Approval Date: August 9, 2002

FREEDOM OF INFORMATION SUMMARY

Abbreviated New Animal Drug Application

ANADA 200-320

EQUELL (ivermectin) Paste

Sponsor:

Virbac AH, Inc.
3200 Meacham Blvd.
Fort Worth, TX 76137

1. GENERAL INFORMATION:

FILE NUMBER:	200-320
SPONSOR:	Virbac AH, Inc. Fort Worth, TX 76137 Drug Labeler Code 051311
ESTABLISHED NAME:	Ivermectin Paste
PROPRIETARY NAME:	EQUELL™ (ivermectin) Paste
DOSAGE FORM:	Oral Paste
HOW SUPPLIED:	Dose syringe containing 6.42 grams of product.
HOE DISPENSED:	OTC
AMOUNT OF ACTIVE INGREDIENTS:	Each milligram of the paste contains 0.0187 milligram (1.87 %) ivermectin.
ROUTE OF ADMINISTRATION:	Oral
SPECIES:	Equine
RECOMMENDED DOSAGE:	The dose rate is 91 mcg ivermectin per pound (200 mcg/kg) of body weight.
PHARMACOLOGICAL CATEGORY:	Antiparasitic
PIONEER PRODUCT:	Eqvalan® (ivermectin) Paste, Merial Ltd., NADA 134-314.

INDICATIONS FOR USE:

Equell is indicated for the effective treatment and control of the following parasites or parasitic conditions in horses:

Large strongyles (adults): *Strongylus vulgaris* (also early forms in blood vessels),

S. edentatus (also tissue stages), *S. equinus*, *Triodontophorus* spp.

Small strongyles including those resistant to some benzimidazole class compounds (adults and fourth stage larvae): *Cyanthostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp., *Cylicodontophorus* spp.

Pinworms (adults and fourth stage larvae): *Oxyuris equi*.
Ascarids (adults and third- and fourth- stage larvae): *Parascaris equorum*.
Hairworms (adults): *Trichostrongylus axei*.
Largemouth stomach worms (adults): *Habronema muscae*.
Neck threadworms (microfilariae): *Onchocerca* spp.
Bots (oral and gastric stages): *Gastrophilus* spp.
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.

2. ANIMAL SAFETY AND EFFECTIVENESS

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act, (53 FR 50460, December 15, 1988; First GADPTRA Policy Letter), 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 data, drug effectiveness data, and human food safety data (other than tissue residue data) are required for approval of an ANADA. An ANADA approval is based on a demonstration that the generic product is bioequivalent to the pioneer product.

The following studies were completed to provide evidence of blood-level bioequivalence of the generic and pioneer ivermectin pastes in horses:

Bioequivalence study 595.04/60001 (GLP)

A BIOEQUIVALENCE STUDY OF VIRBAC'S IVERMECTIN ORAL PASTE AND EQVALAN® IN HORSES

Study Director/Location:	Craig Reinemeyer, D.V.M., Ph.D. East Tennessee Clinical Research, Inc. Knoxville, TN

Summary: After meeting entrance criteria, 28 adult horses (14 castrated males; 14 females) were ranked by weight within each sex. Within each sex, replicates of two

horses were randomly assigned to one of two treatment sequences, generic test article followed by pioneer control article or pioneer control article followed by generic test article. Animals were given the first drug of the assigned sequence during the first treatment period and the second drug of the assigned sequence during the second treatment period. Treatments consisted of a single oral administration of 200 mcg of generic or pioneer ivermectin per kg of body weight. For the second treatment of the sequence, horses received a single oral administration of 200 mcg of generic or pioneer ivermectin per kg of body weight as per treatment assignment. There was a 35-day washout interval between the two periods of the crossover design.

Blood samples for each animal, for each period of the study were taken at the following times, 0 hour and (hours after drug administration), 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 240, 336, and 504. Ivermectin concentrations in plasma were quantified using a validated HPLC method with fluorescence detection (excitation, 360 nm, and emission, 470 nm, wavelengths). The assayed ivermectin plasma levels in the blood of the test animals from the 0 hour sample through the hour 504 sample were statistically analyzed with an analysis of variance procedure, following the 2000 Bioequivalence Guideline.

The area under the plasma concentration curves (AUC estimated from time 0 to last quantifiable concentration) were computed using the trapezoidal method. The maximum concentration measured for all time periods (C_{max}) was determined. Statistical evaluation of AUC and C_{max} values were based upon the Ln-transformed estimates. The corresponding confidence intervals about the ratio of treatment means were conducted in accordance with the algorithms described in the 2000 Bioequivalence Guidance document

Results and Conclusions:

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

Table 1: Results of the *in vivo* bioequivalence study

Variable	Virbac [arithmetic mean (%CV)]	Merial [arithmetic mean (%CV)]	Lower Conf. Lim.	Upper Conf. Lim.
AUC (µg*hr/mL)	2371 (54)	2614 (55)	-18.4%	+3.8%
C_{max} (µg/mL)	37.5 (46)	42.0 (53)	-21.2%	+10.2%

The exponentiated value of the lower confidence limit about the ratio of the test/reference AUC values was ≥0.8 and the corresponding value for the upper limit was ≤1.25. The exponentiated value of the lower confidence limit about the ratio of the test/reference C_{max} values was ≥ 0.7878 and the corresponding value for the upper limit was ≤1.25.

