



Seeing the same dog with the same issue?
There could be a different conclusion.



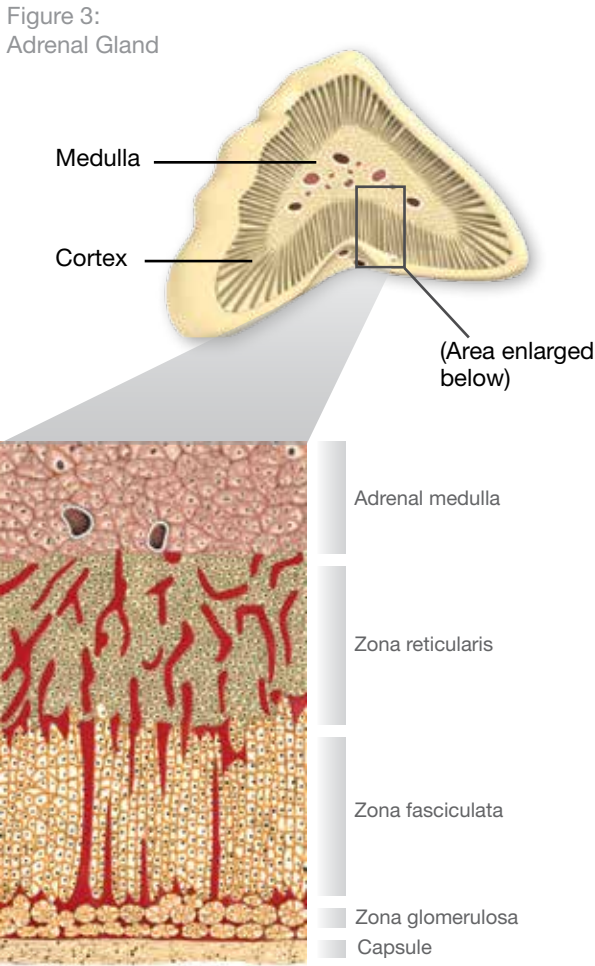
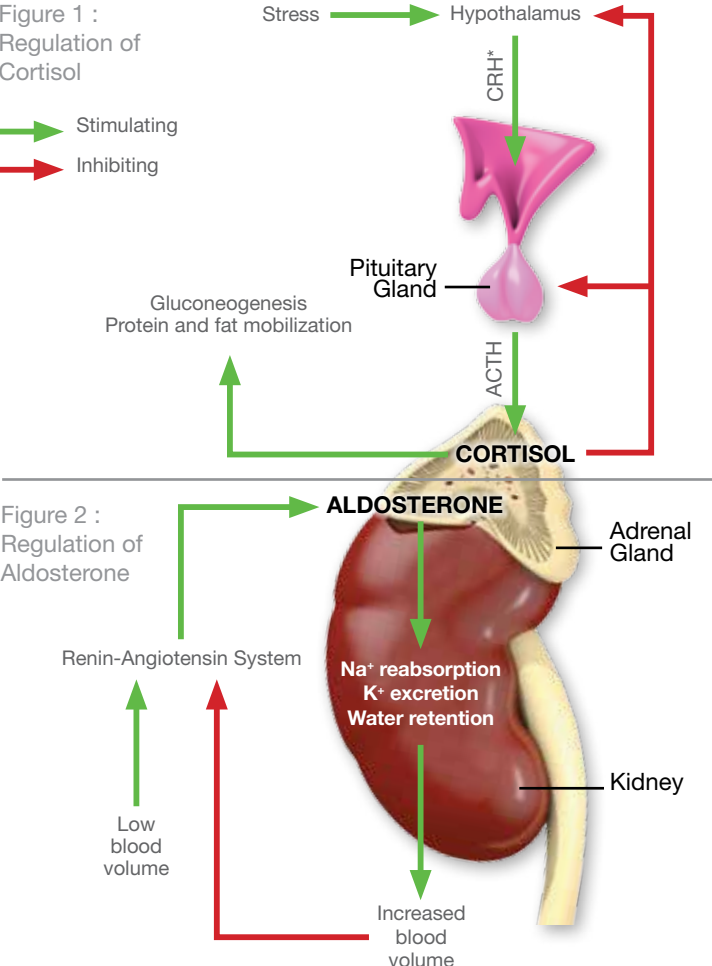
ZYCORTAL[®]
SUSPENSION (desoxycorticosterone
pivalate injectable suspension)

What is Addison's disease (hypoadrenocorticism)?

