Canine Hypoadrenocorticism: Diagnosis and Treatment of an Emerging Disease
Canine Addison’s Disease (hypoadrenocorticism) has always been extremely difficult to diagnose. Its symptoms are so often confused with those of other conditions that it is known as "The Great Pretender." Because Canine Addison’s Disease is so under-diagnosed, it is believed to have a low prevalence. However, with more careful screening, it may emerge as a more common ailment than previously believed.

We at Novartis Animal Health US, Inc. understand the importance of properly diagnosing this serious and potentially fatal disease, and have created this technical monograph to serve as your definitive guide to canine hypoadrenocorticism.

With this monograph, we are proud to educate you about PERCORTEN®-V (desoxycorticosterone pivalate), the only FDA-approved product to treat Addison’s Disease in dogs. If you have any questions, please contact your Novartis Animal Health US, Inc. Representative, or Novartis Animal Health US, Inc. Professional Services at 1-800-637-0281.

* NADA # 141-029, Approved by FDA.
# Table of Contents

1 **Introduction** .............................................................................................................. 3  
   1.1 History of Addison’s Disease ........................................................................... 3  
   1.2 Clinical significance of hypoadrenocorticism .............................................. 3  

2 **Anatomy and pathophysiology** .............................................................................. 5  
   2.1 Adrenal glands in health and disease ......................................................... 5  
   2.2 The role of mineralocorticoids ................................................................. 6  
   2.3 The role of glucocorticoids ....................................................................... 6  

3 **Diagnosis** .............................................................................................................. 7  
   3.1 Predisposing factors .................................................................................. 7  
   3.2 Clinical signs ............................................................................................ 8  
   3.3 Laboratory tests ........................................................................................ 9  

4 **PERCORTEN®-V (desoxycorticosterone pivalate)** .................................. 11  
   4.1 Product description ................................................................................... 11  
   4.2 Pharmacology ........................................................................................... 11  
   4.3 Clinical review .......................................................................................... 12  
   4.4 Dosing and safety ...................................................................................... 13  
   4.5 Addisonian crisis dosing .......................................................................... 14  
   4.6 Product benefits ....................................................................................... 15  

5 **Monitoring and maintenance** ............................................................................... 16  

6 **Frequently asked questions** ................................................................................ 17  

7 **Client information sheet** .................................................................................. 19  

8 **References** ......................................................................................................... 22  

9 **PERCORTEN-V product insert** .......................................................................... Back Cover
1. Introduction

1.1 History of Addison’s Disease
The first human cases of hypoadrenocorticism were described in the mid-1800s by an English physician, Thomas Addison, hence the name “Addison’s Disease.” The clinical syndrome included anemia, lethargy, poor heart function and gastrointestinal upset. It wasn’t until after the 1930s that glucocorticoids and mineralocorticoids, then finally commercially available, were used to treat and save humans from this otherwise fatal disease.

The first canine case of hypoadrenocorticism was reported in 1953. At that time, there were two compounds available for the treatment of Addison’s Disease, DOCA and DOCP; however, neither was approved for use in dogs. By 1960, a new oral drug for treating hypoadrenocorticism was introduced, Florinef® (fludrocortisone acetate), but again approved for human use only. In 1989, Novartis Animal Health US, Inc. (then Ciba-Geigy) provided DOCP to veterinarians for use as an “investigational drug” to treat dogs with Addison’s Disease.

1.2 Clinical significance of hypoadrenocorticism
Hypoadrenocorticism is characterized by inadequate production of glucocorticoids (cortisol) and/or mineralocorticoids (aldosterone) by the adrenal cortex. Primary hypoadrenocorticism, or Addison’s Disease, results from the destruction of the adrenal cortices and is fatal when untreated. Secondary hypoadrenocorticism occurs when the bilateral adrenal cortex atrophies due to insufficient secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland and is associated with only glucocorticoid deficiency.

Hypoadrenocorticism is a serious and potentially life-threatening endocrine disorder. The actual incidence of canine adrenocortical insufficiency at one large veterinary hospital has been calculated at 0.36 dogs per 1000. It has been suggested that these small numbers represent under-diagnosis (rather than minimal occurrence) of the disease. On average, in a typical practice with two veterinarians, each of whom sees approximately 1,500 dogs per year, should expect to diagnose one case of adrenal insufficiency each year.

It has been demonstrated that PERCORTEN-V is well tolerated with a low incidence of side effects. In a small percentage of treated dogs, depression, excessive thirst and urination, digestive, skin and coat changes, weakness, and injection site reactions (pain, abscesses) may occur. Some of these effects may resolve with adjustments in dose or interval of PERCORTEN-V or concomitant glucocorticoid administration. Do not use in pregnant dogs or in dogs that are suffering from congestive heart disease, severe renal disease, or edema. For additional information, please see product insert on back cover.

* Florinef is a registered trademark of Bristol-Myers Squibb.
Because many of the clinical signs of Addison’s Disease resemble those of other illnesses, it has been referred to as “The Great Pretender,”\(^3\) and can be an especially frustrating and challenging situation for the companion animal practitioner.\(^1,2\) Some dogs with Addison’s Disease may appear healthy and active, which can lead to misdiagnosis of the disease. The often obscure presenting signs and the subtle physical abnormalities induced by hypoadrenocorticism complicate an already difficult diagnosis. However, careful observation and a thorough medical history, in conjunction with specific laboratory tests, can reveal an accurate diagnosis. In cases where “classic Addisonian signs” are observed – hyperkalemia, hyponatremia, bradycardia and decreased blood pressure – hypoadrenocorticism should be strongly suspected.\(^2\)

There are many common causes of primary hypoadrenocorticism which include a variety of etiologies. In cases where lymphocyte and plasma cell infiltration is identified in the adrenal cortex, an immune-mediated basis has been suggested.\(^1,3\) Other less common causes include: infections (coccidioidomycosis, blastomycosis, or tuberculosis), hemorrhagic infarctions, granulomatous disease, metastatic neoplasia, trauma, and amyloidosis.\(^1,3\) Primary hypoadrenocorticism is seen most often in young to middle-aged dogs, an interesting contrast to the many other canine endocrinopathies, which tend to affect middle-aged to older dogs.\(^1,3\) Even though any gender can be affected, females seem to be predisposed.

