

## Cushing's Syndrome.

From the dog they thought they'd lost.  
A new vitality found.



# What is canine Cushing's syndrome?

Canine Cushing's syndrome is one of the most commonly diagnosed endocrinopathies in the dog.

Cushing's can be either iatrogenic or naturally occurring (spontaneous):

- Iatrogenic cases result from chronic administration of exogenous glucocorticoids.
- In spontaneous cases there is chronic excessive production of glucocorticoids by the adrenal glands.

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

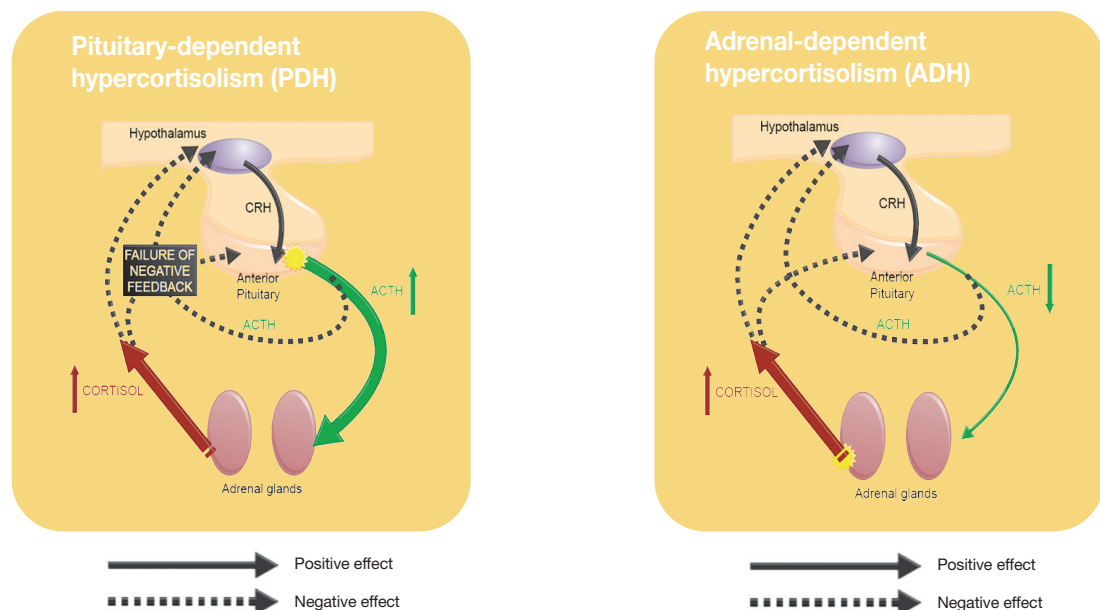
## Types of Cushing's

Most spontaneous cases of hypercortisolism (80-85%) are caused by hypersecretion of ACTH by a lesion in the pituitary gland.

This leads to bilateral adrenal hyperplasia and increased glucocorticoid secretion.

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

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



Did you know that recent research<sup>1</sup> has found that of all dogs treated for Cushing's, a further 57% are never confirmed, despite suspicion? Information in this guide can help you diagnose and treat these cases, improving quality-of-life.

# How to deal with Cushing's syndrome - a three step approach



## Diagnose

The first step in the approach to Cushing's is to use a combination of the clinical signs and laboratory abnormalities to determine if confirmatory testing is required.

The tables below describe the possible findings in detail:

**Table 1. Clinical manifestations of canine Cushing's. Categorisation of frequency is based on identification at the time of initial presentation<sup>a</sup>.**

Common	Less Common	Uncommon
Polydipsia	Lethargy	Thromboembolism
Polyuria	Hyperpigmentation	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		
Systemic hypertension		

**Table 2. Common laboratory abnormalities in dogs with Cushing's<sup>ii</sup>.**

Complete Blood Count	Serum Biochemistry Panel	Urinalysis
Neutrophilic leukocytosis	Increased alkaline phosphatase	Specific gravity $\leq 1.018$ -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 Cushing's that can include diabetes mellitus, systemic hypertension, pancreatitis, urolithiasis and pulmonary thromboembolism<sup>iii</sup>.

However, far before that Cushing's will have significantly affected the quality-of-life of both dog and its owner.



© Dr. S. Galac

**11-year-old Dachshund displaying typical signs of Cushing's.**



**12 year old Labrador showing signs of alopecia and rat-tail.**



© Dr. S. Galac

**10-year-old Boxer displaying typical signs of Cushing's disease.**



**10 year old King Charles Cavalier cross showing lack of hair regrowth.**

**Dechra have worked with Peter Graham BVMS PhD CertVR DipECVCP MRCVS to develop an online app which will help confirm your suspicions of Cushing's. To find out more visit [www.diagnosingcushings.com](http://www.diagnosingcushings.com)**



# Diagnosis of Spontaneous Canine Cushing's

A consensus statement<sup>ii</sup> published in the Journal of Veterinary Internal Medicine in 2013 offers a consensus opinion on the diagnosis of spontaneous Cushing's and the reader is advised to read the statement for further detail.