Addison's disease results from loss of corticosteroid production, principally the mineralocorticoid aldosterone and the glucocorticoid cortisol.

The most common type of canine Addison's disease is primary hypoadrenocorticism, which is nearly always due to an immune-mediated destruction of the adrenal glands. This condition usually results in deficiencies of both mineralocorticoids and glucocorticoids; however, isolated glucocorticoid deficiency has been reported (atypical hypoadrenocorticism).

Secondary hypoadrenocorticism (caused by pituitary dysfunction), results in the deficiency of adrenocorticotrophic hormone (ACTH). This is a very rare cause of canine hypoadrenocorticism and tends to result in glucocorticoid deficiency only. These patients will only need glucocorticoid replacement.



*Corticotropin-Releasing Hormone

If left untreated, Addison's disease can be acutely life-threatening.

How to recognize Addison's disease

When presented with an affected dog, Addison's disease may not be at the top of your rule-out list. Being more aware of this condition and considering it earlier in your diagnostic workup will shorten the length of time it takes to diagnose the disease and deliver appropriate treatment.

Addison's disease is a potentially life-threatening condition.

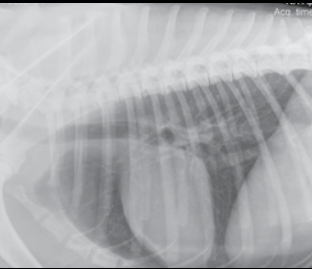
Clinical signs associated with the disease are nonspecific, can wax and wane, and dogs can respond to nonspecific therapy (e.g. intravenous fluid therapy). This condition can be easily mistaken for other diseases (e.g. kidney disease, gastroenteritis, neuromuscular disease and metabolic diseases).

The most common signs of Addison's disease are:

	Almost all cases	Common	Less common
Clinical History	Inappetence Lethargy	Vomiting	Diarrhea +/- Blood Melena (digested blood in stool) Weight loss Polyuria Polydipsia
Physical examination	Depression Weakness	Dehydration	Bradycardia Hypothermia Shivering/muscle stiffness



Depression due to Addison's disease*



Microcardia secondary to hypovolemia*



Bilious vomit**



Melena**



Masticatory muscle loss*



Young puppy with Addison's disease*

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Diagnostic indices of Addison's Disease in descending order of frequency:

Hematology	Serum biochemistry and Urinalysis
Absence of stress leukogram in a stressed/sick animal Neutrophilia Nonregenerative anemia Eosinophilia Lymphocytosis	Hyperkalemia Azotemia Hyponatremia Hyperphosphatemia Urine specific gravity <1.030 Hypochloremia Metabolic acidosis Hypercalcemia Hypoglycemia

Affected dogs can present with a gradual onset of clinical signs or an acute life-threatening state (Addisonian crisis). Animals presenting in Addisonian crisis tend to have clinical signs suggestive of hypovolemic shock such as prolonged capillary refill times, weak peripheral pulses, weakness or collapse.

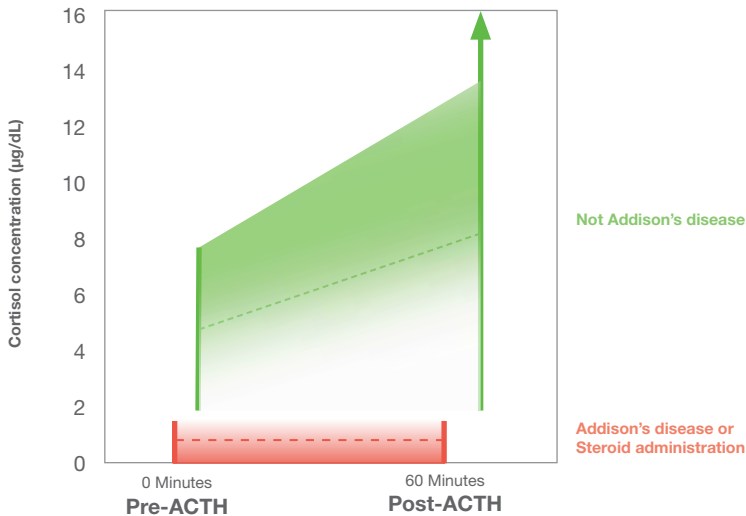
Affected animals may not be tachycardic despite being hypovolemic due to the bradycardic effects of hyperkalemia.

