PERGOLIDE (Veterinary—Systemic)

Commercial pergolide products labeled for human use are no longer available, and there are no veterinary-labeled products in the United States or Canada.

Category: Dopamine agonist.

Indications

Note: Pergolide is not specifically approved for veterinary use. In other USP information monographs, the $^{EL US}$ and $^{EL CAN}$ designations refer to uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of veterinary products and, therefore, product labeling.

Classification as *Accepted, Potentially effective,* or *Unaccepted* is an evaluation of reasonable use that considers clinical circumstances, including the availability of other therapies. The quality of evidence supporting an indication is shown by the evidence rating.

Horses

Accepted

$^{EL US,CAN}$Pituitary pars intermedia dysfunction (treatment)^{EL}—Pergolide is used in the treatment of pituitary pars intermedia dysfunction (PPID; equine Cushing's disease) (Evidence rating: B-3).{R-1-6; 33; 35}

Regulatory Considerations

U.S. and Canada—

There are no commercial veterinary pergolide products. Human pergolide mesylate products previously available in the United States and Canada have been removed from the market due to risk of cardiac valvular damage.{R-7-9} Pergolide prescriptions for veterinary use must either be filled from any remaining supply of the discontinued human product or compounded for veterinary use.

The United States Food and Drug Administration Center for Veterinary Medicine (FDA CVM) issued a statement in May of 2007 that included the following: "FDA is working with the sponsors of the approved products and all other interested parties to ensure that pergolide remains available to treat Cushing's Syndrome in horses until a new animal drug application is approved for that use. This includes trying to make the approved product available through veterinary distribution channels and exercising enforcement discretion as appropriate over the pharmacy compounding of pergolide. Bulk substance used for pharmacy compounding should be labeled for 'animal use only.' All pharmacy compounding must be done under a valid veterinary prescription to treat an affected horse."{R-36} In the United States, refer to the Animal Medicinal Drug Use Clarification Act,{R-10} Food and Drug Administration regulations pertaining to compounding (CFR 21 Part 530.13),{R-11} and the current United States Food and Drug Administration's Compliance Policy Guide on *Compounding of Drugs for Use in Animals.*{R-12} In Canada, refer to the Health Canada Health Products and Food Branch's *Policy on Manufacturing and Compounding Drug Products in Canada* (POL-0051).{R-13}

Chemistry

Chemical group: Ergot derivative dopamine receptor agonist.{R-14}

Chemical Name: Pergolide mesylate—Ergoline, 8-[(methylthio)methyl]-6-propyl-, monomethanesulfonate, (8β)-.{R-15}

Molecular formula: Pergolide mesylate—$C_{19}H_{26}N_2S \cdot CH_4O_3S$.{R-15}

Molecular weight: Pergolide mesylate—410.59.{R-15}

Description: Pergolide Mesylate USP—White to off-white powder.{R-16}

Solubility: Pergolide Mesylate USP—Sparingly soluble in methanol; slighly soluble in water, in dehydrated alcohol, and in chloroform; very slightly soluble in acetone; practically insoluble in ether.{R-16}

Evidence ratings

Evidence Quality	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Insufficient evidence to support a recommendation for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

Evidence Type	
1	Species-specific evidence from at least one large randomized and controlled trial (RCT) or multiple small RCTs
2	Species-specific evidence from a small RCT, disease models, large case studies, pharmacokinetic studies using surrogate endpoints, or evidence from well-designed trials in a different species that is considered appropriate for comparison
3	Dramatic results from either well-designed, species-specific trials without controls, controlled trials without randomization, or small case studies
4	Pharmacokinetic studies without surrogate endpoints or well designed pharmacodynamic studies in healthy animals
5	*In vitro* studies
6	Opinions of respected authorities on the basis of clinical experience or reports of expert committees

Pharmacology/Pharmacokinetics

Note: To date, no bioavailability, pharmacokinetic, or metabolism studies of pergolide have been performed in horses.