## Clinical Presentation: Indications for Diagnostic Testing

- The possibility that a patient has Cushing's is based on the history and physical examination. Endocrine tests should be performed only when clinical signs consistent with Cushing's are present.
- The primary indication for pursuing a diagnosis of Cushing's 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 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 Cushing's.

Biochemical panel, haematology, urinalysis, and urine protein : creatinine ratio results and blood pressure measurement by themselves are not indications to test.

## Screening tests

No test for Cushing's has 100% diagnostic accuracy. Whichever test is chosen, the diagnostic performance of the test will be significantly enhanced by increasing the prevalence of the disease in the population under test by performing endocrine tests only when clinical signs consistent with Cushing's are present.

Diagnosis of Cushing's 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 screening test may be negative in a patient with Cushing's. 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 Cushing's must be considered. Alternatively, the patient may have mild Cushing's and the tests have not yet become positive. It may be worthwhile to retest in 3–6 months if clinical signs progress.

**A confident diagnosis requires consistent endocrine confirmatory test results in a dog with clinical signs compatible with Cushing's.**

## Confirming diagnosis

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

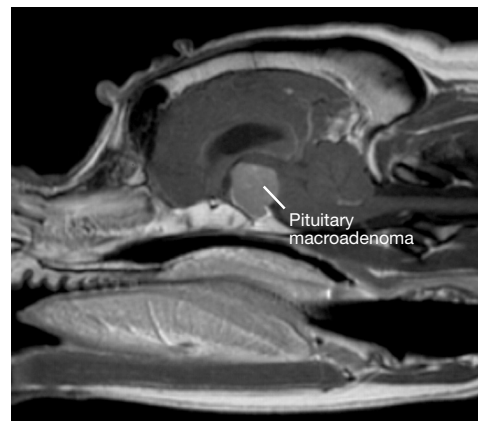
Test	Sensitivity & Specificity	Additional info
Low-Dose Dexamethasone Suppression (LDDST)	<ul style="list-style-type: none"><li>• High sensitivity and moderate specificity test</li><li>• High confidence in a negative test result and false positives can occur</li></ul>	<ul style="list-style-type: none"><li>• Long test (8 hours)</li><li>• In some cases may differentiate between PDH and ADH</li></ul>
ACTH Stimulation (ACTHST)	<ul style="list-style-type: none"><li>• Highest specificity of all these three tests but lacks sensitivity</li><li>• Highest confidence in a positive test result and false negatives are relatively common</li></ul>	<ul style="list-style-type: none"><li>• Relatively short test (1 hour)</li><li>• Test of choice if there is a history of exogenous steroid therapy</li></ul>
Urinary Cortisol to Creatinine Ratio	<ul style="list-style-type: none"><li>• Highest sensitivity of all these three tests but lacks specificity</li><li>• Highest confidence in a negative test result and false positives are relatively common</li></ul>	<ul style="list-style-type: none"><li>• To avoid false-positive results, urine samples should be collected at home at least two days after a visit to a veterinary clinic</li></ul>

For detailed information on performing and interpreting these tests, please refer to the diagnosis flowchart.

## Differentiating between types

It is necessary to differentiate between PDH and 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 measurement of endogenous ACTH, the low- and high-dose dexamethasone suppression tests, ultrasonography, and advanced imaging such as MRI and CT.



