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

EQUINE ENDOCRINOLOGY GROUP

2023

EQUINE ENDOCRINOLOGY GROUP 2023

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

Revised October 2023

Prepared by the PPID Working Group
Kelsey Hart (Group Coordinator; University of Georgia)
François-René Bertin (University of Queensland)
Andy Durham (Liphook Equine Hospital)
Nicholas Frank (Mississippi State University)
Catherine McGowan (University of Liverpool)
Hal Schott (Michigan State University)
Allison Stewart (University of Queensland)

Introduction

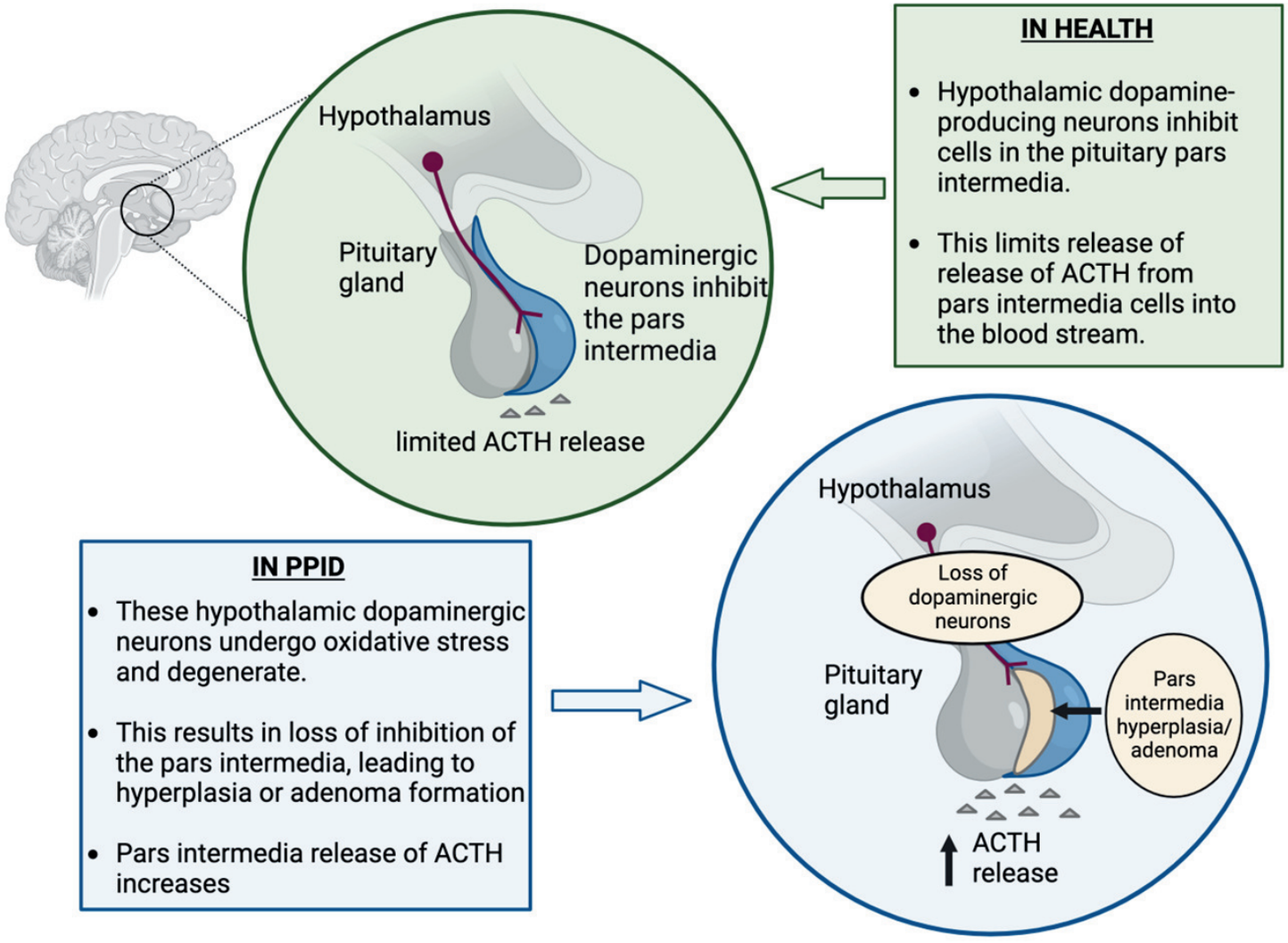
Pituitary pars intermedia dysfunction (PPID) is a slowly progressive age-related degenerative disease of dopaminergic neurons in the hypothalamus. This results in hyperplasia and adenoma formation of the pars intermedia of the pituitary gland, which then releases increased amounts of ACTH (**Figure 1**).