Secondary hypoadrenocorticism in small animals is usually due to excessive or prolonged administration of exogenous glucocorticoids.\(^2\) In these cases, normal adrenal function usually returns within a few months after gradual withdrawal of medication.\(^2\)

1998 marks the year of the first FDA-approved veterinary drug for the treatment of canine hypoadrenocorticism — PERCORTEN-V from Novartis Animal Health US, Inc.

PERCORTEN\(^V\)-V (desoxycorticosterone pivalate), approved by the FDA in 1998, is the only veterinary product approved for treating canine hypoadrenocorticism. It has a well-established safety and efficacy profile.

**Summary – Section 1**
- **Causes of primary hypoadrenocorticism include a variety of etiologies.**
- **Primary hypoadrenocorticism (Addison’s Disease) is fatal if untreated.**
- **Addison’s Disease in dogs is complex and can be difficult to diagnose as the signs often mimic those of other diseases.**
- **Hypoadrenocorticism is often under-diagnosed.**
- **PERCORTEN-V is the only FDA-approved product for the treatment of canine hypoadrenocorticism.**
2. Anatomy and pathophysiology

2.1 Adrenal glands in health and disease

The importance of the adrenal glands is easily recognized by the number of vital substances that they secrete. Many of these hormones are required for normal physiologic function, as well as during times of stress (e.g., cortisol, epinephrine, norepinephrine, estrogen, testosterone, cortisone, aldosterone).

The adrenal gland is a two-part structure located on the cranial pole of each kidney. The inner portion, the medulla, secretes the catecholamines adrenaline and epinephrine. The outer portion, the cortex, consists of three distinct functional zones, each with a particular secretory purpose:

- The outer zona glomerulosa of the cortex is primarily involved with the synthesis and secretion of the mineralocorticoid, aldosterone.
- The middle zona fasciculata synthesizes and secretes glucocorticoids, of which cortisol is the most important in mammals.
- The inner zona reticularis of the adrenal cortex primarily secretes adrenal sex steroids (androgens and estrogens).

Figure 1.

*Gross anatomy of the normal kidney with adrenal glands*
Adrenal cortical functioning is often maintained even in the face of severe compromise. It is estimated that the significant operational reserves of mammalian adrenal glands allow for up to 90% impairment before clinical signs appear. Approximately 10% of animals with hypoadrenocorticism exhibit signs only after stressful situations (e.g., disease, trauma, surgery, travel, kenneling). However, as glandular reserves decline over time, an adrenal crisis (Addisonian crisis) may occur without an obvious precipitating event. This is a life-threatening medical emergency requiring immediate and intensive treatment. (See Section 3.2 Clinical signs and Section 4.5 Addisonian crisis dosing.)

In up to 5% of dogs, other endocrine diseases (i.e., hypothyroidism, diabetes mellitus, hypoparathyroidism) accompany or co-exist with Addison’s Disease.

2.2 The role of mineralocorticoids
All mineralocorticoids control electrolyte regulation and fluid balance. However, aldosterone, the primary adrenal mineralocorticoid, is important in Addison’s Disease because of its specific effect on sodium, chloride, and water resorption. Aldosterone also promotes potassium excretion, leading to extracellular fluid volume expansion and increased blood pressure.

In mineralocorticoid deficiency, potassium excretion is diminished, causing excessive sodium loss and hyperkalemia. Hyponatremia, in turn, leads to decreased circulating blood volume, resulting in prerenal azotemia, hypotension, dehydration, weakness and depression. Hyperkalemia may also lead to myocardial toxicity.

2.3 The role of glucocorticoids
Glucocorticoids, the most important of which is cortisol, affect nearly all somatic tissues. Glucocorticoids are important regulators of glucose, protein, and fat metabolism; they also inhibit inflammation. Glucocorticoids are released in times of stress and are controlled by the hypothalamus (corticotropin-releasing hormone (CRH)) and the pituitary gland (ACTH).

Glucocorticoid deficiency often manifests as anorexia, vomiting, melena, lethargy, and weight loss; it also predisposes to hypoglycemia, and results in impaired excretion of water free of sodium.

Summary – Section 2
- An Addisonian crisis is a life-threatening medical emergency requiring immediate and intensive treatment.
- Severely damaged adrenal glands can continue to function.
- Aldosterone is the most important mineralocorticoid.
- Cortisol is the most important glucocorticoid.
- Glucocorticoid deficiency often manifests as anorexia, vomiting, melena, lethargy and weight loss.
3. Diagnosis

3.1 Predisposing factors
In 1996, a retrospective medical records review of 225 dogs diagnosed with hypoadrenocorticism was conducted to evaluate the clinical and laboratory findings over a 14-year period. In this study, no specific risk factors for Addison’s Disease could be identified; however, results showed correlation with age and breed, and a predisposition in females (approximately 70% to 85% of hypoadrenal dogs are female).

Those breeds at a higher risk of developing Addison’s Disease are listed in Table 1. On the contrary, the breeds less likely to develop the disease are the Lhasa Apso and Yorkshire Terrier.

