Date of Approval: January 24, 2008

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 110-048

VALBAZEN

Albendazole
11.36% suspension
Non-lactating goats

"...for the treatment of adult liver flukes
(*Fasciola hepatica*) in nonlactating goats."

Sponsored by:

Pfizer Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 110-048
B. Sponsor:	Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000069
C. Proprietary Name:	VALBAZEN
D. Established Name:	Albendazole
E. Pharmacological Category:	Antiparasitic
F. Dosage Form:	11.36% suspension
G. Amount of Active Ingredient:	113.6 mg/mL
H. How Supplied:	500 mL/16.9 fl oz, 1 L/33.8 fl oz, and 5 L/169 fl oz containers
I. How Dispensed:	OTC
J. Dosage:	4 mL/100 lb body weight (equivalent to 4.54 mg albendazole/lb, 10 mg/kg)
K. Route of Administration:	Oral (drench)
L. Species/Class:	Non-lactating goats
M. Indication:	For the treatment of adult liver flukes in non-lactating goats.
N. Effect of Supplement:	This supplement provides for the treatment of adult liver flukes (*Fasciola hepatica*) in non-lactating goats.

II. EFFECTIVENESS:

Section 514.1(d) of Title 21 of the Code of Federal Regulations (CFR) permits extrapolation of data from a major species to a minor species to satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act with respect to the effectiveness of a new animal drug. A combination of data from goats (a minor species), cattle (a closely related approved major species), and sheep (a minor species at the time of the albendazole approval, with the exception of human food safety data collection requirements), were used to support the determination of effectiveness, consistent with the "Guidance for Industry: FDA Approval of New Animal Drugs for Minor Uses and Minor Species" (FDA/CVM 2/11/99). As of July 26, 1999, sheep were reclassified as a minor species for all data collection purposes (64 FR 40321).

A. Dosage Characterization:

The dose of 10 mg albendazole/kg body weight for goats was extrapolated from cattle and sheep.

B. Substantial Evidence:

The following dose titration study serves as the required adequate and well-controlled dose confirmation study. The concentration of the albendazole drench used in this study was 5.68%. VALBAZEN (albendazole) is approved at concentrations of 4.55% (NADA 140-934) and 11.36% (NADA 110-048). The original sheep approval (59 FR 65711, December 21, 1994) was a 4.55% albendazole concentration. However, sheep were subsequently added to the label for the 11.36% cattle product (64 FR 1503, January 11, 1999). The increased albendazole concentration was not expected to pose any specific risk hazard to sheep. The actual amount of drug administered to sheep per unit body weight remained the same. CVM concluded that the two formulations should perform in an identical manner when administered to sheep. Accordingly, the sponsor's request for waiver of an *in vivo* study requirement was granted and no additional studies were required to support the approval of the 11.36% oral suspension of albendazole in sheep. The same reasoning is applied to this goat supplement.

"Albendazole Study Against *Fasciola hepatica* in Goats: Safety and Efficacy"

1. Type of Study: Dose titration study serving as a dose confirmation study

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

3. General Design:

   a. Purpose of the study: To determine the effectiveness of albendazole in the control of adult liver flukes (*Fasciola hepatica*) in goats, and to determine an appropriate dosage.

   b. Test animals: Forty weaned male, castrated male, and female goats, approximately 8 weeks of age were allocated for this study. Goats were of several different breeds. The goats were each inoculated *per os* with 250 *Fasciola hepatica* metacercariae in a gelatin capsule.

   c. Dosage Form: 5.68% suspension (drench)

   d. Route of Administration: Oral, with a dosing syringe

   e. Doses: 5 mg/kg, 7.5 mg/kg, 10 mg/kg, or 15 mg/kg body weight

   f. Treatment Groups: The goats were randomly assigned to 5 dose groups (untreated control, 5, 7.5, 10, and 15 mg/kg body weight). The allocation into treatment groups was blocked based on weight. Fourteen weeks after inoculation, albendazole suspension was administered once *per os* to the treated groups at 5 mg/kg, 7.5 mg/kg, 10 mg/kg, or 15 mg/kg body weight.

   g. Controls: The untreated control animals were given a water placebo at a volume equal to that given to the highest treatment group.

   h. Test Duration: 119 days from inoculation with metacercariae to necropsy

   i. Diagnosis: Infection was confirmed by fecal sedimentation 14 weeks after inoculation and at necropsy. The results were recorded as eggs of *F. hepatica* per gram of feces.

   j. Parameter: The efficacy of albendazole relative to the control was calculated using the arithmetic means of the flukes recovered at necropsy. The following formula was used:

$$\text{Efficacy} = \frac{\text{Mean flukes}^{\text{controls}} - \text{Mean flukes}^{\text{albendazole}}}{\text{Mean flukes}^{\text{controls}}} \times 100$$

   k. Results: Refer to Table 1, below.

