Date of Approval: February 17, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-444

ZYCORTAL Suspension

desoxycorticosterone pivalate injectable suspension

Dogs

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

Sponsored by:

Dechra, Ltd.

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I. GENERAL INFORMATION

A. File Number

NADA 141-444

B. Sponsor

Dechra, Ltd.
Snaygill Industrial Estate
Keighley Rd.
Skipton
North Yorkshire, BD23 2RW
United Kingdom

Drug Labeler Code: 043264

US Agent:
Susan L. Longhofer
Dechra, Ltd.
7015 College Blvd
Suite 510
Overland Park, KS 66211

C. Proprietary Name

ZYCORTAL Suspension

D. Established Name

Desoxycorticosterone pivalate injectable suspension

E. Pharmacological Category

Mineralocorticoid

F. Dosage Form

Injectable suspension

G. Amount of Active Ingredient

25 mg/mL

H. How Supplied

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

I. Dispensing Status

Rx

J. Dosage Regimen

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.

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

K. Route of Administration

Subcutaneous injection

L. Species/Class

Dogs

M. Indication

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

II. EFFECTIVENESS

A. Dosage Characterization

The effectiveness of microcrystalline desoxycorticosterone pivalate (DOCP) therapy, administered intramuscularly, was evaluated in 60 dogs with hypoadrenocorticism.[1] Diagnosis was based on clinical signs of the disease, typical electrolyte abnormalities, and ACTH (adrenocorticotropic hormone) stimulation test results. DOCP was administered at a dosage of 2.2 mg/kg (1 mg/lb) of body weight by intramuscular injection on Days 0, 25, and 50. Physical examination was performed, and blood samples were obtained for serum biochemical analysis [sodium (Na^+), potassium (K^+), and blood urea nitrogen (BUN) concentrations] on Days 0, 14, 25, 39, 50, 64, and 75. The frequency of DOCP injections was adjusted based on interpretation of the interim serum biochemical analysis. A final physical examination was performed on Day 75 of the study and the course of treatment was evaluated. Hypoadrenocorticism was not adequately controlled with the recommended dosing regimen in 2 of the 60 dogs. One dog developed severe hyponatremia and hyperkalemia and shock-like signs, and was considered a treatment failure. The other dog was adequately treated when DOCP injections were given every 21 days. All remaining dogs were free of clinical signs associated with hypoadrenocorticism for at least one year after the study ended.

In a separate study, the effectiveness of DOCP, administered subcutaneously, was evaluated in 12 dogs with hypoadrenocorticism.[2] DOCP was administered at

[1] Lynn RC, Feldman EC, Nelson RW. Efficacy of Microcrystalline Desoxycorticosterone Pivalate for Treatment of Hypoadrenocorticism in Dogs. J Am Vet Med Assoc 1993; 202:392-396.
[2] McCabe MD, Feldman EC, Lynn RC, Kass PH. Subcutaneous Administration of Desoxycorticosterone Pivalate for the Treatment of Hypoadrenocorticism. J Am An Hosp Assoc 1995; 31:151-155.

a dosage of 2.2 mg/kg (1 mg/lb) of bodyweight by subcutaneous injection on Days 0, 25, 50, and 75 in a study design otherwise identical to the above described study. All dogs were adequately treated with the recommended dose and dosing interval, with the exception of one dog, which was adequately treated by subcutaneous DOCP injections every 21 days. All dogs were free of clinical signs associated with hypoadrenocorticism for at least one year after the study ended.