Mechanism of action/Effect: The development of pituitary pars intermedia dysfunction appears to be almost exclusively linked to an adenoma or adenomatous hyperplasia of the pituitary pars intermedia. The tumor may also compress or destroy the pars distalis. The pars intermedia tissue in horses with PPID contains one-eighth of the dopamine found in normal horses, probably due to loss of hypothalamic dopaminergic innervation.{R-17-19} Because dopamine inhibits secretion of pro-opiomelanocortin-derived peptides from the pars intermedia, a dopamine agonist is administered to restore control over the marked increase in these peptides and the increase in adrenocorticotrophin hormone (ACTH) in circulation in horses with pituitary pars intermedia dysfunction.{R-6} Pergolide stimulates postsynaptic dopamine receptors D_1 and D_2.{R-14}

Other effects: Pergolide inhibits secretion of prolactin, causes a transient rise in serum growth hormone, and causes a decrease in serum luteinizing hormone.{R-14}

Absorption: Oral—*Human beings:* Bioavailability is 20 to 60%.{R-20}

Protein binding: *Human beings*—95 to 96%.{R-20}

Elimination: *Human beings*—Primarily renal (about 55% of the dose).{R-14; 20}

Precautions to Consider

Reproduction/Pregnancy

Pergolide may adversely affect some species, such as rats, that require pituitary prolactin for luteolysis and the maintenance of early pregnancy.{R-22; 31}

Mice and *rabbits:* Studies of pregnant mice using pergolide mesylate dosages of 5, 16, and 45 mg/kg a day and of pregnant rabbits using dosages of 2, 6, and 16 mg/kg a day showed no evidence of fetal harm.{R-14}

Lactation

Because pergolide reduces prolactin secretion, it may inhibit lactation. It is not known if pergolide is distributed into milk.{R-14}

Mice: Pregnant mice were given pergolide from the fifteenth day of gestation to twenty days after birth at a dose of 0.1, 0.3, 1 or 3 mg/kg a day to evaluate the effects. Although inhibition of lactation in some mice given the 3-mg/kg dose reduced their offspring survival slightly, there were otherwise no evident enduring effects from the treatment.{R-23}

Drug interactions and/or related problems

Note: No drug interactions have been reported in horses. The following are potential interactions, based on the pharmacology of pergolide and reported problems in other species:

Dopamine agonists and/or

Monoamine oxidase inhibitors (MAO-B isoform), including:

Selegiline (L-deprenyl)

(Administration of pergolide concurrently with other dopamine agonists, including medications that prevent the breakdown of dopamine, may exacerbate effects.){R-21}

Dopamine antagonists, including:

Metoclopramide and

Phenothiazines

(These medications may reduce the effectiveness of dopamine agonists, such as pergolide, when administered concurrently.){R-14}

Laboratory value alterations

Note: No significant laboratory value alterations have been reported in association with pergolide treatment in horses.

Medical considerations/Contraindications

Note: No specific medical considerations or contraindications have been reported in association with pergolide treatment in horses.

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition):

Pituitary function tests

(Response to therapy is monitored by intermittent evaluation; see also the *General Dosing Information* section of this monograph.)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Note: Commercial pergolide tablets labeled for use in human patients were removed from the U.S. and Canadian markets because of a cardiac valvulopathy that has not been reported in horses. The presence and severity of damage to heart valves appears to be dependent on the daily and cumulative dose in human beings, for whom the

average total daily dose was 2.8 mg (about 0.04 mg/kg for a 150-pound person).[R-24; 25] Valvular heart disease has been induced in rats with an intraperitoneal dose of 0.5 mg/kg a day for ten to twenty weeks; lower doses have not been studied.[R-26] There is no available evidence of induced cardiac valve disease in horses at the doses generally administered to control pituitary pars intermedia dysfunction.

Those indicating need for medical attention

Incidence unknown

Horses[R-4; 17; 34]

Anorexia; colic; diarrhea; dizziness; dyspnea; dry mouth; sweating

Note: Adverse effects are uncommon in horses administered the low dose of pergolide (0.002 mg/kg a day), although decreased appetite or anorexia has been reported. Beginning treatment at a low dose and gradually increasing it may help to avoid adverse effects when higher doses are necessary.[R-3-5]

Laminitis—When pergolide was first being used in horses, there was some concern about risk of worsening laminitis due to potential vasoconstriction caused by the drug; however, there have been no reported cases. At least one study has suggested an association between pituitary pars intermedia dysfunction (PPID) and chronic laminitis; therefore, in horses with test results indicating PPID, pergolide treatment may assist in control of laminitis.[R-2; 5; 27]

Overdose

For more information in cases of overdose or unintentional ingestion, **contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center** (888-426-4435 or 900-443-0000; a fee may be required for consultation) **and/or the drug manufacturer**.