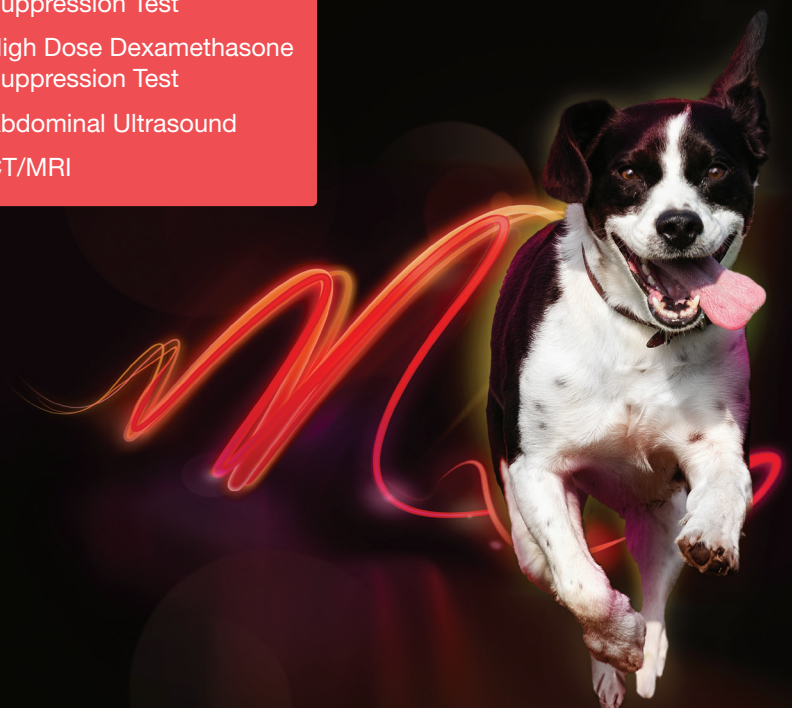
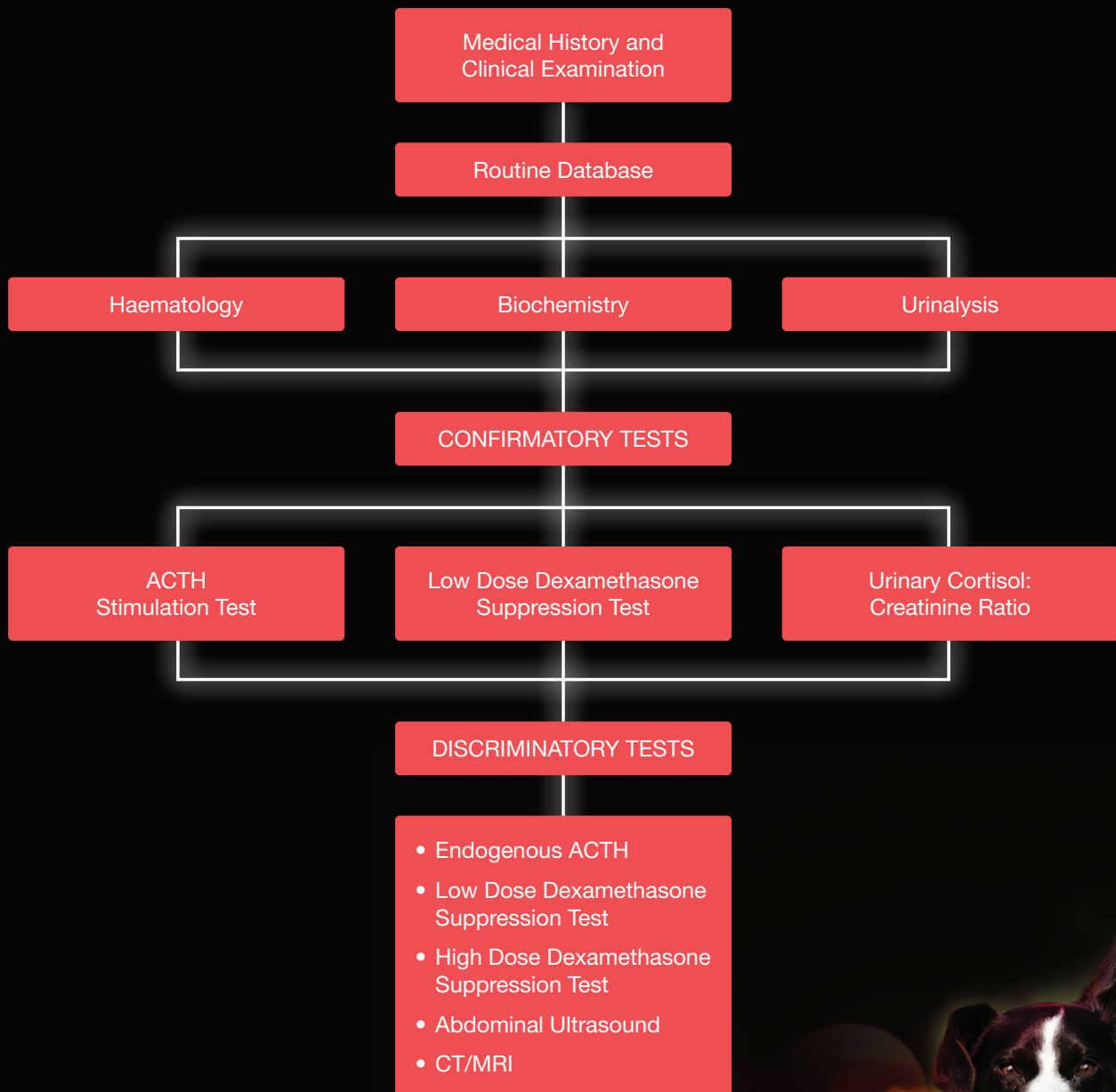
MRI image from a Boxer dog with a pituitary macroadenoma (image courtesy of Ruth Dennis, The Animal Health Trust, UK)

### Did you know that:

- **The 2012 ACVIM Consensus Statement<sup>ii</sup> panel considers the LDDST as the screening test of choice unless iatrogenic Cushing's is suspected?**
- **Because of the ACTHST's low sensitivity its diagnostic usefulness as a screening test for spontaneous Cushing's is inferior to the LDDST?**



To help support the diagnosis all dogs should undergo clinicopathological testing including **haematology, serum biochemistry, urinalysis and specific endocrine testing.**



# A simple guide to diagnosis

## Step 1 - Look

Cushing's is most common in middle-aged to older patients. PDH is most common in small terrier-type breeds, ADH is more common in larger dogs. Regardless of the underlying cause, the clinical signs are the same.

Cushing's  
is the

**P**  
disease:

**P**olydipsia **Alo**pecia  
**P**olyphagia  
**P**ot belly **P**anting **P**oor exercise tolerance  
**P**olyuria

Remember, dogs are being diagnosed increasingly earlier in the disease process and often do not display all the 'P' signs at initial presentation. Any combination of symptoms could indicate disease.