PPID prevalence increases with age, reaching 20% in equids 15 years of age and older and 30% in equids over 30 years of age. Hypertrichosis, a long hair coat that fails to shed, is essentially a pathognomonic clinical sign of PPID, but many other clinical signs are also described (Figures 2 & 3, Table 1).

Documentation of increased plasma ACTH concentrations at rest and/or after TRH stimulation testing is currently the most practical diagnostic test for PPID. However, season and breed can impact ACTH concentrations, and there is some overlap in concentrations between healthy and PPID populations, so interpretation of ACTH results require seasonally adjusted reference ranges and consideration of signalment and severity of signs to decide whether to treat or to monitor and re-test (Figures 4 & 5, Table 2). PPID can also be accompanied by insulin dysregulation so assessing insulin dynamics in concert with PPID testing is recommended (see the EEG 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 and can be found on the EEG website: https://sites.tufts.edu/equineendogroup/

Figure 1 – Overview of PPID Pathogenesis



EQUINE ENDOCRINOLOGY GROUP 2023

Figure 2 – Clinical signs and syndromes with PPID vary in affected equids

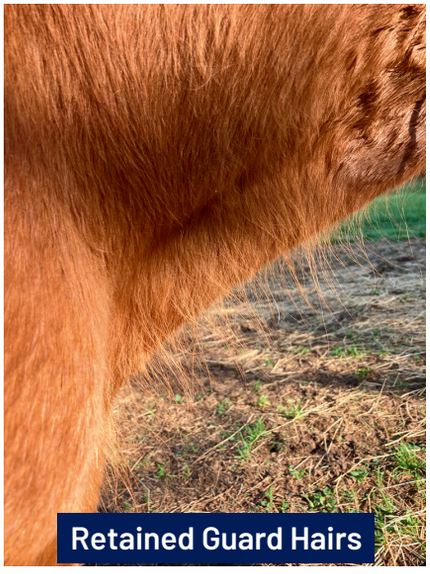


Figure 3 – Clinical spectrum of PPID

Note: affected animals may have only one, several, or many of the listed signs.

Some--but not all--cases may progress from early to advanced clinical signs.

	EARLY/SUBTLE CLINICAL FINDINGS	ADVANCED CLINICAL FINDINGS
Strongly Suggestive	Regional hypertrichosis/delayed shedding	Generalized hypertrichosis
Suggestive	Some loss of topline muscle Change in attitude/lethargy Decreased performance Abnormal sweating (increased or decreased)	Topline muscle atrophy Altered mentation Exercise intolerance Abnormal sweating (increased or decreased) Rounded abdomen Polyuria/polydipsia Recurrent infections
Possible Comorbidities	Infertility Tendon or ligament laxity Desmitis / tendonitis Regional adiposity Hyperinsulinemia-associated laminitis	Infertility Tendon or ligament laxity Desmitis / tendonitis Regional adiposity Hyperinsulinemia-associated laminitis Recurrent corneal ulcers Increased mammary gland secretions

Practice Tip: Increasing animal age and number of clinical signs increase the likelihood that these clinical signs are truly associated with PPID.

Table 1 – Laboratory findings that may accompany PPID

LABORATORY FINDINGS
Hyperglycemia Hyperinsulinemia Hypertriglyceridemia High fecal egg count

EQUINE ENDOCRINOLOGY GROUP 2023

Table 2 – Baseline ACTH and TRH stimulation test protocols and interpretation

Procedure for Baseline ACTH	• Collect into EDTA containing tube (purple top) at any time of the day • Keep samples cool (ice packs or refrigerator) at all times • Centrifuge and separate plasma prior to shipping. Gravity separation of chilled plasma within 4 hours is also acceptable if centrifugation is not available. • Ship via overnight mail with ice packs • Plasma can be frozen (centrifuged samples only) but avoid freeze-thaw cycles
Procedure for TRH Stimulation Test	• Horses can be tested after hay is fed, but not within 12 hours after a grain meal. Testing 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 <250kg) or 1.0 mg (equids>250 kg) of TRH intravenously. Side effects after administration are transient and include coughing, flehmen response, and yawning. • Collect blood into EDTA containing tubes (purple top) at 0 and exactly 10 minutes after TRH administration. A second sample may also be collected 30 minutes after TRH administration if desired. • Submit plasma for measurement of ACTH as described above.

