

## What is Cushing's disease

Cushing's disease, also called Cushing's syndrome or hyperadrenocorticism. Cushing's disease is an overproduction of the hormone cortisol, or an overproduction of steroids. Cortisol is produced by the adrenal glands, located next to the kidneys, and adrenal glands are stimulated to produce cortisol by the pituitary gland located at the base of the brain. There are two types of Cushing's disease. In adrenal-dependent Cushing's disease (ADH), an adrenal gland overproduces cortisol because of an adrenal tumor. In pituitary-dependent Cushing's disease (PDH), the adrenal glands overproduce cortisol because they are overstimulated by a pituitary tumor.

Signs associated with Cushing's disease may include increased thirst and urination, a voracious appetite, an enlarged and sagging belly, hair loss, lethargy/weakness, panting, and sometimes, recurrent infections.

As the name implies Cushing's disease or Cushing's syndrome is a syndrome or disease state with a collection of clinical signs. Cushing's disease is a life-long medical management disease, and is not a disease that is "cured". The goal of medical treatment is to make the pet feel better. Many owners report after starting treatment for Cushing's disease their dog becomes more active, playful and even begins playing with toys they had previously lost interest in.

In human medicine the physician that most commonly suspects Cushing's Disease are psychiatrists. Many people with Cushing's Disease seek psychiatric care because they just feel bad and attribute their signs to depression. After discussing the patient's clinical signs these patients are often referred to an endocrinologist who eventually discover Cushing's disease. This is important to note because we may not be able to "cure" Cushing's disease, but we can work together to make your pet feel better and alleviate clinical signs.

Table 1 Clinical signs of Cushing's Disease

Common	Less Common	Uncommon
Polydipsia (increased thirst)	Lethargy	Thromboembolism
Polyuria (increased urination)	Hyperpigmentation of skin	Ligament Rupture
Polyphagia (excessive hunger)	Comedones	Facial nerve palsy
Panting	Thin Skin	Pseudomyotonia
Alopecia	Urine Leakage	Persistent anestrus
Abdominal distension	Poor Hair growth	Testicular atrophy

Hepatomegaly (liver enlargement)	Insulin resistant diabetes	
Muscle weakness and atrophy	Persistent or recurrent UTI's	
Systemic Hypertension	Persistent / recurrent skin infections	

## Diagnosis

Cushing's disease can be difficult to diagnose, especially in early cases. Diagnosis of Cushing's disease is achieved through history, physical exam identifying several clinical signs listed above as well as confirmatory laboratory tests. Tests that may be needed to diagnose Cushing's disease include:

- Complete blood count (CBC), chemistry panel and urinalysis: These blood and urine tests evaluate the general health of your pet and can help your veterinarian determine if other health problems should be suspected.
- Adrenocorticotrophic hormone (ACTH) stimulation test: This test involves a blood sample, an injection of a hormone (ACTH), an hour of waiting, and then another blood sample. This test is used to diagnose Cushing's disease in a pet.
- Low-dose dexamethasone suppression test: This test takes longer to perform than the ACTH stimulation test and takes place over 8 hours. It involves a blood sample, an injection of a steroid, a few hours of waiting, another blood sample at 4 hours, more waiting, and then another blood sample at 8 hours. This test is used to diagnose Cushing's disease. Sometimes this test can also determine where the problem is in the pet's body (i.e., pituitary or adrenal).
- High-dose dexamethasone suppression test (HDDST): This test is similar to the LDDST except that it uses a higher dose of dexamethasone. It is used to determine where the problem is in the pet's body (i.e. pituitary or adrenal).
- Endogenous adrenocorticotrophic (ACTH) assay, or ACTH level: This test involves a single blood sample. It is used to determine where the problem is in the pet's body (i.e. pituitary or adrenal).
- Radiographs, abdominal ultrasound, or CT scan: Radiographs can help us see changes in other organs that could indicate Cushing's. An abdominal ultrasound can help us see the adrenal glands. Sometimes, a CT scan can be performed to help us evaluate the pituitary gland at the base of the brain.

## **Treatment**

Treatment of Cushing's may be achieved through surgery (adrenalectomy or transphenoidal hypophysectomy) Pituitary irradiation, or medical treatment. Surgery and radiotherapy are complicated and rarely performed. Therefore, Medical Management is the most common and practical approach to managing Cushing's disease.

