Dechra
Veterinary Products

Treat their Hyperadrenocorticism.
Help restore their vitality.

VETORYL® CAPSULES
(trilostane)

01TB-VET50030-0720

What is canine hyperadrenocorticism?

Canine hyperadrenocorticism (HAC), or Cushing's syndrome, is one of the most commonly diagnosed endocrinopathies in the dog.

Hyperadrenocorticism can be either iatrogenic or naturally occurring (spontaneous).

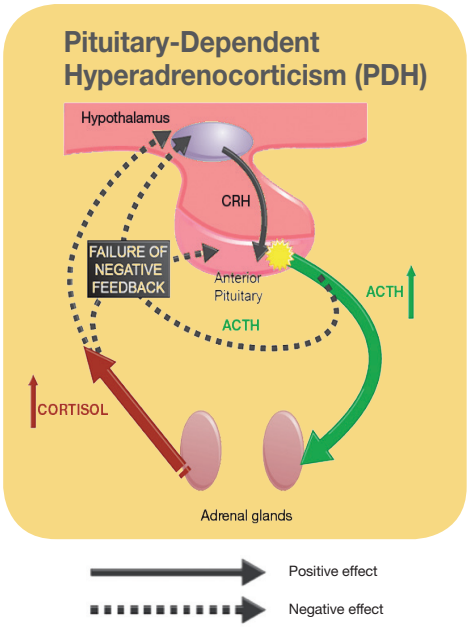
- Iatrogenic cases result from chronic administration of exogenous glucocorticoids.
- Spontaneous cases result from chronic and excessive production of glucocorticoids by the adrenal glands.

Prolonged exposure to high plasma concentrations of glucocorticoids, mainly cortisol, causes a complex of physical and biochemical changes.

Types of hyperadrenocorticism

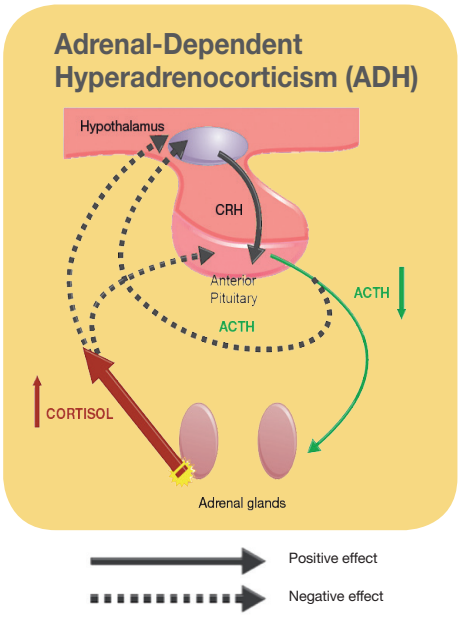
Most spontaneous cases of hyperadrenocorticism (80-85%) are caused by hypersecretion of ACTH (Adrenocorticotropic Hormone) by a lesion in the pituitary gland. The pituitary lesion is typically a microadenoma of the pars distalis. Macroadenomas are less common.

The overproduction of ACTH in the pituitary leads to bilateral adrenal hyperplasia and increased glucocorticoid (cortisol) secretion.



The remainder of spontaneous cases (15-20%) are caused by an autonomous glucocorticoid (cortisol) producing adrenocortical adenoma or carcinoma.

The hypersecretion of cortisol results in suppression of pituitary ACTH secretion and subsequent atrophy of non-tumorous adrenocortical tissue.



How to deal with hyperadrenocorticism - a three step approach

STEP 1 Diagnose | STEP 2 Treat | STEP 3 Monitor

STEP 1 Diagnose

Clinical Signs

The symptoms of hyperadrenocorticism (HAC) are fairly non-specific and never conclusive for diagnosing the disease.

Table 1. Clinical manifestations of canine HAC. Categorization of frequency is based on identification at the time of initial presentation[i].

Common	Less Common	Uncommon
Polydipsia	Lethargy	Thromboembolism
Polyuria	Hyperpigmentation of skin	Ligament rupture
Polyphagia	Comedones	Facial nerve palsy
Panting	Thin skin	Pseudomyotonia
Abdominal distention	Poor hair regrowth	Testicular atrophy
Endocrine alopecia	Urine leakage	Persistent anestrus
Hepatomegaly	Insulin-resistant diabetes mellitus	
Muscle weakness	Persistent or recurrent UTIs	
Systemic hypertension	Persistent or recurrent skin infections	

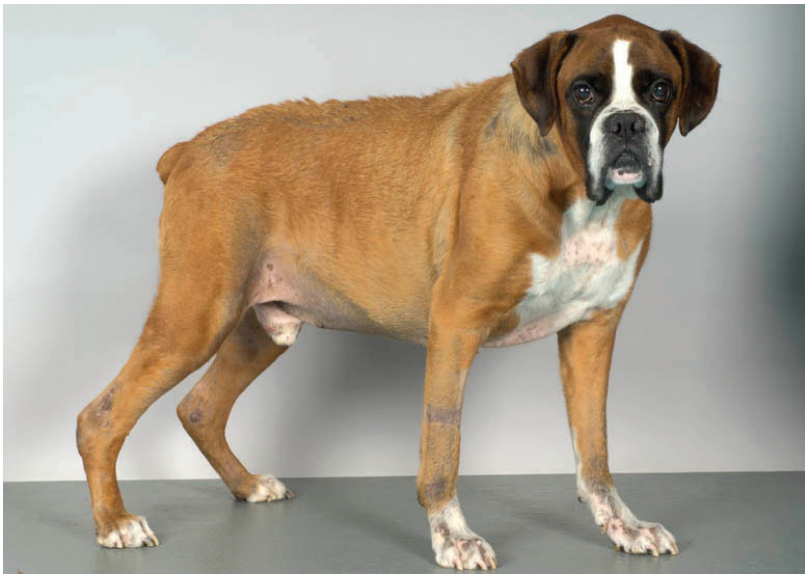
Table 2. Common laboratory abnormalities in dogs with HAC[i].