## Step 2 - Investigate

If signalment and clinical signs raise suspicion of Cushing's disease, the next step is to undertake routine first-line investigations.

The table on the right describes the most common findings:

Haematology	Biochemistry	Urinalysis
Stress Leukogram which includes Lymphopenia Eosinopenia	Increased ALKP (can be well in excess of 1000 IU/L ) Hyperlipidaemia Increased ALT (often mild to moderate - <400 IU/L)	USG <1.020

## Step 3 - Confirm

Once routine diagnostics have revealed non-specific indicators of disease, the next step is to use specific diagnostic testing to confirm Cushing's disease.

### 1. Low Dose Dexamethasone Suppression Test (LDDST)

The 2012 ACVIM consensus statement<sup>ii</sup> considers the LDDST to be the screening test of choice for Cushing's, and it is the best test to use where your suspicion of Cushing's is high.

This test may produce a false positive result, therefore you want to be sure that where a positive result is gained, it is due to true Cushing's, rather than another non-adrenal illness.

Where a negative result is gained, you can be very confident that the dog does not have Cushing's.

### 2. ACTH Stimulation Test (ACTHST)

The ACTHST is best used where there is known concurrent disease, or where Cushing's may be present, but there are other possible differentials high on the list.

The ACTHST is unlikely to give a false positive result, but equally it can provide false negative values.

Where a negative result is gained, further investigations may still be warranted as this test can miss truly Cushingoid dogs.

Cosacthen<sup>®</sup>, Dechra's injectable tetracosactide can be used to undertake an ACTHST. For further information visit XXXX



STEP  
**2**

## Treat

Treatment of Cushing's may be achieved by surgery (adrenalectomy or trans-sphenoidal hypophysectomy), pituitary irradiation, or medical treatment. But since surgery and radiotherapy are complicated, specialist procedures, medical treatment is often the easiest choice.



- Vetoryl is the only veterinary licensed pharmaceutical treatment for both pituitary-dependent and adrenal dependent forms of Cushing's.
- Vetoryl contains trilostane which selectively and reversibly inhibits the enzyme system 3 $\beta$ -hydroxysteroid dehydrogenase, involved in the synthesis of several steroids including cortisol and aldosterone.
- At recommended dose rates, Vetoryl tends to have a more selective effect on glucocorticoid production<sup>iv</sup>, however the potential inhibition of aldosterone must always be borne in mind by the attending clinician.
- Vetoryl reduces circulating cortisol levels, leading to resolution of clinical signs.
- Vetoryl provides flexible and accurate dosing with five strengths, 5 mg, 10 mg, 30 mg, 60 mg and 120 mg capsules, allowing you to significantly improve the quality-of-life for both the dog and the owner.
- Available in blister packs of 30 capsules for ease of dispensing.



Vetoryl should be administered orally, once daily, with food.

The starting dose for treatment is approximately 2 mg/kg, based on available combinations of capsule sizes.

**Once treatment has started, it is important that the owner keeps good home records of their pet. This should include information on thirst, appetite, exercise levels and demeanor.**

## Did you know that:

Dechra has an owner dedicated website which encourages owners to record their dog's progress - [www.canine-cushings.co.uk](http://www.canine-cushings.co.uk)

Encouraging the use of the monitoring sheets will provide you with more clinical information to base dosing decisions on.

Your practice can order printed log books from Dechra, free of charge.

Systematic and frequent record keeping at home could potentially allow an owner to detect changes sooner.



If the dog shows any signs of being unwell advise the owner to stop treatment and contact you immediately.

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





## Treatment with Vetoryl - Frequency of dosing

Most studies on trilostane have examined dogs that are started on once daily administration, as is recommended by Dechra.

A few studies<sup>v,vi,vii,viii</sup> have shown that dogs can be started on trilostane twice daily, however there is no evidence that starting at an increased frequency improves outcome.

Once a patient is started on once daily Vetoryl, the range of capsule sizes gives you the power to restore the dog's health with flexible dosing.

The dose and dose frequency can be adjusted as necessary, according to both clinical signs and monitoring test results.

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

### Did you know that:

In recent owner research<sup>i</sup>,  
48% of dogs received  
Vetoryl more frequently  
than once daily?

48%

## Reasons to treat with Vetoryl - Impact on quality-of-life

Vetoryl gives you the power to bring health and vitality back to dogs suffering with Cushing's syndrome.



“Treatment is worth it, for anyone out there with a dog who's got Cushing's, really go for the treatment because it's great. She's got a great quality-of-life.”

Mary and Missy

“I was given Vetoryl as soon as he was diagnosed and within 48 hours I could see a difference. I know that this is just a medication but for me it's changed our lives.”

Sharon and Benni



# 77%

of owners saw a positive improvement in the quality-of-life of their dog after treatment with Vetoryl.

# 93%

of owners consider their dog's quality-of-life to be important



STEP  
**3**

## Monitor

Vetoryl is a medicine that delivers major clinical benefits to a patient. Every dog with Cushing's is different, in their clinical presentation of the disease as well as in their response to Vetoryl.

