

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-029

B. Sponsor

Novartis Animal Health US, Inc.
Post Office Box 26402
Greensboro, NC 27404-6402

C. Proprietary Name

Percorten™-V

D. Established Name

desoxycorticosterone pivalate

E. Dosage

1. DOSAGE FORM

DOCP is marketed in a 4 mL multiple dose vial. Each mL contains 25 mg desoxycorticosterone pivalate (DOCP) in a sterile suspension for intramuscular injection.

2. ROUTE OF ADMINISTRATION

Before injection, shake the vial thoroughly to mix the microcrystals with the suspension vehicle. DOCP suspension is to be injected intramuscularly. Care should be used to prevent inadvertent intravenous injection, which may cause acute shock and collapse.

3. RECOMMENDED DOSAGES:

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE RESPONSE OF THE PATIENT TO THERAPY. Begin treatment at a dose of 1.0 mg per pound of body weight every 25 days. In some patients, the dose may be reduced. Serum sodium and potassium levels should be monitored to assure the animal is properly compensated. Most patients are well controlled with a dosage of 0.75 to 1.0 mg per pound of body weight, given every 21 to 30 days.

In treating canine hypoadrenocorticism, DOCP replaces the mineralocorticoid hormones only. Glucocorticoid replacement must be supplied by small doses of glucocorticoid hormones (e.g., prednisone or prednisolone). Oral supplementation with salt (NaCl) is not necessary with animals receiving DOCP

F. Dispensing Status

Rx: For use by or on the order of a licensed veterinarian

G. Indication

For use as replacement therapy for the mineralocorticoid deficit in dogs with primary adrenocortical insufficiency.

II. EFFECTIVENESS

Desoxycorticosterone pivalate has a history of use in people and animals. The human-labeled product, which is identical to the veterinary formulation, has been documented in the literature and referenced in text books for the treatment of naturally occurring canine hypoadrenocorticism for at least 20 years. In 1971 Mulnix first reported the use of injectable mineralocorticoids to manage clinical canine hypoadrenocorticism. Veterinary endocrinologists and clinicians, through extensive clinical experience have demonstrated that 1.0 mg/lb body weight is a safe and effective starting dose.^{1,2,3} In addition, all current review articles and text books now list DOCP as a viable treatment option for canine hypoadrenocorticism.^{4,5,6}

Each patient's dose must be carefully titrated to individual DOCP requirement. Serum Na⁺ and K⁺ should be monitored for titration of the dose and dosing frequency with DOCP.

Clinical Field Trials

Two multi-location clinical field trials were conducted to evaluate the efficacy and safety of DOCP in the management of canine hypoadrenocorticism under typical veterinary use conditions.

1. First Well-Controlled Clinical Field Trial

A multi-location controlled clinical field trial was conducted between May, 1989 and May, 1990, to evaluate the efficacy and safety of DOCP in the clinical management of naturally occurring primary canine hypoadrenocorticism. This study included dogs with a history of primary hypoadrenocorticism.

Investigators:

Dr. Edward C. Feldman

¹ Keeton, K.S.; Schechter, R.D.; Schalm, O.W.; Adrenocortical insufficiency in the dog, *California Veterinarian*, 1972; 26(6): 12-18.

² Baarschers, J.J.; Hommes, U.E.; Poll, P.H.A.; Een geval van morbus addison bij de hond [A case of Addison's Disease in a Dog]. *Tijdschr, Diergeneesk*; 1975; 100: 894-896.

³ Harlton, B.W.; Addison's Disease in a Dog., *VM/SAC*; 1976; 71(3): 285-288.

⁴ Feldman, E.C.; Nelson, R.W.; Hypoadrenocorticism (Addison's Disease), *Canine and Feline Endocrinology and Reproduction*, 2nd edition, W. B. Saunders, Philadelphia, 1996, 300.

⁵ Hardy, R.M.; Hypoadrenal Disease, *Veterinary Internal Medicine, Diseases of the Dog and Cat*, fourth edition, W. B. Saunders, Philadelphia, 1995, 1590.

⁶ Feldman, E.C.; Nelson, R.W.; Lynn, R.C.; Desoxycorticosterone pivalate (DOCP) treatment of canine and feline hypoadrenocorticism, *Current Veterinary Therapy XI, Small Animal Practice*, Kirk, R.W.; Bonagura, J.D.; ed W. B. Saunders, Philadelphia, 1992, 353-355.