Complete Blood Count	Serum Biochemistry Panel	Urinalysis
Neutrophilic leukocytosis	Increased alkaline phosphatase	Specific gravity ≤1.018-1.020
Lymphopenia	Increased alanine aminotransferase	Proteinuria
Eosinopenia	Hypercholesterolemia	Indicators of urinary tract infection
Thrombocytosis	Hypertriglyceridemia	
Mild erythrocytosis	Hyperglycemia	

Eventually death may result from the complications of untreated HAC that can include diabetes mellitus, systemic hypertension, pancreatitis, urolithiasis, proteinuria, gallbladder mucocele formation and pulmonary thromboembolism[ii].

However, far before that, HAC will have significantly affected the quality of life of both the dog and its owner.

11-year-old Dachshund displaying typical signs of hyperadrenocorticism.



10-year-old Boxer displaying typical signs of hyperadrenocorticism.

Diagnosis of Spontaneous Canine Hyperadrenocorticism

A consensus statement[i] published in the Journal of Veterinary Internal Medicine in 2013 offers a consensus opinion on the diagnosis of spontaneous canine hyperadrenocorticism and the reader is advised to read the statement for further detail.

Clinical Presentation: Indications for Diagnostic Testing

- The possibility that a patient has hyperadrenocorticism (HAC) is based on the history and physical examination. Endocrine tests should be performed only when clinical signs consistent with HAC are present.
- The primary indication for pursuing a diagnosis of HAC is the presence of one or more of the common clinical signs and physical examination findings (Table 1).
- The more abnormalities identified, the stronger the indication to pursue endocrine testing.
- If less common clinical presentations are identified first, a thorough review of the history, physical examination findings, and routine laboratory test results (Table 2) often provides additional evidence for the disease.
- Failure to identify abnormalities listed in Tables 1 and 2 is a major negative indicator for the presence of HAC.

Abnormal biochemistry, hematology, urinalysis, and urine protein:creatinine (UPC) ratio results and blood pressure measurement by themselves are not indications to perform endocrine tests.

Diagnostic tests

No test for HAC has 100% diagnostic accuracy. Whichever test is chosen, the diagnostic value of the test will be significantly enhanced by performing endocrine testing only when clinical signs consistent with HAC are present.

Diagnosis of HAC depends on demonstration of either:

1) increased cortisol production or
2) decreased sensitivity of the hypothalamic-pituitary-adrenal axis (HPAA) to negative glucocorticoid feedback.

Any diagnostic test may be negative in a patient with HAC. If a test is negative but suspicion for HAC remains, another test should be performed. If more than one test is negative, the possibility that the patient does not have HAC must be considered. Alternatively, the patient may have mild HAC and the tests have not yet become positive. It may be worthwhile to retest in 3–6 months if clinical signs progress.

Confirming the diagnosis

Three endocrine diagnostic tests are available, all with particular advantages and disadvantages:

Summary based on the 2012 ACVIM Consensus Statement on the diagnosis of spontaneous canine hyperadrenocorticism[1].

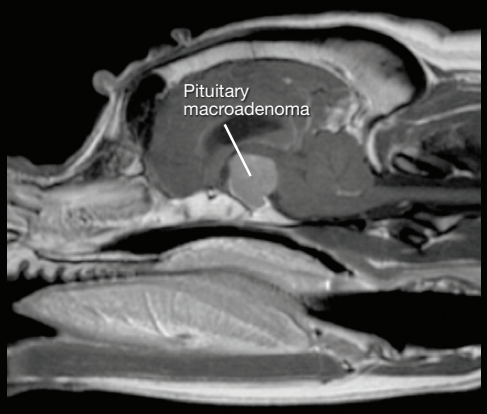
Test	Principles	Sensitivity and Specificity	Protocol	Notes
Urine Cortisol: Creatinine Ratio (UCCR)	Provides an integrated reflection of cortisol production, adjusting for fluctuations in blood concentrations A normal UCCR result is almost 100% consistent with the absence of Cushing's syndrome in the patient. Further endocrine testing is generally not recommended.	Sensitivity: 99% (95% CI, 94-100%) Specificity: 77% (95% CI, 64-87%)	To avoid the influence of stress and false positive results, urine should be collected at home, at least two days after a visit to a veterinary clinic Although a UCCR sample can be collected at any time of day, morning urine is preferred because it usually represents several hours of urine production	A sensitive test to detect cortisol hypersecretion The sensitivity and specificity of this test are greatly reduced when urine collected at a veterinary hospital is tested. (sensitivity ranges from 75-100% and specificity 20-25%) Specificity and sensitivity can be increased when urine from 2-3 days is pooled and collectively tested, and when the test is performed on dogs showing symptoms consistent with HAC
Low-Dose Dexamethasone Suppression (LDDS)	Evaluates the patient's negative feedback mechanism of the hypothalamic/ pituitary/adrenal axis (HPPA) Dogs with HAC have a diminished ability to decrease cortisol production	Sensitivity: 85-100% Specificity: 44-73%	The LDDST should be performed using 0.01-0.015 mg/kg dexamethasone sodium phosphate or polyethylene glycol IV; calculate dose using the parent compound and not the salt Obtain blood samples before dexamethasone administration and 4 and 8 hours after	The ACVIM panel considers the LDDST as the screening test of choice, unless latrogenic HAC is suspected The cortisol concentration 8 hours after dexamethasone administration is evaluated to determine if the patient has cortisol overproduction consistent with HAC If the 8 hour cortisol value is elevated, the 4 hour value can help differentiate between PDH and ADH
ACTH Stimulation	Assesses adrenocortical reserve and is the gold standard for diagnosis of iatrogenic HAC Patients with HAC often have an exaggerated response to ACTH administration	Sensitivity: 57-95% (all forms of spontaneous HAC) 57-63% (ADH) 80-83% (PDH) Specificity: 59-93%	Perform the test using 5 µg/kg of synthetic ACTH with blood samples drawn before and 60 minutes after administration The ACVIM panel prefers IV administration	The gold standard for diagnosis of iatrogenic HAC and monitoring of patients with HAC once they have started treatment Because of its lower sensitivity, its diagnostic usefulness as a confirmatory test for spontaneous HAC is inferior to the LDDST

[1] Behrend et al (2013) Diagnosis of Spontaneous Canine Hyperadreonocorticism: 2012 ACVIM Consensus Statement (Small Animal) JVIM 1-13

Differentiating between types

It is necessary to differentiate between Pituitary Dependent Hyperadrenocorticism (PDH) and Adrenal Dependent Hyperadrenocorticism (ADH) to provide a more accurate prognosis and enable the full range of possible treatments to be discussed with the dog's owner.