To explore the relative drug exposure resulting from intramuscular or subcutaneous administration of ZYCORTAL Suspension (DOCP), a two-treatment, two-period, two-sequence crossover study involving 6 dogs (3 per sequence; 3 males and 3 females) was conducted. Each period was 60 days in duration. An 11 mg/kg dose (5X the target starting dose of 2.2 mg/kg) was used to ensure that the drug could be measured with the analytical method. The study demonstrated similar total desoxycorticosterone (DOC) exposure [estimated as area under the curve (AUC) from time zero through the last quantifiable concentration] when administered by subcutaneous and intramuscular injection (Table 1). Maximum peak concentration (C_{max}) and time to peak concentration (T_{max}) were similar following subcutaneous and intramuscular injection. However, the rate of terminal decline in the respective DOC concentrations was different; concentrations appeared to remain elevated for a longer duration with the subcutaneous route as compared to the intramuscular route. The DOC concentrations at Days 28 and 31 were higher after subcutaneous injection than intramuscular injection. The average time to the last quantifiable concentrations was 49 days and 39 days for the subcutaneous and intramuscular injections, respectively. Although a longer half-life ($t_{½}$) was observed with subcutaneous compared to intramuscular administration, the large fluctuations-induced error associated with these estimates renders these values only approximate.

Table 1: Pharmacokinetics of ZYCORTAL Suspension after subcutaneous (SQ) and intramuscular (IM) administration

Route	AUC (ng*hr/mL)	C_{max} (ng/mL) Average ± SD	T_{max} (days) Average ± SD	[DOC] Day 28 (ng/mL) Average (min – max)	[DOC] Day 31 (ng/mL) Average (min – max)	$t_{½}$ (days) Average ± SD
SQ	204	13.2 ±4.94	10.0 ± 3.52	2.8 (1.9 – 4.2)	2.6 (<LOD – 3.8)	17.0 ± 6.63
IM	207	15.2 ± 3.52	9.7 ± 1.03	2.3 (<LOD – 3.5)	2.1 (<LOD – 3.1)	8.1 ± 4.20

SD = standard deviation
<LOD = analyte not detected (below limit of detection)

Therefore, based on published study results and the study comparing intramuscular and subcutaneous routes of administration, the starting dosage of 2.2 mg/kg (1 mg/lb) of DOCP, administered by subcutaneous injection every 25 days, was selected. Subsequent dose and dosing interval can be adjusted based on individual response.

B. Substantial Evidence

1. Field Study

a. Study Title

A multi-center clinical study of DP300 Suspension (desoxycorticosterone pivalate) for use as replacement therapy for the mineralocorticoid deficiency in dogs with primary adrenocortical insufficiency.

b. Study Dates

February 17, 2012 to September 24, 2013

c. Investigators

Peter Chapman, BVetMed (Hons), Levittown, PA
MaryAnn Crawford, DVM, Paramus, NJ
Jeffrey Dennis, DVM, Overland Park, KS
Mark Dorfman, DVM, Sandy Springs, GA
Samuel Geller, VMD, Quakertown, PA
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Roger Hostutler, DVM, Worthington, OH
Erick Mears, DVM, Tampa, FL
Noemi Benitah, DVM, Tinton Falls, NJ
Howard Robinson, DVM, Fort Collins, CO
Roger Sifferman, DVM, Springfield, MO
Justin Straus, DVM, Fairfield, NJ
Patricia Walters, VMD, West Bridgewater, MA
Auriane Beaufils, DVM, Maisons Alfort Cedex, France
Juan Hernandez, DVM, Arcueil, France

d. Study Design

(1) Objective

To evaluate the effectiveness of ZYCORTAL Suspension for use as a replacement therapy for the mineralocorticoid deficiency in dogs with primary hypoadrenocorticism, and to evaluate field safety.

(2) Study Animals

One hundred and fifty-two (152) dogs of various breeds were enrolled in the study. The dogs ranged in age from 0.5 to 12.4 years and weighed from 2.1 to 134.6 lbs. Seventy-four (74) dogs were male (9 intact, 65 castrated), and 78 were female (10 intact, 68 spayed). Of the 152 dogs enrolled, 133 (87.5%) were newly diagnosed cases and 19 (12.5%) were existing cases that had been treated with short acting mineralocorticoid replacement therapy for at least 30 days prior to enrollment. Dogs eligible for enrollment had a laboratory diagnosis of hypoadrenocorticism based on ACTH (adrenocorticotropic hormone) stimulation test with basal and post-stimulation cortisol values of ≤ 2 mcg/dL (≤ 55.2 nmol/L) and Na^+/K^+ ratio ≤ 27, and had one or more clinical signs consistent with primary hypoadrenocorticism (e.g.,

vomiting, diarrhea, lethargy, inappetence, polyuria/polydipsia, dehydration, or weakness/collapse) within 7 days of the laboratory diagnosis.

