Date of Approval: September 7, 2011

CORRECTED FREEDOM OF INFORMATION SUMMARY

NEW ANIMAL DRUG APPLICATION

NADA 141-331

PRASCEND Tablets

Pergolide Mesylate

Horse

For the control of clinical signs associated with Pituitary Pars Intermedia Dysfunction (Equine Cushing's Disease) in horses

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

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I. GENERAL INFORMATION:

A. File Number: NADA 141-331

B. Sponsor: Boehringer Ingelheim Vetmedia, Inc.

2621 North Belt Highway
St. Joseph, MO 64505-2002

Drug Labeler Code: 000010

C. Proprietary Name: PRASCEND Tablets

D. Established Name: Pergolide mesylate

E. Pharmacological Category: Dopamine receptor agonist

F. Dosage Form: Tablet

G. Amount of Active Ingredient: 1 mg of pergolide (as pergolide mesylate) per tablet

H. How Supplied: PRASCEND tablets are supplied in blister cards containing 10 tablets. The blister cards are supplied in cartons containing 60 or 160 tablets per carton.

I. How Dispensed: RX

J. Dosage: Administer orally at a starting dose of 2 mcg/kg once daily. Dosage may be adjusted to effect, not to exceed 4 mcg/kg daily.

K. Route of Administration: Oral

L. Species/Class: Horses

M. Indication: For the control of clinical signs associated with Pituitary Pars Intermedia Dysfunction (Equine Cushing's Disease)

II. EFFECTIVENESS:

A. Dosage Characterization:

The dosage characterization is based on the published scientific literature described below. Literature was used to establish the dose of pergolide mesylate for further evaluation in the field effectiveness study described in the Substantial Evidence section.

1. Literature Survey

A review of the scientific literature provides information on 181 horses treated with pergolide for Pituitary Pars Intermedia Dysfunction (PPID), also known as Equine Cushing's Disease (ECD). The dosage characterization for pergolide in horses is based on these global references published over the past 26 years. An overview of this literature supports a starting oral dose of 2 mcg/kg with a dose range of 2-4 mcg/kg once daily.

In the literature, horses were administered pergolide at doses ranging from 0.6 to 10 mcg/kg (0.25 mg to 5 mg total daily dose per horse). In 1995, Peters and colleagues reported clinical effectiveness at a dose of 1.7 mcg/kg per day without adverse reactions.[1] Most of the recent clinical trials reported in the literature have used an approximate oral daily dose of 2 mcg/kg.[2,3] At this dose, improvements in clinical signs and relevant diagnostic laboratory tests were reported for the majority of the cases.

The literature reports the target dose of 2-4 mcg/kg to be clinically well tolerated with a low incidence of adverse reactions. Adverse reactions reported were not severe and resolved with a reduction of dose rather than complete discontinuation of pergolide therapy. An increased frequency of anorexia and depression was observed when treatment was initiated at a higher dose (10 mcg/kg/day, 5 mg/horse/day). Additionally, attempts to reduce the dose below 2 mcg/kg can result in treatment failure.[4] Therefore, a minimum initial daily target oral dose of 2 mcg/kg was selected for testing in the clinical field effectiveness study.

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[1] Peters DF, et al. Low Dose Pergolide Mesylate Treatment for Equine Hypophyseal Adenomas (Cushing's Syndrome). *Proceedings 4th Annual Convention American Association of Equine Practitioners* 41: 154-155; 1995

[2] Schott HC, et al. The Michigan Cushing's Project. *Proceedings 47th Annual Convention American Association of Equine Practitioners* 47: 22-24; 2001

[3] Donaldson MT, et al. Treatment with Pergolide or Cyproheptadine of Pituitary Pars Intermedia Dysfunction (Equine Cushing's Disease). *Journal of Veterinary Internal Medicine* 16: 742-746; 2002

[4] Beech J. Treatment of Hypophyseal Adenomas. *Compendium of Continuing Education* 16: 921-923; 1994.

The literature suggests that the effective pergolide dose varies based on severity of disease and variation in individual response to the drug. A target oral dosage regimen of 2-4 mcg/kg given once daily was therefore selected for testing in the clinical field effectiveness study.