Discriminatory tests available to differentiate between PDH and ADH include the low- and high-dose dexamethasone suppression tests, ultrasonography, and advanced imaging such as MRI and CT, and measurement of endogenous ACTH.



MRI image from a Boxer dog with a pituitary macroadenoma (image courtesy of Ruth Dennis, The Animal Health Trust, UK)

Diagnostic summary

A confident diagnosis requires consistent endocrine confirmatory test results in a dog with clinical signs compatible with hyperadrenocorticism.

STEP 2

Treat

Treatment of hyperadrenocorticism (HAC) may be achieved by surgery (adrenalectomy or trans-sphenoidal hypophysectomy), pituitary irradiation, or medical treatment. Surgery and radiotherapy are complicated procedures available only at a few specialty centers, therefore medical treatment is often the most practical and approachable treatment choice.

VETORYL® CAPSULES
(trilostane)

- VETORYL Capsules are the only FDA approved pharmaceutical for the treatment of Pituitary-Dependent Hyperadrenocorticism (PDH) and Adrenal-Dependent Hyperadrenocorticism (ADH) in dogs.
- VETORYL Capsules contain trilostane, which selectively, and reversibly, inhibits the enzyme 3ß-hydroxysteroid dehydrogenase, which is involved in the synthesis of several steroids including cortisol and aldosterone.
- At recommended dose rates, VETORYL Capsules tend to have a more selective effect on glucocorticoid production[iii], however the potential inhibition of aldosterone must always be borne in mind by the attending clinician.
- VETORYL Capsules reduce circulating cortisol levels, leading to improvement in many of the clinical signs of HAC.
- VETORYL Capsules provide flexible and accurate dosing with five strengths (5 mg, 10 mg, 30 mg, 60 mg and 120 mg capsules), allowing you to restore the dog's vitality by reducing the clinical signs associated with HAC.
- Available in blister packs of 30 capsules for ease of dispensing.

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

Approved by FDA under NADA # 141-291.

Important dosage and administration information

VETORYL® CAPSULES (trilostane) should be administered orally, once daily, with food.

The starting dose is 1-3 mg/lb (2.2-6.7 mg/kg) once a day for the treatment of hyperadrenocorticism in dogs. Start with the lowest possible dose based on body weight and available combinations of capsule sizes.

Once treatment has started, the owner should be advised to monitor the dog's demeanor, appetite and water intake. If the dog shows any signs of being unwell, advise the owner to stop treatment and contact a veterinarian immediately.

The dose should be titrated according to individual response as determined by monitoring of clinical signs, physical examination and laboratory test results (ACTH stimulation test and serum biochemistry, including electrolytes).

Should symptoms not be adequately controlled for an entire 24 hour inter-dose period, consideration should be given to dosing with VETORYL Capsules twice daily.

For further information please refer to the treatment and monitoring flowchart and the full prescribing information.

VETORYL Capsules give you the power to treat PDH and ADH in dogs with the quality assurance and consistency of content and bioavailability that comes with FDA approval. Every VETORYL Capsule will deliver an accurate amount of trilostane to your patient that has proven dissolution, bioavailability and pharmacokinetics. The dose can be altered as necessary, according to both clinical signs and monitoring test results.

Most studies on trilostane have examined dogs that are started on once daily administration.

A few studies[iv,v,vi,vii] have shown that dogs can be started on trilostane twice daily. However there is no evidence that doing so improves the outcome. Speed of response may improve, but side effects may increase.

Current evidence would suggest that about 25% of dogs require twice daily trilostane. Conversely 75% of dogs will respond well to once daily dosing.

STEP 3

Monitor

The dose of VETORYL® CAPSULES (trilostane) should be titrated according to individual response as determined by monitoring of clinical signs, physical examination and laboratory test results (ACTH stimulation test and serum biochemistry, including electrolytes).

Once treatment with VETORYL Capsules has been initiated, samples should be taken for biochemistry (including electrolytes) and an ACTH stimulation test 10-14 days later, 30 days later, 90 days later and every 3 months thereafter.

After the administration of VETORYL Capsules with food, cortisol levels are most significantly suppressed for 3 to 8 hours. Therefore, in order to obtain results at the peak time of effect, the ACTH stimulation test should be performed at 4-6 hours post-dosing. This will ensure you are assessing the dog's cortisol levels when they will be at their lowest, thus uncovering any unintended oversuppression of the adrenal glands that would indicate the need to decrease the dose.

A positive response to the administration of VETORYL Capsules will manifest as an improvement in clinical signs and post-ACTH serum cortisol concentration between 1.45-9.1 µg/dL (4-6 hours after dosing with food).

For detailed information on monitoring dogs treated with VETORYL Capsules and guidance on dose changes, please refer to the monitoring and treatment flowchart and the full prescribing information.

