2019

EQUINE
ENDOCRINOLOGY
GROUP

Pituitary Pars Intermedia Dysfunction (PPID)

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Recommendations for the Diagnosis and Treatment of Pituitary Pars Intermedia Dysfunction (PPID)

Revised June 2019

Prepared by the PPID Working Group
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Introduction

Pituitary pars intermedia dysfunction (PPID) is a slowly progressive degenerative disease of hypothalamic dopaminergic neurons. Loss of dopaminergic inhibitory control of pars intermedia (PI) melanotropes leads to hyperplasia and adenoma formation in the PI. Melanotropes in the enlarged PI produce increased amounts of pro-opiomelanocortin, a large prohormone that is subsequently cleaved into smaller peptides, including adrenocorticotropic hormone (ACTH). PPID is uncommon in equids less than 15 years of age but epidemiologic studies have documented a prevalence of about 20% in horses over 20 years of age, increasing to 30% in horses over 30. There is no apparent breed or sex predilection and the only documented risk factor for development of PPID is advancing age. Hypertrichosis, a long hair coat that fails to shed, is essentially a pathognomonic clinical sign for PPID. However, PPID can be manifested by a constellation of other clinical signs/syndromes (Figure 1 and Tables 1-2); consequently, PPID should be considered as a potential contributing factor for many disorders in horses 15 years and older.

Measurement of ACTH concentration is a practical screening test for diagnosis of PPID, although a fall increase in normal equids requires interpretation using seasonally adjusted cutoff values. Because ACTH concentration may not exceed cutoff values in the earlier stages of disease, the dynamic thyrotropin releasing hormone (TRH) stimulation test can also be pursued to support a diagnosis of PPID in equids with suspect clinical signs with a normal baseline ACTH concentration. Because PPID can be accompanied by insulin dysregulation, increasing the risk of laminitis, measurement of insulin concentration is also recommended when testing equids for PPID (see Equine Endocrinology Group Recommendations for Diagnosis and Treatment of Equine Metabolic Syndrome).

The Equine Endocrinology Group (EEG) is composed of experts in the field of equine endocrinology who provide advice in the form of written guidelines to help veterinary practitioners diagnose and manage equine endocrine disorders. Guidelines are updated every two years or when new information becomes available and can be found on the EEG website: **http://sites.tufts.edu/equineendogroup**.

Figure 1 - Clinical signs and syndromes with PPID vary in affected equids and can include the pathognomonic hypertrichosis (left), sometimes with hair color changes (right), loss of topline musculature (middle left) and more devastating musculoskeletal problems such as chronic laminitis (center) and suspensory ligament breakdown (middle right).

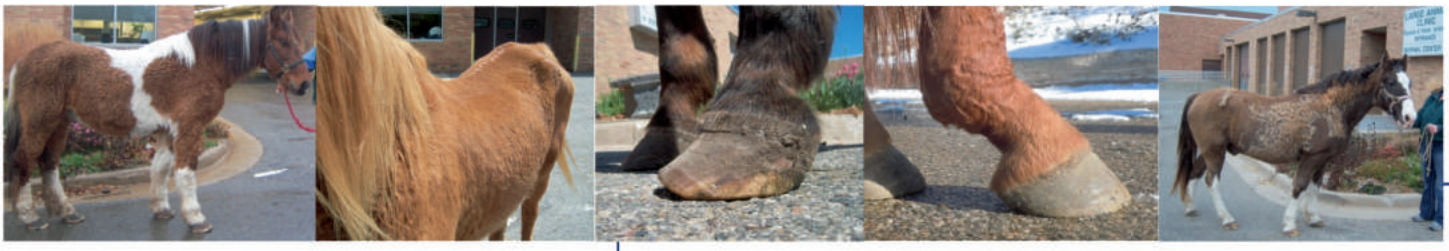

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Table 1. Pituitary Pars Intermedia Dysfunction (PPID) clinical presentation

