Date of Approval: December 16, 2004

FREEDOM OF INFORMATION SUMMARY

NADA 141-241

ZIMECTERIN- EZ
(ivermectin) 0.6% w/w

"for the treatment and control of roundworms, lungworms, and bots"

Sponsored by:

Merial Ltd.

Table of Contents

1. General Information----------Page 1

2. Effectiveness----------Page 2

3. Target Animal Safety----------Page 5

4. Human Safety----------Page 5

5. Agency Conclusions----------Page 6

6. Attachments----------Page 6

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. File Number:	NADA 141-241
b. Sponsor:	Merial Ltd. 3239 Satellite Blvd. Bldg.500 Duluth, GA 30096-4640 Drug Labeler Code: 050604
c. Established Name:	ivermectin
d. Proprietary Name:	ZIMECTERIN-EZ
e. Dosage Form:	meal mixture
f. How Supplied:	ZIMECTERIN-EZ is supplied in a single blister strip containing 5 individual blister cups that in total will treat a horse up to 1250 lb. of body weight. ZIMECTERIN-EZ is also available in a carton containing 6 blister strips each consisting of 5 individual blister cups.
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	Each blister cup contains 36 mg of ivermectin.
i. Route of Administration:	Oral
j. Species/Class:	Equine
k. Recommended Dosage:	136 mcg ivermectin per lb (300 mcg/kg) body weight
l. Pharmacological Category:	Anthelmintic and boticide
m. Indications:	For 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 benzimidazole class compounds) - *Coronocyclus* spp. including: *C. coronatus, C. labiatus,* and *C. labratus, Cyathostomum* spp. including: *C. catinatum, 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.

2. EFFECTIVENESS:

a. Dosage Characterization:

Three crossover trials were completed to compare the plasma kinetics of ivermectin (measured as the ivermectin component, H2B1a) when administered as the corn-cob based meal mixture formulation (0.6% ivermectin) versus the EQVALAN 1.87% oral paste. The fundamental difference between each investigation was the amount of drug administered as the meal mixture formulation. The dose of the reference product remained constant (200 mcg/kg administered orally). The dose of the meal mixture was increased from 200 mcg/kg (study 1) to 220 mcg/kg (study 2), and to 300 mcg/kg (study 3). This increase was needed to compensate for the lower bioavailability of the meal mixture formulation relative to the approved paste. The results of these investigations confirmed that ZIMECTERIN-EZ at a 300 mcg/kg dose provided

equivalent systemic ivermectin exposure as a 200 mcg/kg dose of the EQVALAN oral paste (90% confidence limits, ZIMECTERIN-EZ versus EQVALAN, = 0.82 – 1.07).

b. Substantial Evidence:

(1) Title: Ivermectin/Horse/TopDress/Paste/Oral/Safety/Pharmacokinetics/ Bioequivalence Study (PR&D 0027801)

(2) Purpose of Study: The purpose of this study was to compare the systemic drug exposure of two different formulations of ivermectin in horses when administered once orally: 0.6% ivermectin in a corncob-based meal mixture formulation administered with feed at 300 mcg/kg body weight and ivermectin paste formulation at 200 mcg/kg body weight.

(3) Investigator: Simon Pitt, BvetMED, PhD, MRCVS

(4) Study Location: Highfield Research Centre
Mangrove Lane
Herford, Herfordshire, UK

(5) Study Animals: Sixteen mixed breed horses (eleven female and five male castrate) ranging in age from 2-16 years with a body weight range of 254-470 kg were enrolled. No horses had been treated in the previous three months with avermectin/milbemycin anthelmintics. The animals were housed for treatment on Days 0 and 70 and grazed within paddocks at all other times. Horses were kept separated by treatment groups.

(6) Treatment Groups: The study was conducted in a two period cross-over design. Horses were ranked according to body weight from highest to lowest on Day -3/-4 (for replicates 1-4 and 5-8 respectively) and consecutively assigned to replicates of two animals each until eight replicates were formed. Within each replicate each animal was randomly allocated to a treatment group. Treatment group assignments were reversed on Day 70 from that given on Day 0 for the second period of the study. Horses were fasted at least 6 hours prior to treatment.

For drug administration, the test product was added to a standard ration of 1 kg sweet grain feed. Each horse was monitored to ensure that the ivermectin grain mixture was consumed. The active control paste was presented to the back of the tongue, and dosing was subsequently followed by the administration of 1 kg of feed.

(7) Duration of Study: 105 days

(8) Variables: Plasma samples for ivermectin assay were collected on Days 0 and 70 before treatment, and then at 1.5, 3, 4.5, 6, 7.5, 9, and 12 hours after treatment. Plasma samples were also collected on days 1, 3, 7, 14, 21, 28, 35, 71, 73, 77, 84, and 91, 98, and 105. Additional plasma was taken at Days -17 and -18 to ensure that ivermectin plasma concentrations were zero before the start of the trial.

(9) Analytical method: The analytical method involved a reverse phase HPLC separation with fluorescence detection for determining the concentrations of ivermectin (H2B1a) and an internal standard. The limit of quantification (LOQ) was set at 0.55 ng/mL and the limit of detection was 0.1 ng/mL.

