I. GENERAL INFORMATION

A. File Number

NADA 138-954

B. Sponsor

Pitman-Moore, Inc.
Washington Crossing, New Jersey 08560

C. Proprietary Name

TELMIN™ B Paste Equine Wormer

D. Established Name

mebendazole and trichlorfon

E. Dosage Form(s), Route of Administration and Recommended Dosage

TELMIN B Paste, a paste formulation containing mebendazole and trichlorfon as the active ingredients, is available in an oral dose syringe. Each syringe contains 40 g of paste sufficient to treat up to 1,000 pounds of body weight at the recommended dose of mebendazole (8.8 mg/kg) and trichlorfon (40.0 mg/kg). The syringe, calibrated in 250 pound weight increments, provides this dosage by delivering 10 g of paste for each 250 pounds of body weight.

F. Dispensing Status

Over the Counter (OTC)

G. Indication

TELMIN B Paste is indicated in the treatment of infections caused by bots (*Gastrophilus intestinalis* and *G. nasalis*), large roundworms (*Parascaris equorum*), large strongyles (*Strongylus edentatus*, *S. equinus*, *S. vulgaris*), small strongyles and pinworms (*Oxyuris equi*).

II. EFFECTIVENESS

Substantial evidence of the efficacy of the combination of mebendazole and trichlorfon against infections caused by bots (*Gastrophilus intestinalis* and *Gastrophilus nasalis*) large roundworms (*Parascaris equorum*), large strongyles (*Strongylus edentatus*, *S. equinus*, *S. vulgaris*), small strongyles and pinworms (*Oxyuris equi*) has already been provided in the New Animal Drug Application (NADA 100-402) for the powder dosage form, TELMIN™ B Equine Wormer. TELMIN™ B Paste is recommended for the same indications and at the same dosage level as TELMIN B Equine Wormer. A bioequivalency study was conducted in which the critical efficacy of TELMIN B Paste was compared with that of TELMIN B Equine Wormer. Additionally, clinical field investigations were performed in five different geographic locations to evaluate the efficacy of TELMIN B Paste under practical conditions of use. A summary of the studies conducted is presented below.

A. Bioequivalency Study - Pivotal Study

The anthelmintic activity of TELMIN B Paste Equine Wormer was compared to that of an active treatment control, TELMIN B Powder, in 24 naturally parasitized horses and ponies in a study (Trial No. MEB-99) conducted by B. Seibert, V.M.D., at Pitman-Moore, Inc. Each horse or pony received a single oral treatment of TELMIN B Paste (12 animals) via syringe or TELMIN B Powder (12 animals) mixed in the feed at the recommended rate (8.8 mg mebendazole + 40 mg trichlorfon/kg of body weight). All fecal material was collected for five days after treatment. Five or six days post treatment, the animals were necropsied and the parasites in the gastrointestinal tract were collected, identified and counted. Percent critical efficacy was calculated using the following formula:

% Critical Efficacy = Mean No. Parasites Passed / Mean No. Parasites Passed plus Mean No. Parasites Retained X 100

The mean percent efficacy of both formulations against each parasite is presented in Table 1. In summary, the efficacy of TELMIN B Paste was statistically equivalent to that of TELMIN B Powder against natural infections of parasites claimed in horses and ponies. Clinical signs were limited to two horses treated with TELMIN B Paste and consisted of transient loose feces and mild colic in one horse and rapid breathing and restlessness in the second horse. Each horse recovered uneventfully within 24 hours after the onset of symptoms without the need of symptomatic treatment.

B. Critical Test - Corroborative Studies

Two critical efficacy tests were conducted early in the developmental program using paste formulations of TELMIN™ B that differed slightly from the final proposed commercial formula. The mg/kg dosage levels delivered by each prototype formulation was identical to the final product, namely, 8.8 mg mebendazole and 40 mg trichlorfon per kg of body weight.

