

Date of Approval: July 30, 2004

FREEDOM OF INFORMATION SUMMARY

NADA 141-215

EQUIMAX Paste

ivermectin 1.87%/praziquantel 14.03%

This supplement provides for the use of EQUIMAX Paste in breeding, pregnant or lactating mares without adverse effects on fertility.

Sponsored by:

Virbac AH, Inc.

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1. GENERAL INFORMATION:

- a. File Number: NADA 141-215
- b. Sponsor: Virbac AH, Inc.
3200 Meacham Blvd.
Ft. Worth, TX 76137
- Drug Labeler Code: 051311
- c. Established Name: Ivermectin/praziquantel
- d. Proprietary Name: EQUIMAX
- e. Dosage Form: A paste containing ivermectin 1.87% and praziquantel 14.03%
- f. How Supplied: Individual dose syringe contains sufficient paste to treat one 1320 lb horse orally. Each weight marking on the syringe plunger delivers enough paste to treat 220 lb bodyweight
- g. How Dispensed: OTC
- h. Amount of Active Ingredients: Each milligram of EQUIMAX Paste contains 0.0187 milligram (1.87%) ivermectin and 0.1403 milligram (14.03%) praziquantel. Each syringe contains 120.1 mg of ivermectin and 897.6 mg praziquantel
- i. Route of Administration: Oral
- j. Species/Class: Equine
- k. Recommended Dosage: 91 mcg ivermectin per lb (200 mcg/kg) bodyweight and 0.68 mg praziquantel per lb (1.5 mg/kg) bodyweight
- l. Pharmacological Category: Anthelmintic and Boticide
- m. Indications: Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism. EQUIMAX (ivermectin/praziquantel) Paste is indicated for the treatment and control of the following parasites:

- Tapeworms: *Anoplocephala perfoliata*
 - 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): *Cyathostomum* spp., *Cylicocycylus* 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*
 - Large-mouth Stomach Worms (adults): *Habronema muscae*
 - Bots (oral and gastric stages): *Gasterophilus* 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
 - Dermatitis caused by Neck threadworm microfilariae, *Onchocerca* sp.
- n. Effect of Supplement: This supplement provides for the use of EQUIMAX Paste in breeding, pregnant or lactating mares without adverse effects on fertility.

2. **EFFECTIVENESS:**

The clinical effectiveness of the recommended dosage of 91 mcg ivermectin per pound (200 mcg/kg) of body weight and 0.68 mg praziquantel per pound (1.5 mg/kg) of body weight is contained in the original Freedom of Information Summary for NADA 141-215 dated July 11, 2003. No additional clinical effectiveness data were required for this supplement.

3. **TARGET ANIMAL SAFETY:**

- a. The safety of EQUIMAX Paste in breeding, pregnant or lactating mares was addressed in the study described below.

(1) Type of Study: Target Animal Safety

(2) Study Director: Larry Cruthers, PhD
Professional Laboratory Research Services, Inc.
Corapeake, NC

(3) General Design of the Study:

- (a) Compliance: This study was conducted in accordance with Good Laboratory Practices For Nonclinical Laboratory Studies, U.S. Code of Federal Regulations, Title 21, Part 58, April 1998.
- (b) Purpose of Study: To evaluate the safety and reproductive performance effects of an ivermectin 1.87% / praziquantel 14.03% paste (EQUIMAX Paste) administered orally to healthy mares biweekly with three times (3X) the recommended dosage in breeding, pregnant or lactating mares and assess the viability and growth of the foals produced by these mares.
- (c) Test Animals: Twenty-six healthy, domestic, mares participated in this study. These mares were selected based on a successful foaling in the previous breeding season. After foaling the pre-study foal, mares were randomized to treatment in pairs.
- (d) Dosage Form: Oral paste
- (e) Dose: Mares received either a placebo paste (control group; n=13) or EQUIMAX Paste (test group; n=13) at 3X (0.6 mg/kg ivermectin / 4.5mg/kg praziquantel) the recommended dosage starting 14-17 days after the birth of the pre-study foal and administered biweekly prior to breeding, through gestation, and until their foals reached approximately 90 days of age.
- (f) Route of Administration: Oral
- (g) Test Duration: March 2000 through February 2002
- (h) Variables Measured:

1 Body Weight - Mares: Body weight was determined prior to initial treatment on Day 0 and at 28 day intervals until the end of the study.

Foals: Body weight was determined within 24 hours of birth and at approximately 30, 60, and 90 days thereafter.

2 Physical examinations - Mares: Examinations were performed prior to treatment, Day 90 of gestation, Day of foaling, Day 30 postpartum, Day 60 postpartum, and Day 90 postpartum. Foals: Examinations were performed the day of foaling, Day 30 postpartum, Day 60 postpartum, and Day 90 postpartum.

3 Daily Clinical observations of mares and foals: Daily observations included assessment of general appearance, behavior, attitude and appetite.