**Personalised monitoring** is required to ensure the appropriate dose for that patient is obtained. After initiation of treatment, it needs to be ensured that the prescribed dose of Vetoryl is adequate to control the clinical signs of Cushing's.

**It is important to understand WHY Vetoryl monitoring is needed, and WHAT the results of monitoring can deliver.**

The Vetoryl dose should be titrated according to individual response as determined by monitoring of clinical signs and laboratory test results.

### The aims of Vetoryl monitoring are to:



Ensure improved quality-of-life of dogs and as a result their owner's quality-of-life



Identify whether dogs are on an adequate dose of Vetoryl to control the clinical signs of Cushing's



Identify dogs that are unwell, whether the problem is due to Vetoryl or something else

Assessment should be performed pre-treatment and then at 10 days, 4 weeks, and thereafter every 3 months, following initial diagnosis and after each dose adjustment.

### Did you know that:

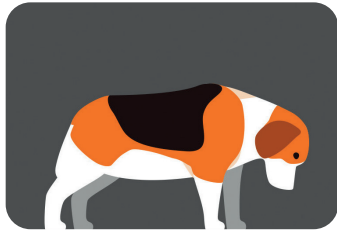
To learn about using the Cushing's Clinical Score and the CushQoL-pet tool visit [xxxxxxxxxxxxx](#), where Professor Stijn Niessen also discusses how to interpret the Cushing's clinical score and the importance of good owner communication in patients receiving ongoing medication for a chronic disease.

# Four steps in monitoring dogs on Vetoryl

For each monitoring consult, work through these four steps:

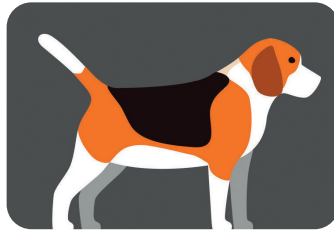
## 1. Cushing's clinical score

This has been developed to make it easy to record and keep track of the most important clinical signs. This can help you answer the following questions:



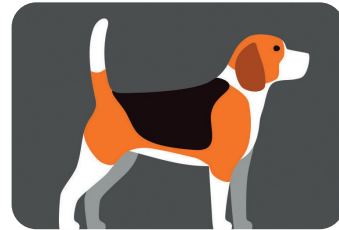
**Is the dog showing signs of being unwell?**

**These include any signs of vomiting, diarrhoea, lethargy and decreased appetite.**



**Is the dog still showing signs of Cushing's?**

**Has there been a change in thirst/urination frequency and volume, appetite, appearance and general demeanour?**



**Is the dog improving as expected following treatment?**

## 2. Physical examination

This provides an opportunity to look for signs that the dog is unwell and/or has concurrent disease. You are also able to check that your physical findings support the clinical history provided by the owner.

## 3. Quality-of-life (QoL) assessment

Consideration of specific treatment needs for individual patients as well as their owners are important to optimise QoL of dogs with Cushing's. The validated CushQoL-pet questionnaire has been developed to help assess QoL within your monitoring consultations.

## 4. Pre-Vetoryl Cortisol

Whilst owner observations and a physical examination are critically important in a monitoring consultation, an objective measure is also required to identify dogs with sub-clinical hypocortisolism and at risk of progressing to an overt iatrogenic hypoadrenocorticism.

For detailed information on Pre-Vetoryl Cortisol, including guidance on result interpretation and subsequent dose changes please visit xxxxxxxxxx or refer to the treatment and monitoring flowchart.

Since the Pre-Vetoryl Cortisol test does not feature on the Vetoryl Summary of Product Characteristics, informed owner consent for 'off-label' monitoring should be obtained.