B. Substantial Evidence:

1. Multi-site Field Effectiveness Study

a. Title and Study Number: An Evaluation of the Clinical Efficacy of Pergolide Mesylate Tablets for the Control of Clinical Signs Associated with Pituitary Pars Intermedia Dysfunction (Equine Cushing's Disease) in Horses. Study Number: 6150-1353-09E-138

b. Type of Study: GCP field study.

c. Study Dates: November 2008 to August 2009

d. Investigators:

Dr. Frank M. Andrews Baton Rouge, LA	Dr. Dianne McFarlane Stillwater, OK
Dr. Ashley M. Stokes Baton Rouge, LA	Dr. Harold C. Schott II East Lansing, MI
Dr. Randy Bimes Quakertown, PA	Dr. Judy Marteniuk East Lansing, MI
Dr. John Hunt Carthage, IN	Dr. Scott Toppin Littleton, CO
Dr. David Kolb Lodi, WI	Dr. Gary W. White Sallisaw, OK

e. Study Design:

This was a multi-site, historical control, open-label field effectiveness study.

1. *Objective*: To evaluate the effectiveness of PRASCEND (pergolide mesylate) in controlling the clinical signs associated with PPID in horses under field conditions. Field safety was also evaluated by monitoring adverse reactions occurring during the study.

2. *Study Animals*: The study enrolled 122 male and female horses, client or university owned, that were diagnosed with PPID. Horses were 10 to 35 years old, weighed 302 to 1370 lb, and represented 16 different breeds.

3. *Treatment Groups*: All horses received PRASCEND orally once daily for 180 days. A concurrent control group was not included in this study due to the life-threatening nature of PPID, the lack of an

adequate active control, and the inability to provide adequate rescue treatment for the life-threatening complications associated with PPID. Based on the natural history of PPID, the disease is expected to continue to progress without spontaneous resolution.

4. *Drug Administration*: Horses were treated with PRASCEND Tablets containing 1.0 mg pergolide (as pergolide mesylate) in each tablet. All horses started treatment at an oral, once daily, target dose of 2 mcg/kg of PRASCEND based on Table 1 below. If the endocrine test results (dexamethasone suppression test (DST) or endogenous adrenocorticotropic hormone (ACTH) test) remained abnormal on Day 90,[1] the target dose was increased to 4 mcg/kg of PRASCEND based on Table 1 below. All doses were rounded to the nearest half tablet.

Table 1. Dosing Table

Body weight (kg)	**Body weight** (lb)	**Treatment**	
		Days 0-90 *(target 2 mcg/kg)*	**Days 91-180 *** *(target 4 mcg/kg)*
136 - 340	300 - 749	0.5 tablet	1 tablet
341 - 568	750 - 1,249	1 tablet	2 tablets
569 - 795	1,250 - 1,749	1.5 tablets	3 tablets
796 - 1022	1,750 - 2,249	2 tablets	4 tablets

* If dose adjustment needed

The most common method of administration reported by the horse owners was dissolving the tablet in water with or without sweetener. Less common methods of administration included placing the tablet in a treat or as a top dressing on feed.

5. *Inclusion Criteria*: The diagnosis of PPID for inclusion in the study was based on a hirsutism score ≥ 1 (regional hirsutism) and an abnormal endocrine test result consistent with PPID.[1] Only one abnormal endocrine test (DST or ACTH) was required for enrollment. Horses were enrolled from November 2008 to January 2009 to avoid endocrine testing during the fall.

6. *Measurements and Observations*: Horses were evaluated by physical examination, clinical pathology, and endocrine testing, and were scored for clinical signs related to PPID (hirsutism, hyperhidrosis, polyuria/polydipsia, abnormal fat distribution, and muscle wasting) on days -7, 90, and 180. The following scoring systems were used to evaluate endocrine test results and clinical signs of PPID:

[1] Endocrine test results at enrollment and on Day 90 were considered abnormal if post-dexamethasone cortisol was ≥ 1mcg/dL for the DST or adrenocorticotrophic hormone concentration was ≥ 50 pg/mL for the endogenous ACTH test.

Endocrine Testing

Horses were evaluated by DST and/or endogenous ACTH tests prior to enrollment (see Inclusion Criteria). At enrollment, investigators chose a single endocrine test (DST or ACTH) to use for post-treatment evaluations.