A thorough clinical history in these cases can increase a clinician's suspicion of this disease and following a detailed physical examination, diagnostic investigations typically include hematology, serum biochemistry (including electrolytes), and potentially radiography, ultrasonography and electrocardiography.

Diagnosis

The gold standard for diagnosing Addison's disease is the ACTH stimulation test, which assesses the ability of the adrenal gland to produce cortisol.

Although a low basal cortisol value can be useful to rule out Addison's disease, it is not adequate for a diagnosis.



Step-by-step diagnosis



*Veterinarians should use the specific reference ranges of their diagnostic laboratory.

Courtesy of Professor Ian Ramsey, University of Glasgow

Addison's disease resembles many other illnesses so it can be challenging to recognize. It is often referred to as 'the great pretender'. Fortunately, once Addison's disease is suspected, confirming the diagnosis is as simple as running an ACTH stimulation test.

Treatment

Once Addison's disease has been confirmed and the patient is hydrated (*i.e.* no continued evidence of vomiting, diarrhea, weakness, depression or dehydration); replacement therapy can begin. Long-term replacement therapy consists of glucocorticoid replacement at physiological doses (very low) and mineralocorticoid replacement.

The recommended therapy for glucocorticoid replacement is oral prednisone/prednisolone at 0.2-0.4 mg/kg/day (0.1-0.2 mg/lb/day).

For mineralocorticoid replacement, the treatment of choice is desoxycorticosterone pivalate (DOCP).

What is DOCP?

Desoxycorticosterone is a corticosteroid with primarily mineralocorticoid activity, similar to aldosterone.

In the kidney, desoxycorticosterone causes sodium and chloride ion retention, and hydrogen and potassium ion excretion, creating an osmotic gradient. The osmotic gradient promotes water absorption from the renal tubules resulting in increased extracellular fluid volume, leading to blood volume expansion, improved venous return to the heart, and increased cardiac output.

Seeing the same dog with the same issues? There could be a different conclusion.



ZYCORTAL Suspension

ZYCORTAL Suspension contains desoxycorticosterone pivalate which is a mineralocorticoid hormone indicated for use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison's disease). ZYCORTAL Suspension was formulated and approved specifically for subcutaneous use.

The desoxycorticosterone pivalate (DOCP) in ZYCORTAL Suspension is a pure mineralocorticoid hormone that regulates electrolytes and water balance, which are impaired in cases of mineralocorticoid deficiency in Addison's disease. DOCP has limited glucocorticoid activity, allowing the independent dose titration of mineralocorticoid without the risk of inducing marked side effects from glucocorticoid oversupplementation *e.g.* polyuria, polydipsia, polyphagia and muscle atrophy.

ZYCORTAL Suspension was formulated and approved specifically for subcutaneous use.

Initial Dose

ZYCORTAL Suspension is intended for long-term administration at intervals and doses dependent upon individual response.

