Date of Approval: December 5, 2008

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-291

VETORYL

Trilostane
Capsules
Dogs

VETORYL Capsules are indicated for the treatment of pituitary-dependent hyperadrenocorticism in dogs. VETORYL Capsules are indicated for the treatment of hyperadrenocorticism due to adrenocortical tumor in dogs.

Sponsored by:

Dechra Ltd.

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I. GENERAL INFORMATION:

A. File Number: NADA 141-291

B. Sponsor: Dechra Ltd.
Dechra House
Jamage Industrial Estate

Talke Pits
Stoke-on-Trent
Staffordshire, ST7 1XW
United Kingdom

Drug Labeler Code: 043264

U.S. Agent:

Karen Bond
Dechra Pharmaceuticals
7015 College Boulevard, Suite 525
Overland Park, KS 66211

C. Proprietary Name(s): VETORYL

D. Established Name(s): Trilostane

E. Pharmacological Category: Adrenocortical suppressant

F. Dosage Form(s): Capsule

G. Amount of Active Ingredient(s): 30 mg and 60 mg

H. How Supplied: Each capsule size comes in a box of three blister cards with 10 capsules/card.

I. How Dispensed: Rx

J. Dosage(s): The starting dose for the treatment of hyperadrenocorticism in dogs is 1.0-3.0 mg/lb (2.2 – 6.7 mg/kg) once a day based on body weight and capsule size. VETORYL Capsules should be administered with food.

Starting Dose

Weight range (pounds)	**Weight range** (kg)	**Starting dose** (mg) **ONCE DAILY**
≥ 10 to < 22	≥ 4.5 to < 10	30
≥ 22 to < 44	≥ 10 to < 20	60
≥ 44 to < 88	≥ 20 to < 40	120 (2 x 60 mg)
≥ 88 to < 132*	≥ 40 to < 60*	180 (3 x 60 mg)

*Dogs over 132 pounds (60 kg) should be administered the appropriate combination of capsules.

K. Route(s) of Administration: Oral

L. Species/Class(es): Dogs

M. Indication(s): VETORYL Capsules are indicated for the treatment of pituitary-dependent hyperadrenocorticism in dogs. VETORYL Capsules are indicated for the treatment of hyperadrenocorticism due to adrenocortical tumor in dogs.

II. EFFECTIVENESS:

A. Dosage Characterization:

The first large study to support the use of trilostane in dogs with hyperadrenocorticism was a study in the United Kingdom (UK) with 78 dogs with pituitary-dependent hyperadrenocorticism (Neiger et al, 2002). The mean starting dose was 5.9 ± 3.0 mg/kg once daily or once every other day, with a range from 1.8 to 20 mg/kg. The range in starting doses was due to the availability of only one capsule size containing 60 mg of trilostane. Based on this study, approximately 6.0 mg/kg/day became a standard starting dose.

The trilostane dose varies between dogs and for an individual dog over time, due to differences in physiological state and progression of disease. Therefore, the starting dose is adjusted based on changes in clinical signs, results of the biochemical testing adrenocorticotropic hormone (ACTH) stimulation test and adverse reactions.

The final dose reported in literature often exceeded 15 mg/kg/day, as shown in Table 1. Although the use of these high doses may have been due to veterinarian preference of the degree of adrenocortical suppression, the availability of only one capsule size resulted in small dogs receiving high doses. To improve dosing accuracy and flexibility, a 30 mg capsule was introduced. With a selection of capsule sizes, the dose could be more accurately titrated to the dog's size and response, thus lowering the recommended starting dose range to 2.2 to 6.7 mg/kg/day. Several studies in dogs with either pituitary- or adrenal-dependent hyperadrenocorticism (Sieber-Ruckstuhl et al, 2006; Eastwood et al, 2003; Benchekroun et al, 2007) supported the effectiveness and safety of this lower dose range. Thus, 2.2 to 6.7 mg/kg/day was selected as the starting dose for the US field study.

Table 1: Starting and Final Trilostane Doses in the Literature

Study	Starting Dose (mg/kg)		Final Dose (mg/kg)	
	Mean ± SD* or Median	Range	Mean ± SD or Median	Range
Neiger et al, 2002	5.9 ± 3.0	1.8-20.0	11.4 ± 4.83	N/A
Ruckstuhl et al, 2002	6.25 (median)	3.9-9.2	6.1 (median)	4.1-15.6
O'Connor, 2002	5.7 ± 2.4	2.7-10.7	13.6 ± 3.4	N/A
Hurley, 1999	N/A	Approx. 4-10	N/A	N/A
Braddock, 2002	6.2	2.8-10.0	19.4	5.3-50
Arenas et al, 2002 (twice daily dosing)	6.0	N/A	N/A	3-16

*Standard deviation

References:

Arenas CB, Melián CL, Pérez Alenza DM (2002). Use of trilostane administered twice daily for the treatment of hyperadrenocorticism. *2002 WSAVA Congress Proceedings.*

Benchekroun G, de Fornel-Thibaud P, Lafarge S, Hérepret D, Rosenbreg D (2007). Trilostane therapy of four dogs with metastatic secreting adrenocortical tumor. *Journal of Veterinary Internal Medicine* **21** (3): 646.