LD_{50}

Oral administration:

Dogs—More than 25 mg/kg.[R-22]

Mice—54 and 87.2 mg/kg for male and female mice, respectively.[R-14; 22]

Rats—8.4 to 33.6 mg/kg, depending on gender and study.[R-14; 22]

Note: In mice and rats, males were consistently more sensitive to acute toxicity than females.[R-22]

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Note: There are no reports of severe overdose in horses.

Dogs

With a single oral dose of 15 to 25 mg/kg:[R-22]

Dilated pupils; relaxed nictitating membranes; vomiting

Human beings[R-14]

Cardiac arrhythmias; central nervous system stimulation; hallucinations; hypotension; vomiting

Mice and *rats*

With a single oral dose of ≥ 7 mg/kg:[R-22]

Aggressive behavior; hyperactivity; increased gnawing; poor grooming; ptosis

Note: For dogs, mice, and rats, the predominant effects of subchronic to chronic toxicity (for dogs, a dose of 2.5 to 10 mg/kg a day, for three months to a year) included decreased weight gain, a mild reduction in erythrocytic parameters (erythrocyte count, hemoglobin, and hematocrit), and, in rats, inhibition of corpora lutea lysis with increased ovarian and uterine weight. A few dogs had decreased prostate weight with focal atrophy with a year of overdosage.[R-22]

Treatment of toxicity

Treatment recommended by the manufacturer in human product labeling consists of the following:[R-14]

- Administering activated charcoal may reduce absorption of pergolide. In some human patients, charcoal has been more successful than emesis or lavage for pergolide overdosage.
- Support airway ventilation and cardiovascular perfusion
- Monitor for potential arrhythmias

Client Consultation

In providing consultation, consider emphasizing the following selected information:

Familiarizing clients with general health care for management of pituitary pars intermedia dysfunction, including body clipping, dental care, dietary changes, hoof care, and watching for signs of secondary infection

Familiarizing clients with signs of potential adverse effects

General Dosing Information

Establishing therapeutic dose

Horses: For horses that have an elevation of plasma endogenous adrenocorticotropin (ACTH) concentration high enough to be considered diagnostic, the test can also be used to evaluate response to treatment.[R-2; 3; 29; 30] ACTH may be reduced to normal level in treated horses (60% of

cases in one report).{R-2} However, horses show improvement in clinical signs with a decline in ACTH, whether or not the plasma level reaches the laboratory reference range.{R-2; 30} ACTH is very labile; therefore, laboratories will have specific instructions on how to collect and transport samples, including type of blood tube, centrifugation and separation of plasma, and immediate freezing for shipment.{R-37} Contact a reliable laboratory for instructions.

Dexamethasone suppression and thyrotropin-releasing hormone stimulation tests have also been used to evaluate treatment response.{R-3; 5; 35}

Clinical response to treatment is always considered in evaluation.

Dosing and Dosage Forms

Note: Pergolide is not specifically approved for veterinary use. In other USP information monographs the EL[US] and EL[CAN] designations indicate uses that are not included in U.S. and Canadian product labeling; however, in this section they reflect the lack of veterinary products and, therefore, product labeling.

Until dosing studies are performed using pergolide prepared by an accepted, standard compounding formula, the most effective dose may depend on how the drug preparation is compounded. Ranges are given reflecting the information available at this time.

DOSAGES

EL[US,CAN] ***Horses***—

For *Pergolide Oral Suspension, Veterinary*

Pituitary pars intermedia dysfunction:

Low dose—0.002 mg per kg of body weight every twenty-four hours (1 mg total dose a day for a 500 kg horse).{R-3; 5; 21; 30}

High dose—0.006 to 0.01 mg per kg of body weight every twenty-four hours (3 to 5 mg total dose a day for a 500 kg horse).{R-1; 2; 4; 17; 21}

Note: There are no pharmacokinetic data on which to base a therapeutic plan. Experienced clinicians suggest beginning with the low dose; if no response is seen, the dose is increased by 0.002 mg/kg every four to eight weeks to a maximum dose of 0.01 mg/kg.{R-1; 17; 21} There are reports that some horses and ponies have been controlled with daily doses as low as 0.001 mg/kg (0.25 to 0.5 mg/kg total dose).{R-32} It is recommended that any regimen begin with the low dose followed by a minimum pause of three to four days between incremental increases to avoid adverse effects.EL{R-4}

DOSAGE FORMS

Oral

PERGOLIDE ORAL SUSPENSION, VETERINARY

Strength(s) usually available: Pergolide oral suspension is not available as a commercial product in the United States or Canada. Therefore, it must be compounded for veterinary use. Utilizing the services of a qualified compounding pharmacist to formulate this dosage form is recommended.