Table 1. Breeds of dogs at greater risk of developing Addison’s Disease

<table>
<thead>
<tr>
<th>Breed</th>
</tr>
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<tbody>
<tr>
<td>Great Dane</td>
</tr>
<tr>
<td>Portuguese Water Dog</td>
</tr>
<tr>
<td>Rottweiler</td>
</tr>
<tr>
<td>Standard Poodle</td>
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<tr>
<td>West Highland White Terrier</td>
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<tr>
<td>Wheaten Terrier</td>
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</tbody>
</table>

Relative to age, research studies show a somewhat higher incidence of Addison’s Disease in the 4- to 7-year age group (average age at diagnosis has been reported as 4.3 to 5.4 years). Then, as dogs age beyond 7 to 10 years, the odds of developing Addison’s Disease begin to decline. For dogs over 10 years old, the odds ratio approaches the level of the 1- to 4-year age group. Dogs younger than 1 year are the least likely to be diagnosed with hypoadrenocorticism. (See Table 2.)

Table 2. Odds of developing hypoadrenocorticism, by age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>0.12</td>
</tr>
<tr>
<td>1 to 4</td>
<td>1.01</td>
</tr>
<tr>
<td>4 to 7</td>
<td>1.90</td>
</tr>
<tr>
<td>7 to 10</td>
<td>1.51</td>
</tr>
<tr>
<td>greater than 10</td>
<td>1.06</td>
</tr>
</tbody>
</table>
3.2 Clinical signs

Hypoadrenocorticism is a chronic disease with a wide range of signs and symptoms. (See Table 3.)

Several of the more frequently observed signs, such as lethargy, weakness, and dehydration, mimic those of many other such common diseases as Renal Failure, Gastrointestinal Disease, etc.\(^1-4\) Additionally, clinical signs are intermittent and are often described as “waxing and waning.”\(^1-4\) Signs may vary between the chronic case and the acute crisis.\(^4\) For example, in some dogs with chronic hypoadrenocorticism, only a few, mild, intermittent clinical signs may be observed. In contrast, the dog in acute Addisonian crisis may exhibit signs that are quite severe and life threatening.\(^4\)

A thorough medical history is crucial in identifying hypoadrenocorticism. Sudden episodes of the more common signs, such as vomiting, diarrhea and weakness, may occur and quickly resolve with fluid and/or glucocorticoid therapy.\(^1,2\) However, over time, a repeated pattern of these signs develops which may suggest progressive adrenal insufficiency.

Table 3. Clinical signs and physical findings of hypoadrenocorticism\(^1-6\)

<table>
<thead>
<tr>
<th>Most commonly found:</th>
<th>May be present:</th>
<th>Less often reported:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression/lethargy</td>
<td>Melena</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Weakness</td>
<td>Hematemesis</td>
<td>Shaking/tremors</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Polyuria/polydipsia (PU/PD)</td>
<td>Painful/sensitive abdomen</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Bradycardia</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>Weak pulse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slow capillary refill</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hair loss</td>
<td></td>
</tr>
</tbody>
</table>

Due to the subtle and intermittent nature of these clinical signs, many dogs with hypoadrenocorticism are not diagnosed until they are presented in crisis. At this point, the veterinarian faces a medical emergency with a severely weak dog that is in hypovolemic shock.\(^1,2\)

The absence of a discrete set of clinical signs for hypoadrenocorticism contributes to the complexity of the disease. The nonspecific nature of abnormalities induced by Addison’s Disease can sometimes mask the actual condition.\(^1\) Therefore, in addition to a thorough medical history and physical examination, the veterinarian should rely on more advanced methods of diagnosis, including laboratory screening. (See Section 3.3 Laboratory tests.)
Table 4. The clinical signs of Addisonian crisis

- Severe weakness/depression
- Hypovolemic shock
  - Pale mucous membranes
  - Prolonged capillary refill time
  - Weak femoral pulse
  - Dehydration
- Bradycardia/arrhythmias
- Acute collapse

3.3 Laboratory tests

Confirmation of primary hypoadrenocorticism is achieved through laboratory analysis, including a complete blood count (CBC), a serum chemistry profile with an electrolyte panel and a serum cortisol concentration. Additionally, a urinalysis can be helpful in supporting the diagnosis, as specific gravity is often less than 1.030 in dogs with adrenal insufficiency. (See Table 5.)

Although a CBC is a valuable reference tool, there may be only minimal changes seen in the hypoadrenal dog. The lack of a stress leukogram, which one would expect to see in an ill dog, should raise the suspicion of hypoadrenocorticism. Common hematological findings in dogs with Addison’s Disease include lymphocytosis and eosinophilia. Often a normocytic, normochromic, non-regenerative anemia is present, which can be masked by dehydration. If dehydration exists, an increased packed cell volume may be seen.

The chemistry profile also may be unremarkable; however, electrolytes are key indicators of insufficient adrenal function. Most hypoadrenal dogs have a sodium/potassium ratio of less than 20:1 (serum sodium is usually <140 milliequivalents per liter (mEq/L), potassium is usually >6.0 mEq/L), although not all hypoadrenal dogs will show these classic electrolyte alterations. However, electrolyte levels alone cannot differentiate between primary and secondary hypoadrenocorticism.

Frequently, hypoadrenocorticism is misdiagnosed as renal failure due to the similar laboratory profiles found in both diseases (i.e., hypotremia, hyperkalemia and hypochloremia). Response to fluid therapy can be used as an indicator; the azotemia associated with Addison’s Disease often completely resolves with rehydration, while only a partial response is observed in cases of primary renal failure.