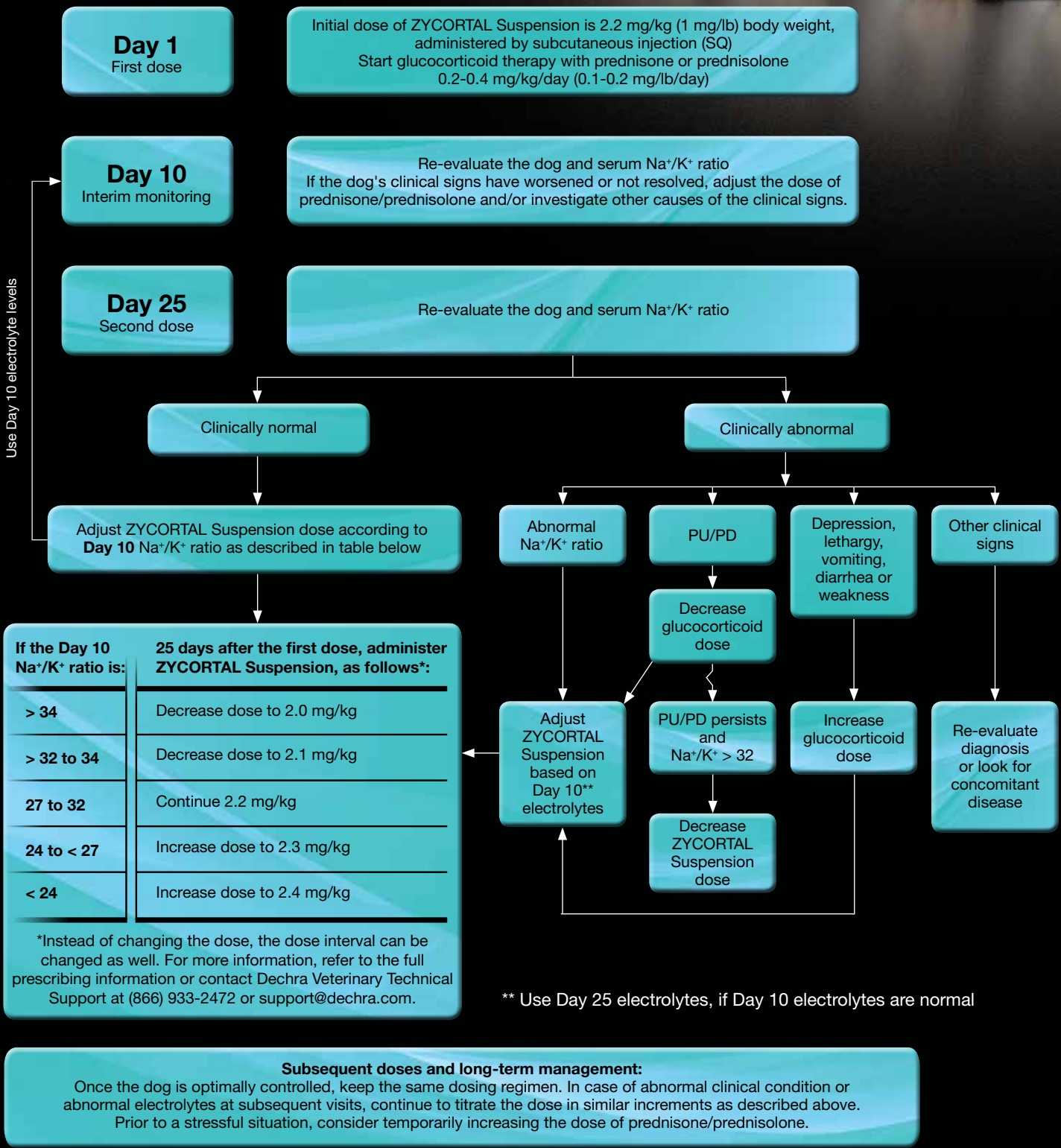
Prognosis

Prognosis for dogs with Addison's disease is excellent if treatment is maintained for life. Glucocorticoid supplementation may need to be increased in times of stress.

Regular monitoring will help ensure the dog's clinical signs are properly managed for the life of the patient.



