for each animal.

Albendazole was effective for each parasite claimed. The study conducted against the deer fluke, *Fascioloides magna*demonstrated 57% efficacy. Albendazole will become the only approved therapy for this highly pathogenic parasite in sheep. The results from major controlled efficacy studies supported the conclusion that when given orally to sheep at 7.5 mg/kg body weight, albendazole is an effective anthelmintic with a wide spectrum of activity against adult and larval stages of gastrointestinal roundworms, lungworms, tapeworms and liver flukes infecting sheep.

The investigators and efficacy against individual parasitic species are given in Tables I, II, III and IV.

Table I SUMMARY OF PIVOTAL DOSE-TITRATION STUDIES Efficacy of Albendazole Against Adult Parasites

Parasite	**% Removal (Range)**	**Investigator**
F. magna 5.0-15.0 mg/kg	22-64	Stromberg
F. hepatica 5.0-15.0 mg/kg	94-99	Gurnell
M. expansa 10.0-15.0 mg/kg	100	Theodorides
T. actinioides 3.8-7.5 mg/kg	54-98	Craig
D. filaria 2.5-10.0 mg/kg	51-94	Theodorides
H. contortus 3.8-10.0 mg/kg	85-99	Craig Theodorides
T. axei 3.8-10.0 mg/kg	100	Craig
N. spathiger 2.5-10.0 mg/kg	94-99	Theodorides

Table II SUMMARY OF PIVOTAL DOSE-TITRATION STUDIES Efficacy of Albendazole Against Fourth-Stage Nematode Larvae

Parasite	% Removal (Range)	Investigator
D. filaria 3.8-7.6 mg/kg	89-96	van Schalkwyk
O. circumcincta 5.0-10.0 mg/kg	99-100	Gurnell
Oe. columbianum 5.0-10.0 mg/kg	94-100	Gurnell
N. spathiger 5.0-10.0 mg/kg	100	Gurnell

Table III SUMMARY OF PIVOTAL DOSE-CONFIRMATION STUDIES Efficacy of Albendazole Against Trematodes, Cestodes and Adult Nematodes

Parasite	% Removal (Range)	Investigator
F. hepatica 4.75 mg/kg	83-86	Johns
T. actinioides 7.5 mg/kg	100	Bergstrom
H. contortus 7.5 mg/kg	100	Craig
T. axei 7.5 mg/kg	100	Craig

Table IV SUMMARY OF DOSE-CONFIRMATION STUDIES Efficacy of Albendazole Against Fourth-Stage Nematode Larvae

Parasite	% Removal (Range)	Investigator
H. contortus 7.5 mg/kg	100	Craig

Location of Investigators in Tables I, II, III and IV

Dr. R. C. Bergstrom, Laramie, WY.
Dr. T. M. Craig, College Station, TX.
Dr. T. O. Gurnell, Terenure, South Africa
Dr. D. R. Johns, New South Wales, Australia
Dr. B. E. Stromberg, St. Paul, MN.
Dr. V. J. Theodorides, West Chester, PA.
Dr. P. C. van Schalkwyk, Terenure, South Africa

A. Dose Titration

Pivotal dose-titration studies were carried out to determine the dose of albendazole needed to control trematodes, cestodes, gastrointestinal and pulmonary nematodes. Approximately 170 sheep were used, three-fourths of which were treated with albendazole. The remaining sheep served as untreated controls. An oral suspension formulation was utilized with dosages ranging from

2.5 to 15 mg/kg. Accepted husbandry practices were duplicated with respect to breeds of sheep, diets, and grazing conditions. Standard procedures were followed for allocating, dosing, collecting samples, enumerating and identifying parasites, and performing necropsies. The parasitic infections were experimentally induced in four (4) of the trials and naturally acquired in the remaining two (2) trials. Based on the data collected, an optimum effective dose of 7.5 mg albendazole per kg body weight was determined.

1. Dose-Titration Study, No. A-8008-75

   T. O. Gurnell
   Terenure Research Farm
   Isando, South Africa

A total of 46 lambs was experimentally infected with metacercariae of *F. hepatica*and divided into five groups. The controls and the first three treatment groups were also experimentally infected with larvae of *O. circumcincta, N. spathiger* and *Oe. columbianum.* One group of nine lambs remained untreated and served as a control. The remaining four groups received albendazole suspension as a single oral dose of 5.0, 7.5, 10.0 or 15.0 mg/kg (8, 11, 11 and 7 lambs, respectively). Ten days after treatment the animals were necropsied. The percent removal in the treatment groups is given below. No adverse reaction was reported.