Table 5. Selected laboratory values in dogs with primary hypoadrenocorticism

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>NUMBER NORMAL VALUE</th>
<th>TESTED</th>
<th>NUMBER MEAN</th>
<th>NUMBER DECREASED (%)</th>
<th>INCREASED (%)</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium</td>
<td>136–50 mEq/L</td>
<td>36</td>
<td>129</td>
<td>22(60)</td>
<td>0(0)</td>
<td>106–146</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>3.5–5.0 mEq/L</td>
<td>36</td>
<td>7.2</td>
<td>0(0)</td>
<td>33(92)</td>
<td>4.7–10.8</td>
</tr>
<tr>
<td>Sodium/potassium ratio</td>
<td>≥27:1</td>
<td>36</td>
<td>19</td>
<td>35(97)</td>
<td>0(0)</td>
<td>11.2–29.1</td>
</tr>
<tr>
<td>BUN (pre-Rx)</td>
<td>9–25 mg/dl</td>
<td>36</td>
<td>84</td>
<td>0(0)</td>
<td>33(92)</td>
<td>12–223</td>
</tr>
<tr>
<td>BUN (after 24-hr Rx)</td>
<td>9–25 mg/dl</td>
<td>9</td>
<td>25</td>
<td>0(0)</td>
<td>4(44)</td>
<td>11–47</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>8.8–11.0 mg/dl</td>
<td>13</td>
<td>11.5</td>
<td>0(0)</td>
<td>8(62)</td>
<td>9.3–14.4</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>70–110 mg/dl</td>
<td>24</td>
<td>81.5</td>
<td>8(33)</td>
<td>4(17)</td>
<td>20–130</td>
</tr>
<tr>
<td>Serum bicarbonate</td>
<td>18–24 mM/L</td>
<td>16</td>
<td>14</td>
<td>13(81)</td>
<td>0(0)</td>
<td>9–19</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>—</td>
<td>25</td>
<td>1.024</td>
<td>—</td>
<td>—</td>
<td>1.008–1.062</td>
</tr>
</tbody>
</table>

The most accurate and reliable laboratory tool for a definitive diagnosis of hypoadrenocorticism is the ACTH stimulation test. This relatively simple assay includes collecting blood samples both before and after ACTH injections. Serum cortisol levels are compared and a positive diagnosis may be made when the concentration is undetectable or remains low (<4 micrograms per deciliter (mg/dl)) after ACTH stimulation. (See Figure 3.)

In cases where electrolyte values are normal, endogenous plasma ACTH concentrations can distinguish primary from secondary hypoadrenocorticism, but only when the blood sample is collected before the administration of glucocorticoids. If glucocorticoids are necessary (e.g., in emergency cases), dexamethasone should be the drug of choice as it does not interfere with the ACTH stimulation test. A high endogenous ACTH level indicates primary disease (i.e., normal pituitary gland functioning), with the lesion in the adrenal gland. Normal values for endogenous ACTH are between 20 picograms per milliliter (pg/ml) and 100 pg/ml. In dogs with primary hypoadrenocorticism, levels as high as 554 pg/ml to 4950 pg/ml have been reported.

Electrolyte levels are also monitored throughout the course of treatment, and are essential for determining dose adjustments of either PERCORTEN®-V (desoxycorticosterone pivalate) and/or supplemental steroids. (See Section 5 Monitoring and maintenance.)

Figure 3. Radioimmunoassay of plasma cortisol concentrations before and after exogenous ACTH stimulation

The ACTH stimulation test
- Plasma cortisol levels are measured before (baseline) and 2 hours after (2.2 U/kg IM gel) or 1 hour after (0.25 mg IV) ACTH administration.
- The normal resting range for healthy dogs is 1.0 µg/dl to 5.0 µg/dl; after stimulation, 6.0 µg/dl to 20.0 µg/dl.
- The pre- and post-ACTH stimulation levels in dogs with Addison’s Disease may be 1.0 µg/dl or less.

Summary – Section 3
- Certain breeds are more likely to develop Addison’s Disease than other breeds.
- Females are diagnosed more often than males.
- 4- to 7-year age group has the highest incidence.
- “Waxing and waning” clinical signs mimic other diseases.
- A repeated pattern of more common signs (vomiting, diarrhea, weakness) may suggest progressive adrenal insufficiency.
- One-third of dogs in Addisonian crisis – a medical emergency – present with bradycardia due to hyperkalemia.
- Electrolytes are key indicators of adrenal insufficiency.
- Response to fluid therapy can be used as an indicator to distinguish between renal failure and hypoadrenocorticism.
- ACTH stimulation test confirms hypoadrenocorticism.
- The lack of a stress leukogram should raise the suspicion of hypoadrenocorticism.
4. PERCORTEN®-V
(desoxycorticosterone pivalate)

4.1 Product description
PERCORTEN-V is indicated for use as replacement therapy in dogs with primary adrenocortical insufficiency (Addison’s Disease).

It is an injectable aqueous solution containing the pure mineralocorticoid, desoxycorticosterone pivalate (DOCP), a long-acting insoluble ester of desoxycorticosterone acetate (DOCA), and is administered intramuscularly as a microcrystalline depot where the crystals dissolve slowly and are absorbed over time.

Please see Sections 4.3 Clinical review and 4.4 Dosing and safety for clinical studies demonstrating the safety and efficacy of PERCORTEN-V.

4.2 Pharmacology
The active ingredient in PERCORTEN-V is desoxycorticosterone pivalate (DOCP), a mineralocorticoid hormone and an analog of desoxycorticosterone acetate (DOCA). The mode of action of DOCP is thought to be like that of other adrenocorticoid hormones; it controls the rate of synthesis of proteins by reacting with the receptor proteins in the cytoplasm to form a steroid-receptor complex. This complex then moves into the nucleus where it binds to chromatin, which results in genetic transcription of cellular DNA to messenger RNA. Steroid hormones like PERCORTEN-V appear to induce this genetic transcription and synthesis of specific proteins. DOCP is recognized as having the same qualitative effects as the natural mineralocorticoid hormone, aldosterone.

The structural formula of PERCORTEN-V

With proper medical management—most dogs suffering from Addison’s Disease may live a normal life span.
The most important therapeutic actions of PERCORTEN®-V (desoxycorticosterone pivalate) are the effects on sodium absorption and potassium excretion.

PERCORTEN-V increases the rate of sodium absorption by the renal tubules and the proximal convoluted tubule (although the latter is less important in sodium retention). It also enhances potassium excretion.