Monitoring and dose adjustment

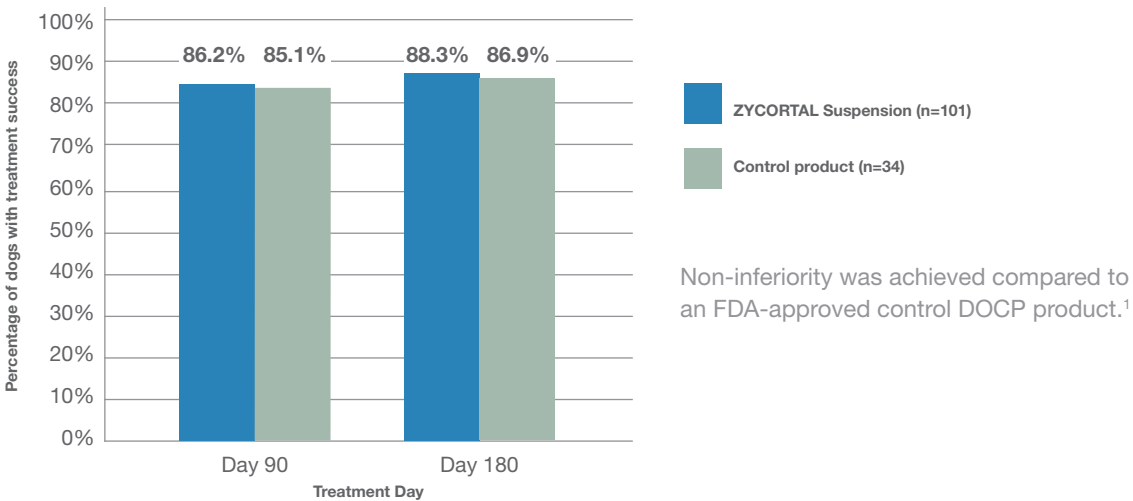


Efficacy

A double-blinded, multi-site, 180-day field study evaluated the effectiveness of ZYCORTAL Suspension compared to an existing FDA-approved desoxycorticosterone pivalate active control.

Non-inferiority was achieved compared to the existing FDA-approved control product containing DOCP.¹

A dog was considered a treatment success if it remained clinically normal or had improved clinical signs compared to baseline and the Na⁺ and K⁺ concentrations were within the reference range of the analyzer, or the Na⁺/K⁺ ratio was between 27-32.



ZYCORTAL Suspension is efficacious, well tolerated and allows tailored dosing for each dog with Addison's disease.

The mean final dose for ZYCORTAL Suspension was 1.9 ± 0.27 mg/kg (range 1.2-2.5 mg/kg) and the mean final dose interval was 38.5 ± 12.5 days (range 20-99 days) with the majority of dogs having a dosing interval between 20 and 46 days.¹

As with all drugs, side effects may occur. In field studies the most common side effects reported were polyuria, polydipsia, depression/lethargy, inappropriate urination, alopecia, decreased appetite/anorexia, panting, vomiting, diarrhea, shaking/trembling, polyphagia, urinary tract infection, urinary tract incontinence and restlessness. ZYCORTAL Suspension should be used with caution in dogs with congestive heart disease, edema, severe renal disease or primary hepatic failure. Dogs presenting in Addisonian crisis must be rehydrated with appropriate intravenous therapy before starting treatment with ZYCORTAL Suspension. Refer to the prescribing information for complete details or visit www.dechra-us.com/zycortal.

Switching dogs from fludrocortisone

Data from the ZYCORTAL Suspension clinical study has shown there is no significant difference in the efficacy of ZYCORTAL Suspension when given to newly diagnosed patients which started treatment with ZYCORTAL Suspension compared to existing patients which started treatment with fludrocortisone and then switched to ZYCORTAL Suspension ($p > 0.05$).²

In the clinical study, 31 dogs were enrolled who were receiving fludrocortisone prior to the administration of ZYCORTAL Suspension. Twelve of these dogs received fludrocortisone for ≥ 30 days; nineteen were treated for ≤ 7 days. When transitioning to ZYCORTAL Suspension, the majority of dogs (17/31) received the last dose of fludrocortisone on the same day of ZYCORTAL Suspension administration (Day 0). A “wash-out” or transition period was not required between the last administration of fludrocortisone and the first administration of ZYCORTAL Suspension.²



Treatment of Addisonian crisis (Acute Hypoadrenocorticism)

Acute and severe signs of Addison’s disease represent a life-threatening emergency. Aggressive intravenous fluid therapy, using isotonic crystalloids (0.9% NaCl, Lactated Ringer’s or Hartmann’s Solution) is critical to reversing the hypovolemic, hypotensive shock these dogs commonly experience. Fluid therapy will also temporarily address the life-threatening electrolyte imbalances. In stable, non-shocky patients, diagnostic samples (CBC, biochemistry, urinalysis and baseline cortisol) can be collected before starting therapy. In shocky, critical patients, priority should be given to stabilizing the patient. Diagnostic samples can be collected once the patient is stable.

In addition to fluid therapy, intravenous administration of dexamethasone may help improve hemodynamically unstable patients. Published dosages for dexamethasone vary widely and range from 0.1 to 2.0 mg/kg. Ideally, an ACTH stimulation test should be performed prior to the administration of dexamethasone. Prednisone, prednisolone, methylprednisolone and cortisone acetate cross-react with the cortisol assay and may artificially elevate serum cortisol results. These steroids should not be used prior to performing an ACTH stimulation test.