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General Design: The specific trial objectives were achieved by comparing the relative effectiveness and safety of DOCP therapy to the reference period (Day 0) in the control of hypoadrenocortical clinical signs. Dogs selected for inclusion in the study were those normally presented to the veterinary hospitals with hypoadrenocortical insufficiency. Only dogs with a definitive diagnosis of primary hypoadrenocorticism were enrolled in the study. A definitive diagnosis was established if three of the following five criteria were met:

- a. serum sodium <135 mEq/l
- b. serum potassium >6 mEq/l

- c. pre ACTH cortisol levels <4 µg/dl
- d. post ACTH cortisol levels <4 µg/dl and/or
- e. endogenous ACTH greater than 300 pg/mL.

Prior to Day 0, six adrenal insufficient animals had received DOCP (many different doses or regimes) and 42 were being maintained on fludrocortisone. Seven of the dogs were newly diagnosed and had received neither drug. Other concomitant therapy with glucocorticoids which did not interfere with study evaluations was permitted.

Animals: A total of 69 dogs were enrolled in this study and 49 (71%) completed the trial; 53% were spayed females, 25% were castrated males, 16% were intact males and 6% were intact females. A total of 23 dog breeds were represented in the trial with Labrador Retriever (16%) being most prevalent. The average age at enrollment was 5.76 years with a range of 9 months to 13.5 years. The average length of clinically apparent adrenocortical insufficiency was one year.

Test material: final market formulation, supplied to investigators in 4 mL glass, multiple-dose vials. Each mL contained 25 mg of microcrystalline DOCP suspension.

Dosage: initial dose was 1 mg/lb every 25 days. The dose and dose interval were adjusted by the clinician to meet the individual patient's needs. Animals that had been previously treated with DOCP began the study at their titrated dose.

Route of administration: deep intramuscular injection

Test duration: 75 days for a total of three DOCP injections (days 0, 25, 50).

Pertinent Parameters measured: Body weight, physical examination, and serum chemistry values [blood urea nitrogen (BUN), serum creatinine, sodium, potassium, and chloride] were obtained on Days 0, 25, 50 and 75. Each animal served as its own control. On Days 14, 39 and 64, the dogs were presented for a monitoring visit at which the same evaluations were repeated.

Results:

Serum chemical and electrolyte values at diagnosis (determined from the medical record) were as follows: average serum sodium (128.4 mEq/l) was below normal; average serum potassium (7.28 mEq/l) was above normal; and average Na⁺/K⁺ ratio (18.09) was below normal.

ACTH stimulation test results at diagnosis: average pre-stimulation plasma cortisol was 0.28 µg/dl (reference range is 0-7 µg/dl); average post-ACTH plasma cortisol was 0.27 µg/dl (reference range 7-15 µg/dl).

Clinical signs observed at diagnosis included, in order of frequency, anorexia, depression/lethargy, weakness, vomiting, weight loss, diarrhea, and shock/collapse.

Efficacy: Both electrolyte levels and serum chemistry values were outside the reference ranges on Day 0 and returned to within normal limits with DOCP

treatment. Serum sodium, potassium, chloride, BUN and the ratio of sodium to potassium had returned to within normal limits by the first monitoring visit on Day 14 and remained within normal limits for the remainder of the study. Body weight increased throughout the study. See Table 1 for clinical trial results.

Table 1 First Clinical Trial: Test Results

	Day 0	Day 14	Day 25	Day 39	Day 50	Day 64	Day 75	Normals
Body Weight (lb.)	54.54	56.03	56.23	57.49	56.72	57.29	57.30	--
Dose DOCP (mg/lb.)	0.97	--	0.96	--	0.94	--	--	--
Serum Na⁺ (mEq/l)	137.4	149.6	146.3	148.2	145.9	147.9	144.5	142-154
Serum K⁺ (mEq/l)	5.61	4.21	5.03	4.31	4.95	4.25	4.92	4.0-5.4
Na⁺/K⁺ ratio	25.18	36.36	29.64	34.94	30.33	35.30	30.32	27-40
Serum Cl⁻ (mg/dl)	100.7	112.7	110.2	110.7	110.4	112.4	110.5	105-116
Serum BUN (mg/dl)	28.75	15.34	20.17	16.16	23.97	17.63	21.45	8-31
Serum Creatinine (mg/dl)	1.34	1.13	1.26	1.19	1.31	1.14	1.25	.8-1.6

Safety: All clinical signs observed are listed in Table 2. Signs of depression/lethargy, polyuria/polydipsia, skin problems and anorexia resolved with low level glucocorticoid supplementation. There were two cases in which loss of hormonal control occurred. These animals exhibited weakness and shock or collapse. Decreasing the DOCP dosage interval resolved these problems in both animals. One dog developed an injection-site abscess which resolved with drainage and antibiotic therapy.