Packaging and storage: Preserve in a tight, light resistant container and store in a refrigerator. See also the *Pergolide Oral Suspension, Veterinary USP (proposed)* monograph.

Stability: A beyond-use date of 14 days, under refrigeration after compounding, has been set for this dosage form, based on evidence of poor stability of a 1-mg-per-mL aqueous preparation when stored at room temperature and exposed to ambient light. See the *Pergolide Oral Suspension, Veterinary USP (proposed)* monograph for more information about the formulation.

Caution: Keep out of the reach of children.

USP requirements: See the *Pergolide Oral Suspension, Veterinary USP (proposed)* monograph.

Developed: 03/12/08

References

1. Sgorbini M, Panzani D. Maccheroni M, et al. Equine Cushing-like syndrome: diagnosis and therapy in two cases. Vet Res Commun 2004; 28: 377-80.
2. Donaldson MT, LaMonte BH, Morresey P, et al. Treatment with pergolide or cyproheptadine of pituitary pars intermedia dysfunction (equine Cushing's disease). J Vet Int Med 2002; 16: 742-46.
3. Schott HC, Coursen CL, Eberhart SW, et al. The Michigan Cushing's project. Proceedings of the Annual Convention of the American Association of Equine Practitioners. San Diego, California; American Association of Equine Practitioners. November 24 to 28, 2001; 47: 22-4.

4. Munoz MC, Doreste F, Ferrer O, et al. Pergolide treatment for Cushing's syndrome in a horse. Vet Rec 1996 Jul 3; 139(2): 41-3.
5. Peters DF, Erfle JB, Slobojan GT. Low-dose pergolide mesylate treatment for equine hypophyseal adenomas (Cushing's syndrome). Proc Ann Conv Am Assoc Equine Prac 1995; 41: 154-5.
6. Orth DN, Holscher MA, Wilson MG, et al. Equine Cushing's Disease: Plasma immunoreactive proopiolipomelanocortin peptide and cortisol levels basally and in response to diagnostic tests. Endocrinology 1982; 110(4): 1430-41.
7. FDA announces voluntary withdrawal of pergolide. J Am Vet Med Assoc 2007 Jun 1; 230(11): 1616.
8. FDA-CVM works to address concerns about pergolide supplies. J Am Vet Med Assoc 2007 Jul 1; 231(1): 20-1.
9. Cease Sale of Permax (pergolide mesylate) in Canada as of August 30, 2007. Available at www.lilly.ca/searchable/media/hcp/permax.pdf. Accessed on November 20, 2007.
10. Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA). Public Law 103-396. Available at http://www.fda.gov/cvm/s340.htm. Accessed November 26, 2007.
11. Office of the Federal Register. Code of Federal Regulations. 21 Part 530.13. US Government Printing Office. Available at www.access.gpo.gov/nara/cfr/waisidx_07/21cfr530_07.html. Accessed on November 26, 2007.
12. Compounding of drugs for use in animals (CPG 7125.40). In: Compliance policy guides manual. Section 608.400. United States Department of Health and Human Services Food and Drug Administration Center for Veterinary Medicine. June, 2003. Available at http://www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg608-400.html. Accessed on November 26, 2007.
13. Manufacturing and compounding drug products in Canada. Health Canada Health Products and Food Branch. 3/28/02. Available at www.hc-sc.gc.ca. Accessed on November 26, 2007.
14. Permax package insert (Lilly, US), Rev 10/02/03. Available at www.fda.gov/cder/foi/label/2003/19385slr030,031,035_permax_lbl.pdf. Accessed on November 26, 2007.
15. USP dictionary of USAN and international drug names, 2007 ed. Rockville, MD: The United States Pharmacopeial Convention Inc. 2007. Available at www.uspusan.com. Accessed on November 26, 2007.
16. The United States Pharmacopeia. The national formulary. USP 30th revision (August 1, 2007). NF 25th ed. (August 1, 2007). Rockville, MD: The United States Pharmacopeial Convention Inc; 2007. Available at www.uspnf.com. Accessed on November 26, 2007.
17. Schott HC. Pituitary pars intermedia dysfunction: equine Cushing's disease. Vet Clin Equine 2002 Aug; 18(2): 237-70.
18. Millington WR, Dybdal NO, Dawson R, et al. Equine Cushing's disease: differential regulation of beta-endorphin processing in tumors of the intermediate pituitary. Endocrinology 1988 Sep; 123(3): 1598-604.
19. MacFarlane D, Dybdal N, Donaldson MT, et al. Nitration and increased α-synuclein expression associated with dopaminergic neurodegeneration in equine pituitary pars intermedia dysfunction. J Neuroendocrinol 2005 Feb; 17(2): 73-80.
20. Kvernmo T, Hartter S, Burger E. A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. Clin Ther 2006 Aug; 28(8): 1065-78.
21. Papich MG. Saunders handbook of veterinary drugs, 2nd ed. St. Louis, Missouri: Saunders Elsevier. 2007. p. 515.
22. Francis PC, Carlson KH, Owen NV, et al. Preclinical toxicology studies with the new dopamine agonist pergolide. Arzneimittelforschung 1994 Mar; 44(3): 278-84.
23. Buelke-Sam J, Cohen IR, Tizzano JP, et al. Developmental toxicity of the dopamine agonist pergolide mesylate in CD-1 mice. II: Perinatal and postnatal exposure. Neurotoxicol Teratol 1991 May-Jun; 13(3): 297-306.
24. Schade R, Andersohn F, Suissa S, et al. Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med 2007 Jan 4; 356(1): 29-38.
25. Zanettini R, Antonini A, Gatto G, et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med 2007 Jan 4; 356(1): 39-46.
26. Droogmans S, Franken PR, Garbar C, et al. In vivo model of drug-induced valvular heart disease in rats: pergolide-induced valvular heart disease demonstrated with echocardiography and correlation with pathology. Eur Heart J 2007; 28: 2156-62.
27. Donaldson MT, Jorgensen JR, Beech J. Evaluation of suspected pituitary pars intermedia dysfunction in horses with laminitis. J Am Vet Med Assoc 2004 Apr 1; 224(7): 1123-7.
29. Couetil L, Paradis MR, Knoll J. Plasma adrenocorticotropin concentration in healthy horses and in horses with clinical signs of hyperadrenocorticism. J Vet Intern Med 1996 Jan-Feb; 10(1): 1-6.
30. Perkins GA, Lamb S, Erb HN, et al. Plasma adrenocorticotropin (ACTH) concentrations and clinical response in horses treated for equine

