I. GENERAL INFORMATION

A. File Number

NADA 131-675

B. Sponsor

Hoechst-Roussel Agri-Vet Co.
Route 202-206; P.O. Box 2500
Seminole, New Jersey 08876-1258

C. Trade Name

Safe-Guard ®

D. Generic Name

fenbendazole

E. Dispensing Status

Over the Counter (OTC)

F. Effect of Supplement

This supplemental approval provides for the minor use claim as a dewormer in specific hoofed zoo and wildlife animals.

II. INDICATIONS FOR USE

Anthelmintic (dewormer) for the removal of internal parasites in hoofed zoo and wildlife animals. See following dosage section for specific claims and parasites.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

20% Type A Medicated Article (Premix) in a 25 lb. box; and 4% and 8% Type A Medicated Articles in 25 lb. paper bags to be administered in mash or pelleted Type C Medicated feeds.

Route of Administration: Oral

Recommended Dosage:

Host Animal	Recommended Treatment for	Mg/Kg/Day x Days of Treatment
Feral Swine (*Suis scrofa*)	kidney worms (*Stephanurus dentatus*), round worms (*Ascaris suum*), nodular worms (*Oesophagostomum dentatum*)	3 mg x 3
Ruminants - **Subfamily antilopinae:** Persian gazelles (*Gazella subgutturosa subgutturosa*) Addra gazelle (*Gazella dama ruficollis*) Slenderhorn gazelle (*Gazella leptoceros*) Kenya impala (*Aepyceros melampus rendilis*) Roosevelt's gazelle (*Gazella granti roosevelti*) Indian blackbuck (*Antilope cervicapra*) Mhorr Gazelle (*Gazella dama mhorr*) Thomson's gazelles (*Gazella thomsoni thomsoni*)	small stomach worm (*Trichostrongylus spp*), Thread necked intestinal worm (*Nematodirus spp*), Barberpole worm (*Haemonchus spp*), whipworm (*Trichuris spp*)	2.5 mg x 3
Ruminants -**Subfamily hippotraginae:** Addax (*Addax nasomaculatus*) Angolan roan antelope (*Hippotragus equinus cottoni*) Fringed-ear oryx (*Oryx gazella callotis*) Arabian oryx (*Oryx leucoryx*)	small stomach worm (*Trichostrongylus spp*), Thread necked intestinal worm (*Nematodirus spp*), Barberpole worm (*Haemonchus spp*), whipworm (*Trichuris spp*)	2.5 mg x 3
Ruminants -Subfamily caprinae: Armenian mouflon (*Ovis orientalis gmelini*) Russian saiga (*Saiga tatarica*)	small stomach worm (*Trichostrongylus spp*), Thread necked intestinal worm (*Nematodirusspp*), Barberpole worm (*Haemonchus spp*), whipworm (*Trichuris spp*)	2.5 mg x 3

IV. EFFECTIVENESS

Background

The usual methods of establishing efficacy in domesticated animals were not feasible in zoo and wildlife animals. Difficulty of restraint for dosing, absence of disease models and inability to necropsy selected animals for worm counts due to the animals' intrinsic value precluded the most direct method of assessing efficacy. Efficacy in exotic ruminants was assessed by the measurement of parasite ova counts determined before and after treatment. The efficacy of fenbendazole in bighorn sheep (Ovis canadensis canadensis) was provided through Public Master File 5071.

1. Suidae

Safe-Guard ® is approved in domestic swine (49 FR 3846, Jan. 31, 1984) with a treatment regimen of 3 mg/kg bw daily for 3 days for removal and control of large roundworms (Ascaris suis), nodular worms (Oesophagostomum dentatum and O. quadrispinulatum), small stomach worms (Hyostrongylus rubidus), kidneyworms (mature and immature Stephanurus dentatus), and lungworms (Metastrongylus apri). Many of these parasites occur in wild suidae.