SEASONAL INTERPRETATION OF RESULTS* (ALSO REFER TO FIG. 5)

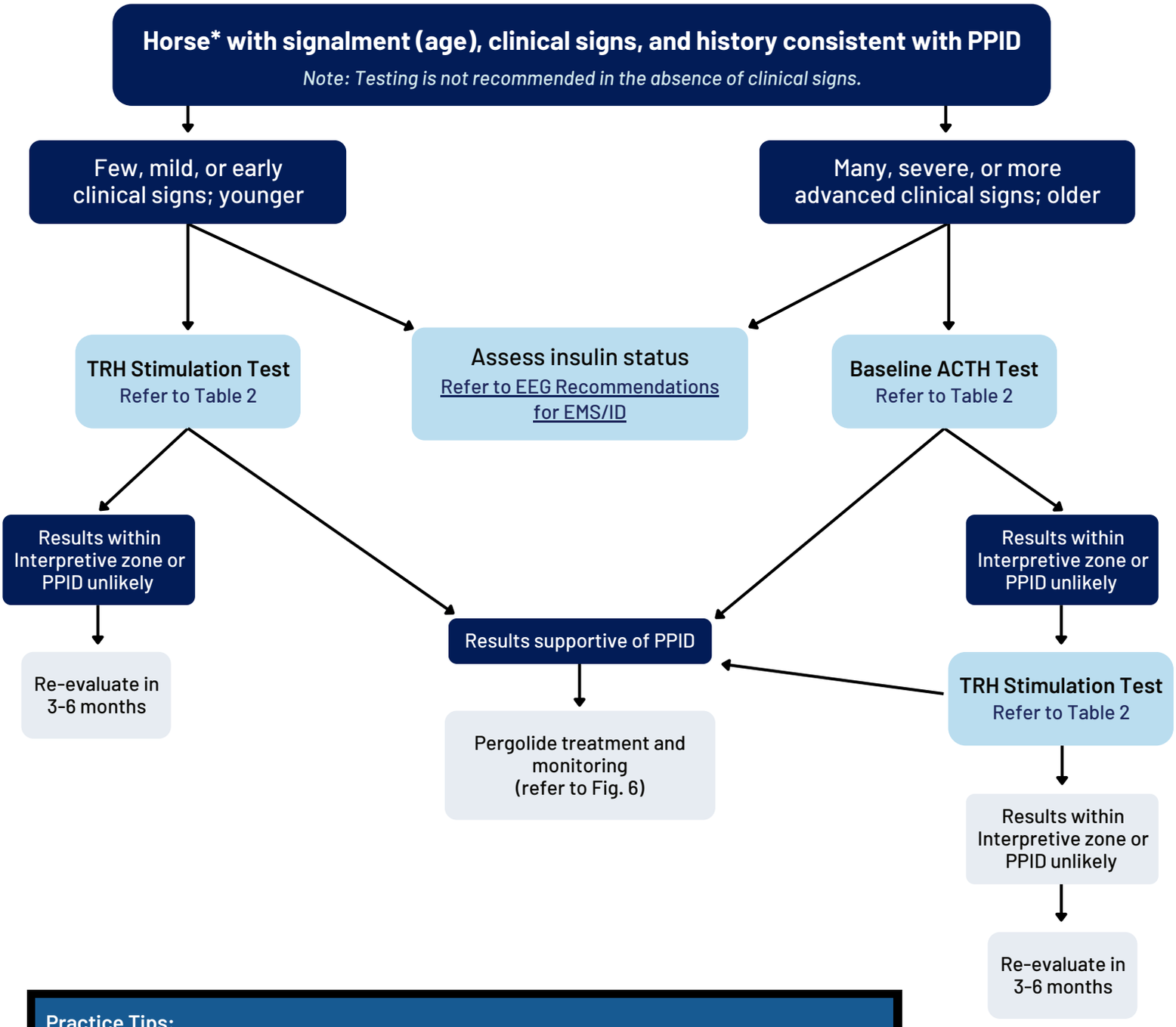
	Time of Year	PPID UNLIKELY	Interpretive Zone - Consider clinical signs and signalment	PPID LIKELY
Baseline ACTH or TRH time 0 (pg/mL)	Dec. - Jan.	< 15*	15 - 40*	> 40
	July & November	< 15*	15 - 50*	> 50
	August	< 20*	20 - 75*	> 75
	Sept. - Oct.	< 30*	30 - 90*	> 90
ACTH 10 min. after TRH (pg/mL)	Jan. - June	< 100	100 - 200	> 200
	July - Dec.	< 100	TRH stimulation testing is best used to identify negative cases in these months due to many false positives	
ACTH 30 min. after TRH (pg/mL)	Jan. - June	< 40	40 - 90	> 90
	July - Dec.	< 40	TRH stimulation testing is best used to identify negative cases in these months due to many false positives	

**ACTH concentrations provided here are based on values determined by the Immulite 2000xpi analyzer. Specific months provided here are accurate for the northern hemisphere, but require seasonal correction for southern hemisphere interpretation.*

Practice Tip: Healthy animals of certain breeds may have results that fall within the equivocal zone, or even the PPID likely range. Specifically, Arabian horses and donkeys may have increased ACTH concentrations in all months. Welsh and Shetland ponies often have increased ACTH concentrations only in the autumn months. Thus, PPID diagnosis should be made with caution in these breeds unless strong clinical signs also present.