Percentage Reduction Relative to Controls

Albendazole

Parasite	**5.0 mg/kg**	**7.5 mg/kg**	**10.0 mg/kg**	**15.0 mg/kg**
F. hepatica (adult)	94	97	98	99
O. circumcincta (larvae)	100	99	99	-
N. spathiger (larvae)	100	100	100	-
Oe. columbianum (larvae)	98	95	99	-

2. Dose-Titration Study, No. A-5180-82A-5180-82

   B. E. Stromberg
   University of Minnesota
   St. Paul, Minnesota

Thirty lambs were experimentally infected with metacercariae of *F. magna*and divided into five groups of six. Albendazole will become the only approved therapy for this highly pathogenic parasite in sheep. Four of the groups received a single oral dose of albendazole suspension at 5.0, 7.5, 10.0 or 15.0 mg/kg. The remaining group remained untreated and served as a control. All

animals were necropsied six weeks after treatment and the percent removal as listed below was recorded. No adverse reaction was reported.

Percentage Reduction Relative to Controls

Albendazole

Parasite	**5.0 mg/kg**	**7.5 mg/kg**	**10.0 mg/kg**	**15.0 mg/kg**
F. magna (adult)	22	57	64	64

3. Dose-Titration Study, No. A-374-78

T. M. Craig
Texas A&M University
College Station, Texas

Thirty lambs harboring natural infections of *T. actinioides, H. contortus* and *T. axei* were divided into three equal groups. Two of the groups were treated with a single oral dose of albendazole suspension at 3.8 or 7.5 mg/kg. The third group remained untreated and served as a control. At necropsy, the following results were recorded. No adverse reaction was reported.

Percentage Reduction Relative to Controls

Albendazole

Parasite	**3.8 mg/kg**	**7.5 mg/kg**
H. contortus (adult)	85	99
T. axei (adult)	100	100
T. actinioides (adult)	54	98

4. Dose-Titration Study, No. A-206-74

V. J. Theodorides
Applebrook Center
West Chester, Pennsylvania

A total of 23 lambs was experimentally infected with *H. contortus, N. spathiger,*and *D. filaria*and divided into four groups. One group of five lambs remained untreated, the other groups of six lambs each received a single oral dose of albendazole suspension at 2.5, 5.0, or 10.0 mg/kg. At necropsy, the following results were reported. No adverse reaction was reported.

Percentage Reduction Relative to Controls

Albendazole

Parasite	**2.5 mg/kg**	**5.0 mg/kg**	**10.0 mg/kg**
H. contortus (adult)	96	99	99
N. spathiger (adult)	94	95	99
D. filaria (adult)	51	83	94

5. Dose-Titration Study, No. Study A-208-74

V. J. Theodorides
Applebrook Center
West Chester, Pennsylvania

Twelve lambs, naturally infected with *M. expansa*, were divided into three groups of four animals each. One group served as an untreated control and the remaining two groups received a single oral dose of albendazole suspension at either 10 or 15 mg/kg. Seven days later the animals were necropsied. The percent removal in the treatment groups is given below. No adverse reaction was reported.

Percentage Reduction Relative to Controls

Albendazole

Parasite	**10 mg/kg**	**15 mg/kg**
M. expansa (adult)	100	100

6. Dose-Titration Study, N0. A-8008-77

P. C. van Schalkwyk
Terenure Research Farm
Isando, South Africa

A total of 31 lambs, experimentally infected with *Oe. columbianum*and *D. filaria*larvae, was divided into three groups. Two of the groups received albendazole suspension as a single oral dose of 3.8 or 7.6 mg/kg (11 lambs each). The third group of nine lambs remained untreated and served as a control. The following results were reported at necropsy. No adverse reaction was reported.

Percentage Reduction Relative to Controls

Albendazole

Parasite	**3.8 mg/kg**	**7.6 mg/kg**
Oe. columbianum (larvae)	84	88
D. filaria (larvae)	89	96

Doses ranging from 2.5 to 15 mg albendazole per kg body weight, were given orally. The results from these studies were used to determine the most effective dose. A dose of 7.5 mg/kg was selected as the most effective level against the greatest number of parasite species infecting sheep. Albendazole will become the only approved therapy for this highly pathogenic parasite in sheep.

B. Dose-Confirmation

Confirmation of the dose selected for gastrointestinal and pulmonary nematodes, trematodes, and cestodes was ascertained in three pivotal controlled trials. A total of 47 sheep was used, approximately one-half of which were treated with albendazole; the remaining sheep served as untreated controls. Infections were acquired naturally in two (2) trials and were experimentally induced in the other trial. All of the sheep were necropsied and parasites remaining were recovered.