Cushing's disease with cyproheptadine or pergolide. Equine Vet J 2002; 34(7): 679-85.
31. Buelke-Sam J, Byrd RA, Johnson JA, et al. Developmental toxicity of the dopamine agonist pergolide mesylate in CD-1 mice. I: Gestational exposure. Neurotoxicol Teratol 1991 May-Jun; 13(3): 283-95.
32. Dybdal NO, Levy M. Pituitary pars intermedia dysfunction in the horse. Part II: diagnosis and treatment. Proc Annu Forum Am Coll Vet Int Med 1997; 15: 470-2.
33. Williams PD. Equine Cushings Syndrome – Retrospective study of twenty four cases and response to medication (abstract). Proc Congr Br Equine Vet Assoc 1995; 34: 41.
34. Beech J. Treatment of hypophyseal adenomas. Compend Contin Educ Pract Vet 1994; 16: 921-3.
35. Watson JL, Dybdal NO, Herrgesell EJ, et al. Equine Cushing's disease and the long-term treatment with oral pergolide mesylate [abstract]. Proc Am Coll Vet Int Med 1998; 16: 710.
36. CVM Update. CVM working to address concerns about supplies of pergolide for horses. Available at http://www.fda.gov/cvm/CVM_Updates/pergolide.htm. Accessed on January 15, 2008.
37. North Carolina State University Clinical Pharmacology - Clinical Endocrinology Laboratory analysis sample menu. Available at www.cvm.ncsu.edu/vth/PDFS/Sample_Menu.pdf. Accessed on January 18, 2008.

Pergolide for the treatment of pituitary pars intermedia dysfunction in horses.

Revision date: December 3, 2007

Back to page 1.