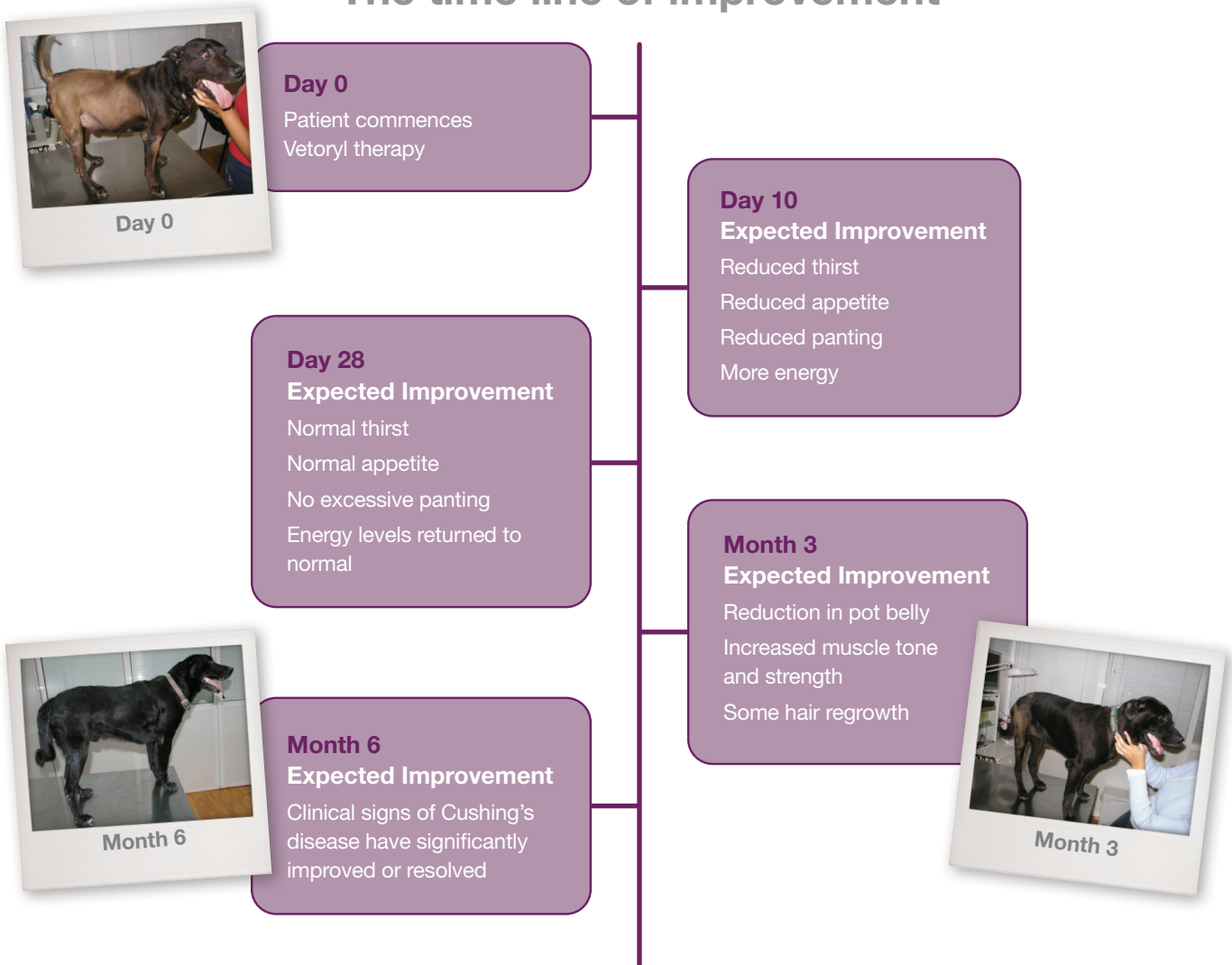
# Efficacy of Vetoryl treatment

According to vets who have treated a number of cases of Cushing's, owners soon notice the difference and comment on the changes in their pet<sup>ix</sup>.

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 3-6 months).

## The time line of improvement



## Is your patient responding as expected?

### YES

Continue to monitor your patient at regular intervals and encourage its owner to maintain good home records. This will ensure the clinical improvement continues.

### NO

If still showing any signs consistent with Cushing's, consider whether a dose increase or an increase in dose frequency would be of benefit to the dog. For further information refer to the treatment & monitoring flowchart.

If your patient is unwell at any time, Vetoryl should be stopped and further investigations undertaken.



## Optimal support of Cushing's syndrome

Cushing's requires medical or surgical intervention to treat the condition. However, some of the common complications of the disease may benefit from supportive measures. Dechra provides products to support the treatment and management of these complicating conditions.

Restoration of the poor skin condition in patients with Cushing's requires sufficient supply of skin supporting nutrients. SPECIFIC™ CED Endocrine Support contains uniquely high concentrations of omega-3 fatty acids and essential skin-supportive nutrients and is especially designed to support the management of endocrine disorders. The high concentrations of omega-3 fatty acids and added beta-glucans can alter the production of eicosanoids and cytokines and support the immune response.

For more information visit:

**[www.specific-diets.co.uk/dog/endocrine-support](http://www.specific-diets.co.uk/dog/endocrine-support)**



**Patients with Cushing's often have dermatological complications.**

**Dechra also offer a complete range of products that can help maintain a healthy skin and coat.**



### **Malaseb® Shampoo**

Topical formulation with the highest level of evidence against cutaneous bacterial Malassezia infection in dogs<sup>x</sup>

- Medicated veterinary licensed shampoo
- Pharmaceutical properties – antifungal and antibacterial action
- Cosmetic properties – conditioning with no added perfumes or colourings
- Contains 2% chlorhexidine digluconate and 2% miconazole nitrate shown to be synergistic against Staphylococcus aureus and Staphylococcus pseudintermedius<sup>xi</sup>



### **DermAllay Oatmeal Spray Conditioner**

- Soothing, moisturising, leave-on skin care spray with oatmeal
- Contains essential fatty acids, ceramides and hydrolysed oatmeal extracts to soothe the skin and support the regeneration of the skin barrier



### **DermAllay Oatmeal Shampoo**

- Soothing, moisturising shampoo with oatmeal extract
- Ideal for use on itchy skin it helps restore coat condition and moisturising the skin
- Contains essential fatty acids, ceramides and hydrolysed oatmeal extracts to support the regeneration of the skin barrier and to soothe skin

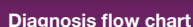
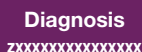


### **DermAllay Sensitive Shampoo**

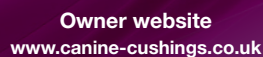
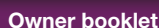
**Ideal for frequent use on sensitive skin**

- Mild shampoo, containing ceramides for sensitive or dry skin
- Contains essential fatty acids in a special formulation for mild cleaning and care of the skin
- Suitable for use on puppies

Dechra provides you with an extensive range of resources to support you with diagnosing, treating and monitoring dogs with Cushing's.