1. Dose-Confirmation Study, No. A-8211-76

   D. R. Johns
   SmithKline Research Station
   Cobbitty, New South Wales
   Australia.

Twenty lambs were experimentally infected with *F. hepatica*metacercariae and divided into two groups. One group of eleven sheep received a single oral dose of albendazole suspension at 4.75 mg/kg; the other group of nine sheep was left untreated and served as a control. At necropsy, the percent removal of the worms was recorded and is given below. No adverse reaction was observed.

Percentage Reduction Relative to Controls

Albendazole

Parasite	**4.75 mg/kg**
F. hepatica (adult)	83

2. Dose-Confirmation Study, No. Study A-368-78

   T. M. Craig
   Texas A&M University
   College Station, Texas

Seven lambs, naturally infected with *H. contortus*, were divided into two groups. One group of three animals received a single oral 7.5 mg/kg dose of albendazole; the remaining four animals were left untreated and served as controls. At necropsy, the results were as follows. No adverse reaction was reported.

Percentage Reduction Relative to Controls

Albendazole

Parasite	**7.5 mg/kg**
H. contortus (adult)	100
H. contortus (larvae)	99
T. axei (adult)	100
C. oncophora (adult)	100
N. spathiger (adult)	100

3. Dose-Confirmation Study, No. A-294-77

R. C. Bergstrom
University of Wyoming
Laramie, Wyoming

Twenty sheep, naturally infected with the fringe tapeworm (*T. actinioides*) were divided into two equal groups. One group received a single oral 7.5 mg/kg dose of albendazole suspension. The other group remained untreated and served as a control. At necropsy, 21 days after treatment, the results were as follows. No adverse reaction was reported.

Percentage Reduction Relative to Controls

Albendazole

Parasite	**7.5 mg/kg**
T. actinioidies (adult)	100

C. Field Trials

Well-documented clinical field trials were conducted in the United States according to an approved protocol which was modified to accommodate the parasite(s) of interest and local management conditions. Groups of sheep with at least a moderate worm infection, as determined by egg counts in their feces, were selected. In one of the trials the same number of animals was treated with albendazole or was left untreated and served as controls. In the other four trials, due to the severity of the infection and the death losses that had occurred, all animals in the flock were treated with albendazole. Worm eggs in fecal samples were counted before and after treatment, and animals were visually observed for side effects.

Five investigators studied albendazole suspension in four states. Sheep of various breeds were treated. Investigators, trial locations and numbers of animals in these studies are tabulated on the following pages. The results of these clinical field trials confirm the results of the studies indicating elimination or reduction of fecal egg counts in virtually all treated sheep. The recommended treatment was found to be safe and practical under field conditions.

Clinical field trials conducted by foreign investigators were also submitted. They further confirm the efficacy of albendazole against a broad spectrum of gastrointestinal roundworm, lungworm, tapeworm and liver fluke infections in sheep.

CLINICAL FIELD TRIALS WITH ALBENDAZOLE SUSPENSION IN SHEEP

United States

Study # (mg/kg)	Investigator/ Location	Total No. of Animals	Type of Parasite Infection	No. of Treated	Average Worm Eggs Before/After Treatment	No. of Controls	Average Worm Eggs Before/After Treatment
A-370 (7.5)	Dr. R. W. Randall Bridger, MT	140	*F. hepatica*	140	298.0/6.60	-	-
A-5090 (7.5)	Dr. D.E. Worley Bozeman, MT	150	*F. hepatica*	150	1020.0/164.0	-	-
A-5108 (5.0)	Dr. H.R. Sherman Dover, MA	100	Tapeworm, G.I. Nematode	100	>400.0/-	-	-/-
A-5121 (7.5)	Dr. R.W. Fish Granton, WI	70	*F. magna*	70	*	-	-/-
A-5099 (7.5)	Dr. R.B. Wescott Pullman, WA	50	Tapeworm, G.I. Nematode	25	0.4/0.04 109.0/1.0	25	0.5/0.7 107.0/140.0

*Since worms do not achieve sexual maturity in this host, no eggs were produced; death losses prior to treatment were 20-40%, no deaths occurred post-treatment.

III. TARGET ANIMAL SAFETY

Studies to evaluate the safety of albendazole in sheep were conducted at SmithKline Animal Health Products in West Chester, Pennsylvania; French's Forest, Brookvale, Australia; and Isando, Transvaal, South Africa, as well as in the laboratories of independent investigators in the United States and other countries.