4 Reproductive observations of mares: Effects of EQUIMAX on breeding, pregnancy and the viability of the study foal were evaluated by calculating and comparing the following variables:

- Number of breeding attempts until pregnancy achieved
- Percentage of mares pregnant at 18, 45, 90 and 135 days following last breeding
- Duration of gestation
- Fertility Index: Number of mares pregnant/number of mares bred
- Gestation Index: Number of pregnant mares with live born study foals/number of pregnant mares
- Foal Viability Index: Number of live foals/number of mares conceived 90 days following birth

Effects of EQUIMAX on the estrous cycle were determined by calculating and comparing the length of estrus and diestrus for three cycles following the birth of the study foal using the following variables:

- Length of estrus in days
- Length of diestrus in days
- Length of estrous cycle in days (estrus + diestrus)

5 Clinical pathology of mares: Blood samples were collected for hematology and serum chemistry evaluation on Day -7 and 0, Day 110 +/- 7 post conception, Day 220 +/- 7 post conception, Within +/- 7 days of parturition, and within two weeks after the final treatment.

6 Adverse Events: Each mare was monitored for signs of adverse drug events during the first hour following each treatment and hourly through six hours post-treatment.

- (i) Statistical Analysis: Repeated measures analysis for mixed models (the MIXED procedure of SAS, SAS Institute, Cary NC) was used to assess variables with continuous outcomes, and assumed a compound symmetric

covariance matrix structure. The statistical model included fixed effects for group and day, and the group by day interaction. Baseline values were included as covariates. If multiple pre-treatment measurements were made, the average of these results was included as the baseline covariate. If the interaction between group and day was significant ($p < 0.10$), within day comparisons were made. If this interaction was not significant, the main effect of group was evaluated. Where results did not follow a normal distribution, data were log transformed prior to analysis. All comparisons were evaluated at $p < 0.10$.

Non-parametric methods of analysis were employed for analysis of length of diestrus, length of estrus, number of breeding attempts until pregnancy, and duration of gestation.

(4) Results:

Twenty-six mares were enrolled in the study. Five mares did not complete the study - three in the placebo group and two in the EQUIMAX group. Two placebo mares were dropped from the study for failure to conceive, and the other placebo mare did not complete the study due to abortion of the study fetus. One EQUIMAX treated mare was dropped from the study for failure to conceive, while another EQUIMAX treated mare was euthanized during a dystocia caused by an oversized, malpositioned, dead foal. Mares that did not conceive or aborted were not examined to determine the cause of the infertility. The cause of death of the foal in the EQUIMAX treated mare with dystocia was not revealed by gross necropsy and was assumed to be due to the dystocia.

(a) Physical examinations and body weights:

Mares: There were no clinically significant or statistically significant treatment related observations in body temperature, respiration rate, or heart rate. A statistically significant group effect was detected for body weight (control = 473.8 kg versus EQUIMAX = 499.4 kg). This difference was due to one EQUIMAX treated draft breed mare that gained 300 kg over the course of the study. The weight gain in this mare was most likely a combination of a regular feeding regimen, the weight gain associated with the developing fetus, and possibly the antiparasitic effect of EQUIMAX. This mare gave birth without problems to a healthy foal. After foaling she lost 100 kg of body weight. There was no other clinically significant weight gain or loss in any other animal in the study, regardless of treatment group.

Foals: There were no clinically significant or statistically significant treatment related observations in body temperature, body weight, respiration rate, or heart rate.

(b) Daily Clinical Observations:

1. Mares:

Conjunctivitis/Uveitis: Three EQUIMAX treated mares had conjunctivitis during the study. Two of these mares were treated for conjunctivitis, and the condition did not reappear despite continuing treatment with the test drug. The other mare had pre-existing conjunctivitis that progressed to anterior uveitis. This mare was treated multiple times for conjunctivitis and anterior uveitis throughout the study; however, the condition never resolved. One control mare was reported with ocular discharge but did not receive treatment.

Mastitis: Two EQUIMAX treated mares developed mastitis post-foaling of the study foal. Both mares were treated with antibiotics and anti-inflammatories, and in both mares the condition resolved.

Colic: Four EQUIMAX treated mares and one control mare experienced at least one episode of colic during the study. One mare experienced colic nine days after being administered EQUIMAX. This mare received 22 additional treatments with EQUIMAX prior to the second colic on the morning of the treatment. Both colic episodes responded to medical treatment and the recovery was uneventful. This mare also had elevated GGT at the time of both colic episodes. By the end of the study GGT had returned to a normal value.

Another EQUIMAX treated mare experienced a total of six episodes of colic while enrolled in the study. Two episodes occurred before EQUIMAX was given and were associated with the pre-study foaling. Four episodes of colic occurred during the treatment phase of the study. The first of these three occurred four days after the 8th treatment. The next colic episode occurred nine days later. The third colic occurred two days following the 26th treatment and the final episode of colic occurred nine days after the 35th treatment. All colic episodes responded to medical treatment. Following the last colic, the mare received six more treatments with EQUIMAX prior to her release from the study. This mare had elevated AST and GGT values during the last episode of colic.