Early	Advanced
Change in attitude/lethargy	Dull attitude/altered mentation
Decreased performance	Exercise intolerance
Regional hypertrichosis	Generalized hypertrichosis
Delayed hair coat shedding	Loss of seasonal hair coat shedding
Loss of topline muscle	Topline muscle atrophy
Abnormal sweating (increased or decreased)	Rounded abdomen
Infertility	Abnormal sweating (increased or decreased)
Desmitis/tendonitis	Polyuria/polydipsia
Regional adiposity	Recurrent infections
Laminitis	Dry eye / recurrent corneal ulcers
	Infertility
	Increased mammary gland secretions
	Tendon and suspensory ligament laxity
	Regional adiposity (bulging supraorbital fat)
	Laminitis/recurrent sole abscesses

Table 2. Laboratory findings that may accompany Pituitary Pars Intermedia Dysfunction (PPID)

Hyperglycemia
Hyperinsulinemia
Hypertriglyceridemia
High fecal egg count

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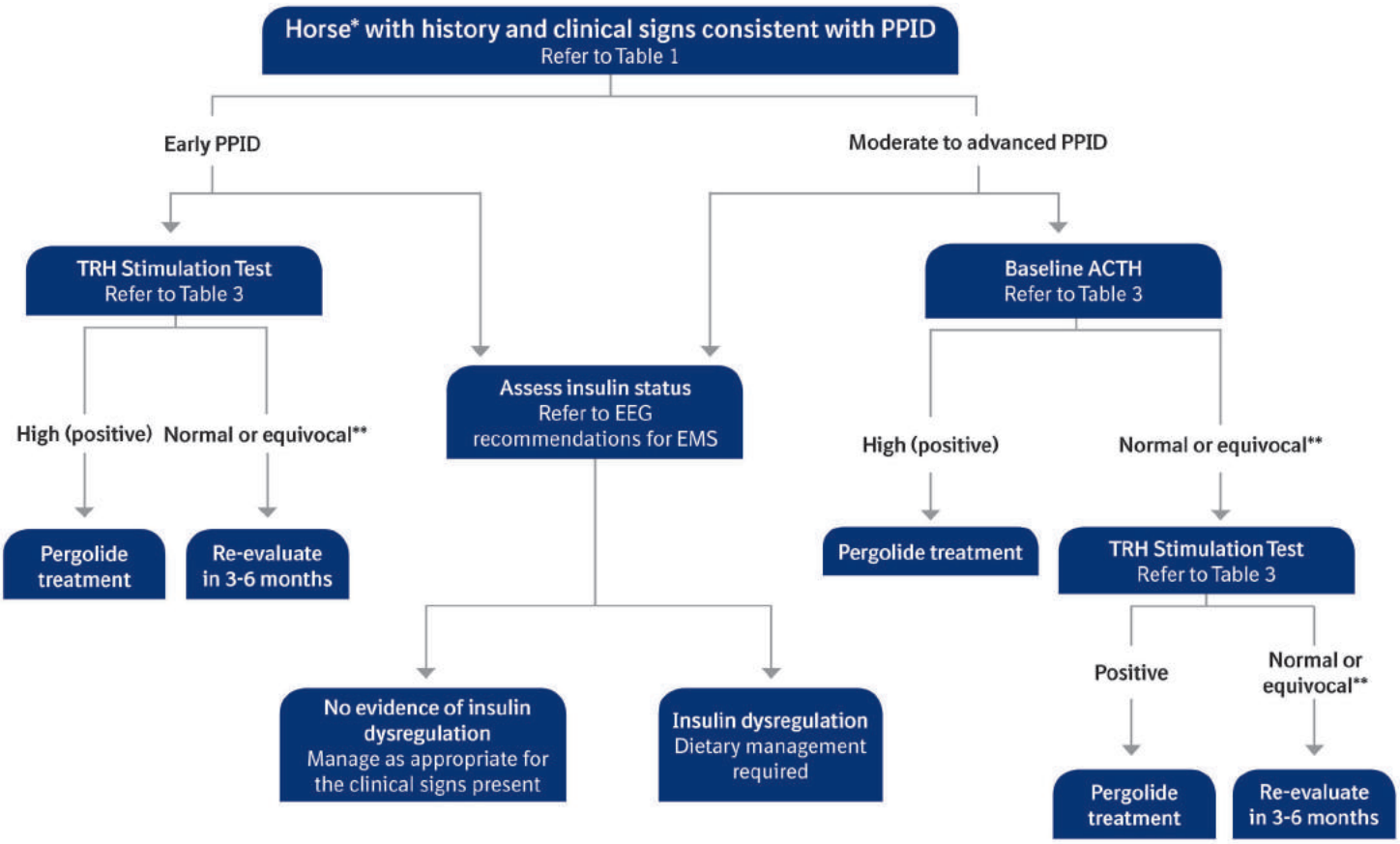
Figure 2 - Algorithm for the diagnosis and management of PPID



* At present this algorithm is largely based on data collected in horses but it can be applied to other equids (ponies, donkeys, and mules) until further data becomes available.