Important details to remember:

- **VETORYL Capsules should be administered with food as this enhances the absorption of trilostane.**
- **Monitoring is important because patients may need lower doses of VETORYL Capsules after they have been on treatment for a period of time.**
- **VETORYL Capsules should be administered on the morning of the follow-up ACTH stimulation testing. Due to the peak time of action of trilostane, an ACTH stimulation test should be performed 4-6 hours after administration of VETORYL Capsules with food.**
- **Hypoadrenocorticism ('Addisonian crisis') is a known adverse reaction.**

Treatment and Monitoring of Hyperadrenocorticism

DAY 1

Start VETORYL® CAPSULES (trilostane) at approximately 1 mg/lb (2.2 mg/kg) once daily as per prescribing information

Give daily by mouth with food in the morning.

DAY 10-14

History, physical examination, serum biochemistry, with electrolytes

Perform ACTH stimulation test 4-6 hours after morning capsule

Ensure morning capsule was given with food

Post-ACTH serum cortisol <1.45 µg/dL (<40 nmol/L) and clinically well

Stop VETORYL Capsules for approximately 7 days

RETURN TO DAY 1 and administer a LOWER DOSE

Repeat ACTH stimulation test in 10-14 days after restarting lower dose

Post-ACTH serum cortisol >1.45 µg/dL (>40 nmol/L) and clinically well

Continue treatment at current dose

It is not recommended to increase dose yet, even if cortisol is >9.1 µg/dL

≥30 DAYS FROM INITIATION OF TREATMENT

History, physical examination, serum biochemistry, with electrolytes

ACTH stimulation test 4-6 hours after morning capsule given with food

Assess degree of clinical improvement

Showing clinical signs consistent with:

1. **Corticosteroid withdrawal syndrome** ("relative" cortisol deficiency characterized by weakness, lethargy, stiff gait, anorexia, fever during first 10 days of therapy)
2. **Hypoadrenocorticism** (*e.g.*, anorexia, lethargy/depression, weakness, shaking/shivering, vomiting, diarrhea, bradycardia, collapse)

STOP VETORYL TREATMENT

Confirm whether clinical signs are due to hypoadrenocorticism with ACTH stimulation test and analysis of serum electrolytes (in particular Na+ and K+)

Treat symptomatically as required, *e.g.*

- dexamethasone to treat hypocortisolemia
- IV 0.9% NaCl to resolve hyperkalemia

SIGNIFICANT IMPROVEMENT

Post-ACTH serum cortisol <1.45 µg/dL (<40 nmol/L) and clinically well

Stop VETORYL Capsules for 7 days depending on the severity of the clinical signs and then

RETURN TO DAY 1 AT LOWER DOSE

Post-ACTH serum cortisol 1.45-5.4 µg/dL (40-150 nmol/L)

Continue treatment at current dose

Post-ACTH serum cortisol >5.4-9.1 µg/dL (>150-250 nmol/L)

Continue on current dose but monitor clinical signs carefully for recurrence

Post-ACTH serum cortisol >9.1 µg/dL (>250 nmol/L)

Continue current dose and recheck in 1-3 months OR RETURN TO DAY 1 and increase morning dose

Continue monitoring history, physical examination, electrolytes and ACTH stimulation test every 90 days.

If dose is altered always recheck ACTH stimulation again 10-14 days later

CLINICAL SIGNS NOT FULLY CONTROLLED

Rule out concurrent illness

If clinical signs are not controlled for a full 24 hour period, twice daily dosing or a dosage increase may be indicated

Post-ACTH serum cortisol >5.4 µg/dL (>150 nmol/L)

Increase dose

RETURN TO DAY 1

To change to twice daily dosing, use combinations of capsule sizes to split the current daily dose into two doses.

If Post-ACTH serum cortisol >9.1 µg/dL (>250 nmol/L), total daily dose can be slowly increased and split into two doses

Continue to monitor as per approved label recommendations

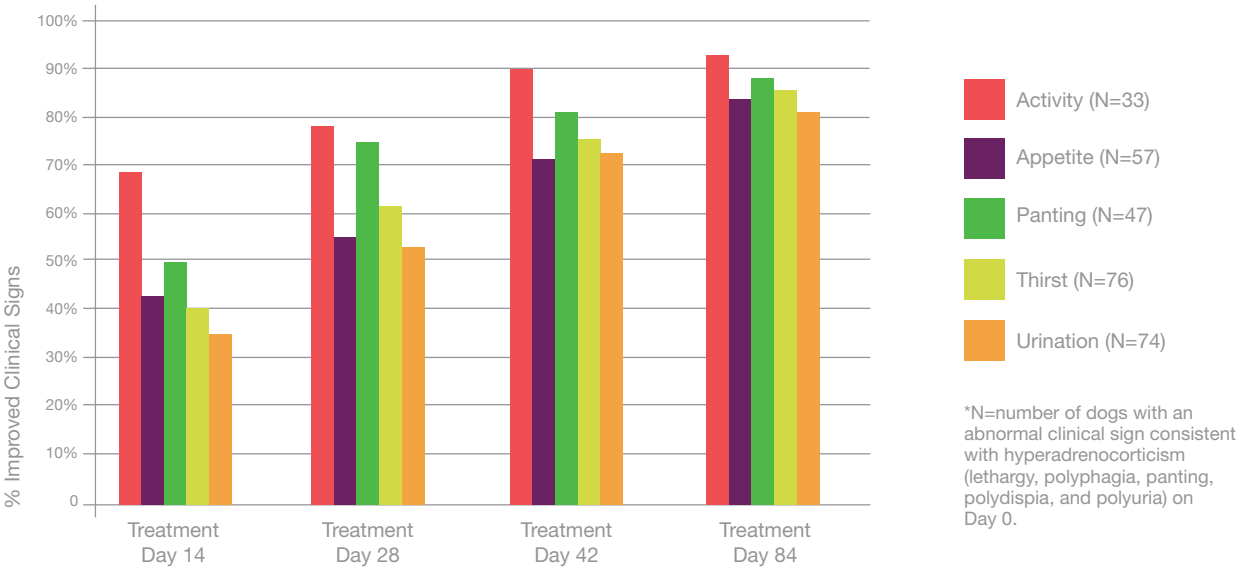
Perform ACTH stimulation test 4-6 hours post morning capsule

If you have questions at any point during patient management, contact Dechra Veterinary Technical Services at (866) 933-2472

Efficacy of VETORYL® CAPSULES (trilostane) treatment

Daily administration of VETORYL Capsules can greatly reduce the clinical signs associated with Cushing's syndrome, helping to restore the dog's vitality. Clinical studies demonstrated that treatment with VETORYL Capsules resulted in decreased thirst, decreased frequency of urination, decreased panting, and improvement of appetite and activity.[viii] Activity levels began to show improvement within 14 days of treatment.