Acute Oral Toxicity Study of Albendazole in Sheep

Investigator:

D. R. Johns
SmithKline Animal Health Products
Cobbitty, New South Wales,
Australia

A-77/3

Purpose: The objective of this study was to determine the maximum tolerated dose of albendazole in sheep.

Methods: Sixteen Merino sheep were divided into four equal groups and received a single oral dose of 26.5 (3.5x), 37.5 (5.0x), 53.0 (7.1x) or 75.0 (10.0x) mg/kg of albendazole suspension. After administration of the compound, all animals were observed daily for clinical signs for a 14-day period.

Results: All animals in the 75 mg/kg group had diarrhea at Day 7. Three of the four animals in the group had wool break and 1 animal died by Day 14. In the 53 mg/kg group, 1 animal exhibited diarrhea. No adverse effects were observed in the 37.5 or 26.5 mg/kg groups.

Conclusion: The maximum tolerated dose in this study was 37.5 mg/kg (5X recommended dose).

Acute Oral Toxicity Study of Albendazole in Sheep

Investigator:

P. C. Van Schalkwyk
SmithKline Animal Health Products
Isando, South Africa

Study A-76/2

Purpose: The objective of this study was to determine the maximum tolerated dose of albendazole, defined here as that dose at which no observable clinical symptoms or gross pathology are noted during a 14 day period, in sheep.

Methods: Twenty Merino male and female lambs weighing 18.5 - 43 kg were assigned to five groups of four lambs each. Albendazole suspension was administered as a single oral dose of 26.5 (3.5x), 37.5 (5.0x), 53.0 (7.1x) or 75.0 910.0x) mg/kg. A similar group of four lambs received the suspension vehicle and served as an untreated control. After administration of the compound, the animals were observed daily for 14 days, then euthanized and necropsied.

Results: No adverse sign was observed in the two lower dose groups. In the two higher dose groups, two of the four animals in each group had appetite depression and decreased activity. One female in the highest dose group had slight wool break. No pathogenic change attributable to administration of albendazole was seen in any of the animals.

Conclusion: The maximum tolerated dose in this study was 37.5 mg/kg (5X recommended dose).

Evaluation of the Safety of Albendazole When Administered Orally to Ewes During Early Pregnancy

Investigator:

J.M. Tesh
G.A. Harper
Life Science Research
Essex, England

Study 77/SAF20/205/UK

Purpose: The objective of this study was to examine the effects of albendazole on the progress and outcome of pregnancy in sheep when administered as a single dose on Day 17 of gestation.

Methods: Approximately 360 Dorset Horn Cross and Clun ewes were mated naturally. After mating, the ewes were randomly assigned to one of five groups. There was a control group and four treatment groups receiving a single dose of albendazole at 7.5 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg 17 days after mating. The numbers of lambs born, mortality rates from the neonatal period through slaughter, initial lamb examination (body weight, general condition, viability estimation, external malformations), lamb index, viability index, mean litter size, live birth, and lamb birth weights were recorded. Maternal factors were pregnancy rate, gestation length, and parturition difficulties.

Results: All the treated groups had lower pregnancy rates than the control group. The lamb index and viability index were much lower for the group receiving 20 mg albendazole/kg body weight. There were teratogenic effects of increasing frequency in the treated groups corresponding to increasing dose. At 20 mg/kg body weight, there were cranial, spinal, and renal defects. At 15 mg/kg body weight, only renal defects were seen. At 10 mg/kg, there was one case of renal agenesis. At 7.5 mg/kg body weight, there were no defects observed that could be related to treatment.

Conclusion: Administration of albendazole at 10 mg/kg (1.3 times the highest recommended therapeutic dose) to ewes on Day 17 of pregnancy was teratogenic.

Evaluation of the Safety of Albendazole When Administered Orally to Ewes During Early Pregnancy

Investigator:

B.C. Farquharson
SmithKline Beecham Animal Health
The Oaks, New South Wales
Australia

Study AUS9251

Purpose: The objective of this study was to investigate the effects of a single dose of albendazole on embryo and fetal development of lambs when administered to pregnant ewes on Day 30 or 45 of gestation.

Methods: Two groups of pregnant ewes received a single oral dose of 11.25 mg/kg on either Day 30 or 45 of gestation. Two additional groups of pregnant ewes serves as controls and received placebo (Valbazen vehicle) at a dosage volume equivalent to that used in treated sheep. Ewes were allowed to lamb naturally and were observed until approximately 21 days after lambing. Lambs were examined and weighed as soon as possible after birth and again at 21 days of age. Necropsies were performed on ewes that died during the trial and on any lambs found dead, underweight, or that did not meeting the growth criteria (if concurrently ill or unhealthy).