## **Vetoryl capsules (Trilostane)**

Vetoryl is the only FDA approved treatment for both Pituitary-Dependent Hyperadrenocorticism (PDH) and Adrenal-Dependent Hyperadrenocorticism (ADH) in dogs. Vetoryl contains Trilostane, which selectively and reversibly, inhibits the enzyme 3 $\beta$ -Hydroxysteroid Dehydrogenase which is involved in the production of several steroids including cortisol and Aldosterone. At current doses Vetoryl works to reduce the amount of circulating cortisol, which will lead to clinical improvement in many of the signs of HAC. Regulating Cushing's disease with Vetoryl is a process that will require frequent follow up testing. Once starting Vetoryl your veterinarian will recommend blood testing at 14 days, 30 days, then 90 days after starting this medication to ensure your pet is being adequately controlled. The dose of Vetoryl will be titrated to manage your pet. Your Veterinarian will also ask you to create a journal of clinical signs as they begin to improve to create a timeline. Once regulated a time may come where a dose change may be needed, and this journal will be crucial in catching these changes early. This journal should include, appetite, demeanor, water consumption and activity. If the pet is showing signs of illness, please contact your veterinarian immediately.

Typically, Vetoryl will be started once daily (75% of cases) at the same time every day and must be given with food. In some instances, your Veterinarian may start twice daily dosing of Vetoryl (25% of cases). For example, twice daily administration may be recommended in diabetics, cases of Calcinosis cutis, or if clinical signs are exceedingly severe.

Monitoring of Vetoryl therapy will typically consist of ACTH stimulation testing, blood chemistries, or resting cortisol levels. Depending on which test your veterinarian recommends, it will dictate when the Vetoryl is given. Please ensure you discuss this prior to dropping off for the test. In MOST cases we recommend dropping off your pet fasted, with their Vetoryl for our staff to administer. These tests typically are timed tests and can take up to 8 hours to complete.

Adverse reactions of Vetoryl that have been reported include anorexia, vomiting, lethargy, diarrhea, and weakness. In severe cases bloody diarrhea, collapse, hypoadrenocorticism and in rare circumstances death.

## **Lysodren:**

Lysodren has been a mainstay of treatment for years but has become harder and hard to find. It is convenient to use and relatively inexpensive, though it does have the potential for serious side effects. Because this medication has been in use for canine Cushing's disease for decades, many veterinarians have extensive experience with its use and with the monitoring tests needed to keep the dose in the therapeutic range. One of the disadvantages of Lysodren therapy is the need for regular monitoring blood tests. Too much Lysodren is toxic and too little is not going to control the Cushing's symptoms. Because of the potential for dose-dependent side effects, monitoring tests are especially important from a safety standpoint.

### ***How this Medication Works***

Lysodren should be considered to be a chemotherapy drug. It actually erodes the layers of the adrenal gland that produce corticosteroid hormones. The pituitary tumor continues to secrete excess stimulation, but the adrenal gland is no longer capable of excess hormone production in response. Instead, if everything has gone according to plan, the adrenal cortex will have been eroded away so as to yield normal - rather than excessive - cortisol production. Over several months all the symptoms of Cushing's syndrome resolve and the patient feels active and happy.

Problems result when too much of the adrenal cortex is eroded. Short-term Lysodren reactions are common (something like 30% of dogs will have one at some point), necessitating the use of a prednisone antidote pill that the veterinarian supplies. In event of such short term reactions, Lysodren® is discontinued until the adrenal gland can re-grow to the desired thickness and therapy is resumed, possibly at a lower dose. Sometimes excess adrenal erosion is permanent and the dog must be treated for cortisone deficiency. This is more serious and the potential for this kind of reaction has been the driving force behind the search for better medications to treat pituitary dependent Cushing's disease (though it is worth noting that in Europe it is common to purposely create a cortisol deficiency; see the section below on [Addison's Disease](#).)

### ***How this Medication is Used***

There are two phases to the treatment of Cushing's disease with Lysodren: an induction phase to gain control of the disease and a lower dose maintenance phase that ideally lasts for the animal's entire life.

#### ***Induction***

During induction, the pet owner receives a prescription for lysodren (usually obtained through a local human pharmacy) plus a bottle of [prednisone](#) tablets to be used as an antidote should any lysodren reactions erupt. Be sure you understand which pill is which. Lysodren is given twice a day with meals during this period so that the plump, excessively stimulated adrenal gland can be rapidly shaved down to the desired size. It is important that lysodren be given with food or it will not be absorbed into your dog's body. A test called an ACTH stimulation test (the same test which may have been used to

diagnose Cushing's disease originally) is used to confirm that the induction endpoint has been reached.

