FOI Summary; NADA 140-439 (original); EQVALAN Liquid (Ivermectin); July 1, 1987
--Editor's abstract

1. General Information

New Animal Drug Application Number: 140-439

Sponsor:

Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0914

Generic Name: Ivermectin

Tradename: EQVALAN Liquid

Marketing Status: Veterinary prescription drug

Date of Approval: July 1, 1987

This FOI Summary provides for a liquid dosage form of ivermectin administered by nasogastric intubation, or as an oral drench, as an addition or alternative to the previously approved products, Eqvalan paste and Eqvalan injection.

2. Indications For Use:

For treatment and control of the following parasites or parasitic conditions in horses:

Bots
Gastrophilus spp., oral and gastric stages

Large mouth stomach worms
Habronema muscae, adults

Neck threadworms
Onchocerca sp., microfilariae

Pinworms
Oxyuris equi, adults and fourth stage larvae

Ascarids
Parascaris equorum, adults

Lungworms
Dictyocaulus arnfieldi, adults and fourth stage larvae

Intestinal threadworms
Strongyloides westeri, adults and fourth stage larvae

Small strongyles - including those resistant to some benzimidazole class compounds
Cyathostomum spp., adults and fourth stage larvae
Cylicocyclus spp., adults and fourth stage larvae
Cylicodontophorus spp., adults and fourth stage larvae
Cylicostephanus spp., adults and fourth stage larvae

Blood worms or large strongyles
Strongylus edentatus, adults and tissue stages
Strongylus equinus, adults
Strongylus vulgaris, adult and arterial larval stages
Triodontophorus spp., adults

Hair worms
Trichostrongylus axei, adults

Summer sores caused by *Habronema* and *Draschia* spp. cutaneous third stage larvae

Dermatitis caused by neck threadworm microfilariae (*Onchocerca* sp.)

3. Dosage Form, Route of Administration and Recommended Dosage

EQVALAN liquid is formulated for administration by stomach tube or as an oral drench. The recommended dosage is 200 micrograms of ivermectin per kilogram of body weight (0.2 mg/kg or 91 mcg/lb). Each ml of EQVALAN liquid contains 10 mg of ivermectin, sufficient to treat 110 lb (50 kg) of horse body weight; 10 ml will treat an 1100 lb (500 kg) horse.

4. Effectiveness:

The New Animal Drug Application for ivermectin liquid for horses contains data demonstrating that the product is the therapeutic equivalent of EQVALAN paste. Therefore, the full spectrum of indications for use of EQVALAN paste (NADA 134-314) is applicable to EQVALAN liquid. The therapeutic equivalence demonstrated in the controlled efficacy confirmation trial and the five field trials is supported by the data from a bioavailability trial where the liquid and paste formulation were compared.

Pivotal Studies

Controlled Efficacy Trial

One controlled efficacy confirmation trial was conducted by Dr. Joseph A. DiPietro at the University of Illinois, Urbana, Illinois, using 15 horses that were given induced ascarid infections. When the infections were 11 days old, horses were randomly allocated to an unmedicated control group, or to treatment with ivermectin liquid as an oral drench or with EQVALAN paste (5 horses per group). No *Parascaris equorum* were found at necropsy, 14 days after treatment, in any ivermectin liquid- or ivermectin paste-treated horse, while all 5 controls were infected with an average of 1136 *P. equorum.* While the immature (migrating) ascarid is not currently included as a claim in the indications for use of ivermectin, it is known to be difficult to control.

Field Trials

Five field trials with 471 horses were conducted in the United States and Canada, one each in Arkansas, Florida, Illinois, Texas and Saskatchewan. The investigators are listed below:

Investigator	Location/Address
Dr. Richard L. Asquith	University of Florida, Ocala, Florida
Dr. Roxanne Bell	Univ. of Saskatchewan Saskatoon, Saskatchewan, Canada
Dr. Joseph A. DiPietro	University of Illinois, Urbana, Illinois
Dr. Ed S. Murray	Spur, Texas

All 471 horses (from 15 days old to 24 years old) in these 5 field trials received ivermectin at use level: 250 horses received ivermectin liquid as a drench, 117 horses received the liquid by stomach tube, and 104 horses got EQVALAN Paste. These numbers include the horses used as concurrent untreated controls and subsequently treated with ivermectin.