Braddock JA (2002). Investigation of some alternative therapies for management of pituitary-dependent hyperadrenocorticism in the dog. Thesis for Master of Veterinary Clinical Studies at The University of Sydney.

Eastwood JM, Elwood CM, Hurley KJ (2003). Trilostane treatment of a dog with functional adrenocortical neoplasia. *Journal of Small Animal Practice* **44** (3): 126-131.

Hurley KJ (1999). Trilostane in the treatment of canine hyperadrenocorticism. *European Society of Veterinary Internal Medicine Newsletter* **9** (2): 11-12.

Neiger R, Ramsey IK, O' Connor JT, Hurley KJ, Mooney CT (2002). Trilostane treatment of 78 dogs with pituitary-dependent hyperadrenocorticism. *The Veterinary Record* **150** (26): 799-804.

O'Connor JT (2002). Clinical, clinicopathological and therapeutic aspects of canine hyperadrenocorticism in Ireland. Thesis for Master of Veterinary Medicine at University College, Dublin.

Ruckstuhl NS, Nett CS, Reusch CE (2002). Results of clinical examinations, laboratory tests and ultrasonography in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. *American Journal of Veterinary Research* **63** (4): 506-512.

Sieber-Ruckstuhl NS, Boretti FS, Wenger M, Maser-Gluth C, Reusch CE (2006). Cortisol, aldosterone, cortisol precursor, androgen and endogenous ACTH concentrations in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. *Domestic Animal Endocrinology* **31** (1): 63-75.

B. Substantial Evidence:

1. UK Field Studies

Two studies are combined in this report. The first study was done when only a 60 mg capsule size was available. After a 30 mg capsule size was available, the second study was conducted in dogs under 10 kg.

Study Titles and Numbers:
Effectiveness Investigation of Trilostane in the Treatment of Canine Pituitary- and Adrenal- Dependent Hyperadrenocorticism. Report No. AVP/EC/TRILO/2005-1.

Efficacy and Safety of VETORYL Capsules in the Treatment of Canine Hyperadrenocorticism in Dogs Weighing Less than 10 kg. Report No. AVP/EC/TRILO/2005-2

Purpose: To assess the safety and effectiveness of trilostane in the treatment of pituitary- and adrenal-dependent hyperadrenocorticism in dogs.

Investigators and Locations:

AVP/EC/TRILO/2005-1
Reto Neiger
London, United Kingdom

Alex German
Bristol, United Kingdom

Grant Petrie
Woking, United Kingdom

David Bentley
Leicester, United Kingdom

AVP/EC/TRILO/2005-2
Reto Neiger
London, United Kingdom

Ian Ramsey
Glasgow, United Kingdom

Luca Ferasin
Bristol, United Kingdom

Animals: Animals recruited into the study were client-owned pet dogs either newly diagnosed with pituitary-dependent or adrenal-dependent hyperadrenocorticism or previously diagnosed, but not treated for at least three months. Diagnosis of hyperadrenocorticism was based on laboratory testing and presence of several of the following clinical signs: polyuria, polydipsia, polyphagia, excessive panting, lethargy, weakness, weight gain, abdominal distension, and alopecia. Laboratory testing included ACTH stimulation test, low-dose dexamethasone suppression test, high-dose dexamethasone suppression test, and endogenous ACTH levels.

Dogs enrolled into the studies: There were 75 dogs enrolled into the two studies.

a) AVP/EC/TRILO/2005-1: There were 60 dogs (11 intact males, 8 intact females, 13 castrated males, and 28 spayed females) enrolled. Ages ranged from 6 to 14.5 years and body weights ranged from 2.7 to 37.4 kg. Cause of hyperadrenocorticism: 46 (76.7%) pituitary-dependent, 7 (11.7%) adrenal-dependent, 7 (11.7%) unspecified.

b) AVP/EC/TRILO/2005-2: There were 15 dogs (5 intact males, 2 intact females, and 8 spayed females) enrolled. Ages ranged from 7 to 13.5 years and body weights ranged from 4.3 and 9.9 kg. Cause of hyperadrenocorticism: 13 (86.7%) pituitary-dependent, 1 (6.7%) adrenal-dependent, and 1 (6.7%) both pituitary- and adrenal-dependent.

Dogs evaluated for effectiveness: Thirty dogs met the criteria for inclusion in the evaluation of effectiveness.

a) AVP/EC/TRILO/2005-1: There were 21 dogs (4 intact males, 9 intact females, 6 castrated males, and 2 spayed females). Ages ranged from 8 to 14 years and body weights ranged from 2.7 to 30.0 kg. Cause of hyperadrenocorticism: 18 (85.7%) pituitary-dependent and 3 (14.3%) adrenal-dependent.

b) AVP/EC/TRILO/2005-2: There were 9 dogs (3 intact males, 1 intact female, and 5 spayed females). Ages ranged from 7 to 12 years and body weights ranged from 5.5 to 9.9 kg. Cause of hyperadrenocorticism: 8 (88.9%) pituitary-dependent and 1 (11.1%) both pituitary- and adrenal-dependent.