Table 2 First Clinical Trial: Clinical Signs Observed

Reaction	No. of Cases
Depression/Lethargy	15
Anemia	2
Polyuria/Polydipsia	13
Behavior Change	2
Skin Problem	9
Hypoalbuminemia	2
Anorexia	7
Otitis	2
Diarrhea	6

Reaction	No. of Cases
Shock/Collapse	2
Weakness	6
Weight Loss	2
Flea Allergy Dermatitis	4
Ascites	1
Incontinence	3
Colitis	1
Electrolyte Abnormality	1
Gingivitis	1
Injection Abscess	1
Low Platelet Count	1
Muscle Spasms	1
Ocular Drainage	1
Panting	1
Shaking	1
Seizure	1
Coughing	1

The average DOCP dose requirement decreased over the 75-day study, from 0.97 mg/lb to 0.94 mg/lb, suggesting that most dogs probably need slightly less than 1.0 mg/lb for maintenance therapy. One animal was not adequately controlled on DOCP, but had not been controlled on fludrocortisone either. No deaths were related to DOCP therapy.

The final evaluation by the clinician was made on study Day 75. In 96% (51/53) of the cases, DOCP was judged to be an effective therapy for hypoadrenocorticism.

Conclusion: This trial demonstrated that desoxycorticosterone pivalate is effective in replacing the mineralocorticoid deficit in dogs suffering from primary hypoadrenocorticism. Adjustment of the DOCP dose or dosage frequency was sometimes necessary. DOCP, given in this regimen, provided control of the biochemical and clinical signs associated with canine hypoadrenocorticism.

2. Second Well-Controlled Clinical Field Trial

A multi-location controlled clinical field trial was conducted to evaluate the efficacy and safety of DOCP in the clinical management of naturally occurring canine primary hypoadrenocorticism.

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General Design: The specific trial objectives were achieved by comparing the relative effectiveness and safety of DOCP therapy at various time points to the reference period (Day 0) in the control of hypoadrenocorticism clinical signs.

Dogs selected for inclusion in the study were those normally presented to the veterinary hospital with newly diagnosed hypoadrenocorticism. A definitive diagnosis of hypoadrenocorticism was established by one of the following two criteria: 1) serum sodium:potassium ratio below 25:1; and/or, 2) abnormal ACTH stimulation test (both pre and post ACTH-stimulation cortisol levels below 7 µg/dl).

Prior to enrollment, fourteen animals received fludrocortisone (78%) and three received DOCP (17%) as replacement therapy for a short time. Three dogs (17%) had received

neither drug at study initiation. Other concomitant therapy with glucocorticoids which did not interfere with study evaluations was permitted.

Animals: A total of 21 dogs were enrolled in this study and 18 (86%) completed the trial; 50% were spayed females, 33% were castrated males, 11% were intact males and 6% were intact females. A total of 13 dog breeds were represented in the trial with Standard Poodle (3), Labrador Retriever (2), German Shepherd Dogs (2), and Rottweiler (2) being most prevalent. The average age at enrollment was 3.76 years; with a range of 18 months to 8 years. The average length of disease was 3 months.

Test material: final market formulation, supplied to investigators in 4 mL glass, multiple-dose vials. Each mL contained 25 mg of microcrystalline DOCP suspension.

Dosage: initial dose was 1 mg/lb every 25 days. The dose and dose interval were adjusted by the clinician to meet the individual patient's needs. Animals that had been previously treated with DOCP began the study at their titrated dose.

Route of administration: deep intramuscular injection Test duration: 75 days for a total of three DOCP injections (days 0, 25, 50).

Pertinent Parameters measured: On Days 0, 25, 50, and 75 all animals received a physical examination and were weighed. Serum chemistries values [blood urea nitrogen (BUN), serum creatinine, sodium, potassium, and chloride] were obtained on Days 0 and 75. Each animal served as its own control.

Results:

Serum chemical and electrolyte values at diagnosis (determined from the medical record) were as follows: average serum sodium (130.72 mEq/l) was below normal; average serum potassium (7.47 mEq/l) was above normal; and average Na⁺/K⁺ ratio (17.86) was below normal.

ACTH stimulation test results at diagnosis: average pre-stimulation plasma cortisol was 0.68 µg/dl (reference range is 0-7 µg/dl); average post-ACTH plasma cortisol was 1.34 µg/dl (reference range 7-15 µg/dl).

Clinical signs observed at diagnosis included, in order of frequency, anorexia, depression, vomiting, weakness, diarrhea, weight loss, shock/collapse, bradycardia, shaking/trembling, dehydration, melena, polyuria, lack of stool, ataxia, muscle atrophy, disorientation.