These trials were run under practical field conditions with the market formulation of EQVALAN liquid to assess the acceptability of the product in horses when administered as an oral drench or by nasogastric intubation, and to confirm its efficacy (by fecal egg counts) when given at 1 ml per 50 kg of body weight (i.e., at 200 mcg/kg).

All of the trials were conducted similarly. Horses had natural infections of internal parasites and no anthelmintics were used on trial animals for at least six weeks before the trial start date. An acclimation period of at least 7 days was provided at each site. Feed, water and housing were given according to the usual practices at each property.

At each U.S. trial location, replicates of four horses were formed based on order of presentation or based on pretreatment fecal egg count. All horses in a replicate were housed, managed, and handled similarly. Within each replicate, 1 horse was assigned to be an unmedicated control, 1 horse was assigned to receive ivermectin liquid by nasogastric tube, and 2 horses were assigned to receive ivermectin liquid as a drench. The Canadian field trial differed from the 4 U.S. trials in that one each of the 4 horses in a replicate was randomly assigned to an unmedicated control group or to treatment with ivermectin liquid as a drench or by stomach tube, or to treatment with EQVALAN paste.

The assigned ivermectin liquid treatments were administered on Day 0, at the rate of 1 ml per 50 kg of horse body weight (200 mcg of ivermectin/kg). Horses were weighed, or had their weights estimated (by girth tape), within a few days prior to Day 0. Ivermectin liquid was administered undiluted. For each horse in the tubing group, at least 200 ml of clean water was flushed through the tubing equipment *in situ* immediately after the administration of ivermectin liquid.

Fecal samples were collected from 471 horses, and examined for parasite eggs on or before Day 0, and most horses were sampled again on Day 13 or 14. At the time of the second sampling, control horses were treated with ivermectin liquid as a drench or with EQVALAN paste. Almost all of these horses had fecal samples taken one more time, usually 2 weeks later, except for the 29 controls in the Canadian field trial.

Fecal samples were generally examined by a modified McMaster procedure. Most samples with a count of 100 or fewer eggs per gram of feces (EPG count) were examined again with a direct flotation technique. Eggs were classified and recorded by type as *Parascaris equorum, Strongyloides westeri* , or strongylids.

For each trial, total EPG counts (i.e., total counts of all types of nematode eggs per horse) were analyzed for differences among treatment groups on Day 13 or 14 using Friedman's test, a nonparametric chi-square test for randomized block designs. Two treatment contrasts were of interest: control vs. ivermectin liquid by stomach tube, and control vs. ivermectin liquid as a drench. In each trial both contrasts were significant at $P<.01$.

Natural parasitic infections were confirmed for 441 of the animals on or before the trial start day. On Day 13 or 14, eggs of parasitic nematodes were found in the feces of 107 of 114 sampled untreated controls, while only 14 of 301 sampled horses that received ivermectin liquid had strongyle type eggs in their feces, and none of 29 horses given EQVALAN paste had parasite eggs. Of the 14 ivermectin liquid-treated horses with positive counts two weeks after treatment, only 2 had counts detectable by the modified McMaster procedure (50 and 300 epg); the others had eggs observed only on the more sensitive direct flotation. Fourteen or 16 days after the controls were treated with ivermectin, strongyle-type eggs were found in the feces of 4 of 41 horses that received ivermectin liquid as a drench, and on 4 of 40 horses that got EQVALAN paste. Included in these trials were 58 horses positive for ascarid eggs prior to treatment with ivermectin liquid (29 tubed, 29 drenched) but negative 14

days after treatment, and 26 horses with *Strongyloides westeri* eggs prior to treatment (8 tubed, 18 drenched) but with none 14 days after treatment).

All horses treated with ivermectin liquid were closely monitored immediately after treatment and observed daily for 13 or 14 days. Also, the oral cavities of all horses receiving ivermectin liquid as an oral drench were examined for abnormalities.

No adverse reactions attributed to ivermectin treatment were reported for any horse. One mare had colic 11 days after treatment and 1 gelding was euthanized on Day 14 suffering from an acute central nervous system disorder; necropsy revealed severe multifocal encephalomalacia consistent with septicemia. No abnormalities were found in the oral cavity of any horse given ivermectin liquid as a drench.