Table 1. Recovery of Adults of *Fasciola hepatica* at Necropsy and Efficacy at Different Dosages

Dosage (mg/kg)	# Goats with Flukes at necropsy (# inf./# examined)	# Flukes recovered		Efficacy
		mean	(range)	
0.0	8/8	75.4	(43 to 117)	--
5.0	8/8	20.1	(6 to 41)	73.3
7.5	7/8	10.1	(0 to 44)	86.6
10.0	7/8	9.8	(0 to 30)	87.0
15.0	5/8	3.1	(0 to 8)	95.9

All goats developed patent infections of *F. hepatica* by 14 weeks post infection.

Clinical observations: No goats died during this trial, and no adverse reactions associated with treatment were observed during the experiment.

Necropsy findings: All 40 of the study goats were euthanized and necropsied at study end (Day 119). Each animal was noted to have biliary hyperplasia and hepatic fibrosis on necropsy. No other post mortem findings were noted.

l. Conclusion:

Based on this study, and on data from the cattle and sheep approvals, the recommended dose of albendazole in non-lactating goats of 10 mg/kg body weight should be effective in the treatment of the adult liver fluke (*Fasciola hepatica*). The sponsor extrapolated the albendazole dose for goats of 10 mg/kg from the cattle and sheep approvals. In this study, the 15 mg albendazole/kg dose shows better efficacy against *Fasciola hepatica* in goats than the 10 mg/kg dose. However, in accordance with the "Guidance for Industry: FDA Approval of New Animal Drugs for Minor Uses and Minor Species" (FDA/CVM 2/11/99), the selection of 10 mg/kg may be based on the following: 1) the efficacy against adult flukes at 87% is similar to that in cattle; and, 2) there is no drug currently approved in goats which has efficacy against adult liver flukes.

III. TARGET ANIMAL SAFETY:

A. Type of Study: Toxicity Study

1. Title: Target Animal Safety of VALBAZEN Oral Suspension (Albendazole) in Goats

2. Investigators: Dr. A.L. Craigmill, Dr. M.A. Payne, and Dr. S.E. Wetzlich
University of California Department of Environmental Toxicology
Davis, California

3. General Design:

   a. Purpose of the study: To provide data necessary to establish the safety of albendazole in goats

   b. Test Animals: Twenty-six (22 female and 4 male) goats of various breeds and crosses, 1 to 5 years of age, weighing 40 to 71 kg

   c. Housing: Goats were housed together in a single outdoor treatment pen.

   d. Dosage Form: VALBAZEN (albendazole) 11.36% suspension (drench)

   e. Route of Administration: Oral, with a dosing syringe

   f. Doses: 10 mg/kg/day body weight (1X the recommended dose of 10 mg/kg), 30 mg/kg/day body weight (3X the recommended dose of 10 mg/kg), and 50 mg/kg/day body weight (5X the recommended dose of 10 mg/kg) administered 3 times, 24 hours apart starting on Day 1

   g. Control: Water was dosed at the volume of the 5X (50 mg/kg/day) group.

   h. Test Duration: 18 days

   i. Pertinent Parameters Measured: Body weights were taken prior to dose initiation and daily during dosing to calculate treatment doses. Daily observations of the study animals were done in the mornings at feeding, from Day -2 to Day 11, and included assessment of general appearance, appetite, and feces. Samples for hematology, serum chemistry, and urinalysis were collected on Day -7, Day 5, and Day 10 of the study.

4. Results:

   The only abnormal finding noted during the daily clinical observations was 2 cases of diarrhea. On the third day after the final treatment, one of the does in the 5X group developed diarrhea, which resolved in 48 hours. On the seventh day after the final treatment, a doe from the 1X group developed diarrhea. The diarrhea in these animals may have been related to albendazole, but it was mild and self-limiting.