Percentages of Dogs with Improved Clinical Signs of HAC After Treatment with VETORYL Capsules as Compared to Day 0



*N=number of dogs with an abnormal clinical sign consistent with hyperadrenocorticism (lethargy, polyphagia, panting, polydispia, and polyuria) on Day 0.

Improvement of clinical signs such as polydipsia, polyuria, polyphagia, panting and lethargy occurs shortly after the start of treatment. Skin, coat and muscle changes take longer to reverse (usually 3-9 months).

As with all drugs, side effects may occur. In field studies and post-approval experience, the most common side effects reported were: anorexia, lethargy/depression, vomiting, diarrhea, elevated liver enzymes, elevated potassium with or without decreased sodium, elevated BUN, decreased Na/K ratio, hypoadrenocorticism, weakness, elevated creatinine, shaking, and renal insufficiency. **In some cases, death has been reported as an outcome of these adverse events.** VETORYL Capsules are not for use in dogs with primary hepatic or renal disease, or in pregnant dogs. Refer to the prescribing information for complete details or visit www.dechra-us.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

What you can expect to see

First recheck at 10-14 days

Owners should have noticed that the dog is drinking and urinating less. The animal should be less ravenous and excessive panting should have reduced. Lethargy is another clinical sign of hyperadrenocorticism that rapidly responds to treatment; even at the first 10-14 day check many owners have noticed that their dog has more energy.

Re-examination at 90 days

Abdominal girth reducing, thus pot belly appearance diminishing. Increased muscle tone and strength. Some hair regrowth may be noticeable.

6 months after starting treatment

Most clinical signs of hyperadrenocorticism should have improved or resolved.

At the end of Dechra's 6 month clinical trial of 60 dogs, no more than 15% of dogs exhibited any of the clinical signs associated with hyperadrenocorticism.

Photographs courtesy of Carlos Mellan, DVM, PhD

If cortisol levels have normalized and the dog is still excessively urinating, check a urinalysis for signs of a silent urinary tract infection (UTI). Dogs with HAC often have silent UTIs that left untreated can cause the polyuria to continue even after the cortisol levels have been controlled.

Additional support for patients with hyperadrenocorticism

Hyperadrenocorticism requires medical or surgical intervention to treat the cortisol overproduction. Some of the common dermatological complications of HAC may benefit from additional supportive measures. Dechra offers a complete line of products to support the restoration of a healthy skin and coat.

MICONAHEX+Triz® Shampoo

A unique combination of 2% miconazole, 2% chlorhexidine, patented USP TrizEDTA®, and ceramide complex

- Miconazole and chlorhexidine provide antibacterial and antifungal activity to aid in the topical therapy of skin conditions
- Potentiated with the antibacterial activity of TrizEDTA® plus epidermal barrier repair therapy with the addition of ceramides

MICONAHEX+Triz® Spray, Mousse and Wipes

- 2% miconazole, 2% chlorhexidine, TrizEDTA® and ceramide complex
- Available in an easy to use leave-on spray or mousse for use between baths
- Available in convenient therapeutic wipes for those harder to reach areas like between the toes and in skin folds.

DERMALLAY™ Oatmeal Shampoo

- A soothing, moisturizing oatmeal shampoo
- Useful in restoring coat condition and moisturizing the skin

DERMALLAY™ Oatmeal Spray Conditioner

- A soothing, leave-on oatmeal spray conditioner
- Useful in restoring coat condition and moisturizing the skin

EICOSA3FF® SnipCaps

- Omega-3 fatty acids, DHA and EPA, in the free fatty acid form
- Omega-3 fatty acids can alter the production of eicosanoids & cytokines & support the immune response

DERMALYTE® Shampoo

- Safflower oil (linoleic acid) aids in skin moisture retention and soothes dry, itchy skin.
- Ceramide complex aids in moisturizing, repairing, and restoring dry, damaged skin.

Dechra Veterinary Technical Services

24-hour support available at (866) 933-2472 or contact us at support@dechra.com for non-urgent questions or concerns.

References

i Behrend *et al* (2013) Diagnosis of Spontaneous Canine Hyperadrenocorticism: 2012 ACVIM Consensus Statement (Small Animal) JVIM 1-13

ii Mooney (2009) Hyperadrenocorticism - to treat or not to treat? UK Vet **14(6):** 1-5

iii Wenger et al (2004) Effects of trilostane on serum concentrations of aldosterone, cortisol and potassium in dogs with pituitary-dependent hyperadrenocorticism. AJVR **65(9):** 245-50

iv Vaughan *et al* (2008) Evaluation of twice-daily, low dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism. JAVMA **232(9):** 1321-132

v Feldman (2011) Evaluation of twice-daily lower-dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism. JAVMA **238:** 1441-1451

vi Augusto *et al* (2012) A comparison of once and twice daily administration of trilostane to dogs with hyperadrenocorticism. *Tierarztliche Praxis Kleintiere* **40:** 415-424

vii Cho *et al* (2013) Efficacy of low- and high-dose trilostane treatment in dogs (< 5 kg) with pituitary-dependent hyperadrenocorticism. JVIM **27:** 91-98

viii http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm049823.htm (accessed December 2014)

Treat their Cushing's Syndrome. Help restore their vitality.