An approach gaining popularity involves reducing the dog's food intake by 30% the day before induction begins to ensure the dog is very hungry for induction. The food is restricted in this way throughout the induction period. The endpoint of induction is determined by a subtle reduction in the patient's appetite (looking up half way through eating the bowl of food, not running to the bowl as quickly as usual, not finishing the meal etc.) Should any of these signs be observed, this would indicate that the endpoint of induction has been reached and it is time for the ACTH stimulation test. Induction proceeds until endpoint has been reached but if 8 to 9 days have passed and a clear endpoint has not been observed, the dog should have the ACTH stimulation test at that time anyway

You should call your veterinarian if any of the following signs of induction endpoint are observed:

- Diarrhea or vomiting
- Appetite loss (this may be as subtle as less enthusiasm towards eating when the food is served, not running for the bowl etc.)
- Decrease in water consumption (it may be helpful for you to measure water consumption during the induction period)
- Lethargy or listlessness

If any of these signs occur, let your veterinarian know. It may be time for an early ACTH stimulation test or possibly even for an antidote pill. It is a good idea to maintain daily telephone contact with your vet after the third day or so of induction as it is at this point that a dog becomes at risk for reaching an early induction endpoint.

If none of the above signs are noted, then the ACTH Stimulation test proceeds as scheduled on the 8<sup>th</sup> or 9<sup>th</sup> day of induction. If this test indicates that sufficient adrenal erosion has taken place, then the Lysodren dose is given once or twice a week instead of twice a day and the dog has successfully entered maintenance. If the test indicates that more adrenal erosion is needed, induction continues. Most dogs are ready for maintenance within the first week of induction but others require more time, especially if they are taking other drugs that alter the metabolism of Lysodren. (Phenobarbital would be the obvious such medication.)

### ***Maintenance***

After achieving maintenance, another ACTH stimulation test is recommended after about a month and then twice a year or so thereafter. Approximately 50% of dogs will experience a relapse at some point and require a second round of induction.

- Full reversal of clinical signs associated with Cushing's disease can be expected after 4 to 6 months of Lysodren therapy. Usually the first, sign to show improvement is the excess water consumption. The last sign to show change will be hair re-growth.

- If appetite loss, vomiting, diarrhea or listlessness occur at any time during maintenance, a Lysodren reaction should be suspected. The veterinarian should be notified; it may be time for one of the prednisone antidote pills. A Lysodren reaction generally reverses within 30 minutes on an antidote pill

### **What is Addison's Disease/Addisonian Crisis?**

Addison's disease, also called hypoadrenocorticism, is the opposite of Cushing's disease; Addison's disease results from a deficiency of cortisone. If Lysodren® erodes away too much of the adrenal gland or if there is an idiosyncratic trilostane response, an Addisonian reaction occurs that can be temporary or permanent. The symptoms mentioned above (vomiting, diarrhea, listlessness, appetite loss) may be seen and if untreated, the patient can go into shock and die. If you suspect an Addisonian reaction is occurring, a dose of prednisone (which has hopefully been provided to keep on hand in case of emergency) should reverse the reaction within 30 minutes, or a couple of hours at most. If no response to prednisone is seen, the dog has some other illness. If the dog is back to normal after the prednisone dose, then contact the veterinarian for further instructions. The prednisone will likely have to be continued for a couple of weeks. In some cases, Addison's disease can be a permanent change. In that case it can be treated and managed.

### Follow up testing

Typically, we monitor Cushing's disease treatment with ACTH stimulation testing. The protocol to do this typically would include feeding and medicating your dog in the morning and then dropping them off at our hospital for a timed blood test. This test is best done at a specific time interval in relation to medication administration. This means your dog will typically spend 4-8 hours at the hospital and the doctor managing your pet's case will call in the following days with results.

### In summary.

1. Cushing's disease is challenging to diagnose and is based on clinical signs as well as blood testing results.
2. Cushing's disease is not curable but can be medically managed to make your pet feel better.
3. There will be frequent follow up blood tests at first to ensure adequate control of the disease.
4. We recommend you keep a journal of your pet's clinical signs through the treatment process to better help treat your pet.
5. If you have any questions, please contact your Veterinarian.