Treatment Groups: This open-label study used a historical control; no control animals were used. The effects of VETORYL Capsules were compared with experience historically derived from the predictable course of hyperadrenocorticism in dogs. Based on the natural history of hyperadrenocorticism, the disease is expected to continue to progress without spontaneous recovery.

Treatment Dosages:

a) AVP/EC/TRILO/2005-1: Dogs weighing >5 and <15 kg started on a 60 mg capsule once daily (4 - 12 mg/kg). Dogs weighing >15 kg and < 40 kg started on 120 mg once daily (3 - 8 mg/kg). The actual starting dose range was 1.9 to 20.7 mg/kg/day.

b) AVP/EC/TRILO/2005-2: All dogs started on a 30 mg capsule once daily (3 - 5.5 mg/kg).

Route of Administration: Oral, given with food.

Frequency of Treatment: All dogs started with once daily dosing. If the post-ACTH stimulation cortisol levels were > 250 nmol/L (> 9.1 µg/dL) and/or clinical signs had not improved by the 9 to 12 day visit, the dose was increased by 30 or 60 mg, depending on the study. Some dogs received twice daily dosing.

Duration of Study: 24 weeks

Study Design: There were five planned visits. Visit 1 was enrollment, testing and initiation of dosing. Subsequent visits were at 9 to 12 days, 4 weeks, 12 weeks, and 24 weeks after starting VETORYL Capsules. At each visit, clinical signs were assessed, and laboratory tests were run. The testing included ACTH stimulation test 4 to 6 hours after dosing, biochemical profile, and hematology. Owners completed daily dosing diaries, including comments on drug tolerability. Interim visits were scheduled 9 to 12 days after any dose increase.

Variables Measured: For a case to be considered a success, improvements needed to be made in both ACTH stimulation test results and clinical signs. An ACTH test was improved if the post-stimulation cortisol was < 250 nmol/L (< 9.1 µg/dL). Safety was evaluated by examining results of hematology and biochemistry testing and owner observations.

Statistical Analysis: The 95% confidence interval was calculated based on binomial distribution of the proportion of success animals.

Results: Treatment with trilostane was considered successful in 26 out of 30 dogs (86.7%) by showing improvement in both ACTH stimulation test results and clinical signs. The confidence interval for the success rate of 86.7% is between 69.3% and 96.2%.

Clinical signs: The clinical signs of polyuria (separated into urine quantity and urine frequency), polydipsia (increased thirst), and polyphagia (increased appetite) improved as early as the 9 to 12 day visit with some additional improvement throughout the study and at visit 5.

Table 2: Percentage of Improved Cases

Clinical Sign	Visit 2 (9 to 12 days)			Visit 5 (week 24)		
	2005-1*	2005-2*	**Combined**	2005-1*	2005-2*	**Combined**
Activity	4.8	11.1	**6.7**	14.3	0.0	**10.0**
Appetite	76.2	77.8	**76.7**	90.4	88.9	**90.0**
Panting	33.3	47.6	**43.3**	66.7	33.3	**56.7**
Thirst	90.5	100.0	**93.3**	90.5	88.9	**90.0**
Urine quantity	81.0	55.6	**73.3**	76.2	88.9	**80.0**
Urine frequency	81.0	77.8	**80.0**	90.5	88.9	**90.0**

* Study AVP/EC/TRILO/2005-1 and Study AVP/EC/TRILO/2005-2

Post-ACTH Cortisol: The post-ACTH stimulation test cortisol levels decreased in all but one dog by the 9 to 12 day visit. Final assessment of improvement was based on lowering the post-ACTH simulation cortisol levels to < 250 nmol/L (< 9.1 µg/dL) at visit 5.

Table 3: AVP/EC/TRILO/2005-1 post-ACTH cortisol (nmol/L)

Visit no.	No. of dogs	Mean	SD	Max	Min
1	21	837.4	326.1	1428	166
2	21	138.5	100.1	359	<20
3	18	115.2	70.6	280	<20
4	21	112.1	108.6	519	<20
5	21	87.6	59.3	212	<20

Table 4: AVP/EC/TRILO/2005-2 post-ACTH cortisol (nmol/L)

Visit no.	No. of dogs	Mean	SD	Max	Min
1	9	1068.9	425.8	1720	451
2	9	358.6	164.1	722	163
3	7	264.4	270.3	839	<20
4	9	257.1	390.0	1274	<20
5	9	99.2	73.0	194	<20

Adverse Reactions: Adverse reactions are reported here using the entire enrolled population of 75 dogs. Five dogs were withdrawn because of adverse reactions including lethargy, anorexia/inappetence, not drinking, vomiting, diarrhea, and muscle tremors. One dog died of pulmonary thromboembolism at week 5.