** Pergolide treatment can still be considered if the horse has equivocal test results, yet exhibits clinical signs consistent with PPID.

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Table 3. Basal ACTH concentration and TRH stimulation test

Procedure for baseline ACTH (also time 0 for TRH stimulation test)

Use glass or plastic tubes containing EDTA (purple top)

Collect at any time of the day

Keep samples cool (ice packs or refrigerator) at all times

Centrifuge and separate plasma prior to shipping

Ship via overnight mail with ice packs

Samples can be frozen (centrifuged samples are preferred over gravity-separated samples)

Procedure for TRH stimulation test

Horses can be tested after hay is fed, but not within 12 hours after a grain meal. Can be performed immediately before an oral sugar test (OST) but do not perform within 12 hours after an OST.

Administer 0.5 mg (equids <250 kg) or 1.0 mg (equids >250 kg) of TRH intravenously. Side effects after administration are transient and include coughing, flehmen response, and yawning.

Blood samples are collected in tubes containing EDTA at 0 and 10 minutes after TRH administration.

Submit plasma for measurement of ACTH (as described above).

Interpretation of results [a]

Non-fall months: mid-November to mid-July

	Negative	Equivocal	Positive
basal ACTH or time 0	<30 pg/mL	30-50 pg/mL*	>50 pg/mL
10 min after TRH	<110 pg/mL	110-200 pg/mL	>200 pg/mL**

Fall months: mid-July to mid-November***

	Negative	Equivocal	Positive
basal ACTH	<50 pg/mL	50-100 pg/mL	>100 pg/mL

[a] Values provided are for laboratories using the Immulite-TM immunoassay for ACTH; reference ranges may vary between different assays as well as different laboratories.

* Equivocal test results for basal ACTH concentration should prompt use of the TRH stimulation test.

** Normal horses, particularly those that are of a thrifty breed, may have results exceeding this value. Breed specific responses are an active area of research and future data may provide breed-specific reference intervals.

*** Fall TRH stimulation testing is an active area of research, but not enough data is currently available to establish accurate cutoff values to support a diagnosis of PPID. Consequently, TRH testing in the fall months is not recommended at this time. However, an ACTH of <110 pg/mL 10 min after TRH administration in fall months can be useful to exclude a diagnosis of PPID.

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Table 4. Diagnostic tests for Pituitary Pars Intermedia Dysfunction (PPID)

RECOMMENDED TESTS

Early PPID: TRH stimulation test with ACTH measured
Moderate to advanced PPID: Basal ACTH concentration

OTHER POTENTIALLY SUPPORTIVE TESTS

Overnight dexamethasone suppression test
Magnetic resonance imaging (MRI) specific for pars intermedia enlargement

NO LONGER RECOMMENDED

Oral domperidone challenge test
Combined dexamethasone suppression/TRH stimulation test with cortisol measured

NOT APPROPRIATE FOR PPID DIAGNOSIS

ACTH stimulation test
Baseline cortisol concentration
Diurnal cortisol rhythm
TRH stimulation test with cortisol measured

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Table 5. Treatment and monitoring of Pituitary Pars Intermedia Dysfunction (PPID)