Once the dog is clinically stable, replace injectable glucocorticoids with physiological doses of oral prednisone or prednisolone, tapering to the lowest effective dose. Once the results of the ACTH stimulation test confirm the presence of hypoadrenocorticism and the patient is hydrated, administer 2.2 mg/kg of ZYCORTAL Suspension subcutaneously.

ZYCORTAL®

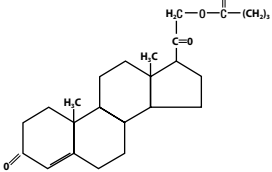
SUSPENSION (desoxycorticosterone pivalate injectable suspension)

For subcutaneous use in dogs only
Mineralocorticoid

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

DESCRIPTION: Desoxycorticosterone pivalate is a mineralocorticoid hormone. Chemically, desoxycorticosterone pivalate is 21-(2,2-dimethyl-1-oxopropoxy)-pregn-4-ene-3,20-dione. The structural formula is:

Molecular Formula: C₂₈H₃₈O₄



ZYCORTAL Suspension is a white aqueous suspension. Each milliliter contains 25 mg of desoxycorticosterone pivalate. Inactive ingredients are 10.5 mg methylcellulose, 3 mg sodium carboxymethylcellulose, 1 mg polysorbate 60, 8 mg sodium chloride, 1 mg chlorocresol and water for injection (to 100%).

INDICATION: For use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison’s disease).

DOSAGE AND ADMINISTRATION: Prior to each use, thoroughly shake the vial to resuspend the product. ZYCORTAL Suspension replaces the mineralocorticoid hormones only. Dogs with combined glucocorticoid and mineralocorticoid deficiency should also be treated with prednisone or prednisolone at an initial dosage of 0.2-0.4 mg/kg/day (0.1-0.2 mg/lb/day). ZYCORTAL Suspension is intended for long-term administration at intervals and doses dependent upon individual response. Tailor the dose of ZYCORTAL Suspension and the concurrently administered glucocorticoid replacement therapy to the individual dog based on clinical response and normalization of Na⁺ and K⁺ concentrations.

Initial dose of ZYCORTAL Suspension: The initial dose is 2.2 mg/kg (1 mg/lb) body weight, administered by subcutaneous injection.

Interim monitoring visit: Re-evaluate the dog and measure the serum sodium/potassium ratio (Na⁺/K⁺ ratio) approximately 10 days after the first dose, which is the time to maximum concentration (T_{max}) of desoxycorticosterone (see **CLINICAL PHARMACOLOGY**). If the dog’s clinical signs have worsened or not resolved, adjust the dose of prednisone/prednisolone and/or investigate other causes of the clinical signs.

Second dose of ZYCORTAL Suspension: At approximately 25 days after the first dose, re-evaluate the dog and repeat the Na⁺/K⁺ ratio.

- If the dog is both clinically normal and has a normal Na⁺/K⁺ ratio on Day 25, adjust the dose based on the Day 10 Na⁺/K⁺ ratio using the guidelines in Table 1, below.
- If the dog is clinically normal and has a Na⁺/K⁺ ratio > 32 on Day 25, either adjust the dose based on the Day 10 Na⁺/K⁺ ratio according to Table 1 or delay the dose (see **Prolonging the dosing interval**).
- If the dog is either not clinically normal or if the Na⁺/K⁺ ratio is abnormal on Day 25, adjust the dose of prednisone/prednisolone or ZYCORTAL Suspension (see **Subsequent doses and long-term management**).

Table 1: Day 25: Administering the Second Dose of ZYCORTAL Suspension

If the Day 10 Na ⁺ /K ⁺ ratio is:	Do not administer Dose 2 on Day 10.	25 days after the first dose, administer ZYCORTAL Suspension, as follows:
> 34		Decrease dose to: 2.0 mg/kg
> 32 to 34		Decrease dose to: 2.1 mg/kg
27 to 32		Continue 2.2 mg/kg
24 to < 27		Increase dose to: 2.3 mg/kg
< 24		Increase dose to: 2.4 mg/kg

Prolonging the dosing interval:

If the dog is clinically normal and the Day 25 Na⁺/K⁺ ratio is > 32 , it is possible to prolong the dosing interval instead of adjusting the dose as described in Table 1. Evaluate the electrolytes every 3-7 days until the Na⁺/K⁺ ratio is < 32 , and then administer 2.2 mg/kg of ZYCORTAL Suspension.