Results: There was no adverse effect upon maternal body weight. The number of ewes that returned to service was similar among the control and the albendazole groups; no ewes returned to service after treatment. The pregnancy rate was similar between the treated and control groups.

The number of lambs born and the number that survived were similar between groups. The following table summarizes the data:

Group #	**1**	**2**	**3**	**4**
Treatment	Vehicle	Vehicle	ABZ	ABZ
Day treated	30	45	30	45
# ewes lambed	17	21	20	22
% ewes bred and pg that lambed	81%	87%	83%	92%
# lambs born	22	29	27	34
Lambing %	129%	145%	135%	155%
# lambs at 21 days	17	21	18	24
Survival %	100%	100%	90%	109%
Death Rate	23%	28%	33%	29%
# lambs abnormal	1	0	0	0

Lambing % = (# lambs born x 100) / # ewes at start of lambing
Survival % = (# lambs alive at Day 21 x 100) / # ewes at start of lambing

Only one congenital abnormality was observed. A lamb from the Day 30 vehicle group had prognathia. There were no developmental abnormalities observed in the ewes nor their lambs attributable to the administration of albendazole.

Conclusion: Administration of albendazole at 11.24 mg/kg (1.5 times the highest recommended therapeutic dose) to ewes on either Day 30 or 45 of pregnancy had no adverse effect on the health of the ewes or on the health and development of their lambs.

Investigations on the Effect of Albendazole on Spermatogenesis. Quality of Semen and Libido in Treated Rams

Investigator:

D. R. Johns
SmithKline Animal Health Products
Cobbitty, New South Wales
Australia

Study A-76-6

Purpose: The objective of this study was to determine the effects of albendazole on spermatogenesis, seminal quality and testicular tissue in rams.

Methods: A single oral dose of 15 mg/kg of albendazole suspension was administered to six 2 year old rams. A similar group of rams were untreated and served as a control. The following parameters were measured over a 56-day period following treatment: semen volume, color, consistency, mobility and proportion of live; dead spermatozoon. Histopathologic examination of stained testicular sections was performed on treated and control animals immediately following the final semen collection (i.e. 56 days following drug administration).

Results: No significant differences could be determined in semen volume, color, consistency, mobility and proportion of line to dead spermatozoa between treated and control groups or between pre- and post- treatment periods within each group. Histopathological examination of stained testicular sections showed no differences between treated and control animals.

Conclusion: Treatment with albendazole suspension at a dose of 15 mg/kg (i.e., 2 times the highest recommended therapeutic dose) exerted no adverse effect on rams.

IV. HUMAN FOOD SAFETY

A. Toxicity Tests

The pivotal toxicity studies conducted to support the safe concentration of albendazole in the edible tissues of sheep are described in the FOI Summary for the approved NADA 110-048 (albendazole suspension for cattle, 54 FR 25114, June 13, 1989).

B. Safe Concentration of Residues

The data from the toxicity studies and the tissue consumption factors for sheep allow assignment of the safe concentrations for residues of albendazole in tissues.

The no-observed-effect level for establishing the safe concentration of the total residues of albendazole is 5 mg/kg/day. This is based on the teratogenic effect in the rat teratology study. The rat is considered the most sensitive species and the teratology study the most sensitive study. Therefore, with a 1000 fold safety factor, the safe concentration for albendazole residues is:

Albendazole Acceptable Daily Intake (ADI) = 5 mg/kg/day (NOEL)/1000 fold safety factor = 0.005 mg/kg/day

Safe Concentration in muscle = ADI X 60 kg (weight of average human)/0.5 kg/day (daily consumption of meat) = 0.005 mg/kg/day X 60 kg / 0.5 kg/day = 0.6 ppm

This is the safe concentration for albendazole residues in muscle derived from treated sheep. Safe concentration of albendazole residues in edible tissues other than muscle is as follows:

Edible Tissue	**Consumption Factor**	**Safe Concentration**
Liver	5	3.0 ppm
Kidney	5	3.0 ppm
Fat	5	3.0 ppm

C. Metabolism and Total Residue Studies

The levels of total drug-related residues of albendazole (ABZ) in the tissues of sheep treated with 14C-albendazole were determined in three studies which varied by dose level and withdrawal schedule. The studies are outlined below, and the animals in each received a single oral dose of the radiotracer by capsule.