PERCORTEN-V also indirectly increases extracellular fluid volume, which expands blood volume and improves the venous return to the heart and cardiac output. This effect prevents the life-threatening hypotensive shock and prerenal azotemia observed in animals suffering from hypoadrenocorticism.

**4.3 Clinical review**

The results of several well-controlled clinical trials demonstrate the tolerability and efficacy of PERCORTEN-V.

The potential toxicity of DOCP was studied using 24 normal dogs. Four groups of six dogs (three male, three female) were injected with the drug on 3 consecutive days every 28 days for 6 months. The doses given represented an approximate total dose of 3 times, 9 times and 15 times the clinically effective dose (e.g., 2.2 mg/kg every 25 days). There were no deaths, and transient significant changes in serum sodium, potassium, and blood urea nitrogen (BUN) levels resolved by the end of the study. The authors concluded that DOCP was well tolerated at up to 15 times the clinically effective dose.

The efficacy of DOCP in the long-term management of canine hypoadrenocorticism (CHAC) was studied in 46 dogs over 75 days. Thirty-eight of the dogs had been diagnosed with CHAC and treated with oral fludrocortisone acetate for 1 month to 9 years prior to DOCP therapy. Eight cases were newly diagnosed. DOCP at 2.2 mg/kg was injected intramuscularly (IM) on days 0, 25, 50 and 75. Twenty-six dogs also received oral prednisolone once every 24 to 48 hours. Forty-four of the 46 dogs responded well to DOCP. One dog suffered a crisis of hypovolemia, hyperkalemia and hypoatremia between days 50 and 75. However, this dog recovered and eventually responded to DOCP therapy. One dog was dropped from the study due to poor response to therapy. It was concluded that DOCP provides adequate control of CHAC via its effect on serum electrolyte concentrations, and by maintaining tissue perfusion.
4.4 Dosing and safety

Dosing

The initial starting dose of PERCORTEN®-V (desoxycorticosterone pivalate) is administered as an IM injection at a rate of 2.2 milligrams per kilogram (mg/kg) of body weight (or 1.0 milligram per pound (mg/lb) of body weight) every 25 days. This dosing schedule may be adjusted depending on response to therapy as measured by serum sodium and potassium levels (see Section 5 Monitoring and maintenance). For most dogs, a dose range of 1.65 mg/kg to 2.2 mg/kg (0.75 mg/lb to 1.0 mg/lb) given every 21 to 30 days is effective.

Because PERCORTEN-V is a pure mineralocorticoid, it must be supplemented with daily oral glucocorticoid hormone replacement (e.g., prednisone or prednisolone) at a rate of 0.2 mg/kg to 0.4 mg/kg every 24 hours. As therapy continues, this dosage should gradually be reduced to the lowest dosage that prevents signs of hypocortisolism (e.g., lethargy, inappetence). Some dogs with primary adrenal insufficiency ultimately do not require glucocorticoid supplementation, except during times of stress (e.g., disease, trauma, surgery, travel, kenneling). It has been recommended that all owners have glucocorticoids available to administer to their dogs in times of stress.

The therapeutic effects of PERCORTEN-V are dependent on functional kidneys. Animals suffering from hypovolemia, prerenal azotemia and inadequate tissue perfusion must be rehydrated with intravenous fluid therapy prior to PERCORTEN-V treatment. Primary renal disease should be ruled out before starting PERCORTEN-V therapy.

PERCORTEN-V should not be given to pregnant dogs or dogs with congestive heart failure or edema. (Excessive doses of PERCORTEN-V may cause increased blood volume and pressure.)

See back cover for the PERCORTEN-V product insert.

Safety

Research has shown that PERCORTEN-V is well tolerated with a low incidence of serious side effects.

In a study of 822 dogs with Addison’s Disease, the following signs were observed, and include many of the same clinical signs that appear with canine hypoadrenocorticism:

- Depression (8%)
- Polydipsia/polyuria (6%)
- Skin and coat changes (5%)
- Anorexia (4%)
- Vomiting (4%)
- Weakness (2%)
- Incontinence (1.7%)
- Weight loss (1%)
- Diarrhea (1%)
- Pain on injection (0.7%)
- Injection site abscess (0.01%)
Most of these side effects resolve with adjustments in PERCORTEN®-V (desoxycorticosterone pivalate) dose or interval, or glucocorticoid dose.\(^9\)

Occasionally, dogs on PERCORTEN-V therapy may develop PU/PD, which may suggest excess glucocorticoids and/or excess PERCORTEN-V. Should this occur, close monitoring and dose adjustments are required. Initially, the glucocorticoid dose should be decreased, followed by, if necessary, a decreased PERCORTEN-V dose at unchanged intervals.

### 4.5 Addisonian crisis dosing

The dog that presents in Addisonian crisis — the end stage of progressively deteriorating adrenal gland disease — is in critical condition with clinical signs signaling a life-threatening situation.\(^1-4\) (See Section 3.2 Clinical signs and Table 4.) This is an extremely grave state that requires immediate attention and intense treatment.\(^1-4\) (See Table 6.)

In almost all crisis cases, the dog is hypovolemic, hyperkalemic and hyponatremic.\(^1-4\) The goal of treatment is to normalize the electrolyte imbalance, correct the hypovolemic shock and re-establish normal homeostasis. This is best accomplished by providing the following:

- Large amounts of intravenous (IV) fluids (i.e., physiologic saline)
- IV glucocorticoids at shock doses (e.g., dexamethasone sodium phosphate (2.0 mg/kg to 4.0 mg/kg) or dexamethasone (0.5 mg/kg to 2.0 mg/kg))
- PERCORTEN-V at 2.2 mg/kg IM

A lead-II electrocardiogram may be useful in monitoring the response to hyperkalemic therapy.

Once the dog is stable, continue PERCORTEN-V treatment and monitoring.