Pivotal study in Feral Pigs

Study No.: 1008/76/1-E
Starting Date: May,1979
End Date: Oct. 1979
Study Director: H.N. Becker, DVM, E. R. Bradley, DVM
Test Substance and Dosage Form: Fenbendazole from 20% premix (Type A Medicated Article)
Animal Species: Feral swine
Number of Animals: 20 feral swine (10 per treatment group)
Drug level tested & Duration of Dosing: 0 and 3 mg/kg bw x 3 days
Route of Administration: Oral, via the feed

A pivotal controlled study in Feral Pigs by Drs. H.N. Becker and E.R. Bradley, College of Veterinary Medicine, University of Florida, Gainesville, FL involved a naturally occurring infestation of Stephanurus dentatus and Ascaris suum. One group of ten (10) feral swine was given 3 mg/kg bw Safe-Guard daily for 3 days in the feed. A second group of 10 animals served as untreated controls. Both groups were necropsied three weeks later and examined for evidence of adult and larval kidney worms. Non-treated pigs showed evidence of infection (live worms) in the perirenal and ureteral areas, while treated animals were devoid of live worms. Live kidneyworm larvae were found in the livers of untreated animals while treated pigs did not harbor such larvae. Urine samples from 8/10 treated animals were devoid of kidneyworm eggs while 8/9 control (non-treated) swine had S. dentatus eggs in their urine.

A complete reduction of ascarid and nodular worm eggs was observed in treated pigs. The results indicated that the drug was 100% effective in reducing the number of ascarid and nodular worm eggs.

2. Ruminants

Ruminants constitute the largest number of animals in zoo and wildlife park environments and represent the class of animals in which fenbendazole has been most thoroughly investigated. Fenbendazole is approved in domestic cattle (53 FR 14788, April 26, 1988) at a level of 5 mg/kg bw against the common nematodes.

Pivotal Study in Ruminant Zoo Animals
Study No.: 1008/76/152-B
Starting Date: Aug. 1986
End Date: Oct. 1987
Study Director: D. Janssen, DVM and J. Allen, DVM
Test Substance & Dosage Form: Fenbendazole from 4% Premix (Type A Medicated Article)
Animal Species: Zoo animals (nondomestic ruminants)
Number of Animals: 55 nondomestic ruminants (37 antilopinae, 12 hippotraginae and 6 caprines)
Drug level tested and Duration of Dosing: 2.5 mg/kg bw x 3 days
Route of Administration: Oral via the feed

A pivotal study was conducted by Dr. Janssen, San Diego Wild Animal Park, Escondido, CA 92027. A total of 55 animals out of a population of 1000 kept in pastures ranging from 20-120 acres were randomly selected for this study. Among the 37 antilopinae were 2 Indian blackbuck, 2 Kenya Impala, 9 Persian Gazelles, 6 Slenderhorn Gazelles, 5 Roosevelt Gazelles, 5 Thompson's Gazelles, 6 Addra Gazelles and 2 Mhorr Gazelles. The hippotraginae sub-family included 3 Addax, 2 Roan Antelope, 5 Fringe Eared Oryx and 2 Arabian Oryx for a total of 12. The third sub-family, caprinae, included 2 Armenian Moufflon and 4 Russian Saiga.

4% Fenbendazole Premix was mixed into the feed and pelleted to provide a level of 7.5 mg/kg bw total dose. This feed, after assay, was available over a 3 day period and consumption/dose ingested measured by dividing the dose of fenbendazole consumed by the estimated biomass for that enclosure. Fecal examinations were conducted 2-14 days before and 5-20 days after treatment ended. Results of treatment are summarized in Table 1.

Efficacy of the premix against endoparasites in the ruminants was determined by comparison with pre- and post-treatment fecal egg counts. Dosages calculated from feed consumption percentages were 3.6 to 8.5 mg/kg. Dosages of less than 5 mg/kg resulted in 80% to 100% reductions in fecal egg counts, and dosages of greater than 5 mg/kg resulted in 98% to 100% reductions in fecal egg counts. With all dosage groups considered, Strongyloides and Nematodirus eggs were the most sensitive to treatment, with 100% reductions in fecal egg counts. Strongyle and Trichuris egg counts were reduced 90% and 96% respectively.

The dose of fenbendazole for exotic ruminants is based on the differences in efficacy noted against the common parasites when comparing a dose of less than 5 mg/kg total dose over a three-day period with a dose of greater than 5 mg/kg total dose over a three-day period (Janssen, D.L 1985. JAVMA 187: 1189). The efficacy surpassed 90% when fenbendazole was administered at greater than 5 mg/kg; whereas, the efficacy was less than 90% when doses less than 5 mg/kg were

administered. In order to assure that a sufficient dose is ingested by each member of a herd, a dose of 7.5 mg/kg over a three-day period (2.5 mg/kg/day) was selected.