EQUINE ENDOCRINOLOGY GROUP 2023

Figure 4 – Algorithm for the diagnosis of PPID



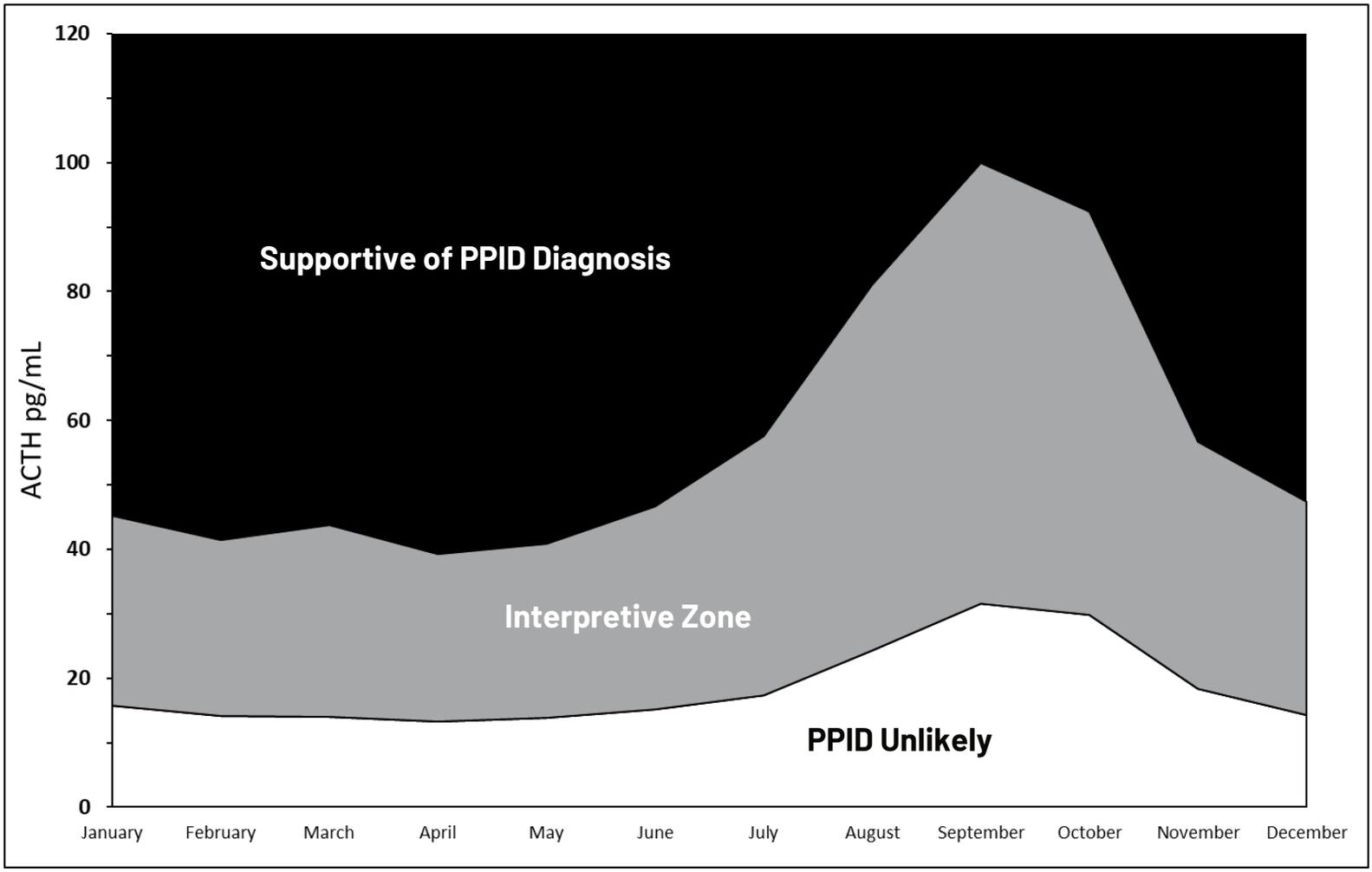
Practice Tips:

- * – This algorithm also can be applied to other equids (ponies, donkeys, and mules).
- In aged horses with generalized hypertrichosis, initiation of treatment without further testing is also appropriate.
- If TRH stimulation testing is not feasible, baseline ACTH alone can be used for diagnosis, but may be less supportive of diagnosis in early stage disease.