VETORYL® CAPSULES
(trilostane)

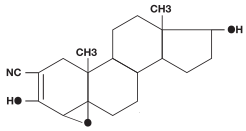
www.dechra-us.com

VETORYL® CAPSULES
(trilostane)

Adrenocortical suppressant for oral use in dogs only.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: VETORYL Capsules are available in 5 sizes (5, 10, 30, 60 and 120 mg) for oral administration based on body weight. Trilostane (4α,5α-epoxy-17β-hydroxy-3-oxoandrostane-2α-carbonitrile) is an orally active synthetic steroid analogue that selectively inhibits 3 β-hydroxysteroid dehydrogenase in the adrenal cortex, thereby inhibiting the conversion of pregnenolone to progesterone. This inhibition blocks production of glucocorticoids and to a lesser extent, mineralocorticoids and sex hormones while steroid precursor levels increase. The structural formula is:



INDICATIONS: VETORYL Capsules are indicated for the treatment of pituitary-dependent hyperadrenocorticism and adrenal-dependent hyperadrenocorticism in dogs.

DOSAGE AND ADMINISTRATION: Always provide the Client Information Sheet with prescription (see **INFORMATION FOR DOG OWNERS**).

1. Starting dose. The starting dose for the treatment of hyperadrenocorticism in dogs is 1-3 mg/lb (2.2-6.7 mg/kg) once a day. Start with the lowest possible dose based on body weight and available combinations of capsule sizes. VETORYL Capsules should be administered with food.

2. Action at 10-14 day evaluation (Table 1). After approximately 10-14 days at this dose, re-examine the dog and conduct a 4-6 hour post-dosing ACTH stimulation test and serum biochemical tests (with particular attention to electrolytes, and renal and hepatic function). If physical examination is acceptable, take action according to Table 1.

Owners should be instructed to stop therapy and contact their veterinarian immediately in the event of adverse reactions such as vomiting, diarrhea, lethargy, poor/reduced appetite, weakness, collapse or any other unusual developments. If these clinical signs are observed, conduct an ACTH stimulation test and serum biochemical tests (with particular attention to electrolytes, and renal and hepatic function).

Table 1: Action at 10-14 day evaluation

Post-ACTH serum cortisol		
µg/dL	**nmol/L**	**Action**
< 1.45	< 40	Stop treatment. Re-start at a decreased dose
1.45 to 5.4	40 to 150	Continue on same dose
>5.4 to 9.1	> 150 to 250	EITHER: Continue on current dose if clinical signs are well controlled OR: Increase dose if clinical signs of hyperadrenocorticism are still evident*
> 9.1	> 250	Increase initial dose

***Combinations of capsule sizes should be used to slowly increase the once daily dose.**

3. Individual dose adjustments and close monitoring are essential. Re-examine and conduct an ACTH stimulation test and serum biochemical tests (with particular attention to electrolytes, and renal and hepatic function) 10-14 days after every dose alteration. Care must be taken during dose increases to monitor the dog's clinical signs.

Once daily administration is recommended. However, if clinical signs are not controlled for the full day, twice daily dosing may be needed. To switch from a once daily dose to a twice daily dose, the total daily dose should be divided into 2 portions given 12 hours apart. It is not necessary for the portions to be equal. If applicable, the larger dose should be administered in the morning and the smaller dose in the evening. For example, a dog receiving 90 mg would receive 60 mg in the morning, and 30 mg in evening.

4. Long term monitoring. Once an optimum dose of VETORYL Capsules has been reached, re-examine the dog at 30 days, 90 days and every 3 months thereafter. At a minimum, this monitoring should include: • A thorough history and physical examination.
• An ACTH stimulation test (conducted 4-6 hours after VETORYL Capsule administration) - a post-ACTH stimulation test resulting in a cortisol of < 1.45 µg/dL (< 40 nmol/L), with or without electrolyte abnormalities, may precede the development of clinical signs of hypoadrenocorticism.
• Serum biochemical tests (with particular attention to electrolytes, and renal and hepatic function).
Good control is indicated by favorable clinical signs as well as post-ACTH serum cortisol of 1.45-9.1 µg/dL (40-250 nmol/L).

If the ACTH stimulation test is < 1.45 µg/dL (< 40 nmol/L) and/or if electrolyte imbalances characteristic of hypoadrenocorticism (hyperkalemia and hyponatremia) are found, VETORYL Capsules should be temporarily discontinued until recurrence of clinical signs consistent with hyperadrenocorticism and ACTH stimulation test results return to normal (1.45-9.1 µg/dL or 40-250 nmol/L). VETORYL Capsules may then be re-introduced at a lower dose.

CONTRAINDICATIONS: The use of VETORYL Capsules is contraindicated in dogs that have demonstrated hypersensitivity to trilostane. Do not use VETORYL Capsules in animals with primary hepatic disease or renal insufficiency (See **WARNINGS** and **PRECAUTIONS**). Do not use in pregnant dogs. Studies conducted with trilostane in laboratory animals have shown teratogenic effects and early pregnancy loss.

WARNINGS: Hypoadrenocorticism can develop at any dose of VETORYL Capsules. In some cases, it may take months for adrenal function to return and some dogs never regain adequate adrenal function.

All dogs should undergo a thorough history and physical examination before initiation of therapy with VETORYL Capsules. Other conditions, such as primary hepatic and/or renal disease should be considered when the patient is exhibiting signs of illness in addition to signs of hyperadrenocorticism (e.g. vomiting, diarrhea, poor/reduced appetite, weight loss, and lethargy). Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of VETORYL Capsules should be considered.

Owners should be advised to discontinue therapy immediately and contact their veterinarian if signs of potential drug toxicity are observed (see INFORMATION FOR DOG OWNERS, DOSAGE AND ADMINISTRATION, PRECAUTIONS, ADVERSE REACTIONS, ANIMAL SAFETY and POST-APPROVAL EXPERIENCE).

In case of overdosage, symptomatic treatment of hypoadrenocorticism with corticosteroids, mineralocorticoids and intravenous fluids may be required.