Another died of congestive heart failure at week 15. Three dogs were euthanized during the study due to renal failure (two dogs) and worsening arthritis and deterioration of appetite (one dog).

The most common adverse reactions were vomiting (17.3 %), lethargy (17.3%), diarrhea/loose stools (14.7%), and anorexia (6.7%). Other adverse reactions were: nocturia, upset stomach, corneal ulcer, cough, persistent estrus, vaginal discharge and vulvar swelling in a spayed female, hypoadrenocorticism, electrolyte imbalance (elevated potassium with or without decreased sodium), collapse and seizure, shaking, constipation, scratching, weight gain, and weight loss.

Conclusions: Trilostane was effective in lowering post-ACTH stimulation cortisol levels and improving clinical signs in dogs with pituitary- and adrenal-dependent hyperadrenocorticism. The most comment adverse reactions were vomiting, lethargy, diarrhea, and anorexia.

Long-term follow-up of cases: Follow-up data, in the form of medical records and case reports, from 49 dogs enrolled in the studies were reviewed for adverse reactions. Sixteen of the dogs were available for formal follow-up evaluation up to 24 months after the studies were completed. Follow-up included clinical evaluation, hematology, serum biochemistry, and ACTH stimulation testing.

The following adverse reactions were seen: hypoadrenocortical episode (including syncope, tremor, weakness, vomiting) in four dogs; hypoadrenocortical crisis or renal failure (including azotemia, vomiting, dehydration, collapse) in three dogs, chronic intermittent vaginal discharge, hemorrhagic diarrhea, occasional vomiting, and distal limb edema. One dog discontinued trilostane and continued to have hypoadrenocorticism when evaluated a year later. Deaths of five dogs were possibly related to trilostane use, including dogs that died or were euthanized because of renal failure, hypoadrenocortical crisis, hemorrhagic diarrhea, and hemorrhagic gastroenteritis.

2. US Field Study

Study Title and Number: A Multi-Center Clinical Study of VETORYL (trilostane) Capsules for the Treatment of Spontaneously Occurring Canine Hyperadrenocorticism
Report No. EC/TRILO2005/PROTO(FDA001)

Purpose: To evaluate the effectiveness of VETORYL Capsules under clinical conditions in dogs with spontaneously occurring hyperadrenocorticism (pituitary- and adrenal-dependent disease).

Investigators and Locations:
Dr. Samuel Geller
Quakertown, PA

Dr. Barrie Yallof
Philadelphia, PA

Dr. David Lukof
Harleysville, PA

Dr. Nancy Sanders
Gaithersburg, MD

Dr. Justin Straus
Fairfield, NJ

Dr. Donna Krochak
Alexandria, VA

Dr. MaryAnn Crawford
Paramus, NJ

Dr. Elizabeth Dole
Syracuse, NY

Dr. Rebecca Green
Tinton Falls, NJ

Dr. Nyssa Reine
New York, NY

Dr. Jason Pintar
Tinton Falls, NJ

Dr. Jennifer Mlekoday
New York, NY

Dr. Roger Sifferman
Springfield, MO

Animals: Animals recruited into the study were client-owned pet dogs either newly diagnosed with pituitary- or adrenal-dependent hyperadrenocorticism or previously diagnosed, but not treated for at least 30 days. Diagnosis of hyperadrenocorticism was based on laboratory testing and a minimum of two clinical signs indicative of hyperadrenocorticism: polyuria/polydipsia, polyphagia, lethargy (exercise intolerance), skin thinning, potbellied appearance, or loss of hair coat. Laboratory testing included ACTH stimulation test, low dose dexamethasone suppression test, endogenous ACTH concentration, and abdominal ultrasound (not all cases).

Dogs enrolled into the study: There were 107 dogs (2 intact males, 1 intact female, 33 castrated males, and 71 spayed females) of various breeds enrolled into the study. Ages ranged from 6 to 16 years and body weights ranged from 3 to 53.5 kg.

Cause of hyperadrenocorticism: 95 dogs (88.8%) were diagnosed with pituitary-dependent hyperadrenocorticism, 5 dogs (4.7%) were diagnosed with adrenal-dependent hyperadrenocorticism, 1 dog (0.9%) was diagnosed with both, and the diagnosis (localization of the disease process) was inconclusive in 6 dogs (5.6%).

Dogs evaluated for effectiveness: 83 dogs met the criteria for inclusion in the evaluation of effectiveness: 74 dogs with pituitary-dependent, 4 dogs with adrenal-dependent, 1 dog with both and 4 dogs with inconclusive localization. Of the 83 dogs that started the study, 80 completed the study. Three dogs were withdrawn due to owner compliance issue or non-trilostane-related medical conditions. A total of 8 dogs were evaluated as treatment failures due to possible trilostane-related adverse reactions.

Dogs evaluated for safety: All 107 enrolled dogs were evaluated for safety.

Treatment Groups: This open-label study used a historical control; no control animals were used. The effects of VETORYL Capsules were compared with experience historically derived from the predictable course of hyperadrenocorticism in dogs. Based on the natural history of hyperadrenocorticism, the disease is expected to continue to progress without spontaneous recovery.