V. ANIMAL SAFETY

Animal safety has been adequately addressed for all species included in the supplemental NADA. Safety studies for bighorn sheep (Ovis canadensis canadensis) are included in Public Master File 5071, and those studies are described in a Freedom of Information Summary. Safety in feral swine (Suis scrofa) is based on data contained in this NADA for domestic swine.

Pivotal Animal Safety Study in Exotic Ruminants

Study No.: 103
Starting Date: July 1991
End Date: Nov.1991
Study Director: R. B. Burns, DVM
Test Substance and Dosage Form: Fenbendazole from 20% Premix (Type A Medicated Article)
Animal Species: Nondomestic ruminants (Zoo animals)
Number of Animals treated: 58 ruminant Zoo Animals
Drug level tested & Duration of Dosing: 0, 37.5 mg/kg bw x 9 days (15X dose), 75 mg/kg bw x 3 days (30X dose).
Route of Administration: Oral, via the feed

The following ruminants were treated in this Target Animal Safety Study:

Thomson's Gazelle (*Gazella thomsoni thomsoni*)
Bongo (*Tragelaphus eurycerus*)
Addax (*Addax nasomaculatus*)
Aoudad (*Ammotragus lervia*)
Pere David Deer (*Elaphurus davidianus*)
Sable Antelope (*Hippotragus niger*)
Guanaco (*Lama glama guanacoe*)
Hartman's Mountain Zebra (*Equus zebra hartman*)
Camel (*Camelus dromedarius*)
Blesbock (*Damaliscus dorcas phillipsi*)

This study was conducted by R. B. Burns, DVM at the Louisville Zoological Gardens, Louisville, KY. A total of 58 animals were given fenbendazole in this study. Fenbendazole premix (Type A Medicated Article) was mixed into the standard supplemental zoo ration in use at the Louisville Zoo. After blending, the medicated ration was pelleted. The pelleted ration was assayed for fenbendazole content. Enough medicated feed was provided to achieve the 15X and 30X dose based on the expected fenbendazole concentration in the feed. Actual fenbendazole recovery from the feed varied from 76.7% to 86.7% of the expected value. Therefore, the actual dose that animals received is based on the feed assay recoveries as summarized in Tables 2 and 3.

The actual excess intake of fenbendazole ranged from 2.3X to 22.5X for the animals (Table 2) in the drug tolerance 30X treatment group (75 mg/kg bw x 3 days). The

excess intake of fenbendazole ranged from 1.6X to 17.7X for the animals (Table 3) in the 15X treatment group (37.5 mg/kg bw x 9 days). Ingestion of both the medicated and non-medicated feed varied resulting in variable intake of fenbendazole as indicated in Tables 2 and 3. Minimum required intakes over 3X and 5X were achieved in all animal groups with the exception of the Pere David Deer. The Pere David Deer also failed to completely consume their usual unmedicated ration.

There were no clinically apparent adverse effects observed in any animal during the trial. The usual methods of establishing safety in domesticated animals, including routine bloodwork and necropsies, were not feasible in the animals in this study due to animals' intrinsic value.

Table 2. Summary of Tolerance Study - Actual Excess Dosage Consumed (Intended dose was 75 mg/kg bw x 3 days)

Animal (Number)	**Animal(s) Total Wt. Lbs.**	**lbs of feed consumed*1**	**FBZ Dose*2**		**Times*3 Normal Dose**
			g	**mg/kg**	
Addax (3)	650 (295.5 kg)	16.5	48.7	164.8	22.0
Thompson Gazelle (6)	195 (88.6 kg)	3.0	8.85	99.9	13.3
Aoudad (1)	250 (113.6 kg)	6.25	18.4	162.0	21.6
Pere David Deer (3)	1800 (818.2 kg)	4.75	14.0	17.1	2.3
Bongo-Female (1)	500 (227.3 kg)	13.0	38.4	168.9	22.5
Bongo- Male (1)	600 (272.7 kg)	15.0	44.3	162.4	21.7