Table 2. Endocrine Test Criteria for Day 90 and 180

Endocrine Test	Outcome	Criteria
DST	Normal/Improved	Post-dexamethasone cortisol <1mcg/dL
	Abnormal/Not improved	Post-dexamethasone cortisol ≥1mcg/dL
ACTH	Normal/Improved	Day 90-ACTH <50 pg/mL Day 180-Decrease in ACTH from enrollment by at least 50% or ACTH <50 pg/mL with a reduction of at least 5 pg/mL
	Abnormal/Not improved	Day 90-ACTH ≥50 pg/mL Day 180-Increase in ACTH from enrollment, decrease in ACTH by <50%, ACTH ≥50 pg/mL, or ACTH <50 pg/mL but with a reduction of <5 pg/mL

The following scoring systems were used for evaluation of clinical signs:

Hirsutism

0 = Normal ……..No unusual hair growth
1 = Regional ……Long hair growth restricted to discrete areas, e.g., the lower jaw, base of neck (jugular area), and palmar/plantar aspects of distal limbs
2 = Generalized ……Slightly to moderately long haircoat that fails to shed out like in previous year
3 = Severe ……Severely long and/or curly haircoat over the entire body

Hyperhidrosis

0 = Normal……..No undue sweating
1 = Mild sweating…….May include regional sweating
2 = Moderate sweating…….Regional to moderate generalized sweating
3 = Severe sweating ……..Generalized sweating over entire body

Polyuria / Polydipsia

0 = Normal .....No excessive drinking or urination noted
1 = Mild .....Slight increase in drinking/urination noted; mild wet stall bedding noted (subjectively)
2 = Moderate .....Moderate increase in drinking/urination noted; moderate wet stall bedding noted (subjectively)
3 = Severe .....Severe increase in drinking/urination noted; severe wet stall bedding noted (subjectively)

Abnormal fat distribution

Horses may show abnormal fat deposition in the supraorbital area, along the crest of the neck, over the tailhead or topline, on the ventral midline, and in the penile sheath.

0 = Normal .....No abnormal fat distribution
1 = Mild .....Mild regional fat deposition in one or more key areas
2 = Moderate .....Moderate regional fat deposition in one or more key areas, with a fatty appearance
3 = Severe .....Severe regional fat deposition in one or more key areas, with a generalized overall fatty appearance

Muscle wasting

0 = Normal .....No muscle wasting
1 = Mild .....Slight muscle wasting and slight loss of overall body condition (thinner appearance)
2 = Moderate .....Moderate muscle wasting and loss of overall body condition, with muscle wasting in the epaxial and rump areas
3 = Severe .....Severe muscle wasting and loss of overall body condition, with muscle wasting in the epaxial and rump areas and a weakening of the abdominal muscles (pot-bellied appearance)

7. *Statistical Methods*:

Each individual horse was considered a treatment success or a treatment failure. Success was based on results of endocrinology testing and/or the investigator's scoring for hirsutism, hyperhidrosis, polyuria/polydipsia, abnormal fat distribution, and/or muscle wasting at scheduled visits. Post-treatment results were compared to pre-treatment assessments for endocrine testing and clinical sign evaluations. Individual horse success was defined as follows:

The DST result returned to normal (<1 mcg cortisol/dL) on Day 180 or the ACTH test result improved on Day 180, i.e., decreasing by at least 50% or returning to normal (<50 pg/mL) by a reduction of at least 5 pg/mL, ***AND*** there was improvement by a score of 1 or more from baseline in at least 1 evaluated clinical sign without worsening of other clinical signs or the development of any new clinical signs among those under assessment.

— Or —

On Day 180, any combination of evaluated clinical signs improved by a score of 3 or more regardless of endocrine test results, without worsening of other clinical signs or the development of any new clinical signs among those under assessment.

f. Results:

One hundred twenty-two horses enrolled in the study resulting in 113 evaluable cases. Individual horse success was based on results of endocrinology testing and/or the investigator's scoring for specified clinical signs related to PPID (hirsutism, hyperhidrosis, polyuria/polydypsia, abnormal fat distribution, and/or muscle-wasting) on the Day 180 evaluation as described above. Based on these definitions, 86 (76.1%) of the 113 evaluable cases were considered treatment successes.

Table 3. Proportion of Treatment Successes on Day 180

Percent success	**Lower bound: one-sided 95% confidence interval**
76.1% (86/113)	68.6%

Of the 9 horses excluded from the effectiveness analysis, 8 died or were euthanized due to worsening of pre-existing conditions (laminitis, dental disease, septic tenosynovitis), or colic (strangulating lipomas, large colon volvulus). The other horse was lost to follow up. Two additional horses were withdrawn from the study by their owners due to a failure to improve and an inability to dose the horse. These 2 horses were included in the effectiveness analysis as treatment failures. All 122 horses receiving PRASCEND were evaluated for safety.