Subsequent doses and long-term management: For subsequent doses, use the following guidelines if the dog is not clinically normal and/or has abnormal Na⁺ or K⁺ concentrations:

- Clinical signs of polyuria/polydipsia: Decrease the prednisone/prednisolone dose first. If the polyuria/polydipsia persists, then decrease the dose of ZYCORTAL Suspension without changing the dosing interval.
- Clinical signs of depression, lethargy, vomiting, diarrhea or weakness: Increase prednisone/prednisolone dose.
- Hyperkalemia, hyponatremia or Na⁺/K⁺ ratio < 27 : Decrease the ZYCORTAL Suspension dosing interval by 2-3 days.
- Hypokalemia or hypernatremia: Decrease the ZYCORTAL Suspension dose.

Prior to a stressful situation, consider temporarily increasing the dose of prednisone/prednisolone.

CONTRAINDICATIONS: Do not use ZYCORTAL Suspension in dogs that have previously had a hypersensitivity reaction to desoxycorticosterone pivalate.

WARNINGS: Use ZYCORTAL Suspension with caution in dogs with congestive heart disease, edema, severe renal disease or primary hepatic failure. Desoxycorticosterone pivalate may cause polyuria, polydipsia, increased blood volume, edema and cardiac enlargement. Excessive weight gain may indicate fluid retention secondary to sodium retention. Do not use desoxycorticosterone pivalate in pregnant dogs.

HUMAN WARNINGS: Not for human use. Keep this and all drugs out of the reach of children. Consult a physician in case of accidental human exposure.

PRECAUTIONS: Any dog presenting with severe hypovolemia, dehydration, pre-renal azotemia and inadequate tissue perfusion (“Addisonian crisis”) must be rehydrated with intravenous fluid (saline) therapy before starting treatment with ZYCORTAL Suspension. The effectiveness of ZYCORTAL Suspension may be reduced if potassium-sparing diuretics, such as spironolactone, are administered concurrently.

ADVERSE REACTIONS: One hundred fifty-two dogs were included in the field safety analysis. Adverse reactions are summarized in Table 2.

Table 2: Percentage of Dogs with Adverse Reactions in the Field Study

Adverse Reaction	ZYCORTAL Suspension (n = 113 dogs)	Active Control (n = 39 dogs)
Polyuria	15.0% (17)	12.8% (5)
Polydipsia	13.3% (15)	15.4% (6)
Depression/lethargy	9.7% (11)	2.6% (1)
Inappropriate urination	8.0% (9)	10.3% (4)
Alopecia	5.3% (6)	5.1% (2)
Decreased appetite/anorexia	4.4% (5)	2.6% (1)
Panting	3.5% (4)	0.0% (0)
Vomiting	3.5% (4)	0.0% (0)
Diarrhea	2.7% (3)	7.7% (3)
Shaking/trembling	2.7% (3)	2.6% (1)
Polyphagia	1.8% (2)	2.6% (1)
Urinary tract infection	1.8% (2)	0.0% (0)
Urinary incontinence	0.9% (1)	2.6% (1)
Restlessness	0.9% (1)	2.6% (1)
Urticaria/facial edema	0.0% (0)	5.1% (2)

One dog with a pre-existing Grade III/IV heart murmur developed congestive heart failure 17 days after the first administration of ZYCORTAL Suspension and was removed from the study. In addition to the adverse reactions reported during the field study, post-approval adverse drug experience reporting for desoxycorticosterone pivalate injectable suspension included reports of anaphylaxis and anemia. To report suspected adverse events, for technical assistance or to obtain a copy of the safety data sheet (SDS), contact Dechra 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/AnimalVeterinary/SafetyHealth>.

