Approval Date: April 2, 2003

FREEDOM OF INFORMATION SUMMARY

EQVALAN® (ivermectin) PASTE 1.87%
for Horses

Supplemental NADA 134-314
Merial Ltd.

Allows for the addition of new parasite species to the Indications

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. NADA Number: 134-314

b. Sponsor: Merial Ltd.
3239 Satellite Blvd.
Bldg. 500
Duluth GA 30096-4640
Drug Labeler Code: 050604

c. Established Name: Ivermectin

d. Proprietary Name: EQVALAN® Paste 1.87%

e. Dosage Form: An oral paste containing 1.87% ivermectin

f. How Supplied: Individual dose syringe contains sufficient paste to treat one 1250 lb horse orally. Each weight marking on the syringe plunger delivers enough paste to treat 250 lb body weight.

g. How Dispensed: OTC

h. Amount of Active Ingredient: Each syringe contains 113 mg of ivermectin.

i. Route of Administration: Oral

j. Species/Class: Equine

k. Recommended Dosage: 91 mcg ivermectin per lb (200 mcg/kg) body weight.

l. Pharmacological Category: Anthelmintic

m. Indications: For the treatment and control of the following parasites in horses:

Large strongyles (adults):

Strongylus vulgaris (also early forms in blood vessels)
Strongylus edentatus (also tissue stages)
Strongylus equinus

Triodontophorus spp. including:
Triodontophorus brevicauda

Triodontophorus serratus

Craterostomum acuticaudatum

Small strongyles: Including those resistant to some benzimidazole class compounds (adults and 4th stage larvae)

Coronocyclus spp. including:
Coronocyclus coronatus
Coronocyclus labiatus
Coronocyclus labratus

Cyathostomum spp. including:
Cyathostomum catinatum
Cyathostomum pateratum

Cylicocyclus spp. including:
Cylicocyclus insigne
Cylicocyclus leptostomum
Cylicocyclus nassatus
Cylicocyclus brevicapsulatus

Cylicodontophorus spp.

Cylicostephanus spp. including:
Cylicostephanus calicatus
Cylicostephanus goldi
Cylicostephanus longibursatus
Cylicostephanus minutus

Petrovinema poculatum

Pinworms (adults and 4th stage larvae) - *Oxyuris equi*

Roundworms or ascarids (adults and 3rd and 4th 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 4th 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. Effect of Supplement: The supplement provides for the use of ivermectin paste for the treatment and control of *Craterostomum acuticaudatum, Petrovinema poculatum,* and *Coronocyclus* spp. including: *Coronocyclus coronatus,* and *Coronocyclus labratus*. Also, the label descriptions of some currently-approved parasite genera are being revised to add included species for which data already exists in the NADA file and to reflect changes in scientific nomenclature.

2. EFFECTIVENESS

Two dose confirmation studies were conducted to confirm the effectiveness of ivermectin paste 1.87% administered at the recommended use level against endoparasites of horses. The endoparasites found at necropsy - including large and small strongyles - were identified to the species level.

Dose Confirmation Study PR&D 0011601

Investigator: Dr. Thomas R. Klei

Study Location: Louisiana State University, Baton Rouge, LA, 70803

Animals: 20 crossbred ponies (13 male, 7 female) aged 2 to 5 years, with natural endoparasite infections

Treatment Groups: Replicates were formed based on baseline strongylid fecal egg counts: within replicates, one animal was randomly allocated to an unmedicated control group, and the other received ivermectin paste 1.87% once at a dosage of 200 mcg of ivermectin per kg body weight.

Route of Administration: Oral

Duration of Study: Animals were necropsied by replicate on Day 14, 15, or 16.

Measurements: Stomach contents and washings, small intestine contents and mucosal washings, cecum and colon were examined for parasites. For each animal with large worm burdens, approximately 2000 or more small strongyles were identified to species.

Statistical Methods:

For each parasite species, differences in worm counts between treated and control groups were compared using a Wilcoxon rank-sum test with a 0.05 significance level.

For each parasite species, percent effectiveness was calculated as follows:

$$\text{Percent effectiveness} = 100[(C - T) / C],$$

where C and T represent the geometric mean of the control and treatment group respectively. The geometric means were computed using the transformation, ln(count+1).

Dose Confirmation Study PR&D 0011602

Investigator: Dr. Steffen Rehbein

Study Location: Kathrinenhof Research Center, Rohrdorf-Lauterbach, Germany

Animals: 20 ponies (9 male, 11 female) aged 2 to 11 years

Treatment Groups: Replicates were formed based on baseline strongylid fecal egg counts: within replicates, one animal was randomly allocated to an unmedicated control group, and the other received ivermectin paste 1.87% once at a dosage of 200 mcg of ivermectin per kg body weight.

Route of Administration: Oral

Duration of Study: Animals were necropsied by replicate on Day 14 or 15.

Measurements: Stomach contents and washings, small intestine contents and mucosal washings, cecum and colon were examined for parasites. For each animal with large worm burdens, several thousand small strongyles were identified to species.

Statistical Methods:

For each parasite species, differences in worm counts between treated and control groups were compared using a Wilcoxon rank-sum test with a 0.05 significance level.

For each parasite species, percent effectiveness was calculated as follows:

Percent effectiveness = 100[(C – T) / C],

where C and T represent the geometric mean of the control and treatment group respectively. The geometric means were computed using the transformation, ln(count+1).

Results of the two dose confirmation studies (PR&D 0011601 and PR&D 0011602:

The parasite species listed below met the following criteria in both of the dose confirmation studies (PR&D 0011601 and PR&D 0011602):

1) Had at least 6 adequately infected control animals per parasite species
2) Had a statistically significant ($p<0.05$) difference in parasite counts between treated and control groups using a Wilcoxon rank-sum test
3) Ivermectin had a >90% effectiveness compared to control

Coronocyclus coronatus
Coronocyclus labiatus
Coronocyclus labratus

Cyathostomum catinatum
Cyathostomum pateratum

Cylicocyclus insigne
Cylicocyclus leptostomum
Cylicocyclus nassatus

Cylicostephanus calicatus
Cylicostephanus goldi
Cylicostephanus longibursatus
Cylicostephanus minutus

Petrovinema poculatum

Strongylus edentatus
Strongylus vulgaris

Triodontophorus brevicauda
Triodontophorus serratus

Craterostomum acuticaudatum

3. TARGET ANIMAL SAFETY

This supplemental NADA does not require re-evaluation of target animal safety data. Please refer to the original NADA 134-314 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. The drug is labeled "Do not use in horses intended for food purposes".

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."

5. AGENCY CONCLUSIONS

The data in support of this supplemental NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 514 of the implementing regulations. The data demonstrates that Eqvalan® (ivermectin) Paste 1.87%, when used under labeled conditions, is safe and effective.

Eqvalan® Paste 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 the Center's supplemental approval policy 21 CFR 514.106(b)(2), this is a Category II change.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, parts of this supplemental approval for non-food producing animals qualify for three years of marketing exclusivity beginning on the date of the supplemental approval because the application contains substantial evidence of the effectiveness of the drug involved, or studies of animal safety required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the treatment and control of the following parasites: *Craterostomum acuticaudatum, Petrovinema poculatum,* and *Coronocyclus* spp. including: *Coronocyclus coronatus,* and *Coronocyclus labratus.*

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Package outsert

Syringe label

Syringe carton