Treatment Dosages: The targeted starting dose of trilostane was 2.2 – 6.7 mg/kg/day (actual range 2.5 – 6.2 mg/kg/day). Starting dosages were based on the following table:

Table 5: Treatment Groups

Weight	Dose	Dosage
≥ 4.5 kg to < 10 kg	30 mg once daily	3.0 – 6.7 mg/kg once daily
≥ 10 kg to < 20 kg	60 mg once daily	3.0 – 6.0 mg/kg once daily
≥ 20 kg to < 40 kg	2 x 60 mg once daily (120 mg)	3.0 – 6.0 mg/kg once daily
≥ 40 kg to < 60 kg	3 x 60 mg once daily (180 mg)	3.0 – 4.5 mg/kg once daily

Route of Administration: Oral, given with food.

Frequency of Treatment: All dogs started with once daily dosing. Dosage changes were based on clinical response and the results of ACTH stimulation and biochemistry tests. If the post-ACTH stimulation cortisol levels were > 9.1 µg/dL and/or clinical signs had not improved by the 14, 28 and 42 day visits, the dose was increased. Dosage decreases were made if the post-ACTH stimulation cortisol value was non-responsive (post-stimulation cortisol < 1.45 µg/dL 4-6 hours post dosing), or if there were clinical signs of oversuppression of adrenal function (for example, poor/reduced appetite, vomiting, lethargy, depression, or diarrhea).

Comparing the final to the initial dose, 55% of dogs required a dose adjustment, 31% with an increased dosage and 24% with a decreased dosage. The mean dose for dogs at the end of the study was 4.84 mg/kg/day (range 1.2-15.6 mg/kg/day). Fifteen dogs (14%) were dosed twice daily at some point during the study. Of those 15, 3 dogs reverted back to once daily dosing. The remaining 12 dogs ended the study with twice daily dosing. Thirty dogs (28%) required a dose discontinuation for at least one day before the treatment was resumed. Ten out of those 30 dogs (33%) required more than one dose discontinuation throughout the study.

Duration of Study: 84 days.

Study Design: There were seven planned visits. Visits 1-3 were enrollment, testing, and initiation of dosing. Subsequent visits were at 14, 28, 42, and 84 days after starting VETORYL Capsules. At each visit, clinical signs were assessed and laboratory tests were run. The testing included an ACTH stimulation test 4 to 6 hours after dosing and a biochemical profile. Hematology and urinalysis were evaluated pre-treatment and on Day 84. Owners completed daily dosing diaries, including comments on drug tolerability. Interim visits were scheduled approximately 14 days after any dose alteration.

Variables Measured to Determine Effectiveness:
- ACTH stimulation test with a post-stimulation cortisol of < 9.1 µg/dL.
- Improvements from the pre-treatment values in hematology and biochemistry test results, clinical signs, overall physical examination, as well as tolerability of the drug as reported by the owner.

Variables Measured to Determine Safety:
- Hematology and biochemistry test results.
- Physical examination parameters.
- Owner observations.

Determination of Success: For each dog, VETORYL Capsules were considered effective in a clinically valid case if on Day 84 **both** the post-ACTH cortisol concentration was <9.1 µg/dL, and the Investigator's clinical assessment documented clinical improvement. Dogs leaving the study were considered treatment failures unless it was clearly documented that the reason for non-completion was not health- or drug-related. The product was considered effective if the lower limit of the one-sided 95% confidence interval for treatment success was > 50%.

Statistical Analysis: Continuous outcome variables measured over time including post-ACTH cortisol and clinical chemistry were evaluated using methods appropriate for repeated measures. The statistical model included time as the only fixed effect. Continuous outcome variables measured once post-treatment were evaluated using analysis of variance. Categorical outcomes including clinical assessment and overall assessment were dichotomized and analyzed using the GLIMMIX procedure.

Results:
Success Rate:
Of the 80 cases remaining for the evaluation of treatment success on Day 84, 64 (80.0%) were considered treatment successes.

Table 6: Treatment Success

Day	No. Clinically Evaluable Cases (N)	Percent Success	Lower Limit of the One-sided 95% Confidence Interval
14	83	69.9%	61.6%
28	83	74.7%	66.9%
42	82	73.2%	65.1%
84	80	80.0%	72.6%

Post-ACTH Cortisol:
The pre-treatment mean post-ACTH cortisol level was elevated, which is consistent with the diagnosis of hyperadrenocorticism. When compared to pre-treatment, the mean post-ACTH cortisol levels at all four post-treatment days were statistically significantly decreased ($p<0.0001$).

Table 7: Post-ACTH Cortisol

Day	N	Mean (µg/dL)	95% Confidence Interval	
			Lower Limit	Upper Limit
Pre-treatment	83	32.3	30.0	34.6
14	79	5.3	4.6	6.1
28	79	5.4	4.8	6.1
42	77	5.4	4.6	6.2
84	72	4.5	3.6	5.4

Clinical Assessment:
Ninety-three percent of animals experienced an improvement in the clinical assessment by Day 84, as shown in the tables below.