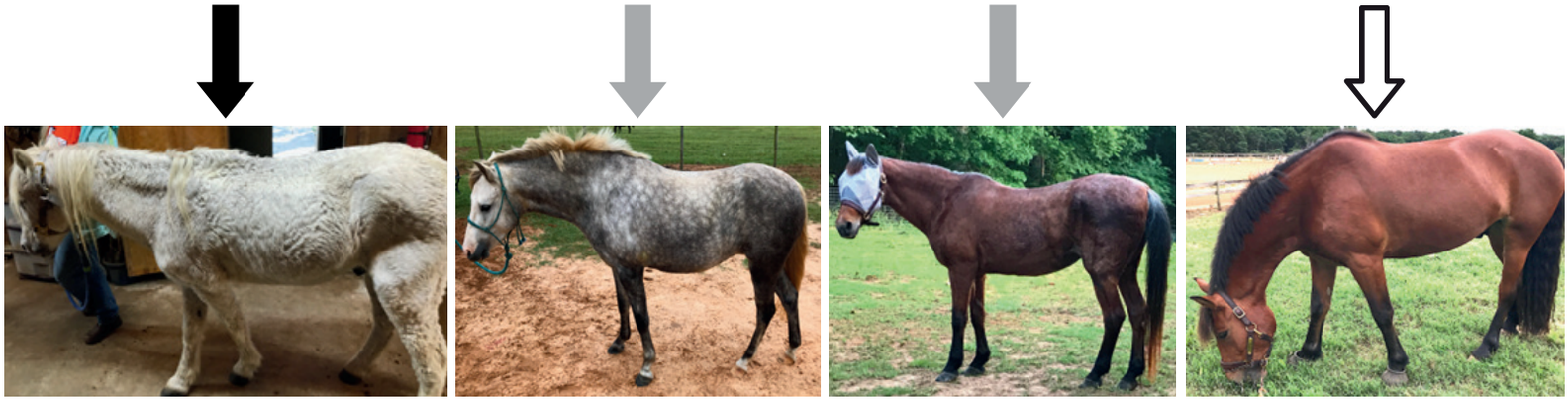
EQUINE ENDOCRINOLOGY GROUP 2023

Figure 5 – Seasonal interpretation of baseline ACTH concentrations

Note: ACTH values presented here were determined using the Immulite 2000xpi analyzer. ACTH concentrations falling in the black shaded area are supportive of PPID diagnosis, and those falling in the white shaded area suggest a PPID diagnosis is unlikely at that time. ACTH concentrations falling in the grey area require further interpretation based on the clinical picture of the animal. The upper and lower limits of the interpretive zone were defined as thresholds that were shown to respectively maximize diagnostic specificity and sensitivity in a study using a large laboratory database of equine plasma ACTH concentrations (Durham et al, Equine Vet J, 2020).