C. Clinical Field Investigations

Clinical field investigations were conducted under the direction of Daniel Ruth, V.M.D., in five veterinary practice locations. The clinical investigators were Michael J. Betley, D.V.M., Carol Stream, Illinois; Thomas E. Goetz, D.V.M., Columbia, Missouri; Joseph G. Merriam, D.V.M., Uxbridge, Massachusetts; Garry L. Stewart, D.V.M., Sulfur, Louisiana; and David L. Varra, D.V.M., Boulder, Colorado. A total of 221 horses and eight ponies of both sexes and of various ages and breeds were included in the trial. Quantitative fecal examinations were performed on all horses five days prior to treatment and repeated five to ten days after treatment. One hundred eighty-one horses were treated with TELMIN™ B Paste by delivering the recommended dose of 8.8 mg/kg mebendazole and 40.0 mg/kg trichlorfon of body weight directly onto the horse's tongue via the syringe, while 48 animals were used as untreated controls. Percent efficacy in reduction of eggs per gram (EPG) was calculated in 175 treated and 47 control cases which had pretreatment positive EPG counts.

The average efficacy ranged from 86% to 95% in the treated horses, compared to 0% to 60% for untreated control animals. The overall efficacy of TELMIN B Paste against nematodes was 91% for treated horses and 32% for untreated controls, as determined by reduction in fecal EPG counts after treatment. Of the 117 treated horses and 33 control animals selected for bot observations, 33% of treated horses and 0% of controls showed bot removal. Five horses developed side effects after treatment. In three cases the clinical signs were self-limiting: excessive salivation in a Quarter horse mare which disappeared in 1.5 hours, low-spiritedness in a mare which returned to normal in 24 hours and abstinence from food and water for 24 hours and from food for six days in a Shetland pony. In the other two cases, anorexia and scant feces were observed in a stallion and acute gastritis was observed in a grade mare, which developed diarrhea persisting for six days. In each case, conservative medical treatment was administered with prompt and complete resolution of clinical signs.

D. Special Issues: Combination Drugs

Data demonstrating the effectiveness of each of the active ingredients, mebendazole and trichlorfon, is contained in the Freedom of Information Summary for TELMIN™ B Equine Wormer (NADA 100-402) shown in Attachment 1. The efficacy of the two active ingredients, mebendazole and trichlorfon, is retained when the combination is used as demonstrated by the critical and clinical studies. Thus, the anthelmintic spectrum of the mebendazole/trichlorfon combination paste is greater than that obtained by the use of each active ingredient alone.

This NADA complies with the combination drug policy stated in 21 CFR 514.1(b)(8)(v). Studies which support the selection of the recommended dosages for mebendazole and trichlorfon are contained in NADA 100-402. Dose titration studies were not required for the combination formulation due to the different spectra of anthelmintic activity for each of the components.

Table 1: Results of Critical Trial Comparisons of TELMIN™ B Paste and TELMIN™ B Powder in Horses

Parasite Species		**Trial No. MEB-77A Paste**	**Trial No. MEB-77A Powder**	**Trial No. MEB-93 Paste**	**Trial No. MEB-93 Powder**	**Trial No. MEB-99 Paste**	**Trial No. MEB-99 Powder**	**Overall Paste**	**Overall Paste**
G. intestinalis	No. Infected	6	5	6	5	9	11	21	21
G. intestinalis	Efficacy (%)	100	97.4	98.9	97.4	99.6	98.5	99.5	97.4
G. nasalis	No. Infected	5	3	5	3	2	2	12	8
G. nasalis	Efficacy (%)	97.9	100	100	100	100	100	99.1	100
Gastrophilus Combined	No. Infected	6	5	6	5	9	11	21	21
Gastrophilus Combined	Efficacy (%)	98.6	97.9	99.1	95.2	99.6	98.5	99.2	97.6
S. vulgaris	No. Infected	5	3	4	5	6	5	15	13
S. vulgaris	Efficacy (%)	100	100	91.3	98.6	100	96.7	97.7	98.2
S. edentatus	No. Infected	4	3	6	5	6	6	16	14
S. edentatus	Efficacy (%)	93.8	95.8	95.6	94.1	100	100	96.8	97.0
S. equinus	No. Infected	3	0	0	0	0	0	3	0
S. equinus	Efficacy (%)	100	100	-	-	-	-	100	-
Strongylus Combined	No. Infected	5	4	6	5	7	8	18	17
Strongylus Combined	Efficacy (%)	99.1	97.4	92.8	96.2	100	99.7	97.4	98.1
Small *Strongylus*	No. Infected	6	6	6	6	12	12	24	24
Small *Strongylus*	Efficacy (%)	95.6	88.4	87.6	90.3	97.7	90.6	94.7	90.0
P. equorum	No. Infected	1	1	1	0	4	4	6	5
P. equorum	Efficacy (%)	100	100	100	-	100	100	100	100
O. equi (Adult)	No. Infected	3	1	1	1	3	2	7	4
O. equi (Adult)	Efficacy (%)	100	100	100	100	100	100	100	100
O. equi (Larval)	No. Infected	2	3	3	1	1	1	6	5
O. equi (Larval)	Efficacy (%)	100	100	100	100	100	100	100	100

