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PRASCEND® TABLETS

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Boehringer Ingelheim

(pergolide mesylate)

Tablets, 1 mg

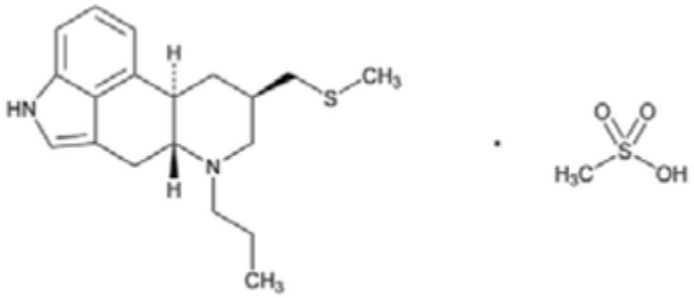
NADA 141-331, Approved by FDA

Dopamine receptor agonist for oral use in horses only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: Prascend Tablets are rectangular light red colored, half-scored tablets embossed with the BI logo and tablet code PRD containing 1 mg pergolide, as pergolide mesylate. Pergolide mesylate is a synthetic ergot derivative and is a potent, dopamine receptor agonist. The chemical name of pergolide mesylate is 8β-[(Methylthio) methyl]-6-propylergoline monomethanesulfonate.

The chemical structure is:



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

Dosage and Administration: Administer orally at a starting dose of 2.0 µg/kg once daily. Dosage may be adjusted to effect, not to exceed 4.0 µg/kg daily. Prascend Tablets should not be crushed due to the potential for increased human exposure.

The tablets are scored and the calculated dosage should be provided to the nearest one-half tablet increment (see Table 1).

Table 1 Dosing Table

	Dosage	
Body weight (lb)	**2.0 µg/kg**	**4.0 µg/kg**
300 - 749	0.5 tablet	1.0 tablet
750 - 1,249	1.0 tablet	2.0 tablets
1,250 - 1,749	1.5 tablets	3.0 tablets
1,750 - 2,249	2.0 tablets	4.0 tablets

Human Warnings: Prascend Tablets should not be crushed due to the potential for increased human exposure. Do not use in horses intended for human consumption.

Precautions: The use of Prascend in breeding, pregnant, or lactating horses has not been evaluated. Prascend is a dopamine agonist which may interfere with reproductive hormones and events in breeding, pregnant, or lactating horses.

Adverse Reactions: A total of 122 horses treated with Prascend Tablets for six months were included in a field study safety analysis.

Table 2 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 26.2% 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.

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

Behavioral changes were noted in 6 horses including aggression, kicking, agitation, nervous behavior and increased activity. One horse required a temporary reduction in dose due to energetic behavior during the first month of the study.

Eight horses died or were euthanized during the study due to worsening of pre-existing conditions (laminitis, dental disease, septic tenosynovitis) or colic (strangulating lipomas, large colon volvulus).

One mare was inadvertently enrolled in the study while pregnant and experienced dystocia resulting in the death of the foal.

To report suspected adverse reactions, to obtain a Material Safety Data Sheet (MSDS), or for technical assistance, call 1-866-638-2226.

Clinical Pharmacology: Pergolide mesylate is a synthetic ergot derivative and is a potent dopamine receptor agonist. As with other dopamine agonists, pergolide inhibits the release of prolactin which suggests that it may interfere with lactation. In horses with PPID, pergolide is believed to exert its therapeutic effect by stimulating dopamine receptors, and has been shown to decrease the plasma levels of adrenocorticotropic hormone (ACTH), melanocyte stimulating hormone (MSH), and other pro-opiomelanocortin peptides.[1]

Pharmacokinetic information in the horse is based on a study by Wright using single oral doses of 10 µg/kg in six healthy mares between 3 and 17 years of age.[2] Pergolide was rapidly absorbed; the mean maximum concentration (Cmax) was 4.05±2.02 ng/mL with the median time to maximum concentration (Tmax) being 0.415 hours. The area under the curve (AUC) was 14.08±7.46 hr.ng/mL. The mean half life (T1/2) was

5.86±3.42 hours; the mean apparent oral clearance (CL/F) was 1204 mL/kg/hr; and the mean apparent volume of distribution (V/F) was 3082±1354 mL/kg.