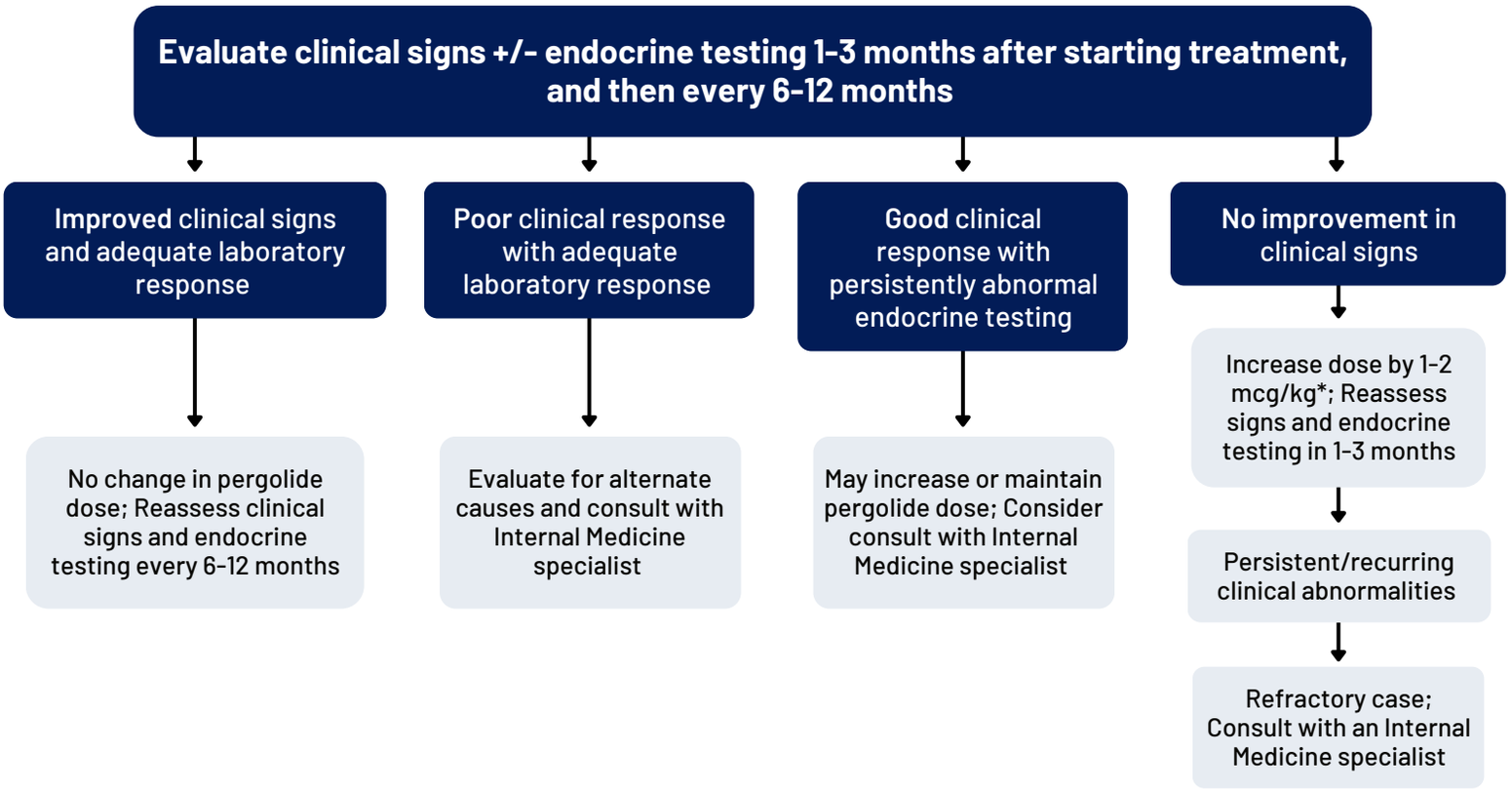
Examples of horses in each zone.



EQUINE ENDOCRINOLOGY GROUP 2023

Figure 6 – Treatment and monitoring of PPID

Initial Treatment Plan	Prascend® (pergolide tablets; Boehringer Ingelheim Animal Health USA, Inc.) is approved for treatment of PPID in horses and is recommended at an initial dose of 2 mcg/kg (0.5 mg for a 250 kg pony and 1.0 mg for a 500 kg horse). The dosage is not to exceed 4 mcg/kg bodyweight once daily. Some horses show a transient reduction in appetite with initial therapy or dose changes – consult with an internal medicine specialist for specific recommendations if inappetence is noted while on pergolide treatment.



Practice Tips:
- Improvement in clinical signs and insulin status are the most important indicator of response to treatment.
- Given the impact of season on ACTH, monitoring in the same season from year to year is important.
- ACTH concentrations may not return to the "PPID unlikely" range despite clinical improvement, and do not always warrant a dose increase.
- Strategies* used by the EEG for refractory cases include:
  - gradually increasing pergolide to 4-6 mcg/kg and adding cyproheptadine (0.25 mg/kg PO BID or 0.5 mg/kg PO SID)
  - OR gradually increasing pergolide to 10 mcg/kg

**These dosages are considered extra-label in the U.S., where the manufacturer's recommendations are not to exceed 4 mcg/kg daily.*

EQUINE ENDOCRINOLOGY GROUP 2023

Table 4 – Other considerations for managing horses with PPID

REMOVING HORSES FROM PERGOLIDE TREATMENT
In the event that a horse on pergolide treatment misses a dose, ACTH concentrations may begin to increase within 48 hours. Drug clearance varies substantially among individual horses and can result in detectable drug levels for much longer than 48 hours in some animals.

USE OF PERGOLIDE IN BREEDING ANIMALS
The safety and efficacy of pergolide in breeding, pregnant, and lactating animals has not been assessed. Group members are aware of pergolide use in a small number of breeding stallions and broodmares, but effects on fertility, lactation, and fetal development are not known. In pregnant mares, withdrawal of pergolide treatment 30-60 days prior to expected parturition may theoretically limit drug suppression of lactation or fetal adrenal axis function, but evidence for this approach is lacking.

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, hoof care, 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.

DIET AND EXERCISE RECOMMENDATIONS
It is important to carefully monitor the weight and body condition in horses with PPID. 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 horses should be fed a lower energy diet and be encouraged to follow an exercise program if soundness permits. 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.

Table 4 (cont.) – Other considerations for managing horses with PPID

MANAGEMENT OF GLUCOSE, INSULIN, AND LIPID DISORDERS
Assessment for insulin dysregulation should also be pursued in all patients with PPID (see Equine Endocrine Group Recommendations for Diagnosis and Management of Equine Metabolic Syndrome). 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 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. Attention should also be paid to the horse's diet and access to pasture (see below).