The following tables are not intended to be in-depth reviews of each article. Instead, they are brief overviews/reviews of the studies, assuming reviewers are already familiar with the cited references. If you would like additional information about these studies, please contact veterinary@usp.org.

Study 1 of 8: Sgorbini M, Panzani D, Maccheroni M, et al. Equine Cushing-like syndrome: diagnosis and therapy in two cases. Veterinary Research Communications 2004; 28: 377-80.

Design • Case reports	**Methods:** • Case 1—Eighteen-year-old Italian saddle horse. History of chronic recurrent laminitis, infertility, progressive hirsutism, hyperhidrosis, pendulous abdomen, lethargy, polyuria, polydipsia, and anorexia. Presented with a fever and increased respiratory rate. Blood work showed hyperglycemia, hypostenuria, hyperinsulinemia, and elevated plasma adrenocorticotrophic hormone (ACTH). Clinical signs resolved and ovarian activity resumed with 6 to 7 weeks of pergolide treatment. ACTH dropped from 155 picograms per mL (pgm/mL) to 26.8 pgm/mL after 45 days and was approximately the same when retested after 14 months of treatment. • Case 2—Twenty-five-year-old French saddle horse with recurrent laminitis, hirsutism, pendulous abdomen, bulging supraorbital fat pads, severe polyuria and polydipsia, and a plasma ACTH of 370 picograms per milliliter (pg/mL). There was no response to 3 mg of pergolide daily for one month. The dose was increased to 4 mg total dose per day and clinical signs were resolved with 6 weeks. ACTH dropped to 59.1 pg/mL. Polyuria and polydipsia significantly improved but did not completely resolve. **Dose:** • Oral pergolide mesylate, initial dose of 0.5 mg total dose every twenty-four hours, gradually increased by 0.5 mg every three days to a final total dosage of 3 mg every twenty-four hours. **Conclusions:** • Pergolide mesylate treatment was effective in these two horses. No side effects were noted.	

Study 2 of 8: Donaldson MT, LaMonte BH, Morresey P, et al. Treatment with pergolide or cyproheptadine of pituitary pars intermedia dysfunction (equine Cushing's disease). Journal of Veterinary Internal Medicine 2002; 16: 742-46.

Design	**Goal:** To investigate the response of horses with pituitary pars intermedia dysfunction (PPID) to cyproheptadine or pergolide.	**Limitations:**
• Retrospec-tive N = 27	**Methods:** • Records of horses evaluated for PPID at University of Pennsylvania Hospital between June 1996 and November 2001. Criteria included plasma ACTH > 50 pgm/mL, at least 1 clinical sign, and evaluation before and after treatment. • ACTH assayed by chemiluminescent immunoassay and insulin by radioimmunosaasay. **Dose:** • Pergolide-treated horses (N = 20)—The median oral dose was 3 mcg/kg (0.003 mg/kg) a day with a range of 1.7 to 5.5 mcg/kg. • Cyproheptadine-treated horses (N = 7)—Oral, 0.25 mg/kg as a total dose every twenty-four hours **Results:** • With pergolide treatment, there was a significant decrease in plasma ACTH, but not insulin or glucose concentration; 60% of horses reached a plasma ACTH within the normal range. There was no significant change in any of the 3 parameters with cyproheptadine treatment. • There was a direct correlation between pergolide dose and ACTH concentration after treatment, as well as between duration of treatment and ACTH concentration. Improvement in clinical signs was reported by 85% of owners of horses treated with pergolide and 28% of owners of horses treated with cyproheptadine. • Treatment with pergolide significantly decreased the number of horses with laminitis ($P < 0.001$). **Conclusions:** • Results suggest pergolide is more effective than cyproheptadine in the treatment of PPID.	• Evaluation of cyproheptadine administered twice a day or at higher dose may have given different results. Also, mechanism of action of cyproheptadine may not include suppression of ACTH secretion. • Retrospective studies have inherent biases; selection for treatment group is not randomized, etc.

Study 3 of 8: Schott HC, Coursen CL, Eberhart SW, et al. The Michigan Cushing's project. Proceedings of the Annual Convention of the American Association of Equine Practitioners. San Diego, California November 24 to 28, 2001; 47: 22-4.