Table 8: Clinical Assessment

Day	N	% Improved*	Lower Limit of the 95% One-sided Confidence Interval
14	79	84.8	76.6
28	79	92.4	85.6
42	77	93.5	86.8
84	72	93.1	86.0

*Percent of dogs considered to have improved relative to baseline (Day 0).

Clinical signs:
The clinical signs of hyperadrenocorticism (polyuria, polydipsia, polyphagia, panting, and lethargy) improved as early as Day 14 with continued improvement throughout the study through Day 84.

Table 9: Percentages of Animals with Improved Clinical Signs of Hyperadrenocorticism Compared to Day 0

Clinical Sign (N*)	Day	% Improved (N Improved/N Total for Day)
Activity (N=33)	14	67.7% (21/31)
	28	77.4% (24/31)
	42	90.0% (27/30)
	84	92.9% (26/27)
Appetite (N=57)	14	42.6% (23/54)
	28	55.6% (30/54)
	42	71.7% (38/53)
	84	83.7% (41/49)
Panting (N=47)	14	48.9% (22/45)
	28	75.6% (34/45)
	42	81.8% (36/44)
	84	87.8% (36/41)
Thirst (N=76)	14	40.3% (29/72)
	28	61.1% (44/72)
	42	75.7% (53/70)
	84	86.2% (56/65)
Urination (N=74)	14	35.2% (25/71)
	28	63.4% (45/71)
	42	72.5% (50/69)
	84	81.3% (52/64)

*N=number of dogs with an abnormal clinical sign consistent with hyperadrenocorticism (lethargy, polyphagia, panting, polydipsia, and polyuria) on Day 0.

Clinical Pathology:
Clinically significant changes between the pre- and post-treatment serum chemistry included decreases in alanine aminotransferase, aspartate transferase, alkaline phosphatase, Na/K ratio, and cholesterol ($p < 0.0001$), which are an indication of improvement of hyperadrenocorticism. Similarly, evaluation of the pre- and post-treatment complete blood counts revealed an increase in eosinophils (counts and percent), lymphocytes (counts and percent), and a decrease in segmented neutrophils (counts and percent) ($p < 0.0001$), which represents an improvement to the "stress leukogram" associated with hypercortisolemia.

Complete blood counts conducted pre- and post-treatment revealed a statistically significant ($p < 0.005$) reduction in red cell variables (HCT, HGB, and RBC), but the mean values remained within the normal range. Additionally, approximately 10% of the dogs had elevated BUN values ($\geq$ 40 mg/dL) in the absence of concurrent creatinine elevations. In general, these dogs were clinically normal at the time of the elevated BUN.

Adverse Reactions: Adverse reactions are reported here using the total population of 107 dogs.

Adrenal necrosis/rupture (2 dogs) and hypoadrenocorticism (2 dogs) were the most severe adverse reactions in the study. One dog died suddenly of adrenal necrosis, approximately 1 week after starting trilostane therapy. One dog developed an adrenal rupture, believed to be secondary to adrenal necrosis, approximately 6 weeks after starting trilostane therapy. This dog responded to trilostane discontinuation and supportive care.

Two dogs developed hypoadrenocorticism during the study. These two dogs had clinical signs consistent with hypoadrenocorticism (lethargy, anorexia, collapse) and post-ACTH cortisol levels $\leq$ 0.3 µg/dL. Both dogs responded to trilostane discontinuation and supportive care, and one dog required continued treatment for hypoadrenocorticism (glucocorticoids and mineralocorticoids) after the acute presentation.

Additional adverse reactions were observed in 93 dogs. The most common of these included diarrhea (31 dogs), lethargy (30 dogs), inappetence/anorexia (27 dogs), vomiting (28 dogs), musculoskeletal signs (lameness, worsening of degenerative joint disease) (25 dogs), urinary tract infection (UTI)/hematuria (17 dogs), shaking/shivering (10 dogs), otitis externa (8 dogs), respiratory signs (coughing, congestion) (7 dogs), and skin/coat abnormality (seborrhea, pruritus) (7 dogs).

Five dogs died or were euthanized during the study (1 dog secondary to adrenal necrosis, discussed above, 2 dogs due to progression of pre-existing congestive heart failure, 1 dog due to progressive central nervous system signs, and 1 dog due to cognitive decline leading to inappropriate elimination). In addition to the 2 dogs with adrenal necrosis/rupture and the 2 dogs with hypoadrenocorticism, an additional 4 dogs were removed from the study as treatment failures due to possible trilostane-related adverse reactions, including collapse, lethargy, inappetence, and trembling.

Conclusions: VETORYL Capsules were effective in lowering post-ACTH stimulation cortisol levels and improving clinical signs in dogs with hyperadrenocorticism. The most severe adverse reactions were adrenal necrosis/rupture, which resulted in the death of 1 dog, and hypoadrenocorticism. In addition, the most common adverse reactions included vomiting, lethargy, diarrhea, and anorexia.