Angiotensin converting enzyme (ACE) inhibitors should be used with caution with VETORYL Capsules, as both drugs have aldosterone-lowering effects which may be additive, impairing the patient's ability to maintain normal electrolytes, blood volume and renal perfusion. Potassium sparing diuretics (e.g. spironolactone) should not be used with VETORYL Capsules as both drugs have the potential to inhibit aldosterone, increasing the likelihood of hyperkalemia.

HUMAN WARNINGS: Keep out of reach of children. Not for human use.

Wash hands after use. Do not empty capsule contents and do not attempt to divide the capsules. Do not handle the capsules if pregnant or if trying to conceive. Trilostane is associated with teratogenic effects and early pregnancy loss in laboratory animals. In the event of accidental ingestion/overdose, seek medical advice immediately and take the labeled container with you.

PRECAUTIONS: Mitotane (o,p'-DDD) treatment will reduce adrenal function. Experience in foreign markets suggests that when mitotane therapy is stopped, an interval of at least one month should elapse before the introduction of VETORYL Capsules. It is important to wait for both the recurrence of clinical signs consistent with hyperadrenocorticism, and a post-ACTH cortisol level of > 9.1 µg/dL (> 250 nmol/L) before treatment with VETORYL Capsules is initiated. Close monitoring of adrenal function is advised, as dogs previously treated with mitotane may be more responsive to the effects of VETORYL Capsules.

The use of VETORYL Capsules will not affect the adrenal tumor itself. Adrenalectomy should be considered as an option for cases that are good surgical candidates. The safe use of this drug has not been evaluated in lactating dogs and males intended for breeding.

ADVERSE REACTIONS: The most common adverse reactions reported are poor/reduced appetite, vomiting, lethargy/dullness, diarrhea, and weakness. Occasionally, more serious reactions, including severe depression, hemorrhagic diarrhea, collapse, hypoadrenocortical crisis or adrenal necrosis/rupture may occur, and may result in death.

In a US field study with 107 dogs, adrenal necrosis/rupture (two dogs) and hypoadrenocorticism (two dogs) were the most severe adverse reactions in the study. One dog died suddenly of adrenal necrosis, approximately one week after starting trilostane therapy. One dog developed an adrenal rupture, believed to be secondary to adrenal necrosis, approximately six weeks after starting trilostane therapy. This dog responded to trilostane discontinuation and supportive care.

Two dogs developed hypoadrenocorticism during the study. These two dogs had clinical signs consistent with hypoadrenocorticism (lethargy, anorexia, collapse) and post-ACTH cortisol levels ≤ 0.3 µg/dL. Both dogs responded to trilostane discontinuation and supportive care, and one dog required continued treatment for hypoadrenocorticism (glucocorticoids and mineralocorticoids) after the acute presentation.

Additional adverse reactions were observed in 93 dogs. The most common of these included diarrhea (31 dogs), lethargy (30 dogs), inappetence/anorexia (27 dogs), vomiting (28 dogs), musculoskeletal signs (lameness, worsening of degenerative joint disease (25 dogs), urinary tract infection (UTI)/hematuria (17 dogs), shaking/shivering (10 dogs), otitis externa (8 dogs), respiratory signs (coughing, congestion) (7 dogs), and skin/coat abnormality (seborrhea, pruritus) (8 dogs).

Five dogs died or were euthanized during the study (one dog secondary to adrenal necrosis, discussed above, two dogs due to progression of pre-existing congestive heart failure, one dog due to progressive central nervous system signs, and one dog due to cognitive decline leading to inappropriate elimination). In addition to the two dogs with adrenal necrosis/rupture and the two dogs with hypoadrenocorticism, an additional four dogs were removed from the study as a result of possible trilostane-related adverse reactions, including collapse, lethargy, inappetence, and trembling.

Complete blood counts conducted pre- and post-treatment revealed a statistically significant ($p < 0.005$) reduction in red cell variables (HCT, HGB, and RBC), but the mean values remained within the normal range. Additionally, approximately 10% of the dogs had elevated BUN values (≥ 40 mg/dL) in the absence of concurrent creatinine elevations. In general, these dogs were clinically normal at the time of the elevated BUN.

In a long term follow-up study of dogs in the US effectiveness study, the adverse reactions were similar to the short term study. Vomiting, diarrhea and general gastrointestinal signs were most commonly observed. Lethargy, inappetence/anorexia, heart murmur or cardiopulmonary signs, inappropriate urination/incontinence, urinary tract infections or genitourinary disease, and neurological signs were reported. Included in the US follow-up study were 14 deaths, three of which were possibly related to trilostane. Eleven dogs died or were euthanized during the study for a variety of conditions considered to be unrelated to or to have an unknown relationship with administration of trilostane.

In two UK field studies with 75 dogs, the most common adverse reactions seen were vomiting, lethargy, diarrhea/loose stools, and anorexia. Other adverse reactions included: nocturia, corneal ulcer, cough, persistent estrus, vaginal discharge and vulvar swelling in a spayed female, hypoadrenocorticism, electrolyte imbalance (elevated potassium with or without decreased sodium), collapse and seizure, shaking, muscle tremors, constipation, scratching, weight gain, and weight loss. One dog died of congestive heart failure and another died of pulmonary thromboembolism. Three dogs were euthanized during the study. Two dogs had renal failure and another had worsening arthritis and deterioration of appetite.

In a long term follow-up of dogs included in the UK field studies, the following adverse reactions were seen: hypoadrenocortical episode (including syncope, tremor, weakness, and vomiting), hypoadrenocortical crisis or renal failure (including azotemia, vomiting, dehydration, and collapse), chronic intermittent vaginal discharge, hemorrhagic diarrhea, occasional vomiting, and distal limb edema. Signs of hypoadrenocorticism were usually reversible after withdrawal of the drug, but may be permanent. One dog discontinued VETORYL Capsules and continued to have hypoadrenocorticism when evaluated a year later. Included in the follow-up were reports of deaths, at least 5 of which were possibly related to use of VETORYL Capsules. These included dogs that died or were euthanized because of renal failure, hypoadrenocortical crisis, hemorrhagic diarrhea, and hemorrhagic gastroenteritis.