CLINICAL PHARMACOLOGY: Desoxycorticosterone is a corticosteroid with primarily mineralocorticoid activity, similar to aldosterone. In the kidney, desoxycorticosterone causes sodium and chloride ion retention, and hydrogen and potassium ion excretion, creating an osmotic gradient. The osmotic gradient promotes water absorption from the renal tubules resulting in increased extracellular fluid volume, leading to blood volume expansion, improved venous return to the heart, and increased cardiac output. After subcutaneous administration of 11 mg/kg body weight (five times the labeled starting/initial dose of 2.2 mg/kg) of ZYCORTAL Suspension, the plasma half-life (mean \pm standard deviation) is approximately 17 ± 7 days, with a maximum concentration (C_{max}) of 13.2 ± 5 ng/mL, and time to maximum concentration (T_{max}) of 10 ± 3.5 days.

EFFECTIVENESS: A double-blinded, multi-site, 180-day field study evaluated the effectiveness of ZYCORTAL Suspension compared to an FDA-approved desoxycorticosterone pivalate active control. One hundred fifty-two (152) dogs of various breeds, 0.5-12.4 years of age and weighing 0.95-61.2 kg were enrolled. One hundred thirteen (113) dogs were treated with ZYCORTAL Suspension and 39 dogs were treated with the active control. Both groups were administered an initial dose of 2.2 mg/kg. Subsequent doses administered and/or frequency of administration were adjusted according to the clinical needs of the dog. A dog was considered a treatment success if it remained clinically normal or had improved clinical signs compared to baseline and the Na⁺ and K⁺ concentrations were within the reference range of the analyzer, or the Na⁺/K⁺ ratio was between 27-32. Success rates for ZYCORTAL Suspension were 86.2% and 88.3% on Days 90 and 180, respectively; success rates for the active control were 85.1% and 86.9% on Days 90 and 180, respectively. The mean final dose for ZYCORTAL Suspension was 1.9 ± 0.27 mg/kg (range 1.2-2.5 mg/kg) and the mean final dose interval was 38.5 ± 12.5 days (range 20-99 days) with the majority of dogs having a dosing interval between 20 and 46 days.

ANIMAL SAFETY: In a laboratory study, ZYCORTAL Suspension was administered via subcutaneous injection to 32 Beagle dogs (four groups of 8 dogs each) at doses of 0, 1, 3 and 5 times the labeled starting dose (1X = 2.2 mg/kg), once every 21 days for 6 months, for a total of 9 injections. The volume injected in 3X and 5X dogs was equally divided between three and five sites, respectively. Dogs in the 1X group were dosed at a single injection site. Control dogs (0X) received subcutaneous injections of 0.9% sodium chloride at a volume equivalent to the 5X dose. The most frequently noted abnormal clinical observations were injection site reactions in treated dogs, characterized by erythema and edema. Clinical pathology findings considered related to ZYCORTAL Suspension treatment included: decreased mean corpuscular volume in 3X and 5X groups; increased globulin concentrations in all treated groups; decreased potassium concentrations in all treated groups; increased sodium concentrations in all treated groups; decreased chloride concentrations in the 3X group; decreased blood urea nitrogen concentrations in all treated groups; and decreased urine specific gravity concentrations in all treated groups. Gross necropsy findings considered treatment-related included: subcapsular and cortical renal cysts, corresponding histologically with vascular tunica media hyperplasia; and irregular white plaques in the injection site subcutaneous tissue, corresponding histologically with granulomatous inflammation. Additional histology findings considered treatment-related included: chronic inflammation of the renal cortices, cortical tubular basophilia, cortical tubular dilation, glomerulopathy (3X and 5X groups), and adrenal gland vacuolation (zona glomerulosa).

STORAGE INFORMATION: Store at controlled room temperature 25°C (77°F) with excursions between 15-30°C (59-86°F) permitted. Do not freeze. Use within 120 days of first puncture.

HOW SUPPLIED: ZYCORTAL Suspension is supplied in a clear glass vial with 4 mL (100 mg) desoxycorticosterone pivalate (25 mg/mL).

NADA 141-444, Approved by FDA
NDC 17033-382-04

Manufactured for: Dechra Veterinary Products
7015 College Boulevard, Suite 525, Overland Park, KS 66211
Manufactured in the United Kingdom.

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ZYCORTAL®

SUSPENSION (desoxycorticosterone pivalate injectable suspension)

Dechra Veterinary Technical Services

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

References

1. <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM488818.pdf> (accessed May 2016)
2. Data on file

Further reading

1. Scott-Moncrieff, J. C (2015) Canine and Feline Endocrinology, 4th Edition 485-520

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