(3) Treatment Groups

Table 2: Treatment groups

Treatment Group	Initial Dosage	Route	Number of Dogs treated
ZYCORTAL Suspension	2.2 mg/kg (1 mg/lb)	Subcutaneous	113
Active control	2.2 mg/kg (1 mg/lb)	Intramuscular	39

(4) Drug Administration

Dogs were administered an initial dose of 2.2 mg/kg (1 mg/lb) of either ZYCORTAL Suspension or an FDA-approved desoxycorticosterone pivalate active control. Following the initial dose, the amount administered, or the frequency of administration, could be adjusted to individualize the dosage according to the clinical needs of the dog.

The mean final dose was 1.9 ± 0.27 mg/kg (range 1.2 - 2.5 mg/kg) and 2.0 ± 0.27 mg/kg (range 1.4 - 2.8 mg/kg) in the ZYCORTAL Suspension and active control groups, respectively. The mean final dose interval was 38.5 ± 12.5 days (range 20 - 99 days) and 38.8 ± 11.6 days (range 23 - 70 days) in the ZYCORTAL Suspension and active control groups, respectively.

Every dog received glucocorticoid replacement therapy during the study. The starting dosage of prednisone or prednisolone ranged from 0.1 to 1 mg/kg/day, with the majority of investigators using 0.2 to 0.4 mg/kg/day. The dose was decreased over time for most dogs to avoid adverse effects while maintaining therapeutic levels.

(5) Exclusion criteria

Specifically excluded from enrollment were pregnant or lactating bitches; dogs with iatrogenic hypoadrenocorticism; dogs with concurrent endocrine or metabolic disease; dogs receiving drugs that could interfere with the diagnostic ACTH stimulation test (e.g., etomidate or parenteral steroids within 30 days, topical or oral steroids within 14 days, and dexamethasone within 24 hours) and/or serum electrolyte concentrations (e.g., trimethoprim, amphotericin B, potassium depleting diuretics).

(6) Measurements and Observations

Dogs were evaluated at Day 25 ± 3, and Days 60, 90, 120, 150 and 180 ± 14 with a physical examination, clinical assessment, evaluation of in-house serum Na^+ and K^+ concentrations, and calculation of the Na^+/K^+ ratio. Hematology and chemistry samples were collected and evaluated on Day 25 ± 3. Hematology, chemistry, and urinalysis samples were evaluated on Days 90 and 180 ± 14. Safety observations (adverse events) were recorded throughout the study.

(7) Determination of Success

Effectiveness was evaluated at Day 90 ± 14. A dog was considered a treatment success if: 1) the investigator determined that the dog had remained clinically normal or had reduced clinical signs compared to baseline, and 2) the Na^+ and K^+ concentrations were within the reference range of the analyzer or the Na^+/K^+ ratio was between 27 and 32.

(8) Statistical Analysis

Non-inferiority of ZYCORTAL Suspension to the active control was evaluated by calculating a two-sided 95% confidence interval on the difference between the success rates at Day 90 ± 14 in the two groups. If the upper bound of this confidence interval was within the set margin (15%), ZYCORTAL Suspension was considered non inferior to the active control. The GLIMMIX procedure in SAS (SAS Institute, Cary NC) was used to evaluate non-inferiority. Treatment group was included as the only fixed effect in the model, and study site and the site-by-treatment interaction were included as random effects. A binomial distribution was assumed, and a logit link was used.

e. Results

Of the 152 dogs enrolled in the study, 135 dogs (101 ZYCORTAL Suspension and 34 active control) were included in the statistical analysis for Day 90 effectiveness. The percent success was 86.2% and 85.1% in the ZYCORTAL Suspension and active control groups, respectively. The upper bound of the 95% confidence interval for the difference of success rates between the active control and ZYCORTAL Suspension groups at Day 90 ± 14 was 13.6%, lower than the acceptance margin of 15%, thus supporting a conclusion of non-inferiority.