Long-term follow-up of cases: Follow-up data, in the form of medical records and case reports, from 91 dogs enrolled in the study was reviewed for adverse reactions. Follow-up included clinical evaluation, hematology, serum biochemistry, and ACTH stimulation testing.

The adverse reactions were similar to the short-term study. Vomiting, diarrhea and general gastrointestinal signs were most commonly observed. Lethargy, inappetence/anorexia, heart murmur or cardiopulmonary signs, inappropriate urination/incontinence, urinary tract infections or genitourinary disease, and neurological signs were reported. Included in the US follow-up study were 14 deaths, 3 of which were possibly related to trilostane. Eleven dogs died or were euthanized during the study for a variety of conditions considered to be unrelated to or to have an unknown relationship with administration of trilostane.

III. TARGET ANIMAL SAFETY:

A. Margin of Safety Study:

Study Title and Number: A 3-Month Oral Safety Study in Dogs Using Trilostane. Laboratory Study Number 9744-06

Type of Study: Laboratory safety study following Good Laboratory Practices (GLP)

Study Dates: May 17, 2006 to August 22, 2006

Investigator and Location: Janice O. Kuhn, PhD, CABT
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General Design:
Purpose of the Study: To evaluate the safety of trilostane in dogs after oral administration at 1X, 3X, and 5X the recommended maximum starting dosage (6.7 mg/kg) twice daily for 3 consecutive months (90 days).

Description of Test Animals: Thirty-two 6-month old Beagles; the females weighed 5.0 to 8.9 kg and males weighed 6.4 to 10.3 kg at the start of the study.

Control and Treatment Groups: The 1X dose was based on an average starting dose of 6.7 mg/kg.

Table 10: Treatment Groups

Treatment Group	Dose	Number and Sex of Animals
Group I	0 (5 empty capsules) twice daily	8 (4M/4F)
Group II	1X (6.7 mg/kg) twice daily	8 (4M/4F)
Group III	3X (20.1 mg/kg) twice daily	8 (4M/4F)
Group IV	5X (33.5 mg/kg) twice daily	8 (4M/4F)

Inclusion Criteria/Exclusion Criteria: Satisfactory clinical pathology values, satisfactory size, body weight, and physical examination.

Dose Administration: Dogs were dosed twice daily for 90 days. The drug was given with food and dosage was adjusted for weight gain.

Variables Measured: General health status observations were made twice daily. Food consumption was measured twice daily and body weights were recorded weekly. Physical examinations and blood samples (serum chemistry panel, hematology, and coagulation values) were performed pre-treatment and on days 30, 60, (63 for blood tests) and 91. ACTH stimulation test was performed pre-treatment and day 90 or after observing signs of hypoadrenocorticism. Necropsy, including gross and microscopic examination, and organ weights was performed at the end of the study. Urine samples were collected but results were invalid because of processing errors.

Statistical Methods: Body weight, food consumption, physical examinations, urinalysis, hematology, and serum chemistry were analyzed using a repeated measures analysis of covariance. The fixed effects were gender, day, dose

group, and their 2- and 3-way interactions. The random effect was weight blocked within gender. The pre-treatment values of the dependent variables were included as covariates in the models. Organ weights relative to the body weight were analyzed using an analysis of variance. The fixed effects were gender, dose group, and gender-by-dose group, as appropriate. The random effect was weight blocked within gender. Data transformations were applied when necessary (log transformed). Categorical outcomes with multiple observations were analyzed using a generalized linear mixed model.

Results:
Deaths: Three dogs from the 3X and five dogs from the 5X group died between 23 and 46 days on the drug. They showed one or more of the following clinical signs: decreased appetite, decreased activity, weight loss, dehydration, soft stool, slight muscle tremors, diarrhea, lateral recumbency, and staggering gait. Bloodwork showed hyponatremia, hyperkalemia, and azotemia, which are consistent with hypoadrenal crisis.

Clinical signs, body weight, and food consumption: The dogs in the 3X and 5X groups had decreased activity. The 5X dogs had less weight gain than dogs in the other groups and food consumption was the same among all the groups.

Hematology: There were several hematology variables that showed statistical differences ($p<0.1$) in the study, both by study day and by dose. The 3X and 5X dogs had lower mean corpuscular volume than the 0X dogs. Other differences seen in the high dose groups were not clinically significant. There were no differences in the coagulation profiles among groups.

Serum Chemistry: There were several serum chemistry variables that showed statistical differences ($p<0.1$) in the study, both by study day and by dose. The 3X and 5X dogs had lower sodium, albumin, total protein, and cholesterol compared to the 0X dogs. There was a dose-dependent increase in the amylase in all treated groups. There was sporadic elevated potassium in those groups.

ACTH stimulation tests: The dogs in the 3X and 5X groups had no stimulation. The 1X dogs mean pre-stimulation cortisol was similar to the 0X groups. The 1X mean post-stimulation cortisol was lower than the 0X, but still showed some stimulation.