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<thead>
<tr>
<th>Table 6. Therapeutic management of an acute adrenal crisis(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Collect blood for CBC, chemistry profile, urinalysis, resting cortisol</td>
</tr>
<tr>
<td>2. Intravenous 0.9% saline IV (20–40 ml/lb) initially</td>
</tr>
<tr>
<td>3. ACTH stimulation test</td>
</tr>
<tr>
<td>A. 1 U/lb ACTH gel IM-sample at 0 and 2 hours in dogs</td>
</tr>
<tr>
<td>B. 0.25 mg synthetic ACTH IM in dogs sample at 0 and 1 hour</td>
</tr>
<tr>
<td>4. Glucocorticoid replacement</td>
</tr>
<tr>
<td>A. Hydrocortisone hemisuccinate or phosphate, 1–2 mg/lb IV slowly or</td>
</tr>
<tr>
<td>B. Prednisolone sodium succinate, 2–10 mg/lb IV or</td>
</tr>
<tr>
<td>C. Dexamethasone sodium phosphate, 0.25 to 1.0 mg/lb IV 5. Add 100 ml of 50% dextrose to each liter of saline if hypoglycemic</td>
</tr>
<tr>
<td>5. Mineralocorticoid replacement</td>
</tr>
<tr>
<td>A. Desoxycorticosterone pivalate, 1 mg/lb IM or SQ every 25 days or</td>
</tr>
<tr>
<td>B. Fludrocortisone acetate, 0.1 mg/10 lb/day once hydrated and not vomiting or having diarrhea or</td>
</tr>
<tr>
<td>C. Hydrocortisone sodium succinate or phosphate as above</td>
</tr>
<tr>
<td>6. Sodium bicarbonate-replacement needs calculated as follows: Body weight (kg) x 0.5 x base deficit. Give 1/4 of this amount IV over the first 6 hours of therapy. Administer only if TCO(_2) is &lt;12 mEq/L</td>
</tr>
<tr>
<td>7. Monitor:</td>
</tr>
<tr>
<td>A. ECG</td>
</tr>
<tr>
<td>B. Serum electrolytes</td>
</tr>
<tr>
<td>C. BUN, creatinine and urine output</td>
</tr>
<tr>
<td>D. Blood glucose, if low initially</td>
</tr>
</tbody>
</table>
4.6 Product benefits

Because PERCORTEN®-V (desoxycorticosterone pivalate) is a pure mineralocorticoid, it is readily absorbed by the body with a rapid onset of action. Therapeutic effect is usually observable shortly after the initial IM dose (often within 24–48 hours). To date, thousands of dogs with Canine Addison’s Disease have been successfully maintained with PERCORTEN-V, and provide documented proof of product safety as well as efficacy. Easy-to-follow dosing schedules – one injection every 25 days – plus simple dose adjustments, when necessary, are important advantages only PERCORTEN-V offers.

It has been estimated that the average duration of Canine Addison’s Disease is 4.9 years from time of diagnosis. However with proper medical management, hypoadrenal dogs may live a normal life span comparable to the life expectancy of dogs without adrenal insufficiency.

PERCORTEN-V, the only FDA-approved veterinary product for Canine Addison’s Disease, is clearly the drug of choice for treating this serious and life-threatening condition.

It has been demonstrated that PERCORTEN-V is well tolerated with a low incidence of side effects. In a small percentage of treated dogs, depression, excessive thirst and urination, digestive, skin and coat changes, weakness, and injection site reactions (pain, abscesses) may occur. Some of these effects may resolve with adjustments in dose or interval of PERCORTEN-V or concomitant glucocorticoid administration. Do not use in pregnant dogs or in dogs that are suffering from congestive heart disease, severe renal disease, or edema. For additional information, please see product insert on back cover.

Summary – Section 4

- PERCORTEN-V is the only FDA-approved veterinary product indicated for Canine Addison's Disease.
- PERCORTEN-V is fast-acting, safe and effective.
- PERCORTEN-V is administered once every 25 days.
- PERCORTEN-V is a pure mineralocorticoid and should be supplemented with daily glucocorticoid hormone replacement.
- The therapeutic effect of PERCORTEN-V is dependent upon functional kidneys.
- PU/PD in a dog receiving PERCORTEN-V may suggest excessive glucocorticoids.
- PERCORTEN-V can be used in emergency situations.
- With proper medical management, dogs with Addison's Disease may live a normal life span.
5. Monitoring and maintenance

Because dogs with hypoadrenocorticism require continuous treatment for the rest of their lives, regular monitoring is necessary to maintain adequate control of the disease.

Although a safe and efficacious dose of PERCORTEN®-V (desoxycorticosterone pivalate) has been established, some dogs may require dose adjustments throughout their treatment, a common practice in hormonal therapy. In order to measure the response to therapy, several repeat serological tests are performed at regular intervals. These frequent reassessments allow the veterinarian to properly adjust the dose of PERCORTEN-V, supplemental steroids or both, if necessary, to effect a positive outcome.

The most critical laboratory indicators of proper PERCORTEN-V dosing are electrolyte values. During the initial 2 to 3 months of PERCORTEN-V therapy, electrolytes should be checked at day 14 and 25. Dosing frequency may be adjusted based on these results (see **Table 7**). Once the dog is stabilized, repeat electrolyte analysis should be completed every 3 to 4 months.

**Table 7. Dosing guidelines and frequency adjustments**

- If all electrolyte values are normal at day 14 and normal at day 25, change to 30-day dosing frequency.
- If all electrolyte values are normal at day 14 but abnormal at day 25, change to 21-day dosing frequency.
- Once stable, check electrolytes every 3 to 4 months.

It is important to note that the most common cause for PERCORTEN-V treatment failure is insufficient supplemental gluocorticoid administration. In times of stress (e.g., disease, trauma, surgery, travel, kenneling), additional amounts of supplemental corticosteroids may be required. Signs of cortisol deficiency include profound depression, vomiting and diarrhea.