Effectiveness on Days 25, 60, and 180 was evaluated but not subjected to statistical analysis. Success rates for the ZYCORTAL Suspension and active control groups, respectively, were: 91.5% and 86.1% on Day 25; 81.6% and 86.1% on Day 60; and 88.3% and 86.9% on Day 180.

Throughout the study, there were no unusual findings in hematology, chemistry, and urinalysis values compared to baseline in either treatment group.

f. Adverse Reactions

All 152 dogs (113 ZYCORTAL Suspension and 39 active control) enrolled in the field study were evaluated for adverse reactions. See adverse reactions in Table 3, below.

Table 3: Adverse reactions

Adverse reaction	ZYCORTAL Suspension (n = 113)	Active Control (n = 39)
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/VI heart murmur was removed from the study after it developed congestive heart failure 17 days after the first administration of ZYCORTAL Suspension.

g. Conclusions

This study supports that subcutaneous administration of ZYCORTAL Suspension is safe and effective in controlling the clinical signs and electrolyte imbalance associated with primary hypoadrenocorticism in dogs.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

1. Study Title

A 6-month subcutaneous safety study in dogs using desoxycorticosterone pivalate (DOCP)

2. Location

Sinclair Research Center, LLC
Auxvasse, MO

3. Study Design

a. Objective

To evaluate the safety of desoxycorticosterone pivalate in dogs when administered subcutaneously once every 21 days for 6 months.

b. Study Animals

Male and female Beagle dogs, approximately 5.5 to 6 months of age, weighing between 7.3 to 9.7 kg.

c. Treatment Groups

Table 4: Treatment Groups

Treatment Group	Dose (mg/kg)	Number and Sex of Dogs
1	Negative control Saline (0 mg/kg)	4 M / 4 F
2	1X DOCP (2.2 mg/kg)	4 M / 4 F
3	3X DOCP (6.6 mg/kg)	4 M / 4 F
4	5X DOCP (11 mg/kg)	4 M / 4 F

d. Drug Administration

The test article was administered subcutaneously in the intrascapular area as five separate injections in 5X dogs, three separate injections in 3X dogs, and one single injection for 1X dogs. Dogs in the negative control group received five separate subcutaneous injections of saline. Dogs were dosed once every 21 days in a 6-month period, for 9 total doses.

e. Measurements and Observations

(1) Animal observations

Body weights, technician assessments, and veterinary physical examinations.

(2) Clinical pathology

Hematology, clinical chemistry, urinalysis, and coagulation parameters (prothrombin time (PT) and activated partial thromboplastin time (aPTT)).

(3) Gross necropsy and histopathology

A complete gross necropsy was performed for all dogs. Histopathology was performed for all routine collected tissues in the 0X and 5X groups. Only the adrenal glands, injection sites, kidneys, tissue masses, and any gross lesions were evaluated histologically in the 1X and 3X groups.

f. Statistical Analysis

The study was conducted as a completely randomized design with a three-way treatment structure, dose with four levels (0X, 1X, 3X, and 5X), sex with two levels (female, male), and time with the number of sampling events dependent on the response variable. In all analyses, the experimental unit was the individual animal. Differences were deemed significant if the p-value was < 0.10.

For continuous variables measured only once during the study, the data were analyzed using a linear model for a completely randomized design structure with a two-way treatment structure that included the fixed effects, treatment, sex, and the sex-by-treatment interaction.

For continuous variables measured more than once, the data were analyzed using a linear mixed model for a completely randomized design structure with repeated measures and a covariate. The fixed effects were treatment, sex, day, treatment-by-sex, sex-by-day, treatment-by-day, and treatment-by-sex-by-day. The pretreatment value nearest to the first day of treatment was used as the covariate.