III. TARGET ANIMAL SAFETY

One safety study was conducted by B. Seibert, V.M.D., at Pitman-Moore, Inc. in which the effects of TELMIN™ B Paste administered orally at 2.2 times the recommended

dose were determined in horses. This study is summarized below. The toxicity of the combination of mebendazole and trichlorfon in horses has already been proven in the currently approved New Animal Drug Application (NADA 100-402) for the powder formulation of TELMIN™ B Equine Wormer, dated March 6, 1975, and approved February 19, 1980. These studies have been summarized in the Freedom of Information Summary for NADA 100-402 included in Attachment 1.

A. Safety Study of TELMIN B Paste Equine Wormer

A total of 12 horses, including eight mares and four geldings, representing various breeds or breed mixtures and ranging in age from approximately two to 11 years, were used in the study. The horses were allocated to two groups with each group consisting of two geldings and four mares. To one group of six horses, TELMIN B Paste was administered in a single oral dose via syringe at the rate of 22 g/250 lb representing 2.2 times the recommended dose of 10 g/250 lb or 8.8 mg of mebendazole and 40 mg of trichlorfon/kg of body weight. The remaining six horses each received a placebo paste, formulated without mebendazole or trichlorfon, administered orally via syringe at the rate of 22 g/250 lb. Parameters examined in this study were clinical observations, hematology, serum chemistry, sulfobromophthalein clearance (a liver function test), and red blood cell cholinesterase activity.

Results from the hematological, serum chemical and sulfobromophthalein clearance tests did not reveal any drug-related changes. Diarrhea was the most prevalent clinical sign observed in the TELMIN B Paste treated horses. Other side effects that occurred infrequently and in mild form in this group included incoordination, salivation, restlessness and pawing. A brief period of quiet recumbency was also observed in one treated horse. Clinical signs were absent by eight hours post treatment. There were no side effects in the placebo-treated horses except for mild diarrhea observed in one horse four hours after treatment.

Erythrocyte (RBC) cholinesterase determinations were made on blood samples collected twice before treatment and at four hours, and 1, 2, 4, 8, 16 and 32 days following treatment. In the TELMIN B Paste treated group, depression of cholinesterase activity was evident at the one hour post treatment sampling time (23%) and the maximum depression (56%) was observed one day after treatment. Mean values were 36% less than pretreatment levels at the final 32 day sampling time. In this study, TELMIN B Paste significantly reduced (P less than 0.01) cholinesterase activity when compared to the placebotreated control horses. This finding was comparable to the results of a previous safety trial in which the powder formulation of TELMIN B, when administered at 2.2 times the recommended dose, also significantly reduced cholinesterase levels (P less than 0.01) in horses when compared to placebo control group. Cholinesterase depression is an expected pharmacological response following the administration of a cholinergic drug such as trichlorfon.