**Summary – Section 5**

- Routine electrolyte monitoring is an integral part of treatment.
- Stress increases the amount of steroid supplementation needed.
- During the initial two to three months of therapy, electrolytes should be checked at day 14 and at day 25.
- Some dogs may require dose adjustments throughout treatment.
1. Q. What is the vial size and concentration of PERCORTEN®-V (desoxycorticosterone pivalate)?
   A. PERCORTEN-V comes in a 4-ml sterile vial at a concentration of 25.0 mg/ml (a total of 100 mg of active ingredient).

2. Q. What is the appropriate dose of PERCORTEN-V?
   A. PERCORTEN-V should be administered by intramuscular (IM) injection at an initial rate of 2.2 mg/kg (1.0 mg/lb), approximately every 25 days. (See questions 6 and 7 for additional dosing information.)

3. Q. Does PERCORTEN-V need to be refrigerated?
   A. No. PERCORTEN-V may be stored at room temperature between 15° C and 30° C (59° F and 86° F). It should, however, be protected from light and freezing. Each unopened vial has a two-year shelf life from the date of manufacture.

4. Q. Does PERCORTEN-V require reconstitution?
   A. No. The PERCORTEN-V vial contains an aqueous suspension at the given concentration. The vial should be shaken thoroughly before each use.

5. Q. Can one vial of PERCORTEN-V be used for multiple injections?
   A. Yes. Each PERCORTEN-V vial is designed for multiple use. As with any injectable drug, proper sterile technique should be observed.

6. Q. Should PERCORTEN-V be supplemented with a corticosteroid, such as prednisone or prednisolone? If so, what is the standard dose?
   A. Yes. An oral corticosteroid supplement, such as prednisone or prednisolone, should be given every day while the dog is receiving PERCORTEN-V. The usual starting dose for glucocorticoid hormone replacement is 0.2 mg/kg to 0.4 mg/kg daily. For example, a 30- to 60-pound dog would require an initial dose of 5.0 mg/day. During times of stress, additional amounts of supplemental steroids are required to maintain adequate control of the disease. (Note: The most common cause for treatment failure is insufficient supplemental glucocorticoid administration. Signs of cortisol deficiency include profound depression, vomiting and diarrhea.)
7. Q. Will corticosteroid supplementation be required indefinitely?
   A. As therapy continues, the dosage of prednisone or prednisolone should be gradually reduced to the lowest dose that prevents signs of hypocortisolism (e.g., lethargy, inappetence). Many dogs can be maintained on relatively small doses of prednisone, supplementing as needed during times of stress.

8. Q. How often should electrolytes be monitored?
   A. During the initial 2 to 3 months of PERCORTEN®-V therapy, electrolytes should be checked at day 14 and day 25. The following guidelines should be used for adjusting PERCORTEN-V dosing:
   • If all values are normal at day 14 and normal at day 25, change to 30-day frequency
   • If all values are normal at day 14 but abnormal at day 25, change to 21-day frequency
   • Once stable, check electrolytes every 3 to 4 months

9. Q. What are the necessary steps for transitioning from Florinef® (fludrocortisone acetate) to PERCORTEN-V?
   A. No weaning is required when switching from Florinef to PERCORTEN-V. Follow these simple steps simultaneously:
   Step 1 – Discontinue all oral salt supplements
   Step 2 – Begin PERCORTEN-V injections and discontinue Florinef
   Step 3 – Begin daily corticosteroid supplement
   (See question 6 for more details on corticosteroid dosing.)

10. Q. How safe is PERCORTEN-V?
    A. Through extensive clinical trials lasting nearly 6 years (and including over 1,000 cases), PERCORTEN-V has demonstrated a wide margin of safety. Please see back cover for the PERCORTEN-V product insert and Section 4.3 Clinical review.

    It has been demonstrated that PERCORTEN-V is well tolerated with a low incidence of side effects. In a small percentage of treated dogs, depression, excessive thirst and urination, digestive, skin and coat changes, weakness, and injection site reactions (pain, abscesses) may occur. Some of these effects may resolve with adjustments in dose or interval of PERCORTEN-V or concomitant glucocorticoid administration. Do not use in pregnant dogs or in dogs that are suffering from congestive heart disease, severe renal disease or edema.

11. Q. How quickly does PERCORTEN-V work and when can I expect my patients to return to normal?
    A. The therapeutic effects of PERCORTEN-V is usually observed shortly after the initial IM dose (often within a few days). For optimal disease control, and to ensure that your patients are receiving the most appropriate PERCORTEN-V dose, follow the recommended dosing guidelines. (See questions 2, 6, and 7 for additional dosing information.)

* Florinef is a registered trademark of Bristol-Myers Squibb.
7. Client information sheet

The following two pages may be photocopied and given to your clients when you prescribe PERCORTEN®-V (desoxycorticosterone pivalate) for their dogs. This information offers a simple explanation of the basics of Canine Addison’s Disease and what is required of pet owners whose dogs are in treatment.
What dog owners need to know about Canine Addison’s Disease

Your veterinarian has just prescribed PERCORTEN\textsuperscript{®}-V (desoxycorticosterone pivalate) for your dog. PERCORTEN-V is the only FDA-approved treatment for Canine Addison’s Disease, and your veterinarian knows that it’s fast-acting, safe and effective.

Although Canine Addison’s Disease is a serious and potentially fatal condition, with regular injections of PERCORTEN-V and proper medical care, your dog should live a normal, happy life.

Caring for a dog with Canine Addison’s Disease will require frequent visits to your veterinarian and some extra attention from you. Because this disease is so complex, your veterinarian may occasionally need to adjust the dosage of PERCORTEN-V as well as the daily supplements you give your dog. It’s important that you pay careful attention to the veterinarian’s instructions. Here’s what you need to do:

Medication approximately every 25 days

Your dog will be receiving a medication, PERCORTEN-V, given by your veterinarian approximately every 25 days. It is essential to your dog’s health that this measure be taken seriously. Make appointments with your veterinarian and keep them in your calendar.