Supporting Data

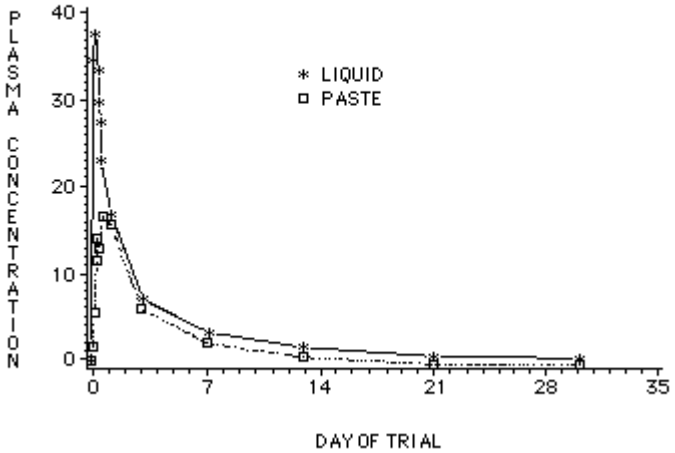
Bioavailability

A bioavailability trial was conducted by Dr. Richard L. Asquith at the University of Florida, Ocala, Florida, utilizing 13 healthy pregnant mares. One horse was randomly selected to be an unmedicated control whose plasma was used to verify the absence of ivermectin. Pairs of horses were formed based on breed, body condition and weight. Within pairs, one horse received EQVALAN paste orally at 200 mcg/kg and the other received ivermectin liquid by nasogastric intubation at 200 mcg/kg. Blood samples were collected from each mare prior to treatment and at appropriate intervals following treatment.

Plasma samples were assayed for ivermectin. Area under the plasma time curve (AUC) was computed for each animal. The natural logarithm transformation was found to help homogeneity of variance for AUC; plasma concentration data and time-to-peak were not transformed. Peak plasma value, log (AUC), and time-to-peak were analyzed, with and without a rank transformation, using analysis of variance for a repeated measures design, to investigate whether the treatment profiles were similar. The conclusions were the same whether or not the rank transformation was used.

All plasma samples for the control horse and all pretreatment samples were free of ivermectin. Ivermectin liquid had a higher and earlier peak plasma ivermectin concentration than EQVALAN paste. The differences between formulations were confined to the first 24 hours after dosing (see Figure 1). After that time, the profiles of the two formulations were almost identical and the difference in area under the plasma time curves was only 12%. Ivermectin liquid provides equivalent parasite exposure to ivermectin and, therefore, equivalent efficacy against the same spectrum of equine parasites as the paste.

FIGURE 1
MEAN PLASMA CONCENTRATION (NG/ML) OVER TIME
IVERMECTIN LIQUID VS PASTE, AT 200 MCG/KG



Conclusion

The therapeutic equivalence of ivermectin liquid to EQVALAN paste was confirmed in one controlled efficacy confirmation comparison trial and in 5 field trials. The efficacy was demonstrated as a drench or by nasogastric tube.

EQVALAN liquid has the same indications for treatment and control of parasites and parasitic conditions as has EQVALAN paste.

5. Safety in the Target Animal

Pivotal Studies

NADA 134-314 and 127-443

The safety of ivermectin in horses has been established in trials included in previous submissions (EQVALAN paste; NADA 134-314 and EQVALAN injection; NADA 127-443). Information on these studies is included in the Freedom of Information Summaries for these previously approved products.

Breeding Animal Safety - Horses

Two teratology trials were conducted in which mares were given ivermectin paste at 600 mcg/kg six times at two-week intervals during the period of organogenesis. Two additional trials were conducted where mares were treated six or seven times with ivermectin injection at 600 mcg/kg at two months of pregnancy. A stallion breeding safety trial was also conducted in which stallions received a single treatment of ivermectin injection at 600 mcg/kg. No adverse effects on reproduction were seen in these trials and it was concluded that ivermectin may be used safely in breeding stallions and in pregnant mares. These trials are more fully described in the Freedom of Information Summary for EQVALAN paste.

Supporting Data

Ivermectin liquid for horses has been tested in a tolerance trial conducted using repeated administrations at 3 and 5 times use level. The clinical field trials discussed in the previous section also demonstrated safety and acceptability of ivermectin liquid under commonly experienced field conditions.