Study No. I

A-S-4028-83, Total Residue Study

T. Wishousky
Applebrook Center
West Chester, Pennsylvania

Dose: 7.5 mg/kg (the recommended dose)

Total number of sheep in study: 2 male and 2 female sheep

Withdrawal Schedule: 5 and 8 days post dosing

Study No. II

No trial number, Metabolic Fate of Albendazole in Sheep Tissues

W. Colman
Applebrook Center
West Chester, Pennsylvania

Dose: 10 mg/kg (1.3 times the recommended dose)

Total number of sheep in study: 7 male and 2 female sheep

Withdrawal schedule: 1, 2, 4, 6, and 8 days post dosing

Study No. III

No trial number, Pharmacokinetic and Residue Studies of Albendazole-14C in Sheep

J. Miller
Applebrook Center
West Chester, Pennsylvania

Dose: 16.2 mg/kg (2.16 times the recommended dose)

Total number of sheep in study: 11 male and 7 female sheep

Withdrawal schedule:1, 2, 4, 6, 10, 20, 30 and 45 days post dosing

Tissue samples of muscle, liver, kidney and fat from each of the animals were radioassayed for total drug related residues. The results from the three studies are shown collectively in the two tables that follow.

Total Radioactivity (ppm) in the Edible Tissues of Sheep Receiving the Indicated Dose of 14C-Albendazole

Withdrawal Days 1 through 10

	1	**2**	**4**	**5**	**6**	**8**	**10**
Muscle (16.2 mg/kg)	2.5 (±0.26)	0.18 (±0.045)	0.017 (±0.001)		0.015 (±0.003)		0.017 (±0.005)
Muscle (10 mg/kg)	1.21 (*)	0.067 (*)	0.029 (±0.012)		0.025 (±0.015)	0.011 (±0.0015)	
Liver (16.2 mg/kg)	15.8 (±4.29)	7.9 (±2.45)	0.66 (±0.18)		0.56 (±0.25)		0.32 (±0.05)
Liver (10 mg/kg)	9.31 (*)	3.7 (*)	1.37 (±0.367)		0.77 (±0.464)	0.339 (±0.125)	
Liver (7.5 mg/kg)				0.347 (±0.024)		0.251 (±0.076)	
Kidney (16.2 mg/kg)	14.4 (±2.10)	3.8 (±0.57)	0.20 (±0.03)		0.16 (±0.11)		0.14 (±0.05)
Kidney (10 mg/kg)	5.6 (*)	0.67 (*)	0.27 (±0.083)		0.19 (±0.123)	0.069 (±0.015)	
Fat (16.2 mg/kg)	0.97 (±0.48)	0.10 (±0.023)	0.014 (±0.009)		0.021 (±0.019)		0.012 (±0.009)
Fat (10 mg/kg)	1.04 (*)	0.05 (*)	0.12 (±0.037)		0.035 (±0.011)	0.013 (±0.004)	

Total Radioactivity (ppm) in the Edible Tissues of Sheep Receiving the Indicated Dose of 14C-Albendazole

Withdrawal Days 20, 30 and 45

	20	**30**	**45**
Muscle (16.2 mg/kg)	0.011 (±0.003)	0.005 (±0.001)	0.007 (±0.000)
Liver (16.2 mg/kg)	0.17 (±0.030)	0.046 (±0.021)	0.065 (±0.0004)
Kidney (16.2 mg/kg)	0.04 (±0.012)	0.020 (±0.004)	0.020 (±0.005)
Fat (16.2 mg/kg)	0.009 (±0.002)	0.007 (±0.001)	0.004 (±0.000)

Livers from sheep in the residue studies previously described were subjected to wet chemistry procedures to establish the profiles of 14C-albendazole metabolites present in those samples. A number of extraction procedures were used with liver tissue which varied in the extraction solvent and the use of sample pretreatment with enzymes or acid hydrolysis. The techniques used to isolate and quantitate metabolites included thin layer chromatography, autoradiography, and reverse isotope dilution. In general, the qualitative profiles of the major metabolites present in liver were very similar regardless of the profiling procedure used. There were, however, significant variations in the amounts of the individual metabolites observed because metabolite stability and solubility parameters varied. The greatest single factor affecting the quantitative profile was the use of acid hydrolysis, which released metabolites, particularly the 2-aminosulfone metabolite, from the bound residue present in liver.

The extractable radioactivity in the liver samples ranged between 13% and 99% of the total radioactivity present in the tissue depending upon the extraction procedure used and the length of the withdrawal time. At one day withdrawal, 99% of the 14C-albendazole residues in sheep liver was freely extractable into ethyl acetate. That percentage declined to about 37% by four days of withdrawal and to 13% by eight days of withdrawal.