Your next appointment is on: ______________________

Daily supplements

Your dog needs supplements of glucocorticoid hormone replacement. These are given orally, every day. Over the next few months, your veterinarian will adjust the daily dosage. To begin with, follow these instructions.

**Daily dosage:** ____________

**How to administer:**

- ______________________
- ______________________
- ______________________

Watch your dog closely

It’s important that you note any symptoms your dog may have and report them to your veterinarian on your next visit. Use this chart to keep track.

- loss of appetite
- depression
- diarrhea
- frequent urinating
- frequent drinking
- lethargy
- vomiting
- weakness
- other: ____________

Note: If your dog experiences shock or collapse, call your veterinarian immediately. In scientific studies of PERCORTEN-V, a small percentage of dogs experienced such symptoms when beginning the treatments, but these symptoms were never fatal.
Answering dog owners’ questions about PERCORTEN®-V
(desoxycorticosterone pivalate)

1. Q. What is Canine Addison’s Disease?
   A. Canine Addison’s Disease is a condition in which a dog’s adrenal glands aren’t working properly. Adrenal glands produce chemicals called corticoids, which help regulate the body’s use of food and water.

2. Q. How does PERCORTEN-V work?
   A. PERCORTEN-V is a corticoid supplement. It replaces corticoids that your dog’s adrenal glands aren’t producing.

3. Q. How effective is PERCORTEN-V?
   A. PERCORTEN-V is very effective. In fact, one clinical study found PERCORTEN-V to be 100% effective in treating Canine Addison’s Disease. In a separate study, PERCORTEN-V was found to be 96% effective.

4. Q. How soon will PERCORTEN-V start to work?
   A. The effects of PERCORTEN-V can usually be seen within 24–48 hours.

5. Q. Is PERCORTEN-V safe?
   A. Yes. Rigorous clinical testing has proven how safe PERCORTEN-V is.

   You should speak to your veterinarian about possible side effects. It has been demonstrated that PERCORTEN-V is well tolerated with a low incidence of side effects. In a small percentage of treated dogs, depression, excessive thirst and urination, digestive, skin and coat changes, weakness, and injection site reactions (pain, abscesses) may occur. Some of these effects may resolve with adjustments in dose or interval of PERCORTEN-V or concomitant glucocorticoid administration. Do not use in pregnant dogs or in dogs that are suffering from congestive heart disease, severe renal disease or edema.

   Please see brief summary at bottom of page for more information.

6. Q. Is PERCORTEN-V recommended for pregnant dogs?
   A. Pregnant dogs should not be treated with PERCORTEN-V.

7. Q. Will my dog have Addison’s Disease for the rest of its life?
   A. Yes, but with proper medical management, your dog may live a normal life span compared to dogs without Addison’s Disease.

**Brief Summary:** Please consult full package insert for more information. **Indications:** PERCORTEN-V (desoxycorticosterone pivalate) Injectable Suspension is indicated as replacement therapy for the mineralocorticoid deficit in dogs with primary adrenocortical insufficiency. **Warnings:** Do not use this drug in pregnant dogs. Do not use in dogs suffering from congestive heart disease, severe renal disease or edema. **Precautions:** Some patients may exhibit side effects if dosage is too high or prolonged. Some of these effects may resolve with adjustments in dose or intervals of PERCORTEN-V or concomitant glucocorticoid medication. **Adverse Reactions:** The following adverse reactions have been reported following the use of PERCORTEN-V: depression, polyuria, polydipsia, anorexia, skin and coat changes, diarrhea, vomiting, weakness, weight loss, incontinence, pain on injection and injection site abscess. **Caution:** U.S. Federal law restricts this drug to use by or on the order of a licensed veterinarian. **How Supplied:** PERCORTEN-V is available in 4 ml multiple-dose vials and packed one vial per carton, each ml contains 25 mg desoxycorticosterone pivalate. **Storage Conditions:** PERCORTEN-V should be stored at room temperature between 59° F and 86° F (15°-30° C).
8. References


*PERCORTEN-V is a registered trademark of Novartis AG.*
PERCORTEN-V is a white aqueous suspension. Each ml contains 25 mg of desoxycorticosterone pivalate. Inactive ingredients are water for injection, methylcellulose, sodium carboxymethylcellulose, polysorbate 80, sodium chloride, and thimerosal.

CLINICAL PHARMACOLOGY:

Desoxycorticosterone pivalate (DOCP), like other adrenocorticoid hormones, is thought to act by controlling the rate of synthesis of proteins. It reacts with receptor proteins in the cytoplasm to form a steroid/receptor complex. This complex moves into the nucleus where it binds to chromatin that results in genetic transcription of cellular DNA to messenger RNA. The steroid hormones appear to induce transcription and synthesis of specific proteins which produce the physiologic effects seen after administration.

DOCP is a long-acting ester of desoxycorticosterone acetate (DOCA) which is recognized as having the same qualitatively effective as the natural mineralocorticoid hormone aldosterone.

The most important effect of DOCP is to increase the rate of renal tubular absorption of sodium. This effect is seen most intensely in the thick portion of the ascending limb of the loop of Henle. It also increases sodium absorption in the proximal convoluted tubule but this effect is less important in sodium import. Chloride follows the sodium out of the renal tubule.

Another important effect of DOCP is enhanced renal excretion of potassium. This effect is driven by the resorption of sodium that pulls potassium from the extracellular fluid into the renal tubules, thus promoting potassium excretion.

DOCP also acts to increase extracellular fluid volume. The enhanced retention of sodium, chloride and bicarbonate creates an osmotic gradient that promotes water absorption from the renal tubules. The retention of sodium, chloride and bicarbonate creates an osmotic gradient that promotes water absorption from the renal tubules. The percolation of sodium, chloride and bicarbonate creates an osmotic gradient that promotes water absorption from the renal tubules.

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