Two additional EQUIMAX treated mares experienced an episode of colic after treatment, one had colic two days after being treated and another had colic ten days after being treated. These colics were mild and responded to medical treatment.

One control mare experienced an episode of colic ten days after receiving placebo.

2. Foals:

Two foals born to EQUIMAX treated mares had gastrointestinal dysfunction (loose stools, diarrhea) and depression that required supportive treatment. These foals also had transient ocular discharge. All of these abnormal observations occurred in the first few weeks of life and responded to medical treatment.

- (c) Reproductive observations: There were no clinically significant differences in the groups with respect to number of breeding attempts to achieve pregnancy, and duration of gestation. The 21 mares that completed the study gave birth to live, healthy study foals and exhibited normal lactation and maternal care. The indices below demonstrate that there was no clinically or statistically significant difference in the groups with respect to the fertility index, gestation index and foal vitality at 90 days.

Group	Fertility Index	Gestation Index	Foal Vitality Index 90 days
Control	84.6%	90.0%	90.9%
Test	92.3%	91.7%	83.3%

There were no statistically significant differences in these variables ($p > 0.10$).

- (d) Estrus & Diestrus Observations: The first post partum diestrus was more variable in the treated mares than in the control mares and was statistically different ($p \leq 0.0571$). There were no statistically significant group effects for subsequent diestrus periods or for estrous cycle length. There were two treated mares with abnormally short diestrus periods in the first post partum estrous cycle, which explains the statistically significant finding. One of these mares also failed to ovulate in the following two estrous cycles.
- (e) Clinical pathology (mares only):

1. Hematology: There were no clinically significant abnormalities in the hematology variables.

2. Serum Biochemistry: A statistically significant group effect was detected for AST ($p \leq 0.0090$), and GGT ($p \leq 0.0111$). Test group values were higher than control group values for these two variables. The clinical significance of these findings is discussed below.

AST was sporadically elevated above the normal range in three EQUIMAX treated mares and in one control mare over the course of the study. One EQUIMAX treated mare had two instances of elevated AST, one on Day 110 post conception and another two weeks after the final treatment. This mare also had elevated GGT on Day 110 post conception. Another EQUIMAX treated mare had an elevated AST on Day 220 post conception, which was accompanied by mildly elevated GGT, which remained mildly elevated until the end of the study. The remaining EQUIMAX treated mare had a mildly elevated AST five days after foaling, along with an elevated GGT, and also an

episode of colic. One control mare had an elevated AST on Day 110 post conception, and she also had an elevated GGT on that day.

GGT was above the normal range in at least four of the eleven EQUIMAX treated mares and in two of the ten control mares. These increases all appeared on Day 110 post conception in both the test and control groups. One EQUIMAX treated mare had elevated GGT values throughout the study and had two episodes of colic during the study. The two control mares with elevated GGT values had ongoing disease, one with chronic laminitis, and the other with Cushing's disease complicated by laminitis.

In conclusion, there was a greater incidence of elevated AST and GGT values in the EQUIMAX treated mares. The majority of the elevations in these enzymes were sporadic; however, the fact that two EQUIMAX treated horses had elevated enzymes at the same time of the episodes of colic is a finding that should be noted.

- (f) Adverse Drug Events: There were no adverse drug events reported in mares during the first hour after each treatment and hourly through 6 hours post treatment.
- (5) Conclusions: This study demonstrated that EQUIMAX Paste administered orally at three times the recommended dosage does not adversely affect the fertility of breeding, pregnant or lactating mares; however, there were other clinically significant observations in the EQUIMAX treated mares and their foals.

Mares: Two EQUIMAX treated mares had an abnormally short diestrus period in the first post-partum estrous cycle. One of these mares did not ovulate in the next two cycles. An increased incidence of colic was observed in EQUIMAX treated mares as compared to control mares. In addition, elevations of GGT and AST were more frequent in the EQUIMAX treated mares, and in two of these mares these enzymes were elevated at the time of colic episodes.

Foals: In the first few weeks of life, foals born to the EQUIMAX treated mares had a higher incidence of transient ocular discharge and gastrointestinal disturbances (loose stools, diarrhea) and depression requiring medical intervention as compared to foals born to control mares.

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 supplement.

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

Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users, to obtain more information, or to obtain a MSDS, contact Pfizer at 1-800-366-5288.” The Virbac product is distributed by Pfizer.

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 EQUIMAX Paste when used under the labeled conditions of use, is safe and effective for the treatment and control of roundworms (ascarids, strongyles and lungworms), tapeworms and bots in horses.

The drug is available over-the-counter for lay use because adequate directions for use are provided and oral antiparasitic treatments in horses are routinely performed by the layperson.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the use of EQUIMAX in breeding, pregnant and lactating mares without adverse effects on fertility. New Target Animal Safety data was generated to demonstrate that EQUIMAX is safe for use in breeding, pregnant and lactating mares, which forms the basis for exclusivity.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

EQUIMAX Paste is under the following U.S. patent number:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
5,824,653	11/27/2015

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Package Insert
Syringe Label
Carton Label