Date of Approval: June 20, 2006

FREEDOM OF INFORMATION SUMMARY

Original Abbreviated New Animal Drug Application

ANADA 200-390

Ivermectin Paste
(ivermectin)

Anthelmintic

For use in horses for treatment and control of large strongyles, small strongyles, pinworms, roundworms (ascarids), hairworms, new threadworms, large-mouth stomach worms, and bots.

Sponsor:

Med-Pharmex, Inc.

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. File Number:	ANADA 200-390
b. Sponsor:	Med-Pharmex, Inc. 2727 Thompson Creek Rd. Pomona, CA 91767-1861 Drug Labeler Code: 054925
c. Established Name:	Ivermectin
d. Proprietary Name:	Ivermectin Paste 1.87%
e. Dosage Form:	Paste
f. How Supplied:	Individual 6 mL syringe containing 0.21 oz (6.08 g) of 1.87% ivermectin
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	1.87% ivermectin
i. Route of Administration:	Oral
j. Species/Class:	Horses, not intended for human consumption
k. Recommended Dosage:	6 mL syringe (6.08 g): This syringe contains sufficient paste to treat one 1250 lb horse at the recommended dose rate of 91 mcg ivermectin per lb (200 mcg/kg) body weight. Each weight marking on the syringe plunger delivers enough paste to treat 250 lb body weight. (1) While holding plunger, turn the knurled ring on the plunger ¼ turn to the left and slide it so the side nearest the barrel is at the prescribed weight marking. (2) Lock the ring in place by making a ¼ turn to the right. (3) Make sure the horse's mouth contains no feed. (4) Remove the cover from the tip of the syringe. (5) Insert the syringe tip into the horse's mouth at the space between the teeth. (6) Depress the plunger as far as it will go, depositing paste on the back of the tongue. (7) Immediately raise the horse's head for a few seconds after dosing.

l. Pharmacological Category: Anthelmintic

m. Indications: Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism. Ivermectin Paste provides effective treatment and control of the following parasites in horses. **Large Strongyles** (adults) – *Strongylus vulgaris* (also early forms in blood vessels), *S .edentatus* (also tissue stages), *S. equinus*; *Triodontophorus* spp. including *T. Brevicauda* and *T. serratus*, and *Craterostomum acuticaudatum*; **Small Strongyles** (adults, including those resistant to some benzimidizole class compounds) – *Coronocyclus* spp. including *C. coronatus, C. labiatus* and *C. labratus*; *Cyanthostomum* spp. including *C. catinatum* and *C. pateratum*; *Cylicocyclus* spp. including *C. insigne*, *C. leptostomum*, *C. nassatus* and *C. brevicapsulatus*; *Cylicodontophorus* spp.; *Cylicostephanus* spp. including *C. calicatus*, *C. goldi*, *C. longibursatus* and *C. minutus*, and *Petrovinema poculatum*; **Small Strongyles** – Fourth-stage larvae; **Pinworms** (adults and fourth-stage larvae) – *Oxyuris equi*; **Ascarids** (adults and third- and fourth-stage larvae) – *Parascaris equorum*; **Hairworms** (adults) – *Trichostrongylus axei*; **Large-mouth Stomach Worms** (adults) – *Habronema muscae*; **Bots** (oral and gastric stages) – *Gasterophilus* spp. including *G. intestinalis* and *G. nasalis*; **Lungworms** (adults and fourth-stage larvae) – *Dictyocaulus arnfieldi*; **Intestinal Threadworms** (adults) – *Strongyloides westeri*; **Summer Sores** caused by *Habronema* and *Draschia* spp. cutaneous third-stage larvae; Dermatitis caused by neck threadworm microfilariae, *Onchocerca* sp.

n. Pioneer Product: EQVALAN Paste 1.87%; ivermectin; NADA 134-314; Merial, Ltd.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

Med-Pharmex, Inc. has demonstrated *in vivo* bioequivalence via a blood-level bioequivalence study comparing the generic product to the pioneer product to support the safety and efficacy of the generic product for use in the treatment and control of large strongyles, small strongyles, pinworms, roundworms (ascarids), hairworms, new threadworms, large-mouth stomach worms, and bots in horses.

Blood-level Bioequivalence Study: One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and pioneer formulations of ivermectin paste.

Testing Facility: Colorado Animal Research Enterprises, Inc. (CARE)
6200 East County Road 56
Fort Collins, CO

Objective: The objective of this study was to determine the comparative blood-levels of Med-Pharmex, Inc.'s Ivermectin Paste 1.87% and EQVALAN (ivermectin) Paste 1.87% sponsored by Merial, Ltd. in a two-period crossover study in horses.

Summary: The design of this study is a comparative bioavailability study using healthy adult horses in a single-dose, two-period, crossover design with randomization of experimental units to two treatments. Thirty-two domestic breed adult horses (16 nonpregnant females and 16 gelded males) were randomly assigned in equal numbers to either of two treatment sequences (8 male, 8 female each sequence) separated by a 35-day washout interval; Med-Pharmex Inc.'s oral ivermectin paste test article followed by Merial Ltd.'s ivermectin paste reference product or vice-versa. Venous blood samples for plasma ivermectin analysis were collected one hour prior to dosing and at 1, 3, 5, 6, 7, 8, 9, 10, 12, 15, 18, 24, 36, 48, 72, 168, 336, and 504 hours after treatment.

Results: The AUC was computed using the trapezoidal rule from time 0 out to the last sampling time associated with quantifiable drug concentration ($AUC_{0\text{-}LOQ}$). The natural logarithm of AUC was computed and used as the variable for analysis. The maximum concentration measured for all time periods (C_{max}) was determined and the natural logarithm of C_{max} was computed and used as the variable for analysis.

The criteria for determining bioequivalence, as described in CVM's Bioequivalence Guidance, is

to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the log scale of AUC and C_{max} and then take the anti-log of the confidence limits multiplied by 100. The resulting bounds should be between 80.00% and 125.00%. As seen in the table below both AUC and C_{max} fall within those bounds.

Variable	Generic Mean	Pioneer Mean	Lower Bound	Upper Bound
Time to Max. Concentration (hours)	4.41	4.78	NA[1]	NA[1]
Log_e(AUC)	8.20	8.30	80.1%	103.6%
$Log_e(C_{max})$	4.15	4.20	82.6%	108.6%

[1]Not Applicable

The variable time to maximum concentration (T_{max}) is permitted to be interpreted by clinical judgment. In this case, there is no reason to expect the difference in T_{max} will affect the efficacy of the drug, since both AUC and C_{max} are bioequivalent and the product is administered as a single dose. Therefore, the study objective to determine the bioequivalence of the generic and pioneer ivermectin products was achieved.

3. HUMAN SAFETY:

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

Human warnings are provided on the package label as follows: **Warning: Do not use in horses intended for human consumption. Not for use in humans. Keep this and all drugs out of the reach of children. Refrain from smoking and eating when handling. Wash hands after use. Avoid contact with eyes.**

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that Ivermectin Paste 1.87%, when used under the proposed conditions of use, is safe and effective for its labeled indications.

Safety and effectiveness for this generic new animal drug, Ivermectin Paste 1.87%, were established by the demonstration of blood-level bioequivalence to the pioneer product, EQVALAN Paste 1.87% sponsored by Merial, Ltd. under NADA 134-314.

5. ATTACHMENTS:

Facsimile generic labeling and currently approved pioneer labeling are attached as indicated below:

Generic Labeling: Container label; Package insert; Carton label

Pioneer Labeling: Container label; Package insert; Carton label