(10) Data Analysis: Area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal method from either hr zero to the last sampling time associated with concentrations at or exceeding the LOQ of the analytical method ($AUC_{0\text{-last}}$), from hr zero to hr 24 postdose ($AUC_{0\text{-}24}$) or from hr 24 to the last sampling time associated with concentrations at or exceeding the LOQ ($AUC_{24\text{-last}}$). Other values of interest were the observed peak concentration (Cmax) and the time to Cmax (Tmax). Statistical comparisons of the test and reference blood level values were based upon the 2 one-sided test procedure described in the CVM Bioequivalence Guidance (revised 10/09/02). Tmax values were considered non-pivotal and were compared solely on a qualitative basis.

(11) Results: The meal mixture and oral paste formulations resulted in comparable ivermectin systemic exposure ($AUC_{0\text{-last}}$). Slight differences in Cmax values were observed (as indicated by the lower confidence limit of 0.74). Since the product did not meet traditional bioequivalence criteria for Cmax, the sponsor was asked to justify basing an approval primarily upon AUC estimates. In response, Merial Ltd. provided data from clinical effectiveness trials generated with EQVALAN oral paste in ponies, and presented a corresponding Emax model that was fitted to the log parasite counts. This information confirmed that the small difference observed in Cmax values (without corresponding differences in AUC) will not compromise product effectiveness. In addition, Merial provided published information confirming that avermectins in general exhibit activities that are dependent upon the duration of the parasite exposure to active drug concentrations (Lifschitz, et al., 1999)[1]. Therefore, to confirm equivalent exposure over time, the data were partitioned into two partial AUC values: $AUC_{0\text{-}24}$ and $AUC_{24\text{-last}}$. Based upon these AUC estimates, plus $AUC_{0\text{-last}}$, it was

[1] Lifschitz, A., Virkel, G., Imperials, F., Sutra, J.G., Galtier, P., Lanusse, C., and Alvinerie, M. (1999a). Moxidectin in cattle: correlation between plasma and target tissues disposition. J. Vet. Pharmacol. Therap., 22: 266-273.

concluded that the relative bioavailability study provided an acceptable surrogate for demonstrating the comparability of product effectiveness.

The results of the *in vivo* relative bioavailability study are provided in Table 1.

Table 1: Blood level values resulting from a single dose of EQVALAN paste (200 mcg/kg) or meal mixture product (300 mcg/kg).

Parameter	Units	Paste (Ref)	Meal mixture (Test)	Ratio Test/Ref	Lower Conf Lim#	Upper Conf Lim#
$AUC_{0\text{-}last}$	ng*hr/mL	124.39	116.54	0.94	0.82	1.07
$AUC_{0\text{-}24}$	ng*hr/mL	37.56	34.64	0.92	0.79	1.08
$AUC_{24\text{-}last}$	ng*hr/mL	85.32	80.82	0.95	0.83	1.08
Cmax	ng/mL	65.48	58.50	0.89	0.74	1.08
Tmax	hrs	3.94	5.06			

lower and upper bounds for the 90% confidence limits, as determined on the basis of the 2 one-sided tests procedure.

(12) Conclusions: Based upon an equivalence of extent of absorption ($AUC_{0\text{-}24hr\text{-}last}$) and the comparability of the partitioned systemic ivermectin exposure (as defined by $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}24hr\text{-}last}$,), ivermectin 0.6% in a corn cob meal mixture, when administered once with feed at 300 mcg/kg, demonstrated comparable systemic drug exposure to ivermectin paste 1.87% when administered once orally at 200 mcg/kg.

3. TARGET ANIMAL SAFETY

This NADA does not require evaluation of target animal safety data due to bioequivalence of ZIMECTERIN EZ (ivermectin) 0.6% w/w to EQVALAN (ivermectin 1.87%) Paste. Please refer to the original NADA 134-314 for EQVALAN (ivermectin) Paste, FOI Summary, dated May 29, 1984.

4. 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 NADA.

Human Warnings are provided on the product label as follows: “Not for use in humans. Keep this and all drugs out of reach of children. Refrain from smoking and eating when handling. Wash hands after use. Avoid contact with eyes.”

The Material Data Safety Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users, to obtain more information, or to obtain a MSDS, contact Merial at 1-888-637-4251.

5. 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 of the implementing regulations. The data demonstrate that ZIMECTERIN-EZ, when used under labeled conditions of use, is safe and effective for the treatment and control of various species of internal parasites.

ZIMECTERIN-EZ is labeled for OTC use. Routine deworming of horses is a widely accepted and recommended practice performed by the lay person. A diagnosis of parasite infection prior to deworming is not necessary.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The basis for exclusivity is the bioequivalence study which demonstrated comparable systemic drug exposure of the approved ivermectin paste and the corn cob meal mixture formulation of ivermectin.

ZIMECTERIN-EZ is under the following U.S. patent number:

U.S. Patent Number	Date of Expiration
Patent Pending	

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Single blister strip carton
Multi-unit containing either six individual cartons or six blister strips
Blister strip label