The corresponding T_{max} values were 4.6 hr and 3.2 hrs for the test and reference products respectively.

Due to the very large within-subject variability observed with these products (residual errors from the ANOVA, expressed as %CV for AUC and C_{max}, were 26.9% and 38% respectively), the 11% difference in C_{max} prevented the confidence limits from being contained within the strict 0.80 – 1.25 boundary defining product bioequivalence. Importantly, it was noted that the intersubject variability was similar across treatment groups (refer to Table 1). In a similarly conducted study on 28 horses for the European regulatory authorities (see below), the test and reference products (which were manufactured in a manner identical to that used for the US formulations) succeeded in meeting US-type bioequivalence criteria (0.80 – 1.25). Therefore, given the high variability associated with the test and reference products, the 1% deviation from traditional US bioequivalence criteria for C_{max}, and the success of the European bioequivalence investigation, the US FDA concludes that Equell and Eqvalan are bioequivalent. "

Adverse events observed during the study included transient tremors, pawing and agitation in one horse and fasciculation of muscles in all limbs in another. Both horses had received the generic product and in both cases the clinical signs resolved spontaneously without medical intervention.

Supportive Bioequivalence Study 595.04/4001

DETERMINATION OF THE BIOEQUIVALENCE OF TWO IVERMECTIN FORMULATIONS IN HORSES.

Investigator/Study Location: Bruce Chick B.V.Sc., Dip. Ag. Econs., Dip. Diag. Path
Veterinary Health Research PTY Ltd.
Colin Blumer Animal Health Laboratory
West Armidale, NSW. Australia

Summary: After meeting entrance criteria, 28 adult horses (14 castrated males; 14 females) were ranked by weight within each sex. Within each sex, replicates of two horses were randomly assigned to one of two treatment sequences, generic test article followed by pioneer control article or pioneer control article followed by generic test article. Animals were given the first drug of the assigned sequence during the first treatment period and the second drug of the assigned sequence during the second treatment period. Treatments consisted of a single oral administration of 200 mcg of generic or pioneer ivermectin per kg of body weight. For the second treatment of the

sequence, horses received a single oral administration of 200 mcg of generic or pioneer ivermectin per kg of body weight. There was a 35-day washout interval between the two periods of the crossover design.

Blood samples for each animal, for each period of the study were taken at the following times, 0 hour and (hours after drug administration), 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 240, 336, and 504. Ivermectin concentrations in plasma were quantified using a validated HPLC method with fluorescence detection (excitation, 360 nm, and emission, 470 nm, wavelengths). The assayed ivermectin plasma levels in the blood of the test animals from the 0 hour sample through the hour 504 sample were statistically analyzed with an analysis of variance procedure, following the 2000 Bioequivalence Guideline.

The area under the plasma concentration curves (AUC estimated from time 0 to last quantifiable concentration) were computed using the trapezoidal method. The maximum concentration measured for all time periods (C_{max}) was determined. Statistical evaluation of AUC and C_{max} values were based upon the Ln-transformed estimates and the corresponding confidence intervals about the ratio of treatment means were conducted in accordance with the algorithms described in the 2000 Bioequivalence Guidance document

Results and Conclusions: The exponentiated value of the lower confidence limit about the ratio of test/reference AUC values was ≥0.8 and the corresponding values for the upper limit was ≤1.25. The exponentiated value of the lower confidence limit about the ratio of test/reference C_{max} values was ≥ 0.80 and the corresponding values for the upper limit was ≤1.25. Therefore, the study objective to determine the bioequivalence of generic and pioneer ivermectin 1.87% paste by serum bioavailablity was achieved. T_{max} did not satisfy the criteria in the *Bioequivalence Guidance*, but 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.

3. HUMAN SAFETY:

Human Safety Relative to Food Consumption:

None required as Ivermectin Paste 1.87% is intended for use only in horses. The labeling includes the statement:

"WARNING: Do not use in horses intended for food purposes."

Human Safety Relative to Possession, Handling, and Administration:

Labeling contains adequate caution/warning statements.

4. AGENCY CONCLUSIONS:

This is an Abbreviated New Animal Drug Application (ANADA) filed under section 512(b)(2) of the Federal, Food, Drug and Cosmetic (FFD&C) Act.

Safety and effectiveness for this generic animal drug, Ivermectin Paste1.87% were established by demonstration of bioequivalence to the pioneer product, Eqvalan® Paste for Horses (NADA 134-314, Merial Ltd.).

This generic product and the pioneer product have identical labeling indications for the use in horses. The route and method of administration of the two drugs are identical. Both drugs are administered orally. The generic and pioneer products contain the same active ingredients.

This ANADA satisfies the requirements of section 512 of the Act and demonstrates that Ivermectin Paste 1.87 % is safe and effective for its labeled indications when used under the proposed conditions of use.

5. LABELING (Attached)

1.Generic labeling:

Package Insert
Container Label
Carton Label

2.Pioneer Labeling

Package Insert
Container Label
Carton Label