Foreign Market Experience: The following events were reported voluntarily during post-approval use of VETORYL Capsules in foreign markets. The most serious adverse events were death, adrenal necrosis, hypoadrenocorticism (electrolyte alterations, weakness, collapse, anorexia, lethargy, vomiting, diarrhea, and azotemia), and corticosteroid withdrawal syndrome (weakness, lethargy, anorexia, and weight loss). Additional adverse events included: renal failure, diabetes mellitus, pancreatitis, autoimmune hemolytic anemia, vomiting, diarrhea, anorexia, skin reactions (rash, erythematous skin eruptions), hind limb paresis, seizures, neurological signs from growth of macroadenomas, oral ulceration, and muscle tremors.

POST-APPROVAL EXPERIENCE: As of June 2013, the following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data. The following adverse events are listed in decreasing order of reporting frequency: anorexia, lethargy/depression, vomiting, diarrhea, elevated liver enzymes, elevated potassium with or without decreased sodium, elevated BUN, decreased Na/K ratio, hypoadrenocorticism, weakness, elevated creatinine, shaking, renal insufficiency. **In some cases, death has been reported as an outcome of the adverse events listed above.**
For a cumulative listing of adverse reactions for trilostane reported to the CVM see: http://www.fda.gov/ADEreports

This listing includes Adverse Events reported to CVM for products, such as VETORYL Capsules, that contain the active ingredient trilostane. Listings by active ingredient may represent more than one brand name.

To report suspected adverse events and/or obtain a copy of the SDS or for technical assistance, call Dechra Veterinary Products at (866) 933-2472.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at: http://www.fda.gov/reportanimalae

INFORMATION FOR DOG OWNERS: Owners should be aware that the most common adverse reactions may include: an unexpected decrease in appetite, vomiting, diarrhea, or lethargy and should receive the Client Information Sheet with the prescription. Owners should be informed that control of hyperadrenocorticism should result in resolution of polyphagia, polyuria and polydipsia. **Serious adverse reactions associated with this drug can occur without warning and in some cases result in death (see ADVERSE REACTIONS and POST-APPROVAL EXPERIENCE).**

Owners should be advised to discontinue VETORYL Capsules and contact their veterinarian immediately if signs of intolerance such as vomiting, diarrhea, lethargy, poor/reduced appetite, weakness, or collapse are observed. Owners should be advised of the importance of periodic follow-up for all dogs during administration of VETORYL Capsules.

CLINICAL PHARMACOLOGY: Trilostane absorption is enhanced by administration with food. In healthy dogs, maximal plasma levels of trilostane occur within 1.5 hours, returning to baseline levels within twelve hours, although large inter-dog variation occurs. There is no accumulation of trilostane or its metabolites over time.

EFFECTIVENESS: Eighty-three dogs with hyperadrenocorticism were enrolled in a multi-center US field study. Additionally, 30 dogs with hyperadrenocorticism were enrolled in two UK field studies. Results from these studies demonstrated that treatment with VETORYL Capsules resulted in an improvement in clinical signs (decreased thirst, decreased frequency of urination, decreased panting, and improvement of appetite and activity). Improvement in post-ACTH cortisol levels occurred in most cases within 14 days of starting VETORYL Capsules therapy.

In these three studies, there were a total of 10 dogs diagnosed with hyperadrenocorticism due to an adrenal tumor or due to concurrent pituitary and adrenal tumors. Evaluation of these cases failed to demonstrate a difference in clinical, endocrine, or biochemical response when compared to cases of pituitary-dependent hyperadrenocorticism.

ANIMAL SAFETY: In a laboratory study, VETORYL Capsules were administered to 8 healthy 6 month old Beagles per group at 0X (empty capsules), 1X, 3X, and 5X the maximum starting dose of 6.7 mg/kg twice daily for 90 days. Three animals in the 3X group (receiving 20.1 mg/kg twice daily) and five animals in the 5X group (receiving 33.5 mg/kg twice daily) died between Days 23 and 46. They showed one or more of the following clinical signs: decreased appetite, decreased activity, weight loss, dehydration, soft stool, slight muscle tremors, diarrhea, lateral recumbency, and staggering gait. Bloodwork showed hyponatremia, hyperkalemia, and azotemia, consistent with hypoadrenocortical crisis. Post-mortem findings included epithelial necrosis or cystic dilation of duodenal mucosal crypts, gastric mucosal or thymic hemorrhage, atrial thrombosis, pyelitis and cystitis, and inflammation of the lungs.

ACTH stimulated cortisol release was reduced in all dogs treated with VETORYL Capsules. The dogs in the 3X and 5X groups had decreased activity. The 5X dogs had less weight gain than the other groups. The 3X and 5X dogs had lower sodium, albumin, total protein, and cholesterol compared to the control dogs. The 5X dogs had lower mean corpuscular volume than the controls.
There was a dose dependent increase in amylase. Post-mortem findings included dose dependent adrenal cortical hypertrophy.

STORAGE INFORMATION: Store at controlled room temperature 25°C (77°F) with excursions between 15°-30°C (59°-86°F) permitted.

HOW SUPPLIED: VETORYL Capsules are available in 5, 10, 30, 60 and 120 mg strengths, packaged in aluminum foil blister cards of 10 capsules, with 3 cards per carton.

VETORYL Capsules 5 mg	NDC 17033-105-30
VETORYL Capsules 10 mg	NDC 17033-110-30
VETORYL Capsules 30 mg	NDC 17033-130-30
VETORYL Capsules 60 mg	NDC 17033-160-30
VETORYL Capsules 120 mg	NDC 17033-112-30

TAKE TIME  OBSERVE LABEL DIRECTIONS

Approved by FDA under NADA # 141-291

Manufactured for: Dechra Veterinary Products
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Method of use covered by US patent No. 9,283,235.

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F1612 Rev. January 2019

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