It was concluded in this study that the side effects observed were mild and self-limiting and that cholinesterase depression is not unexpected following a double dose of trichlorfon. These reactions were comparable to that of the powder formulation of TELMIN B when administered at 2.2 times the recommended dose.

B. Clinical Field Trial Safety

The safety of TELMIN B Paste was further confirmed in the clinical field trial of TELMIN B Paste in which a total of 181 horses and ponies of both sexes and of various ages and breeds were treated with TELMIN B Paste. Side effects were elicited in five horses (3%). Excessive salivation was observed in a Quarter horse mare, but this reaction disappeared 1.5 hours later. An aged mare was low in spirit, but was clinically normal within 24 hours. A Shetland pony refused food and water for 24 hours and was off feed for six days before returning to normal. No medication was administered to any of these horses and recovery was complete. Anorexia and scant feces were observed in a 10-month old Lipizzaner stallion and colic, loss of spirit and appetite and diarrhea were observed in an aged mare. Conservative medical treatment was administered. In both these cases, the clinical signs were regarded to have been a result of effective worm treatment in the presence of heavy parasitism.

C. Reproductive Safety

Information to support the safe use of TELMIN B Paste in stallions and pregnant mares up to the last month of pregnancy is based on the fact that the active ingredients in the combination product, mebendazole and trichlorfon, are individually approved for such use. These products are currently on the market with approved New Animal Drug Applications, i.e., TELMIN™ (mebendazole) Equine Wormer, NADA 91-736, approved March 7, 1973, and ANTHON® (trichlorfon) Horse Wormer, Bayvet Division of Cutter Laboratories, Inc., NADA 15-161, approved May 13, 1964. Further evidence was provided by B.M. Cooley, D.V.M., Lafayette, Louisiana, who participated in a clinical trial in which the commercial formulations of mebendazole (TELMIN) and trichlorfon (ANTHON) were administered concurrently to 30 pregnant mares beyond the mid-point of pregnancy. The drugs were either mixed in the feed or given as a top dressing on the feed at the label recommended doses for mebendazole (8.8 mg/kg) and trichlorfon (40 mg/kg). There were no adverse effects in any of the pregnant mares and all deliveries reported were uneventful.

IV. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this New Animal Drug Application. This drug is approved for use only in horses that are not to be used for food and is to be labeled:

WARNING: Not for use in horses intended for food.

With regard to human safety relative to possession, handling and administration, there is a very slight risk of dermal absorption from handling this drug and an appropriate warning appears on the label to wash hands after use. The label further states: If swallowed by a human, immediately call physician, poison control center or hospital emergency room. Additional emergency medical advice for induction of vomition is provided.

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V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that mebendazole/ trichlorfon oral paste combination when used as labeled is safe and effective.

This product has an adequate margin of safety for use by the layman and the possible adverse reactions that may occur are usually mild and reversible. The label carries the description of side effects that may be encountered so that the laymen can distinguish them from other signs of unrelated pathology. The drug poses no problem with disease organisms, immunosuppression by steriod agents or change in intestinal flora. The label warns that trichlorfon, one of the active ingredients, is a cholinesterase inhibitor and should not be used simultaneously or within a few days before or after treatment with other cholinesterase inhibiting drugs, pesticides or chemicals. Other drugs that this product may have interaction with are prescription items and should pose no problem for the layman who does not have access to them. No special handling is necessary to ensure humane treatment of the animal.

All horses carry a parasite burden and this is generally recognized by the professional horseman and lay public, interested in horses. This product is a broad spectrum anthelmintic which is effective against the major parasites of horses. Therefore, the layman will not be required to make a specific diagnosis to use this product. However, if the layman has a serious problem with parasitism in horses, the label bares the statement: "Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism."

The product is for oral administration to horses with adequate directions for use which, in our judgement, the layman can reasonably be expected to follow for the conditions of use, prescribed, recommended or suggested in the approved labeling and will be followed in practice. Accordingly, we have concluded that the product be categorized as an over-the-counter product (OTC).

VI. ATTACHMENTS

Copies of applicable 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.

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