

HFA-305
Dockets
Management Plan

FEB 14 2000

FREEDOM OF INFORMATION SUMMARY

Public Master File

5582

Albendazole Suspension

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

Sponsored by:

NRSP-7

FOIS |

I. GENERAL INFORMATION

PMF Number: 5582

Sponsor: NRSP-7
Western Region
College of Veterinary Medicine
University of California
Davis, California 95616

Accepted Name: Albendazole

Supplemental Effects: The approval of a supplement to an already approved product will allow for the use of albendazole suspension for the treatment of adult liver flukes (*Fasciola hepatica*) in nonlactating goats.

Minor Species Classification Goats are classified as a minor species. Therefore, this Public Master File addresses minor species requirements with respect to effectiveness and target animal safety data collection.

II. INDICATION FOR USE

Albendazole suspension is indicated for the treatment of adult liver flukes (*Fasciola hepatica*) in nonlactating goats.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

- A. *Dosage Form*: Albendazole liquid is an 11.36% suspension.
- B. *Route of Administration*: Oral (drench)
- C. *Recommended Dosage*: Administer albendazole suspension to nonlactating goats at the dosage of 10 mg per kg body weight.

IV. 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, cattle (a closely related approved major species), and sheep, 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).

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

A summary of a study demonstrating the effectiveness of albendazole in goats is provided.

A. Type of Study: Dose Titration

B. Name and Address of Investigator:

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

C. General Design of the Investigation:

- 1) 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.
- 2) 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. These goats were each inoculated per os with 250 *F. hepatica* metacercariae in a gelatin capsule.
- 3) 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. 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. The untreated control animals were given a water placebo at a volume equal to that in the highest treatment group.
- 4) Diagnosis: Infection was confirmed by fecal sedimentation and examination for eggs of *F. hepatica*, 14 weeks after inoculation and at necropsy.

- 5) Dosage Form: 5.68% suspension (drench)
- 6) Route of Administration: Oral (drench).
- 7) Dosages used: 0, 5, 7.5, 10, and 15 mg albendazole/kg of body weight.
- 8) Test Duration: 119 days from inoculation with metacercariae to necropsy.
- 9) 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:

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

D. Results: Refer to Table 4.1, below.

Table 4.1. 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		% Reduction
		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)	88.3
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, hepatic fibrosis, and on necropsy. No other post mortem findings were noted.

E. Conclusion:

Based on this study, and on data from the cattle and sheep approvals, the recommended dose of albendazole in nonlactating goats of 10 mg/kg bodyweight should be effective in the control of 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 adult liver fluke in goats than the 10 mg/kg dose. 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 88.3% is similar to that in cattle; and, 2) there is no drug currently approved in goats which has efficacy against adult liver

flukes. As the Target Animal Safety study (see part V) was inconclusive regarding safety of albendazole in goats at the 50 mg/kg dose, the 10 mg/kg dose should provide a wider margin of safety.

V. TARGET ANIMAL SAFETY

The following multiple dose target animal safety study was conducted.

A. Title: Target Animal Safety of VALBAZEN® (albendazole) in Goats.

B. Name and Address of Investigators:

Dr. A.L. Craigmill
Dr. M.A. Payne
Dr. S.E. Wetzlich
Department of Environmental Toxicology
University of California
Davis, California 95616

C. General Design of the Investigation:

- 1) Purpose of the study: To provide data necessary to establish the safety of albendazole in goats
- 2) Test Animals: Twenty-six (22 female and 4 male) goats of various breeds and crosses were used in this study. Body weight ranged from 40 to 71 kg. Age ranged from 1 to 5 years.
- 3) Test Article: VALBAZEN® (albendazole)
- 4) Procedure: There were 4 treatment groups. Group A (control) were dosed with water at the volume of the 5x (50mg/kg/day) group. Albendazole was administered orally to each of the remaining 3 groups at 10, 30, or 50 mg/kg/day (i.e., 1, 3, or 5 times the recommended dose). These treatments were administered 3 times, 24 hours apart starting on Day 0. Samples for hematology, serum chemistry, and urinalysis were collected on Day -7, Day 2, and Day 7 of the study.
- 5) Dosage Form: 11.36% suspension (drench)
- 6) Route of Administration: Oral (drench)
- 7) Test Duration: 18 days
- 8) Parameters: daily clinical observations, hematology, serum chemistry, and urinalysis