TESTING IN THE FACE OF LAMINITIS PAIN AND OTHER STRESS
Stress, excitement, and trailering can result in a transient increase in ACTH concentrations. Samples for PPID diagnosis via baseline ACTH should not be collected within 30 minutes of trailering, or in an animal that is visibly excited. Low to moderate pain of at least 24 hours duration does not appear to impact diagnostic testing with baseline ACTH or TRH stimulation testing. Testing may be performed in laminitic horses, but it is ideal to postpone until severe pain is controlled.

TESTING AFTER SEDATION
Sedation may impact endocrine responses. Diagnostic testing with baseline ACTH concentration only can be performed immediately (within 5-10 minutes) after sedation with xylazine or detomidine, with or without butorphanol, without substantial impact on the test interpretation. TRH stimulation testing and assessment of insulin status are impactedby sedation for at leastseveral hours. Thus, it is ideal to avoid diagnostic testing for PPID and insulin status within 24-48 hours of sedation.

Disclosures

Andy Durham is affiliated with the Liphook Equine Hospital and this institution offers endocrine testing.

Boehringer Ingelheim facilitates the development of EEG guidelines by supporting travel expenses for participants but does not influence the recommendations made by the group.

Acknowledgements

The authors thank Rachel Lemcke of Amwell Data Services LLC for helping design this document.

EQUINE ENDOCRINOLOGY GROUP 2023

Table 5 – Suggested further reading

1. Adams AA, Siard-Altman MH, Reedy SE, Barker D, Elzinga S, Sanz MG, Urschel K, Ireland JL. Evaluation of seasonal influences on adrenocorticotropic hormone response to the thyrotropin-releasing hormone stimulation test and its accuracy for diagnosis of pituitary pars intermedia dysfunction. Vet J. 2023 Oct 5;300-302:106035. doi: 10.1016/j.tvjl.2023.106035.

2. Bamford NJ, Stewart AJ, El-Hage CM, Bertin FR, Bailey SR. Investigation of breed differences in plasma adrenocorticotropic hormone concentrations among healthy horses and ponies. Vet J. 2023 Jun-Jul;296-297:105995. doi: 10.1016/j.tvjl.2023.105995.

3. Durham AE, Potier JF, Huber L. The effect of month and breed on plasma adrenocorticotropic hormone concentrations in equids. Vet J. 2022 Aug;286:105857. doi: 10.1016/j.tvjl.2022.105857.

4. Durham AE. The effect of pergolide mesylate on adrenocorticotrophic hormone responses to exogenous thyrotropin releasing hormone in horses. Vet J. 2022 Jul;285:105831. doi: 10.1016/j.tvjl.2022.105831. Epub 2022 Apr 25. PMID: 35477010.

5. Durham AE, Clarke BR, Potier JFN, Hammarstrand R, Malone GL. Clinically and temporally specific diagnostic thresholds for plasma ACTH in the horse. Equine Vet J. 53(2): 250-260. 2021. DOI: 10.1111/evj.13292

6. Gehlen H, Jaburg N, Merle R, Winter J. Can endocrine dysfunction be reliably tested in aged horses that are experiencing pain? Animals. 10: 1426. 2020. DOI: 10.3390/ani10081426

7. Hodge E, Kowalski A, Torcivia C, Lindborg S, Stefanovski D, Hart K, Frank N, van Eps A. Effect of thyrotropin-releasing hormone stimulation testing on the oral sugar test in horses when performed as a combined protocol. J Vet Intern Med. 2019 Sep;33(5):2272-2279. DOI: 10.1111/jvim.15601.

8. Horn R, Stewart AJ, Jackson KV, Dryburgh EL, Medina-Torres CE, Bertin FR. Clinical implications of using adrenocorticotropic hormone diagnostic cutoffs or reference intervals to diagnose pituitary pars intermedia dysfunction in mature horses. J Vet Intern Med. 2021 Jan;35(1):560-570. DOI: 10.1111/jvim.16017

9. Kam YN, McKenzie K, Coyle M, Bertin FR. Repeatability of a thyrotropin-releasing hormone stimulation test for diagnosis of pituitary pars intermedia dysfunction in mature horses. J Vet Intern Med. 2021 Nov;35(6):2885-2890. doi: 10.1111/jvim.16281.

10. Menzies-Gow NJ, Banse HE, Duff A, Hart N, Ireland JL, Knowles EJ, McFarlane D, Rendle D. BEVA primary care clinical guidelines: Diagnosis and management of equine pituitary pars intermedia dysfunction. Equine Vet J. 2023 Oct 5. doi: 10.1111/evj.14009.