In addition to supporting you we also provide an extensive range of resources to help support your clients following their pets diagnosis.



Contact us: Dechra Veterinary Products Limited, Sansaw Business Park,  
Hadnall, Shrewsbury, Shropshire SY4 4AS. Tel: +44 (0) 1939 211200





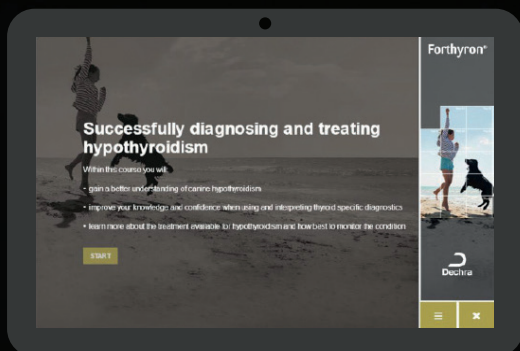
## Experts in endocrinology

The Dechra Academy gives you free access to a number of educational topics, allowing you to learn at a time or place that suits you.

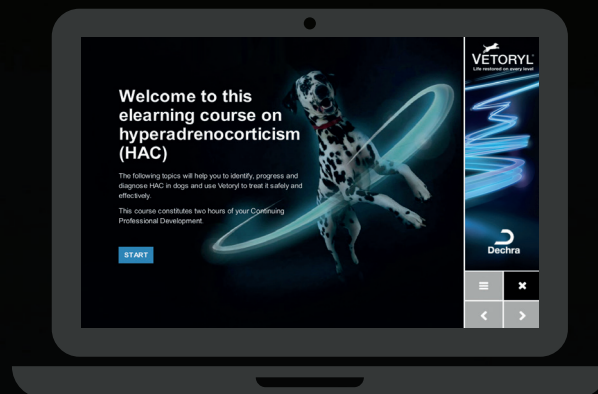
Our Academy has case studies, videos, interactive eLearning and digital books which all count towards your CPD.



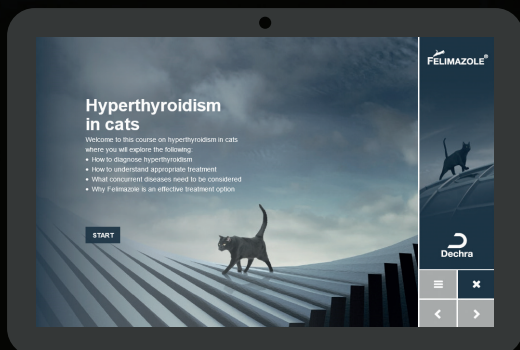
**Canine and feline diabetes mellitus: more than just insulin**



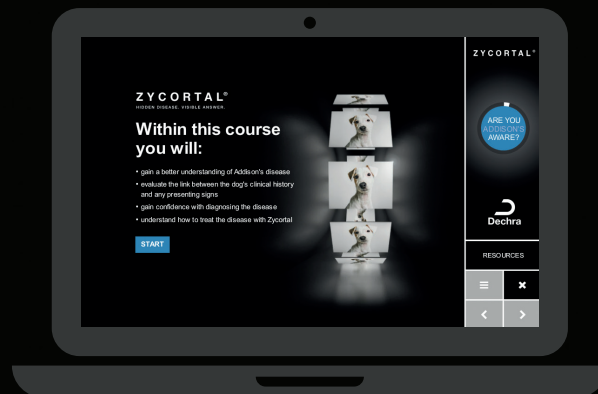
**Forthyron: Successfully diagnosing and treating hypothyroidism**