The use of more vigorous extraction procedures, particularly the use of acid hydrolysis as noted earlier, effected the release of increasing amounts of drug-related residues from the bound residue. This effort resulted in the isolation and identification of the albendazole sulfoxide, sulfone, and 2-aminosulfone metabolites in liver tissue. Parent albendazole and the 2-aminosulfoxide metabolite were also shown to be present but in small amounts and only at short withdrawal times. The table below presents the quantitation of the major metabolites as percentages of the extractable radioactivity present in liver tissue.

Percentages of the Major 14C-Albendazole Metabolites in the Extractable Radioactivity Present in Sheep Liver

Days Post Dosing	ABZ	ABZ Sulfoxide	ABZ Sulfone	ABZ 2-Amino-Sulfone
1	NQ*	57.6%	15.3%	1.3%
2	NQ*	57.0%	16.0%	7.4%
4	-	41.6%	16.9%	13.0%
6	-	12.4%	5.2%	34.1%
8	-	12.2%	10.5%	17.8%

* NQ = Present but not quantitated

Metabolite profiles of albendazole in the urine of rats and mice were also determined using similar extraction procedures. The following table presents the quantitation of the major metabolites as percentages of the extractable radioactivity present in urine. The extractable radioactivity ranged between 39% and 82% of the total radioactivity present in urine depending upon the extraction procedure used.

Percentages of the Major 14C-Albendazole Metabolites in the Extractable Radioactivity Present in 0-24 Hour Urine of Rats and Mice

Species	ABZ	ABZ Sulfoxide	ABZ Sulfone	ABZ 2-Amino-Sulfone	ABZ Hydroxypropyl-sulfones Metabolite E	ABZ Hydroxypropyl-sulfones Metabolite G
Rat	2	5	27	15	14	24
Mouse	<1	1	29	4	22	30

A comparison was made of the metabolite patterns present in sheep liver with those present in the urine collected from the rats and mice. The comparison showed that parent albendazole and all other metabolites identified at any time period in sheep liver were also present in the urine of the laboratory species. Therefore, the test species were exposed to all of the metabolites shown to be present in the liver from sheep treated with albendazole.

D. Assignment of Marker Residue, Target Tissue and Rm (Tolerance)

The data in the tables of total residue values shown on two of the previous pages established that liver contains the highest levels of total drug-related residues of albendazole and that it is the tissue in sheep from which residues are the slowest to deplete to the safe concentration. These observations suggested liver as the likely choice of target tissue for albendazole in sheep.

The metabolism data summarized in Section B confirmed liver as the target tissue and led to the selection of the 2-aminosulfone metabolite as the marker residue. Those data demonstrated that the 2-aminosulfone metabolite was present in sufficiently high concentration in liver and had the proper depletion characteristics to serve as the marker substance in that tissue.

The Rm (tolerance) for albendazole in sheep liver was set from the liver total residue data in Study No. II and the marker residue depletion (cold) study described in Section D. In the latter study, residues of the marker residue were assayed by the determinative procedure of the regulatory method. That assay is based on HPLC and is described in Section E.

An overlay of the total radioactivity and marker residue decline curves demonstrated that the albendazole 2-aminosulfone metabolite (marker residue) is at a concentration of approximately 250 ppb when total 14C-albendazole residues in sheep liver are at the safe concentration of 3.0 ppm. Accordingly, the Rm (tolerance) for the marker residue in sheep liver is established at 250 ppb.

E. Studies Demonstrating a Withdrawal Time

The withdrawal time for the suspension formulation of albendazole in sheep was calculated from the marker residue depletion data in a study which involved 20 treated sheep. Those animals each received a single 7.5 mg/kg dose of the albendazole suspension formulation and were euthanized in groups of 6, 4, 4, or 6 sheep (equal sex distribution per group) at 2, 5, 8 or 11 days, respectively, post dosing.

1. Marker Residue Depletion Study in Liver from Sheep Treated with Albendazole

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   Applebrook Center
   West Chester, Pennsylvania

   The livers (target tissue) were collected at the time of slaughter and were assayed for the marker residue (the 2-aminosulfone metabolite) using the determinative procedure. The results are presented in the following table.

   Residue Levels (ppb) of the Albendazole Marker Residue in the Livers of Sheep Following a 7.5 mg/kg Dose of The Suspension Formulation of Albendazole

   Days Post Dosing

	2	**5**	**8**	**11**
Range ppb	331 (±89)	61.2 (±17.2)	37.9 (±13.6)	23.2 (±1.6)

   A statistical analysis of the depletion data using the upper tolerance limit containing a 99 percentile of the population with 95% confidence limits yielded a withdrawal period of seven days for the albendazole suspension formulation.