11. Stewart AJ, Ireland JL, Durham AE, McGowan CM. Diagnosis of equine pituitary pars intermedia dysfunction. Vet J. 2023 Oct 5:106036. doi: 10.1016/j.tvjl.2023.106036.

12. Tadros EM, Fowlie JG, Refsal KR, Marteniuk J, Schott HC. Association between hyperinsulinemia and laminitis severity at the time of pituitary pars intermedia dysfunction diagnosis. Equine Vet J. 51: 52-56. 2019. DOI: 10.1111/evj.12963

13. Tatum RC, McGowan CM, Ireland JL. Evaluation of the sensitivity and specificity of basal plasma adrenocorticotrophic hormone concentration for diagnosing pituitary pars intermedia dysfunction in horses: A systematic review. Vet J. 2021 May 21:105695. DOI: 10.1016/j.tvjl.2021.105695

14. Tatum RC, McGowan CM, Ireland JL. Efficacy of pergolide for the management of equine pituitary pars intermedia dysfunction: A systematic review. Vet J. 2020 Dec:266:105562. DOI: 10.1016/j.tvjl.2020.105562

15. Thane K, Uricchio C, Frank N. Effect of early or late blood sampling on thyrotropin releasing hormone stimulation test results in horses. J Vet Intern Med. 2022 Mar;36(2):770-777. doi: 10.1111/jvim.16362.

16. Vaughn SA, Norton NA, Hart KA. Circulating Hypothalamic-Pituitary-Adrenal Axis Hormones and Insulin Concentrations in Horses and Ponies. J Equine Vet Sci. 2022 Apr;111:103810. doi: 10.1016/j.jevs.2021.103810.

17. Vorster DM, Wang W, Kemp KL, Bamford NJ, Bertin FR. Clinical implications of imprecise sampling time for 10- and 30-min thyrotropin-releasing hormone stimulation tests in horses. Equine Vet J. 2023 Aug 30. doi: 10.1111/evj.13991.

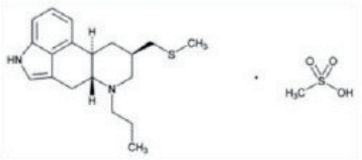
EQUINE ENDOCRINOLOGY GROUP 2023

Notes

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 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 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	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).

In some cases, adverse events were reported after a dose increase (see **Post-Approval Experience**).

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.

Keep PRASCEND in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Dogs have eaten PRASCEND tablets that were placed in food intended for horses or dropped during administration of the tablets to the horses. Adverse reactions may occur if animals other than horses ingest PRASCEND tablets (see **Post-Approval Experience**).

Human Warnings: Not for use in humans. Do not ingest the product. 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.

Pergolide, like other ergot derivatives, may cause emesis, dizziness, lethargy or low blood pressure.

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. Store this product separately away from human medicinal products and handle this product with care to avoid accidental ingestion.

In case of accidental ingestion seek medical advice immediately and show the package leaflet or the label to the physician.

Precautions: Treatment with PRASCEND may cause inappetence.

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:
Pre-Approval Experience: 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

Inappetence 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 inappetence or decreased appetite as compared to the 32.8% of horses that experienced inappetence or decreased appetite during the study. Most cases of inappetence were transient and occurred during the first month of treatment; however, some horses experienced sporadic inappetence throughout the study. Two horses required a temporary reduction in dose due to inappetence 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.

51747031-05/21

Post-Approval Experience (2019):

The following adverse events are based on post approval adverse drug experience reporting for PRASCEND. Not all adverse events are reported. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.

The following adverse events in horses are categorized in order of decreasing reporting frequency by body system and in decreasing order of reporting frequency within each body system:

General: anorexia, lethargy, weight loss
Gastrointestinal: diarrhea, abdominal pain/colic
Dermatological: alopecia, hyperhidrosis, dermatitis
Musculoskeletal: laminitis, muscle stiffness/soreness
Neurological: ataxia, seizure, muscle tremors
Behavioral: aggression (to other horses and humans), hyperactivity (anxiety, agitation), other behavioral changes (stud-like behavior, spooky, unpredictable, confused)
Clinical pathology: anemia, elevated liver enzymes, thrombocytopenia

The above adverse events were reported in some horses at starting dose levels, while in the others following a dose increase.

Death (including euthanasia) has been reported.

Adverse events have been reported in dogs following ingestion of tablets prepared for administration to horses.

To report suspected adverse reactions, to obtain a Safety Data Sheet (SDS), or for technical assistance, contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

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

Approved by FDA under NADA # 141-331

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.

Marketed by:
Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

Origin Czech Republic

448901-03
Revised 05/2021

US-EQU-0289-2021

US-EQU-0368-2023