Tolerance

The tolerance trial was conducted by Dr. Joseph A. DiPietro, University of Illinois, Urbana, IL, in young foals because they are considered to be the most sensitive age of horse based on studies with EQVALAN paste. Young foals were given repeated doses of ivermectin liquid at 0, 3 or 5 times use level, i.e., at 0, 600 or 1000 mcg/kg. This trial was conducted using 18 standardbred foals that were from 24 to 92 days old on Day 0.

The foals were kept on pasture and received a dietary supplement. Well water was available. Replicates of 3 foals were formed based on sex and pretreatment weight. Within replicates, foals were randomly allocated to receive a water treatment (placebo control), or ivermectin liquid as a drench at 600 or at 1000 mcg/kg. Assigned treatments were administered on Days 0, 14 and 28 to each foal. The dose for each foal was calculated based on the weight obtained 2 days prior to each of the 3 treatment administrations. Procedures were followed during dosing to ensure that the drug was retained.

Thorough physical examinations were made of each foal before treatment and on Day 35; clinical observations were made daily. The foals were closely monitored and examined for toxic signs for several days following each treatment. If any one of the observations in the examination for primary toxic signs was other than "normal", a more detailed examination for secondary toxic signs was conducted.

None of the 6 foals given 3 exposures to 5 times the use level of ivermectin liquid had adverse reactions or toxic signs.

Those reactions which were considered not related to ivermectin treatment at 3 times use level included respiratory infections, a submandibular lymph node enlargement and diarrhea. Reactions similar to these were observed in the control foals.

Two of the foals given ivermectin liquid at 3 times use level had front limb lameness after their third exposure to the drug. The cause of this lameness could not be determined. In both foals, all signs resolved completely.

Laboratory Animals - Teratology

Ivermectin has been shown to be teratogenic in rats, rabbits, and mice at or near maternotoxic dose levels. At these high doses, evidence of a teratogenic effect is limited to cleft palate that occurs at a low frequency in all three species and clubbing of the forepaws which occurs only in rabbit fetuses. Mice are the most sensitive species to the effects of ivermectin with maternotoxicity at a dose of 200 mcg/kg/day and teratogenicity at 400 mcg/kg/day. In rabbits 6000 mcg/kg/day was maternotoxic and teratogenic, and teratogenicity was also evident at a dose of 3000 mcg/kg/day. The threshold for both maternotoxicity and teratogenicity in rats was 10,000 mcg/kg/day.

Breeding Animal Safety - Other Domestic Animals

The Freedom of Information Summaries for IVOMEC injection for cattle, IVOMEC injection for swine, IVOMEC paste for cattle and HEARTGARD 30 Tablets for dogs describe various breeding safety studies in the respective target animals. In each of these species ivermectin has been found safe for use in breeding animals.

Conclusions

There are insufficient data to determine safety of ivermectin liquid in foals less than 4 months old.

Demonstration of the safety and acceptability of ivermectin liquid in horses was found in the 5 field trials conducted using 471 horses. Ivermectin liquid was given once, at use level, to 367 of these horses (250 were drenched, 117 were tubed). No adverse reactions attributable to ivermectin liquid were observed. Both routes of administration were satisfactory.

The safety seen in these trials was expected, based on the previously reported safety trials where high levels of ivermectin, up to 12 mg/kg (12,000 mcg/kg), were administered to horses by intramuscular injection or orally. These studies demonstrate that EQVALAN liquid is safe for use in horses, including breeding animals.

6. Human Safety

As labeled the drug poses no hazard to human safety pertaining to drug residues, because it is labeled "not for use in horses intended for food". The labeling contains adequate caution statements and instructions for the safe use of EQVALAN liquid by experts (veterinarians).

7. 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 EQVALAN (ivermectin) liquid when used under its labeled conditions of use is safe and effective.

Because the route and techniques for administration (nasogastric intubation and drenching) require the expertise of a veterinarian, EQVALAN (ivermectin) liquid is labeled for prescription use even though the efficacy of the product covers all the economically important parasites of the horse.

8. Labeling

1. EQVALAN® (ivermectin) Oral Liquid for Horses package label
2. EQVALAN® (ivermectin) Oral Liquid for Horses package insert

Copies of these labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855