Efficacy: As a result of DOCP treatment, sodium, potassium, chloride, BUN and the ratio of sodium to potassium were in the normal range on Day 75. Body weight rose throughout the study and appeared to reach a plateau after Day 50. (see Table 3).

Table 3 Second Clinical Trial: Test Results

	Day 0	Day 25	Day 50	Day 75	Normals
Body Weight (lb.)	54.54	57.65	59.14	58.85	--

	Day 0	Day 25	Day 50	Day 75	Normals
Dose DOCP (mg/lb.)	0.99	0.99	0.97	--	--
Serum Na⁺ (mEq/l)	139.61	--	--	148.00	142-154
Serum K⁺ (mEq/l)	5.40	--	--	4.92	4.0-5.4
Na⁺/K⁺ ratio	26.42	--	--	30.59	27-40
Serum Cl⁻ (mg/dl)	105.94	--	--	112.39	105-116
Serum BUN (mg/dl)	28.41	--	--	17.23	8-31
Serum Creatinine (mg/dl)	1.13	--	--	1.16	0.8-1.6

Safety: All clinical signs observed are listed in Table 4. The depression and anorexia resolved with low level supplementation with glucocorticoids. Lowering the dose of glucocorticoids corrected the two cases of polyuria/polydipsia observed. Pain on injection was noted in two animals; and one animal collapsed immediately after the first injection, possibly due to inadvertent intravenous administration. No deaths were related to DOCP therapy.

Table 4 Second Clinical Trial: Clinical Signs Observed

Reaction	Number of Cases
Anorexia	3
Polyuria/Polydipsia	2
Skin Problem	3
Pain on Injection	2
Depression	1
Diarrhea	1
Elevated Liver Enzymes	1
Incontinence	1
Shock/Collapse	1

The final evaluation by the clinician was made on study Day 75. In all cases, DOCP was judged to be an effective therapy for hypoadrenocorticism.

Conclusion: This trial demonstrated that desoxycorticosterone pivalate is effective in replacing the mineralocorticoid deficit in dogs suffering from primary hypoadrenocorticism. Adjustment of the DOCP dose or dose frequency was necessary, as was occasionally the addition of glucocorticoid therapy.

III. ANIMAL SAFETY

A. Six-month Chronic Toxicity Study in Dogs with DOCP

Study Director: Dr. Edward Chow & Dr. John Turnier
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General Design: The objective of the study was to determine the safety of desoxycorticosterone pivalate in healthy Beagle dogs. DOCP was administered by intramuscular injection at 1X, 3X and 5X the intended labeled dose for three consecutive days at the beginning of each 28-day dosing interval for six months.

Animals: Five-month old pure bred Beagle dogs. Groups of six dogs (three of each sex) were assigned to each treatment group (total 12 males and 12 females).

Test material: 4 mL multi-dose vial of Percorten™-V as a 25 mg/mL suspension.

Dosage: 0, 2.2, 6.6 and 11 mg/kg administered for the first three days of each 28-day dosing interval.

Route of administration: Parenterally by deep intramuscular injection.

Test duration: Six months for a total of 18 doses

Pertinent parameters measured: Clinical signs, body weight, ophthalmic observations, food consumption and water consumption were evaluated throughout the study. Clinical chemistry tests and urinalysis were performed at monthly intervals. A complete necropsy and histopathology were performed on all dogs at termination.

Results: Administration of Percorten™-V did not affect survival or significantly alter clinical signs.

Urine Volume and Urinalysis: Polyuria and polydipsia were observed and urine creatinine concentration decreased (14-89 mg/dl) in all of the treated dogs.

Histopathology: Treatment-related changes were only observed in the kidneys when DOCP was administered at > 6.6 mg/kg. The primary renal

lesion consisted of glomerulonephropathy seen in all males at > 6.6 mg/kg, in one female at 6.6 mg/kg, and in all females at 11 mg/kg. Other possible treatment-related lesions in the kidney, observed sporadically in the 6.6 and 11.0 mg/kg groups, were tubular hyperplasia, inflammation and tubular dilatation.

Conclusions: Injections of Percorten™-V at doses as high as five-fold the monthly dose administered for 3X the use duration (3 days/month) for six months resulted in no mortality or any significant effects on body weight, food consumption, and ophthalmic observations at any dose level. However, polyuria and polydipsia were noted and creatinine concentration decreased in the 1X, 3X, and 5X groups. Histopathological treatment related results indicated renal changes at 6.6 mg/kg doses and higher.

IV. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is to be labeled for use in dogs, which are non-food animals.

V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations, and demonstrate that Percorten™-V, when used under labeled conditions of use, is safe and effective.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient of the drug (including any ester or salt of the active ingredient) has been approved in any other application. The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to diagnose and treat this disease condition in dogs.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.