4. Results

a. Clinical Observations

Injection site reactions, characterized by erythema and edema, were the most common treatment-related abnormal finding. Injection site reactions were observed across all groups; however, dogs in the 5X group were more frequently affected (0X= 5 dogs, 1X= 2 dogs, 3X= 5 dogs, 5X= 7 dogs).

b. Clinical Pathology

(1) Hematology

Decreased mean corpuscular volume was observed in 3X and 5X group dogs. This finding is considered treatment-related.

(2) Clinical Chemistry

The following findings are considered treatment-related:

a) Elevated mean globulin concentrations were observed in dogs in all treated groups compared to the control dogs on Days 85 and 180. Elevated mean globulin concentrations corresponded with decreased

albumin/globulin ratios in the 3X and 5X group dogs, and elevated total protein concentrations in dogs in all treated groups.

b) Mean potassium concentrations were decreased in dogs in all treated groups compared with the control dogs on Days 85 and 180.

c) Mean sodium concentrations were elevated in dogs in all treated groups compared with the control dogs on Days 85 and 180.

d) Mean chloride concentrations were decreased in 3X group dogs compared to the control dogs on Day 180.

e) Decreased blood urea nitrogen (BUN) concentrations were observed in dogs in all treated groups when compared with the control dogs on Days 85 and 180.

(3) Urinalysis

Decreased mean urine specific gravity concentrations were reported in all treated group dogs compared to the controls on Days 85 and 180. This finding is considered treatment-related.

c. Gross Necropsy

The following findings are considered treatment-related:

(1) Kidneys

Three dogs in the 3X group and all 8 dogs in the 5X group had subcapsular and/or cortical renal cysts. No 1X or control dogs were affected. The subcapsular cysts corresponded histologically with vascular tunica media hyperplasia.

(2) Injection sites

Irregular white plaques in the subcutaneous tissue were observed in three 1X dogs, five 3X dogs, and five 5X dogs. No control dogs were affected. This finding corresponded histologically with granulomatous inflammation.

d. Histopathology

The following findings are considered treatment-related:

(1) Kidneys

Minimal to moderate chronic inflammation of the renal cortices was observed in no control dogs, three 1X dogs, six 3X dogs, and seven 5X dogs. Minimal to moderate cortical tubular basophilia was observed in one control dog, three 1X dogs, six 3X dogs, and eight 5X dogs. Minimal to moderate cortical tubular dilation was observed in no control dogs, three 1X dogs, five 3X dogs, and eight 5X dogs. Minimal

to slight glomerulopathy was observed in no control or 1X dogs, two 3X dogs, and two 5X dogs. Slight to moderate subcapsular vascular hyperplasia was seen in no control dogs, one 1X dog, two 3X dogs, and two 5X dogs.

(2) Adrenal Glands

Minimal to moderate adrenal gland vacuolation (zona glomerulosa) was observed in two control dogs, five 1X dogs, four 3X dogs, and four 5X dogs.

(3) Injection site

Minimal to slight chronic-active inflammation of the subcutis was observed in no control dogs, one 1X dog, no 3X dogs, and two 5X dogs. Minimal to marked granulomatous inflammation of the subcutis was observed in no control dogs, three 1X dogs, seven 3X dogs, and five 5X dogs. Slight myofiber degeneration of the muscle subjacent to the injection site was observed in one 5X dog.

5. Conclusions

This laboratory study supports the safe use of ZYCORTAL Suspension at a dosage of 2.2 mg/kg once every 21 days. Treatment-related findings include: injection site changes characterized by erythema and edema, electrolyte changes, decreased BUN concentrations, adrenal gland vacuolation, and renal changes on gross pathology and histopathology.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ZYCORTAL Suspension:

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.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that ZYCORTAL Suspension, when used according to the label, is safe and effective for use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison's disease).

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is needed in the diagnosis and treatment of hypoadrenocorticism and the monitoring and treatment of any adverse reactions.

B. Exclusivity

ZYCORTAL Suspension, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of ZYCORTAL Suspension.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.