Design	**Goal:** To evaluate the response of horses with equine Cushing's disease to pergolide and cyproheptadine, including effectiveness of laboratory tests. **Methods:** • Horses with naturally occurring disease presented to Michigan veterinarians and enrolled in this field study administered by Michigan State University from 1997 to 1999. Enrollment criteria included clinical signs and diagnostic low-dose dexamethasone test (DST) or thyrotropin-releasing hormone stimulation test (TRH). **Dose:** • Control group—No treatment (N = 5) • Treatment group 1—Oral pergolide, 2 mcg/kg every twenty-four hours (N = 20). • Treatment group 2—Oral cyproheptadine, 1.2 mg/kg every twenty-four hours (N = 7). **Duration:** 6 to 12 months **Results:** • Clinical improvement was reported more often with pergolide treatment. Normal DST and TRH results were found in more horses treated with pergolide than in horses treated with cyproheptadine. There was no significant difference between cyprophetadine-treated and untreated horses in normalization of DST and TRH. • Decreased appetite was seen in several pergolide-treated horses during the first week of treatment, but resolved with a transient reduction in dose. **Conclusions:** • In this study, cyproheptadine had little benefit over no treatment in horses with Cushing's disease. Pergolide treatment had demonstrable clinical and laboratory effects. • Plasma ACTH may show false positives and false negatives, based on comparison with DST or TRH. • A subgroup of horses with normal DST and TRH, without hirsutism, but with abnormal fat deposition, laminitis, and elevated serum insulin may have peripheral Cushing's disease and, therefore, would not respond to pergolide.	**Comments:** • Allocation to treatment group was not randomized. "Treatments were selected through client discussions with their primary care veterinarians." (Communication with Dr. Schott on December 1, 2007) • 77 horses were enrolled, but only 32 completed the study.
• Prospective, open study, with active and negative controls N = 32		

Study 4 of 8: Watson JL, Dybdal NO, Herrgesell EJ, et al. Equine Cushing's disease and the long-term treatment with oral pergolide mesylate [abstract]. Proceedings of the American College of Veterinary Internal Medicine 1998; 16: 710.

Design • Case series N = 6	**Methods:** • DST was used to evaluate Cushing's disease and treatment efficacy. Pituitary gland mass was evaluated in two horses: one by magnetic resonance imaging and one at postmortem. **Dose:** Oral pergolide mesylate, 1.8 to 2.8 mcg/kg every twenty-four hours. **Duration:** 6 to 26 months **Results:** • All 6 horses responded to treatment, as measured by clinical signs and DST. Improvements in clinical signs were seen before test results responded. • No side effects of treatment were noted. **Conclusions:** • Pergolide can be effective for extended periods (>2 years) at these doses.	

Study 5 of 8: Munoz MC, Doreste F, Ferrer O, et al. Pergolide treatment for Cushing's syndrome in a horse. Veterinary Record 1996 Jul 3; 139(2): 41-3.

Design	**Methods:**	**Comments:**
• Case report	• Male, Hanoverian horse, 16 years of age, with a history of weight loss, hirsutism, supraorbital fat stores, dermatophilosis, distended abdomen, polyuria, and polydipsia over 3 months. Lab results included hyperglycemia and elevated AST and GGT. Combined DST with ACTH-stimulation and TRH tests supported the diagnosis of PPID. **Dose:** • Oral pergolide, 3 mg total dose every twenty-four hours. When side effects occurred, the dose was discontinued and treatment restarted at 0.5 mg total dose a day, increased by 0.5 mg every three days to reach the 3-mg-a-day dose. • After seven months, the total daily dose was reduced to 2 mg every forty-eight hours. **Results:** • Clinical improvement was noted over one to six months and the horse was still participating in sporting events two years after treatment began. No side effects were reported after the initial dose was reduced.	• The authors report positive biochemical results, but did not publish the details of laboratory results.

Study 6 of 8: Peters DF, Erfle JB, Slobojan GT. Low-dose pergolide mesylate treatment for equine hypophyseal ademonas (Cushing's syndrome). Proceedings of the Annual Convention of the American Association of Equine Practitioners. 1995; 41: 154-5.