F. Regulatory Methods

Albendazole Determinative Assay Scheme

The determinative assay for detecting residues of albendazole in sheep liver involves measurement of the 2-aminosulfone metabolite by high performance liquid chromatography (HPLC) with fluorescence detection. The assay is based on the method developed for monitoring residues of albendazole in cattle liver (NADA 110-048), with the only differences being modifications in the standard curve range (5 - 1600 ppb) and fortification level (200 ppb) of the internal standard to better accommodate the higher Rm (tolerance) for the 2-aminosulfone metabolite in sheep liver.

Albendazole Confimatory Assay Scheme

The confirmatory procedure for residues of the albendazole 2-aminosulfone metabolite in sheep liver is identical to the confirmatory procedure developed for residues of albendazole in cattle. That method involves formation of the t-butyl dimethylsilyl (t-BDMS) derivative which is then subjected to gas liquid chromatography/mass spectrometry (GC/MS) analysis.

Validation

The determinative and confirmatory procedures as developed for residues in cattle are filed in the Food Additives Manual on display in FDA's Freedom of Information Public Room (Room 12A-30, 5600 Fisher's Lane, Rockville, MD 20857).

V. USER SAFETY

The drug was also evaluated for untoward effects which might result from physical contact with it:

Albendazole was not irritating when applied directly to abraded or non-abraded rabbit skin (500 mg applied to each side). Similarly, no irritation was observed in either non-irrigated (non-washed) or irrigated eyes of any rabbit immediately, 24, 48 or 72 hours after instillation of 100 mg of albendazole.

A single oral dose of 3000 mg/kg of albendazole failed to produce death when administered to mice. This dose represents approximately 300 times the highest recommended therapeutic dose.

The studies demonstrated that the drug would have no ill effects on persons handling it if it is used according to label recommendations.

VI. AGENCY CONCLUSIONS

The data submitted in support of this original NADA comply with the requirements of section 512 of the Act and demonstrate that albendazole (4.55%) when used under the proposed conditions of use, is safe and effective. These data from the controlled studies demonstrate the effectiveness of albendazole for its labeled indications as an

anthelmintic for sheep when administered as an oral suspension at a dosage level of 7.5 mg/kg of body weight. These studies demonstrate the efficacy of a single dose of albendazole for removal and control of the following parasites:

A. Adult Liver flukes:

Fasciola hepatica, Fascioloides magna (adults)

B. Tapeworms:

Common tapeworms: *Moniezia expansa*

Fringed tapeworms: *Thysanosoma actinioides*(heads and segments)

C. Lungworms:

Dictyocaulus filaria(adults and 4th stage larvae)

D. Stomach worms:

Barberpole worms: *Haemonchus contortus* (adults and 4th stage larvae)
Brown stomach worms:*Ostertagia circumcincta, Marshallagia marshalli*(adults and 4th stage larvae)
Small stomach worms: *Trichostrongylus axei*(adults and 4th stage larvae)

E. Intestinal worms:

Thread-necked intestinal worms: *Nematodirus spathiger, N. filicollis*(adults and 4th stage larvae)
Cooper's worms: *Cooperia oncophora* (adults and 4th stage larvae)
Bankrupt worms: *T. colubriformis*(adults and 4th stage larvae)
Nodular worms: *Oesophagostomum columbianum*(adults and 4th stage larvae)
Large-Mouth Bowel Worms: *Chabertia ovina*(adults and 4th stage larvae)

The safe concentration for albendazole in uncooked edible sheep tissues is 0.6 ppm in muscle, 3.0 ppm in liver, 3.0 ppm in kidney and 3.0 ppm in fat. The tolerance for the albendazole marker compound, 2-aminosulfone metabolite, is established at 0.25 ppm in sheep liver. The withdrawal time for sheep is 7 days.

Albendazole is currently approved in cattle as an over-the-counter product. 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 for sheep shall also, have over-the-counter marketing status.

Under Section 512(c)(2)(F)(ii) of the FFDCA, this approval for food-producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains reports of new clinical or field investigations

essential to the approval of the application and conducted or sponsored by the applicant.

VII. ATTACHMENTS

Front Panel: Valbazen Broad-Spectrum Sheep Dewormer Suspension, 4.55% albendazole, l liter (1,000 mL) bottle.
Front Panel: Valbazen Broad-Spectrum Sheep Dewormer Suspension, 4.55% albendazole, 500 mL bottle.

Copies of these 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.