Improvement was noted in assessment scores for all clinical sign categories. Mean scores for each clinical sign are presented in Table 4. The percent of animals with improved clinical assessment scores relative to baseline at Day 90 and Day 180 are presented in Table 5. For each evaluated clinical sign, 21.2% (abnormal fat distribution) to 36.3% (muscle wasting) of horses received an improved score on the Day 90 evaluation relative to baseline. At Day 180, hyperhidrosis, polyuria/polydipsia, abnormal fat distribution, and muscle wasting had improved in 33.3% to 46.0% of horses as compared to baseline, and 89.2% of horses showed improvement in hirsutism.

Table 4. Clinical Assessment Mean Scores

Clinical Sign	Day -7	Day 90	Day 180
	N=113	N=113	N=111*
Hirsutism	1.96	1.62	0.54
Hyperhidrosis	0.64	0.34	0.08
PU/PD	0.58	0.14	0.10
Fat distribution	0.81	0.63	0.43
Muscle wasting	0.92	0.58	0.36
Total score	4.90	3.31	1.51

*Two horses were withdrawn from the study prior to day 180

Table 5. Percent of Animals with Improvement in Clinical Signs Relative to Baseline Scores

Clinical sign	**Day 90** (%)	**Day 180** (%)
	N=113	N=111*
Hirsutism	32.7%	89.2%
Hyperhidrosis	27.4%	42.3%
Polyuria / polydipsia	31.0%	34.2%
Abnormal fat distribution	21.2%	33.3%
Muscle wasting	36.3%	46.0%

*Two horses were withdrawn from the study prior to day 180

ACTH and DST results changed significantly over time (P≤0.05) with values lower on Days 90 and 180. For horses enrolled based on ACTH results (n=20), the mean ACTH concentration decreased from 73.53 pg/mL at baseline to 51.12 pg/mL on Day 90 and 45.08 pg/mL on Day 180. For horses enrolled based on DST results (n=93), the mean post-dexamethasone cortisol concentrations decreased from 3.12 mcg/dL at baseline to 1.39 mcg/dL on Day 90 and 1.47 mcg/dL on Day 180.

Of the 113 horses included in the effectiveness database, 47 horses (41.6%) had abnormal endocrine test results on Day 90 resulting in a dose increase to 4 mcg/kg. Sixty-six (58.4%) horses did not require a dose increase based on the Day 90 endocrine test results and remained on a dose of 2 mcg/kg throughout the study.

Mean direct and total bilirubin, insulin, glucose, and SDH values had statistically significant decreases post-treatment. Mean insulin concentrations were above the reference range (≤300pmol/L) both pre-(483 pmol/L) and post-treatment (319 pmol/L) and showed a decreasing trend during the study.

g. Adverse Reactions:

A total of 122 horses treated with PRASCEND for six months were evaluated for adverse reactions.

Table 6. Summary of the most common adverse reactions (N=122)

Clinical sign	# Cases	Cases (%)
Decreased appetite	40	32.8
Lameness	22	18.0
Diarrhea/Loose stool	12	9.8
Colic	12	9.8
Lethargy	12	9.8
Abnormal Weight Loss	11	9.0
Laminitis*	10	8.2
Heart murmur	10	8.2
Death	8	6.6
Tooth disorder	8	6.6
Skin abscess	7	5.7
Musculoskeletal pain	6	4.9
Behavior change	6	4.9

* Three new cases and 7 pre-existing, recurring cases

Inappetance or decreased appetite occurred at one or more meals in 40 of 122 horses treated with PRASCEND. At the baseline evaluation 1.6% of owners reported a history of inappetance or decreased appetite as compared to the 32.8% of horses that experienced inappetance or decreased appetite during the study. Most cases of inappetance were transient and occurred during the first month of treatment; however, some horses experienced sporadic inappetance throughout the study. Two horses required a temporary reduction in dose due to inappetance during the first month of the study. Both horses returned to their original dose within 30 days.

Weight loss occurred in more than half of the horses in this study; however, weight loss that was considered abnormal was only reported in 11 horses. Two of these horses lost between 50 and 100 pounds, and 3 lost ≥100 pounds. The other 6 cases that had documented adverse reactions of weight loss either did not lose >50 pounds or lost weight early in the study and regained the weight by Day 180. In the total 122 horse study population, 22 horses lost between 50 and 100 pounds and 14 horses lost ≥100 pounds by Day 180. In four of the cases that lost ≥100 pounds, the losses were noted to be healthy changes in body composition. The other horses that lost ≥50 pounds were noted to have a normal general appearance on the Day 180 physical examination.