Necropsy examinations: Dose-dependent adrenal hypertrophy was seen in all treated groups. Histopathology showed adrenal cortical hypertrophy with increased size of the epithelial cells and disarray of the linear patterns of the zona glomerulosa and zona fasciculata. Three of the eight dogs that died had duodenal lesions. There was minimal cystic dilatation of mucosal crypts and multifocal minimal deep necrosis in the epithelial mucosa. Other findings in the dogs that died included diffuse hemorrhage of the stomach mucosa, thymic hemorrhage, atrial thrombosis, pyelitis and cystitis, and inflammation of the lungs.

Conclusions: Trilostane administered at 6.7 mg/kg twice daily for 90 days was generally well-tolerated by healthy Beagle dogs. Trilostane administered at higher doses of 20.1 mg/kg and 33.5 mg/kg twice daily resulted in significant morbidity and mortality due to the drug's inhibition of cortisol, corticosterone and aldosterone production. The dogs that died showed typical physical and

biochemical evidence of hypoadrenocorticism. The VETORYL label advises the veterinarian to carefully monitor the dog whenever the dose is increased.

B. Dose Tolerance Study:

Study Title and Number: Evaluation of the Oral Toxicity of Trilostane (WIN 24540) after being administered for 3 months to the Beagle dog

This study was conducted at the Winthrop Research Center in Longvic/Dijon, France from April to August 1979, to determine the oral safety of trilostane. Thirty-two, healthy, 5- to 6-month-old Beagles weighing 7.4 to 10.8 kg were enrolled and dosed once daily for 90 days based on the following groups:

Table 11: Treatment Groups

Treatment Group	Dose*	Number and Sex of Animals
Group I	0X (Control) once daily	8 (4M/4F)
Group II	1.2X (8 mg/kg) once daily	8 (4M/4F)
Group III	4.8X (32 mg/kg) once daily	8 (4M/4F)
Group IV	19X (128 mg/kg) once daily	8 (4M/4F)

*Final market formulation was not used. Capsules were emptied and contents suspended in tragacanth gum for oral administration. The control group was the same volume of tragacanth gum without drug.

Results:
Deaths: Four of the high dose group dogs died during the study. During the 4 to 15 days prior to death, the dogs were in poor condition with anorexia, vomiting, and weight loss. Death was preceded by prostration and hemorrhagic diarrhea. The deaths occurred as early as 38 days or up to 76 days on the drug.

Body weight: There was delayed weight gain in all the treated dogs compared to control dogs.

Hematology: There was a dose-dependent decrease in red blood cell count, hematocrit, and hemoglobin in the treated dogs. The bone marrow of all treated groups showed delayed maturation of the red blood cell line.

Serum Chemistry: The blood urea nitrogen was elevated in a dose-dependent manner in the treated groups. The 128 mg/kg group had elevated potassium and decreased sodium, cholesterol, and albumin.

Necropsy examinations: All doses caused gross hypertrophy of the adrenal glands with a dose-dependent hyperplasia of the zona fasciculata and zona reticularis. Hyperplasia was diffuse with some nodular areas. At 128 mg/kg, the zona glomerulosa was affected as well. There was an increase in the weights of the ovaries and decrease in the weights of the testes in the 32 mg/kg group. All treated dogs had hyperplasia of the cortical and medullary layers of the thymus.

Conclusions: There were dose-related drug effects seen in all treated groups, including poor weight gain, elevated BUN, electrolyte imbalances, decreased red cell parameters, and hypertrophy of the thymus and adrenal glands. At the highest dose group, four dogs died of hemorrhagic gastroenteritis.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. 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 VETORYL Capsules:

"Keep out of reach of children. Not for human use.

Wash hands after use. Do not empty capsule contents and do not attempt to divide the capsules. Do not handle the capsules if pregnant or if trying to conceive. Trilostane is associated with teratogenic effects and early pregnancy loss in laboratory animals.
In the event of accidental ingestion/overdose, seek medical advice immediately and take the labeled container with you."

The human user warnings are based on scientific articles, safety studies in human subjects, case reports, toxicological studies in laboratory species, and the material safety data sheets.

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 and 21 CFR part 514. The data demonstrate that VETORYL Capsules, when used according to the label, is safe and effective for the treatment of pituitary- and adrenal-dependent hyperadrenocorticism in dogs.

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 required to properly diagnose hyperadrenocorticism and to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity:

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 the approval because no active ingredient of the new animal drug has previously been approved.

VETORYL, as approved for the treatment of hyperadrenocorticism due to adrenocortical tumor in dogs, qualifies for SEVEN years of exclusive marketing rights beginning on the date of the approval. This drug qualifies for exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it is a designated new animal drug under section 571(a) of the act. Except as provided in section 573(c)(2) of the act, CVM may not

approve or conditionally approve another application submitted for such new animal drug with the same designated intended use as VETORYL.

C. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Facsimile Labeling:
- Package Insert
- Dog Owner Information about VETORYL (trilostane) CAPSULES
- Blister Label (30 mg)
- Blister Label (60 mg)
- Dispensing Container Carton Label (30 mg)
- Dispensing Container Carton Label (60 mg)