Design • Prospective, open, clinical study without controls N = 5 horses and 4 ponies	**Goal:** To study the efficacy of pergolide in the treatment of pituitary gland ademonas in horses and ponies **Methods:** • Horses presented for evaluation of symptoms indicative of equine Cushing's syndrome. Laboratory testing included a DST to verify loss of pituitary responsiveness. **Dose and duration:** • Oral pergolide, 0.0017 mg/kg a day (1.7 mcg/kg), divided to be administered twice a day. • Average of 13.6 months (range, 1 to 23 months) study duration **Results:** • Eight of nine horses showed clinical improvement within 14 to 35 days and seven of those had ongoing improvement for 5 to 52 weeks. • DST results improved or returned to normal in seven animals. Hyperglycemia resolved in five. • Two of three horses presenting with laminitis were reported to be markedly improved within 2 weeks after treatment started. • One horse showed no clinical improvement but did show improved DST results. • No adverse effects of treatment were noted. **Conclusions:** • The results for this low dose are similar to those reported for higher doses of pergolide mesylate in the treatment of equine Cushing's disease.	

Study 7 of 8: Williams PD. Equine Cushings Syndrome – Retrospective study of twenty four cases and response to medication (abstract). In: Proceedings of the 34th Congress of the British Equine Veterinary Association. 1995. p. 41.

Design • Case series N = 24	**Methods:** • Diagnosis of Cushing's disease in these equine cases was by TRH stimulation and clinical signs. Treatment response was evaluated by resolution of clinical signs and return to normal serum glucose concentration. In horses treated for a significant period of time, TRH and cortisol levels were monitored. **Duration:** • 3.5 years **Dose:** • Low dose oral pergolide, maximum of 1 to 2 mg total dose a day. • High dose oral pergolide, maximum of 4 to 5 mg total dose a day. • Cyproheptadine (dose not specified) • Untreated (N = 10) **Results:** • Four of the untreated animals were euthanized within six months. • Cyproheptadine caused little improvement and the animals that survived were changed to pergolide treatment. • High-dose pergolide caused immediate improvement, but the cost of this regimen was prohibitive. • The response to low-dose pergolide was encouraging. **Conclusions:** • Low-dose pergolide treatment appears to be a good alternative to cyproheptadine treatment or no treatment.	

Study 8 of 8: Orth DN, Holscher MA, Wilson MG, et al. Equine Cushing's Disease: Plasma immunoreactive proopiolipomelanocortin peptide and cortisol levels basally and in response to diagnostic tests. Endocrinology 1982; 110(4): 1430-41.

Design • Case report (only one horse was given pergolide)	**Goal:** This is an investigation of two cases of equine Cushing's disease, with additional data from normal horses. **Methods:** • Case 1—A 7-year-old mare with clinical signs of severe Cushing's disease. Blood tests were performed, and the horse was then euthanized because no effective treatment was available. Necropsy revealed a pars intermedia adenoma and hyperplastic adrenal glands. • Case 2—A 12-year-old mare with clinical signs of Cushing's disease, including laminitis. Blood tests were performed, and the horse was successfully treated (therapy not specified). • Tests performed in Cases 1 and 2 included radioimmunoassays for ACTH, cortisol, and pars intermedia proopiolipomelanocortin (proOLMC) peptides (including αMSH, βMSH, corticotrophin-like intermediate lobe peptide [CLIP], β-lipotropin [β-LPH], and β-endorphin), low and high dose dexamethasone suppression tests, ACTH stimulation, glucose tolerance, and insulin tolerance. • Additional tests performed in Case 2 included the response of plasma cortisol and pituitary peptides to insulin, vasopressin, dopamine-HCL, bromocriptine, or pergolide mesylate. • Normal horses—A single blood sample was taken from 10 horses between 8 and 10 a.m. to establish a standard for pituitary peptide concentrations. **Dose:** • Intravenous dopamine hydrochloride, 4 mcg/kg/min for 150 minutes • Oral and subcutaneous bromocriptine, 100 mg total dose • Oral pergolide, 5 mg total dose alone and in combination with dexamethasone **Results:** • Basal ACTH in the two horses was similar to that seen in human Cushing's disease (hyperplasia of ACTH-secreting cells in the pars distalis); however, the proOLMC peptides were disproportionately increased. • Agents that affect secretion from the pars distalis (glucocorticoids, vasopressin and hypoglycemia) had little or no effect on proOLMC secretion. Dopamine and dopamine agonists (bromocriptine, pergolide) inhibited proOLMC secretion from the pars intermedia tumor in this horse. • Dopamine caused a rapid fall in hormone levels. Bromocriptine and pergolide caused rapid and sustained decreases in hormones to normal levels. **Conclusions:** • The results of this study support the potential for dopamine agonists to treat equine Cushing's disease.	