D. Results:

The only abnormal findings noted during the daily clinical observations were 3 cases of diarrhea, and 2 cases of respiratory tract infection. On day 3 after treatment, one of the does in the 5x group developed diarrhea, which resolved in 48 hours. On day 6 after treatment, a doe from the 1x group developed diarrhea. By day 7 post treatment (last day of observation), another doe in the 5x group had developed a respiratory tract infection and diarrhea, with a body temperature of 106°F. The study veterinarian felt that the diarrhea in the 2 goats from the 5x group may have been related to the albendazole treatment, and that in the case of goat from the 1x group it was likely to have been unrelated to treatment. Based on these observations, the study veterinarian concluded that when albendazole is administered at the 5x dose for 3 days, it may occasionally cause a mild, self-limiting diarrhea. No abnormal behavior associated with toxicity was noted during the daily clinical observations.

The investigator noted statistically significant decreases in phosphorus across all treatment groups (including controls), from pretreatment samples to post treatment samples. Similar falls in sodium, chloride, potassium, total protein, and hematocrit were across groups and felt to be indicative of hemoconcentration due to high ambient temperatures. Fluctuations in glucose were felt to be stress mediated.

In order to find treatment-related effects, if any, CVM compared the means between groups at each timepoint by analysis of variance. No dose-related effects were found with the differences in Phosphorus, Sodium, Chloride, Potassium, Total Protein, and Hematocrit among groups. For the 7 day post treatment samples, CVM found that the 5x group mean values for White Blood Cell count and Total Bilirubin were statistically significant from the means of the other groups at this time point. The slightly higher bilirubin may have been due to anorexia in the does of the 5x group, though feed intake was not recorded. One doe had a low WBC (3600 cells/microliter with 0 neutrophils), which helped decrease the mean WBC for the 5x group. Another doe in the group had a normal WBC with 0 neutrophils, and a fibrin of 500. This increase in fibrin was most likely due to an inflammatory process. The slightly lower mean WBC and the slightly increased TBR in the 5x group appeared to be due to respiratory infection in 2 of the does, and were not clinically significant in terms of safety of albendazole. The results of this TAS study were inconclusive regarding the safety of albendazole in goats at the 5X dose.

E. Conclusion:

The data demonstrate that albendazole is safe for nonlactating goats at the recommended dose of 10 mg/kg body weight.

VI. HUMAN FOOD SAFETY

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

Name and Address of Investigator:

Dr. Arthur Craigmill
Department of Environmental Toxicology
University of California
Davis, California 95616

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 6.1

Table 6.1. Liver Concentrations of Albendazole (Mean \pm SD) on Days 5 through 25

Withdrawal period (days)	Residues (ppb)
5	138.50 \pm 24.93
10	78.70 \pm 16.53
15	50.69 \pm 15.82
20	29.48 \pm 2.17
25	26.43 \pm 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 nonlactating 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.

VII. AGENCY CONCLUSIONS

The data submitted in this Public Master File (PMF) satisfy in part the requirements of Section 512 of the Food, Drug, and Cosmetic Act with regard to the proposed use of albendazole for the treatment of Fascioliasis caused by *Fasciola hepatica* in nonlactating goats. Goats are a minor species of animal as defined under 21 CFR 514.1(d). The data submitted meet the requirements of that regulation, and FDA's "Guidance for Industry -- FDA Approval of Animal Drugs for Minor Uses and Minor Species" (2/99). This guidance document (number 61), supersedes Guideline 26, "Guidelines for the Preparation of Data to Satisfy the Requirements of Section 512 of the Act Regarding Minor Use of Animal Drugs."

The human food safety data indicate that domestic goats treated with albendazole at the recommended dosage will require 7 days for the depletion of albendazole residues from the tissues. The studies in this file do not support the use of albendazole in lactating goats. Therefore, a milk tolerance and withholding period have not been assigned to the use of the product in goats.

FDA is publishing a notice of availability of data for this PMF, to encourage sponsors to file New Animal Drug Applications (NADAs) for the use of albendazole covered by this PMF. Sponsors will need to include in their application, in addition to a reference to the PMF, drug labeling and other information needed for approval, such as data supporting extrapolation from a major species in which the drug is currently approved, or authorized reference to such data, data concerning manufacturing methods, facilities, and controls, and information addressing the potential environmental impacts (including occupational) of the manufacturing process associated with the product.

VALBAZEN[®] (albendazole) is currently approved for use in cattle and sheep (see 21 CFR 520.45a).

cc:

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