   There were statistically significant decreases in phosphorus noted across all treatment groups (including controls), from pretreatment samples to post-treatment samples. Similar, but not statistically significant, decreases in sodium, chloride, potassium, total protein, and hematocrit were found across all treatment groups. There was a statistically significant difference between the 5X and control group for white blood cell count and total bilirubin on Day 7 post-treatment. However, the differences were considered to be clinically insignificant.

5. Conclusion:

Oral administration of albendazole at the recommended dosage is safe in goats.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summary for the original approval of NADA 110-048 dated March 30, 1989, contains a summary of all toxicology studies.

B. Residue Chemistry:

1. Summary of Residue Chemistry Study

Tissue Residue Depletion Study in Goats Treated with Albendazole (11.36% suspension). In accordance with 21 CFR part 58, this study was conducted in compliance with Good Laboratory Practices.

Dr. Arthur Craigmill
Department of Environmental Toxicology
University of California
Davis, California

Twenty-one commercial breed female goats (6 Lamancha and 15 Alpine) were allocated for this study. The goats ranged in age from 1 to 8 years. Twenty were treated with a single dose of 10 mg albendazole/kg body. One Alpine doe was used as an untreated control. Treated goats were divided into five groups of four goats each. The groups were slaughtered at 5, 10, 15, 20, and 25 days after treatment. Samples of liver were taken from each animal after slaughter. Tissue residues were determined using a modified version of the regulatory analytical method. Results are shown Table 2.

Table 2. Liver Concentrations of Albendazole (Mean ±SD) on Days 5 through 25

Withdrawal period (days)	Residues (ppb)
5	138.50±24.93
10	78.70±16.53
15	50.69±15.82
20	29.48±2.17
25	26.43±8.17

Using a liver tolerance value of 250 ppb (*i.e.*, the sheep tolerance established following review of a full human food safety package for sheep), and a statistical tolerance limit algorithm, the Agency concludes that non-lactating goats treated orally with up to 10 mg albendazole oral suspension/kg body weight will have tissue residues below tolerance if they are withheld from slaughter at least 7 days following drug administration.

2. Target Tissue and Marker Residue Assignment

The target tissue and marker residue assigned for the supplemental approval for sheep under NADA 110-048 dated December 2, 1998, apply to this approval in goats. Liver is assigned as the target tissue and the marker residue is albendazole 2-aminosulfone.

3. Tolerance Assignments

The tolerance assigned for the supplemental approval for sheep under NADA 110-048 dated December 2, 1998, applies to this approval in goats. A tolerance of 250 ppb is assigned for residues of albendazole 2-aminosulfone in goat liver.

4. Withdrawal Time

Based on the data provided in the residue depletion study titled "Tissue Residue Depletion Study in Goats Treated with Albendazole (11.36% suspension)" summarized above and using our statistical tolerance limit algorithm, a preslaughter withdrawal time of 7 days is assigned for non-lactating goats treated with a single dose of 10 mg albendazole oral suspension/kg body weight.

C. Microbial Food Safety:

CVM considered the impact of the use of 10 mg/kg VALBAZEN (albendazole) oral suspension (11.36%) in non-lactating goats on antimicrobial resistance development in bacteria of public health concern. A microbial food safety assessment was not necessary at this time.

D. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 110-048 dated March 30, 1989, contains the analytical method summaries for VALBAZEN in cattle. The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 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 VALBAZEN:

For Use in Animals Only. Not for human use. Keep This and All Medication Out of Reach of Children.

Studies to evaluate the safety of albendazole to users are discussed in the FOI Summary for NADA 110-048, approved March 30, 1989.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that VALBAZEN, when used according to the label, is safe and effective for the treatment of adult liver flukes (*Fasciola hepatica*) in non-lactating goats. Additionally, the data demonstrate that residues in food products derived from non-lactating goats treated with VALBAZEN will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity:

Under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the Act), this approval qualifies for SEVEN years of exclusive marketing rights beginning on the date of approval because the new animal drug has been declared a designated new animal drug by FDA under section 573(a) of the Act.

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

D. Patent Information:

The sponsor did not submit any patent information with this application.