Lethargy was reported in 9.8% of horses during the study, and was not reported in any horses at the baseline evaluation.

New cases of laminitis developed in 3 horses during the study and 7 horses had recurrences of pre-existing laminitis.

Behavioral changes were reported in 6 horses including aggression, kicking, agitation, nervous behavior, and increased activity. One horse required a temporary reduction in dose due to energetic behavior and was

returned to the original dose within 9 days.

Twelve horses experienced colic during the study, and 12 horses experienced at least one episode of diarrhea or loose stool. Three of the colics were severe and not likely related to treatment with PRASCEND (strangulating lipomas, large colon volvulus). The other colics were mild and resolved with treatment. One case of diarrhea was related to Potomac Horse Fever. All other episodes of diarrhea were mild and self-limiting.

One mare was inadvertently enrolled in the study while pregnant and experienced dystocia at foaling on Day 179 of treatment. Her pregnancy was not discovered until foaling. The dystocia was due to malpositioning resulting in the death of the full term foal.

h. Conclusions:

This study supports the effectiveness of PRASCEND for the control of clinical signs associated with Pars Pituitary Intermedia Dysfunction in horses. Adverse reactions associated with PRASCEND treatment included inappetance, weight loss, lethargy, and behavioral changes.

III. TARGET ANIMAL SAFETY:

A. Six Month Margin of Safety Study

1. Title: Evaluation of the Margin of Safety of Orally Administered Pergolide Mesylate in Horses (Study Number 6150-1353-09E-137)

2. Type of Study: GLP Laboratory Study

3. Study Dates: July 2009 to February 2010

4. Study Director and Location: Dr. Matthew Edmonds
Parma, Idaho

5. Study Design:

a. *Objective:* To evaluate the margin of safety of 1.0 mg pergolide (as pergolide mesylate) tablets when administered once daily for 180 days at oral dosages of 0 mcg/kg (0X), 4 mcg/kg (1X), 6 mcg/kg (1.5X), and 8 mcg/kg (2X).

b. *Study Animals:* Thirty-two healthy grade, Paint, and Appaloosa horses ranging from 3 to 10 years of age and 460 to 582 kg.

c. *Treatment Groups and Drug Administration:*

Table 7. Treatment Groups and Doses

Treatment Group	Dose (mcg/kg)	Dose Multiple*	Number (male/female)
1	0	0X	4/4
2	4	1X	4/4
3	6	1.5X	4/4
4	8	2X	4/4

*The 1X dose represents the upper end of the recommended dose range of 2-4 mcg/kg

Horses were administered PRASCEND Tablets containing 1.0 mg pergolide (as pergolide mesylate) in each tablet. Horses received 0X, 1X, 1.5X, or 2X the maximum recommended dose of PRASCEND orally, once daily for 180 to 183 days. Doses were rounded up to the nearest half tablet and the tablets were dissolved in approximately 10 mL of a 50% sugar water solution. Control horses received an oral dose of sugar water. Drug administration occurred prior to concentrate consumption each day.

Pergolide mesylate may cause inappetance in horses when treatment is initiated. In order to maintain horses on study with consistent dosing, the administration of PRASCEND Tablets was initiated as follows: Horses in the 1X group received PRASCEND Tablets at a dose of 4 mcg/kg for the entire study period. Horses in the 1.5X group were dosed at 4 mcg/kg on Days 0–14, and then at 6 mcg/kg from Day 15 through the end of the study. Horses in the 2X group were dosed at 4 mcg/kg on Days 0–14, at 6 mcg/kg on Days 15–30, followed by 8 mcg/kg from Day 31 through the end of the study.

d. *Measurements and Observations:*

Table 8. Measurements and Observations

Measurements and Observations	**Day of Study**
Twice Daily Health Observations	-14 to 180[1]
Estimation of Concentrate Consumption	-14 to 180[1]
Physical Exams	-2, 0, 30, 60, 90, 120, 150, 180
Body Weight	-2, 0, 30, 60, 90, 120, 150, day of necropsy
Clinical Pathology, Urinalysis, Fecal Exam	-4, (-2)[2], 30, 60, 90, 120, 150, 180
Cardiac Exam by board certified veterinary cardiologist (including echocardiography and electrocardiography)	-7, 175
Gross Necropsy and Histopathology	180-184

[1] Horses were euthanized on Days 180-184. Test article administration and general health observations continued until the day of euthanasia.