*1 Feed contained 2.95 9 fenbendazole (FBZ)/lb. based on average of 4 feed assays. Recommended dosage is 2.5 mg x 3 days (total dose 7.5 mg).
*2 Lbs. consumed x 2.95 = 9 FBZ consumed
*3 (mg FBZ/kg) / 7.5 = actual excessive dosage

Table 3. Summary of Safety Study - Actual Excess Dosage Consumed (Intended dose was 37.5 mg/kg bw x 9 days)

Animal (Number)	Animal(s) Total Wt. Lbs.	lbs of feed consumed*1	FBZ Dose*2		Times*4 Normal Dose*3
			g	mg/kg	
Addax (3)	650 (295.5 kg)	27.5	71.8	81.0	10.8
Blesbock (3)	400 (181.8 kg)	24.25	63.3	116.1	15.5
Camel (1)	1000 (454.5 kg)	26.0	67.9	50.0	6.7
Bongo-Female (1)	500 (227.3 kg)	25.0	65.3	95.8	12.8
Bongo- Male (1)	600 (272.7 kg)	30.0	78.3	95.7	12.8
Sable (1)	350 (159.1 kg)	7.75	20.2	42.3	5.6
Sable (4)	1550 (704.5 kg)	56.25	146.8	69.4	9.3
Aoudad (1)	250 (113.6 kg)	9.75	25.4	74.5	9.9
Aoudad (6)	1500 (681.8 kg)	67.5	176.2	86.1	11.5
Zebra-Dillon (1)	800 (363.6 kg)	32.0	83.5	76.5	10.2
Zebra-Kindra (1)	700 (318.2 kg)	21.25	55.5	58.1	7.7
Zebra-Shani (1)	800 (363.6 kg)	14.25	37.2	34.1	4.5
Zebra-Joann (1)	850 (386.4 kg)	36.00	94.0	81.1	10.8
Pere David Deer (3)	1800 (818.2 kg)	11.5	30.0	12.2	1.6
Thompson's Gazelle (1)	50 (22.7 kg)	2.25	5.9	86.6	11.5
Thompson Gazelle (6)	195 (88.6 kg)	13.50	35.2	132.4	17.7
Guanaco (8)	2100 (954.5 kg)	45.00	117.5	41.0	5.5

*1 Feed contained 2.61 9 fenbendazole (FBZ)/lb. based on average of 4 feed assays. Recommended dosage is 2.5 mg x 3 days (total dose 7.5 mg).
*2 Lbs. consumed x 2.61 = 9 FBZ consumed
*3 mg/kg = average dose given every 3 days of nine day period
*4 (mg FBZ/kg) . 7.5 =-actual excessive dose given every 3 days of 9 day period.

VI. HUMAN SAFETY

This supplement is for use of fenbendazole in hoofed zoo and wildlife animals. Because these types of animals do not constitute a component of the human diet, residue and metabolism studies were not required to support approval of this supplement to NADA 131-675. To cover the possibility that the fenbendazole premix may be used to treat animals in the wild that are hunted, the product is restricted from use for 14 days prior to and during the hunting season. The 1 4-day period provides an interval for residues of fenbendazole to deplete from animals that might be hunted and then used for food purposes.

VII. AGENCY CONCLUSIONS

The data in support of this supplemental NADA complies with the requirements of Section 51 2 of the Act and Section 514.111 of the implementing regulations. It demonstrates that Safe-Guard ® medicated premix (4%, 8%, and 20% fenbendazole premix) when used under the labeled conditions in indicated zoo and wildlife species is safe and effective.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. This supplement provides for the minor use claim as a dewormer in zoo and wildlife animals. The approval of this change has no adverse effect on the safety and effectiveness of the animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Under section 51 2(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for non-food producing animals qualifies for THREE 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 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 new species and claims for which the supplemental application was approved.

The original NADA is labeled for OTC distribution. The current supplement maintains OTC status. The statement, "Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism", appears on the labeling.

The product will be used primarily by individuals with specialized training in the care and management of rare and exotic species and wildlife animals. If a condition develops that could be confused with parasitic infection, this statement addresses recommendations to assist these individuals.

VIII. ATTACHMENTS

1. 4% Fenbendazole Type A Medicated Article.
2. 8% Fenbendazole Type A Medicated Article.
3. 20% Fenbendazole Type A Medicated Article.

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

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.