Initial treatment plan	The FDA-approved pergolide [Prascend® (pergolide tablets); Boehringer Ingelheim Animal Health, USA, Inc.] is recommended at an initial dosage of 0.5 mg for a 250-kg pony and 1.0 mg for a 500-kg horse (approx. 2 mcg/kg) q24h orally. Perform baseline diagnostic testing before starting treatment. Some horses show a transient reduction in appetite. To address this problem, stop treatment until appetite returns and or decrease by half for 3 to 5 days and then titrate back up in 1 mcg/kg increments every 2 weeks until the desired dose is achieved.
Initial response (first 30 days)	Improved attitude/performance Increased activity Improvement in polyuria/polydipsia Improved sweating Decreases in basal ACTH and ACTH 10 minutes after TRH administration (but not necessarily to below cutoff values) Potentially improved glucose and insulin dynamics
Long-term response (1-12 months)	Improved hair coat shedding Increased skeletal muscle along topline Less pronounced rounding of the abdomen Less likely to develop infections Potentially fewer/milder episodes of laminitis
Timeline	A period of 2 months is required before conclusions should be drawn about changes in clinical signs. The test used to diagnose PPID (e.g., basal ACTH concentration or TRH stimulation test) can be rechecked 4-8 weeks after starting treatment to assess the response to treatment.

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Table 6. Treatment and monitoring of Pituitary Pars Intermedia Dysfunction (PPID) cont.

Treatment strategies	**Adequate laboratory response with good clinical response** If test results are normal at recheck and clinical signs have improved or are stable, the dosage is held constant and the patient is placed on an every 6 month recheck schedule, with one appointment occurring in the fall season. This allows assessment of the patient during the seasonal increase in ACTH concentration and ensures that treatment is adequate during this period. **Adequate laboratory response with poor clinical response** If test results are normal at recheck, but there has been recurrence or development of new problems (i.e., laminitis, bacterial infection, or weight loss), then reassess patient for additional medical problems including insulin dysregulation before assuming that an increase in pergolide dosage is required. **Inadequate laboratory response with good clinical response** If test results are abnormal at recheck, yet the patient is responding well clinically, the dosage can be held at the same level or increased, according to the veterinarian's preference. This may be observed more commonly when testing is performed in fall months. **Inadequate laboratory response with poor clinical response** If test results remain abnormal at recheck and the patient is not responding well clinically, increase the daily dosage by 0.5 to 1.0 mg for a 500-kg horse (1-2 mcg/kg/day) and recheck after 2-4 weeks. Treatment strategies used by the group for refractory cases include gradually increasing the pergolide dosage to 3 mg for a 500-kg horse (6 mcg/kg) daily and adding cyproheptadine (0.25 mg/kg orally twice daily or 0.5 mg/kg once daily) or gradually increasing the pergolide dosage up to 5 mg for a 500-kg horse (10 mcg/kg) daily.

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Table 7. Other considerations for managing horses with pituitary pars intermedia dysfunction (PPID)

Switching horses from compounded pergolide	It may be possible to reduce the dosage of pergolide when switching from compounded pergolide to Prascend® (pergolide tablets). First consider the current status of the horse. If PPID is well controlled, consider a lower dosage of PRASCEND (maximum recommended reduction of 50%). Retest the horse after 2-4 weeks (consider history and physical examination findings) to assess response to treatment.
Removing horses from pergolide treatment	In the event that a horse on pergolide treatment misses a dose or is removed from treatment for exhibition/competition, ACTH concentrations may begin to increase within 48 hours, but the risk of clinical signs worsening during this period is low.
Quality of life	The majority of horses with PPID are aged and therefore susceptible to non-PPID conditions. Therefore, horse owners should be advised that while medical management of PPID improves quality of life, it does not necessarily prolong lifespan.
Wellness care	In addition to medical management, horses with PPID should receive regular wellness care. Special attention should be paid to body condition, dentistry, and parasite control. Inadequately controlled PPID horses are also at risk for bacterial infections. Adequate water should be available if polydipsia and polyuria are persistent problems.
Glucose and insulin dysregulation	If hyperglycemia (type II diabetes mellitus) is a concurrent problem, assessment for insulin dysregulation should also be pursued (see Equine Endocrine Group Recommendations for Diagnosis and Management of Equine Metabolic Syndrome). Control of blood glucose concentration should be assessed in response to pergolide treatment before other treatments for hyperglycemia are considered. Special attention should also be paid to the horse's diet and access to pasture (see below).
Diet and exercise recommendations	Feed selection should be based upon body condition score and evidence for insulin dysregulation. Some PPID horses are lean and have normal insulin status, and senior feeds and pasture grazing are appropriate in these cases. Obese (BCS≥7/9) horses should be fed a lower energy diet and an exercise program, and those with insulin dysregulation require lower non-structural carbohydrate feeds and limited access to pasture. Feed requirements of aged horses, especially those with PPID, may change over time and monthly monitoring of BCS by owners is recommended. Dietary supplements have also been suggested for the management of PPID, but to date, scientific evidence for their efficacy is lacking.
Management of glucose, insulin, and lipid disorders	Insulin dysregulation is detected in approximately one-third of cases and is most likely a result of PPID developing in equids genetically predisposed to EMS. Less commonly, diabetes mellitus develops in horses with PPID and is characterized by persistent hyperglycemia and glucosuria. Hypertriglyceridemia is detected in some diabetic horses and blood lipid concentrations markedly increase if the animal enters negative energy balance. Pergolide treatment has been associated with improved glycemic control and normalization of blood triglyceride concentrations in some of these cases with positive effects often seen within 48-72 hours.