[2] Clinical pathology was performed on Day -2. Urinalysis and Fecal Exams were not performed on Day -2.

e. *Statistical Methods:*

The individual horse was the experimental unit in the statistical analysis.

Continuous variables measured only once on a horse (e.g., organ weights) during the study were analyzed using the analysis of variance. The model included treatment, sex and the sex-by-treatment interaction as fixed effects. Continuous outcomes measured multiple times on a horse during the study (e.g., clinical pathology variables) were analyzed using repeated measures analysis of covariance, with treatment, sex, day, and treatment-by-sex, sex-by-day, treatment-by-day, and treatment-by-sex-by-day terms in the model as fixed effects. The pretreatment value was used as a covariate. All main effects and interaction terms were tested at alpha=0.10, except for the treatment-by-sex-by-day interaction which was tested at alpha=0.05. For all variables, appropriate mean contrasts between each PRASCEND dosed group and the control group were performed at an unadjusted alpha=0.10 to follow up on significant treatment effects in two-way interactions or main effects.

For categorical variables, Fisher's exact test was used to compare each PRASCEND dosed group to the control group at alpha = 0.10.

6. Results:

During the 6 month study, one 1.5X horse experienced a mild episode of spasmodic colic on Day 3 that resolved after treatment with flunixin meglumine.

Another 1.5X horse was noted to have mildly icteric sclera on the Day 90 physical exam. This horse also had an elevated GGT value of 74 U/L on that day (reference range 5-15 U/L). The icterus was resolved by the Day 120

physical exam and the horse's GGT values slowly decreased over the course of the study and were within the reference range by Day 180. The horse did not exhibit any other abnormal clinical signs. One control horse also had an elevated GGT value of 73 U/L on Day 60, but did not exhibit icterus. The cause of icterus and the GGT elevation in either horse could not be determined.

PRASCEND treated groups had lower mean heart rates and higher mean temperatures than the control group. Mean heart rates were statistically significantly different for geldings in all PRASCEND treated groups and for mares in the 2X group when compared to the control group. Mean heart rate was reduced by approximately 10 (1X group), 18 (1.5X group) and 16 (2X group) beats per minute for geldings and 8 beats per minute for mares in the 2X group. Mares in the 1X and 1.5X groups also had numerically lower mean heart rates; however, the differences were not statistically significant. The minimum heart rates for individuals in all treated groups were within the normal range (24-44 beats per minute). Mean temperatures were statistically significantly different for all PRASCEND treated groups and higher when compared to the control group. The differences between groups were less than 0.5°F and the temperature of all individuals remained below 101.5°F.

Mean red blood cell counts and hemoglobin values were lower in PRASCEND treated groups as compared to the control group. Other hematology parameters including hematocrit, white blood cells, absolute neutrophils, and absolute lymphocytes exhibited mild, transient decreases as compared to the control group. The hematology parameters generally decreased over the first 30 to 60 days after treatment initiation and then returned to values similar to pre-treatment levels. No treatment related alterations were identified on histopathology evaluation of bone marrow.

7. Conclusions:

   This study supports the safety of PRASCEND Tablets when administered orally to horses at a dose of up to 4 mcg/kg once daily.

IV. HUMAN FOOD 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, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PRASCEND:

Not for use in humans. Keep this and all medications out of reach of children. PRASCEND should not be administered by persons who have had adverse reactions

to ergotamine or other ergot derivatives. Pregnant or lactating women should wear gloves when administering this product. It has been reported that pergolide tablets may cause eye irritation, an irritating smell, or headache when PRASCEND Tablets are split or crushed. PRASCEND Tablets should not be crushed due to the potential for increased human exposure and care should be taken to minimize exposure when splitting tablets. Consult a physician in case of accidental ingestion by humans.

VI. 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. The data demonstrate that PRASCEND Tablets, when used according to the label, is safe and effective for the control of clinical signs of Pituitary Pars Intermedia Dysfunction (Equine Cushing's Disease).

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian. Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose and monitor the treatment of horses with Pituitary Pars Intermedia Dysfunction.

B. Exclusivity:

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database (formerly the Green Book) on the FDA CVM internet website.