Effectiveness: An open-label, historical control, field study evaluated the effectiveness of Prascend for the control of clinical signs of PPID. A total of 122 horses with PPID were enrolled in the study, 113 of which were included in effectiveness evaluations. The success of each horse was based on results of endocrinology testing (dexamethasone suppression test or endogenous ACTH test) and/or improvement in clinical signs related to PPID (hirsutism, hyperhidrosis, polyuria/polydypsia, abnormal fat distribution, and/or muscle-wasting) on the Day 180 evaluation. Based on endocrine testing and investigators' clinical assessment scores, 86 (76.1%) of the 113 evaluable cases were 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%

Enrolled horses were diagnosed with PPID based on the presence of hirsutism and an abnormal pre-study endocrine test result. All horses were treated with 2 µg/kg Prascend (to the nearest one-half tablet) orally once daily for the first three months. If the endocrine test result on Day 90 was normal or adequately improved, the horse continued on the same dose through Day 180. If the endocrine test result on Day 90 was abnormal, the dose increased to 4 µg/kg given once daily through Day 180. Forty-seven of the 113 horses included in the effectiveness database required a dose increase at Day 90.

Improvement was noted in scores for all clinical sign categories and in mean results for endocrine tests.

Table 4 Percent of Animals with Improvement in Clinical Signs Relative to Baseline Scores

Clinical sign	Day 90±7 (%)	Day 180±7 (%)
Hirsutism	32.7%	89.2%
Hyperhidrosis	27.4%	42.3%
Polyuria / polydypsia	31.0%	34.2%
Abnormal fat distribution	21.2%	33.3%
Muscle wasting	36.3%	46.0%

Table 5 Endocrine test results (mean values)

Test	# Animals	Baseline	Day 90	Day 180
ACTH (pg/mL)	20	73.53	51.12	45.08
DST (µg/dL)	93	3.12	1.39	1.47

*Dexamethasone suppression test

Animal Safety: A 6-month target animal safety study was conducted to determine the effects of Prascend administered orally to horses at 0X, 1X, 1.5X, and 2X the labeled dosage (0, 4, 6, and 8 µg/kg) once daily. There were eight healthy horses (four males and four females) per treatment group. Clinical abnormalities seen during the study that are treatment-related include decreased heart rate and increased body temperature. However, minimum heart rates and maximum body temperatures were all within the normal ranges for horses.

Respiratory rates for geldings were lowered by the test article, but remained within the normal range. There were no treatment-related changes in body weights, concentrate consumption, urinalysis, electrocardiograms, echocardiograms, gross pathology, and histopathology. Overall mean red blood cell counts and hemoglobin showed a progressive trend towards lower

values in the 1X, 1.5X, and 2X dose groups compared to the control 0X group. Additionally, hematocrit showed a dose-related decrease at several time points. Despite the statistically significant findings for these hematology parameters, the pre-dose baseline values were similar in magnitude to the day-180 values. The group averages and most individual results were within the clinical pathology laboratory's reference ranges. Moreover, histological examination of paraffin sections provided no evidence of treatment-related bone marrow alteration.

Storage: Store at or below 25°C (77°F).

How Supplied: Prascend (pergolide mesylate) Tablets are available in 1.0 mg strength - packaged 10 tablets per blister and 60 or 160 tablets per carton.

NDC 0010-4489-01 - 60 tablets

NDC 0010-4489-02 - 160 tablets

References:

[1.] Orth, D.N., Holscher, M.A., Wilson, M.G., et al. (1982) Equine Cushing's Disease: Plasma Immunoreactive Proopiolipomelanocortin Peptide and Cortisol Levels Basally and in Response to Diagnostic Tests. Endocrinology. 110(4):1430-41

[2.] Wright A, Gehring R, Coetzee H (2008.) Pharmacokinetics of pergolide in normal mares. American College of Veterinary Internal Medicine Forum, Abstract #36, San Antonio, TX.

Manufactured for: **Boehringer Ingelheim Vetmedica, Inc.**, St. Joseph, MO 64506 U.S.A.

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