**Vetoryl: Cushing's syndrome**



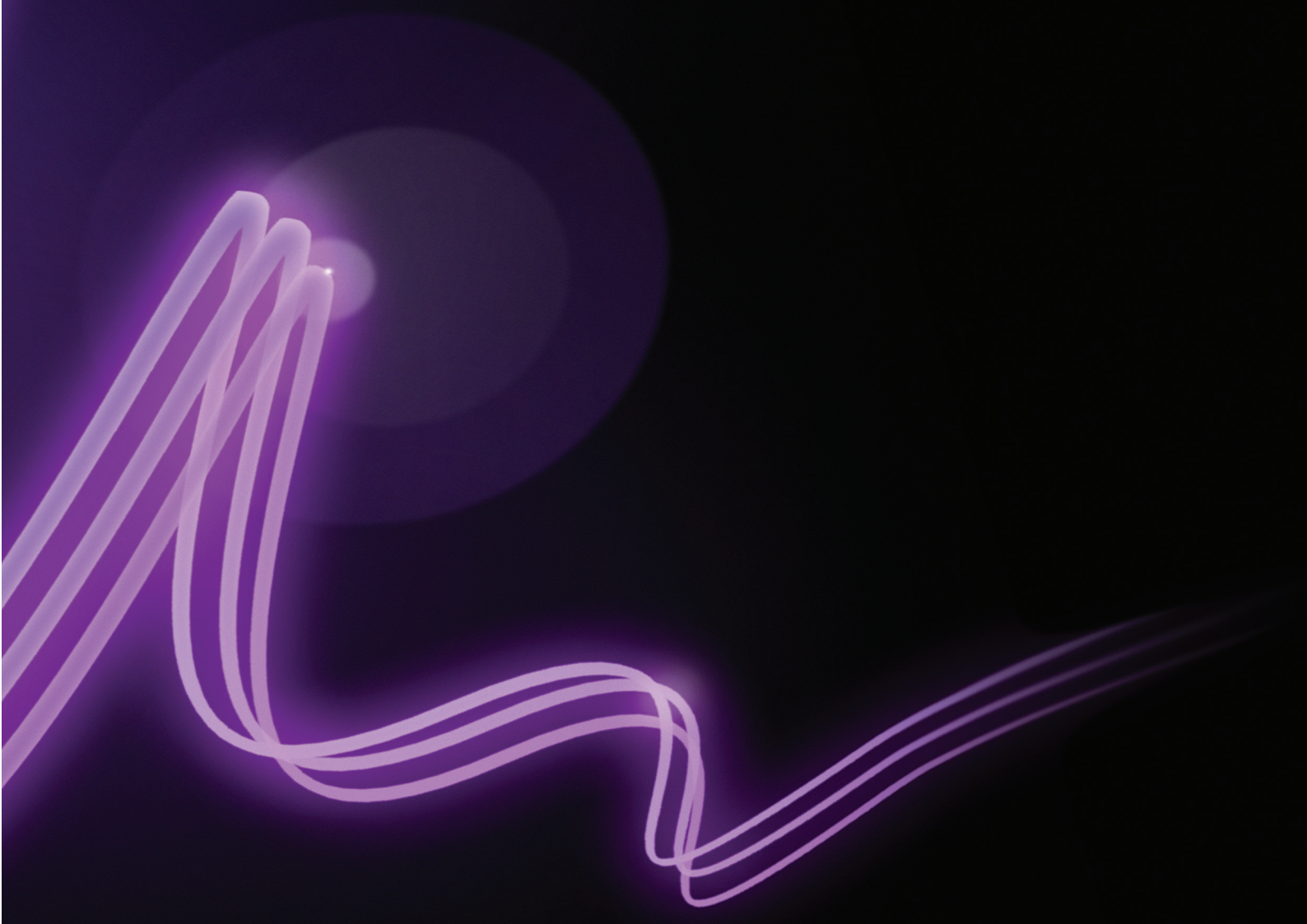
**Felimazole: Feline hyperthyroidism**



**Zycortal: Introduction to hypoadrenocorticism**

Visit <https://academy.dechra.com> to find out more.





## References

- i Internal Report VET0818
- ii Behrend *et al* (2013) Diagnosis of Spontaneous Canine Hyperadrenocorticism: 2012 ACVIM Consensus Statement (Small Animal) JVIM 1-13
- iii Mooney (2009) Hyperadrenocorticism - to treat or not to treat? UK Vet **14(6)**: 1-5
- iv 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
- v 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
- vi Feldman (2011) Evaluation of twice-daily lower-dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism. JAVMA **238**: 1441-1451
- vii Augusto *et al* (2012) A comparison of once and twice daily administration of trilostane to dogs with hyperadrenocorticism. Tierärztliche Praxis Kleintiere **40**: 415-424
- viii Cho *et al* (2013) Efficacy of low- and high-dose trilostane treatment in dogs (< 5 kg) with pituitary-dependent hyperadrenocorticism. JVIM **27**: 91-98
- ix Internal report VET60
- x Muller *et al* (2012) A review of topical therapy for skin infections with bacteria and yeast. Veterinary Dermatology **23**: 330-362
- xi Clark *et al* (2015) Susceptibility in vitro of canine methicillin-resistant and -susceptible staphylococcal isolates to fusidic acid, chlorhexidine and miconazole: opportunities for topical therapy of canine superficial pyoderma. Journal of Antimicrobial Chemotherapy **70(7)**: 2048-2052

**MALASEB:** Malaseb Shampoo contains 2% w/v chlorhexidine and 2% w/v miconazole UK: POM-V IE: POM

**VETORYL:** Vetoryl contains trilostane UK: POM-V IE: POM

**COSACTHEN:** Cosacthen contains tetracosactide UK: POM-V IE: POM

For further information contact: Dechra Veterinary Products Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire, SY4 4AS T +44 (0)1939 211200 F +44 (0)1939 211201 [www.dechra.co.uk](http://www.dechra.co.uk) [www.dechra.ie](http://www.dechra.ie) Registered Office: 24 Cheshire Avenue, Cheshire Business Park, Lostock Gralam, Northwich CW9 7UA. Registered in England and Wales, Company Registration No.5385888. Dechra Veterinary Products Limited is a trading business of Dechra Pharmaceuticals PLC