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Boehringer Ingelheim

NADA 141-331, Approved by FDA

Prascend®

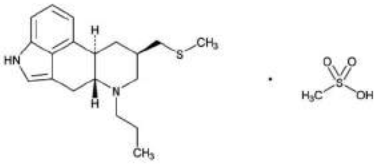
(pergolide tablets)

1 mg

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 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 8B-[(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 mcg/kg once daily. Dosage may be adjusted to effect, not to exceed 4 mcg/kg daily. 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.

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

Body weight	Dosage 2 mcg/kg	Dosage 4 mcg/kg
136 - 340 kg (300 - 749 lb)	0.5 tablet	1 tablet
341 - 567 kg (750 - 1,249 lb)	1 tablet	2 tablets
568 - 795 kg (1,250 - 1,749 lb)	1.5 tablets	3 tablets
796 - 1,022 kg (1,750 - 2,249 lb)	2 tablets	4 tablets

Dosing should be titrated according to individual response to therapy to achieve the lowest effective dose. Dose titration is based on improvement in clinical signs associated with Pituitary Pars Intermedia Dysfunction (PPID) and/or improvement or normalization of endocrine tests (for example, dexamethasone suppression test or endogenous ACTH test). If signs of dose intolerance develop, the dose should be decreased by half for 3 to 5 days and then titrated back up in 2 mcg/kg increments every 2 weeks until the desired effect is achieved.

Contraindications: Prascend is contraindicated in horses with hypersensitivity to pergolide mesylate or other ergot derivatives.

Warnings: Do not use in horses intended for human consumption.

Human Warnings: Not for use in humans. Keep this and all medications out of the 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.

Precautions: Treatment with Prascend may cause inappetance.

The use of Prascend in breeding, pregnant, or lactating horses has not been evaluated. The effects of pergolide mesylate on breeding, pregnant, or lactating horses are not known; however, the pharmacologic action of pergolide mesylate suggests that it may interfere with reproductive functions such as lactation.

Prascend is approximately 90% associated with plasma proteins. Use caution if administering Prascend with other drugs that affect protein binding. Dopamine antagonists, such as neuroleptics (phenothiazines, domperidone) or metoclopramide, ordinarily should not be administered concurrently with Prascend (a dopamine agonist) since these agents may diminish the effectiveness of Prascend.

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 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.

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 using single oral doses of 10 mcg/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 mcg/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 mcg/kg given once daily through Day 180. Forty-seven (41.6%) 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** (mcg/dL)	93	3.12	1.39	1.47

** Dexamethasone suppression test: Post dexamethasone cortisol concentration

Animal Safety: In a six month target animal safety study healthy adult horses received Prascend administered orally, once daily, at doses of either 0 mcg/kg, 4 mcg/kg, 6 mcg/kg, or 8 mcg/kg (0X, 1X, 1.5X, or 2X the maximum recommended dose). There were eight healthy horses (four males and four females) in each treatment group. Doses were prepared by dissolving tablets in approximately 10 mL of a 50% sugar water solution.

Prascend treated groups had lower mean heart rates and higher mean temperatures than the control group. Horses in all treatment groups had minimum heart rates within the normal range and maximum temperatures below 101.5°F. One 1.5X horse experienced a mild episode of spasmodic colic on Day 3 that resolved after treatment with flunixin meglumine.

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.

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

How Supplied: Prascend Tablets are available in 1 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.

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