

HFA 2009-0665  
FOIS request

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# 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

FOIA-2009-N-0665

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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**

<b>Weight range (pounds)</b>	<b>Weight range (kg)</b>	<b>Starting dose (mg) ONCE DAILY</b>
≥ 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  $5.9 \pm 3.0$  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 adrenocorticotrophic 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, Boretta 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

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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
<b>Activity</b>	4.8	11.1	<b>6.7</b>	14.3	0.0	<b>10.0</b>
<b>Appetite</b>	76.2	77.8	<b>76.7</b>	90.4	88.9	<b>90.0</b>
<b>Panting</b>	33.3	47.6	<b>43.3</b>	66.7	33.3	<b>56.7</b>
<b>Thirst</b>	90.5	100.0	<b>93.3</b>	90.5	88.9	<b>90.0</b>
<b>Urine quantity</b>	81.0	55.6	<b>73.3</b>	76.2	88.9	<b>80.0</b>
<b>Urine frequency</b>	81.0	77.8	<b>80.0</b>	90.5	88.9	<b>90.0</b>

\* 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 common 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).

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Investigators and Locations:

Dr. Samuel Geller  
Quakertown, PA

Dr. Barrie Yallop  
Philadelphia, PA

Dr. David Lukof  
Harleysville, PA

Dr. Nancy Sanders  
Gaithersburg, MD

Dr. Justin Straus  
Fairfield, NJ

Dr. Donna Krochak  
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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  $> 9.1 \mu\text{g/dL}$  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  $< 1.45 \mu\text{g/dL}$  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  $< 9.1 \mu\text{g/dL}$ .
- 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  $< 9.1 \mu\text{g/dL}$ , 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**

<b>Day</b>	<b>N</b>	<b>% Improved*</b>	<b>Lower Limit of the 95% One-sided Confidence Interval</b>
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  $\leq 0.3$   $\mu\text{g/dL}$ . 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.

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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  
 Stillmeadow, Inc. Sugarland, TX

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**

<b>Treatment Group</b>	<b>Dose</b>	<b>Number and Sex of Animals</b>
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**

<b>Treatment Group</b>	<b>Dose*</b>	<b>Number and Sex of Animals</b>
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)

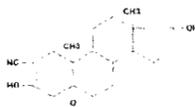
Dispensing Container Carton Label (60 mg)

 **VETORYL® CAPSULES**  
(trilostane)

Adrenocortical suppressant for oral use in dogs only.

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

**DESCRIPTION:**  
VETORYL Capsules are available in 2 sizes (30 and 60 mg) for oral administration based on body weight. Trilostane (4 $\alpha$ , 5 $\alpha$ -epoxy-17 $\beta$ -hydroxy-3-oxoandrostane-2 $\alpha$ -carbonitrile) is an orally active synthetic steroid analogue that selectively inhibits 3 $\beta$ -hydroxysteroid dehydrogenase in the adrenal cortex, thereby inhibiting the conversion of pregnenolone to progesterone. This inhibition blocks production of glucocorticoids and to a lesser extent, mineralocorticoids and sex hormones while steroid precursor levels increase. The structural formula is:



**INDICATIONS:**  
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.

**DOSAGE AND ADMINISTRATION:**  
Always provide the Client Information Sheet with prescription.  
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 (see Table 1). VETORYL Capsules should be administered with food.

**Table 1: 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.

After approximately 10-14 days at this dose, re-examine the dog and conduct a 4-6 hour post-dosing ACTH stimulation test. If physical examination is acceptable, take action according to Table 2.

**Table 2: Action at 10-14 day evaluation**

Post-ACTH serum cortisol		Action
µg/dL	nmol/L	
< 1.45	< 40	Stop treatment. Re-start at a decreased dose
1.45 to 5.4	40 to 150	Continue on same dose
> 5.4 to 9.1	> 150 to 250	<b>EITHER:</b> Continue on current dose if clinical signs are well controlled <b>OR:</b> Increase dose if clinical signs of hyperadrenocorticism are still evident*
> 9.1	> 250	Increase initial dose

\* Combinations of capsule sizes should be used to slowly increase the once daily dose.

**Individual dose adjustments and close monitoring are essential.** Re-examine and conduct an ACTH stimulation test 10-14 days after every dose alteration. Care must be taken during dose increases to monitor the dog's clinical signs and serum electrolyte concentrations. Once daily administration is recommended. However, if clinical signs are not controlled for the full day, twice daily dosing may be needed using combinations of capsule sizes to slowly increase the dose. For once daily doses up to 90 mg, increase the total daily dose by 30 mg and divide into 2 doses given 12 hours apart. For once daily doses ≥120 mg, increase the total daily dose by 60 mg and divide into 2 doses given 12 hours apart.

**Long Term Monitoring**

Once an optimum dose of VETORYL Capsules has been reached, re-examine the dog at 30 days, 90 days and every 3 months thereafter. At a minimum, this monitoring should include a thorough history and physical examination, ACTH stimulation test (conducted 4-6 hours after VETORYL Capsule administration), and serum biochemical tests (with particular attention to electrolytes, renal and hepatic function). A post-ACTH stimulation test resulting in a cortisol of < 1.45 µg/dL (< 40 nmol/L), with or without electrolyte abnormalities, may precede the development of clinical signs of hypoadrenocorticism. Good control is indicated by favorable clinical signs as well as post-ACTH serum cortisol of 1.45-9.1 µg/dL (40-250 nmol/L).

If the ACTH stimulation test is < 1.45 µg/dL (< 40 nmol/L) and/or if electrolyte imbalances characteristic of hypoadrenocorticism (hyperkalemia and hyponatremia) are found, VETORYL Capsules should be temporarily discontinued until recurrence of clinical signs consistent with hyperadrenocorticism and test results return to normal (1.45-9.1 µg/dL or 40-250 nmol/L). VETORYL Capsules may then be re-introduced at a lower dose.

Owners should be instructed to stop therapy and contact their veterinarian immediately in the event of adverse reactions or unusual developments.

**CONTRAINDICATIONS:**

The use of VETORYL Capsules is contraindicated in dogs that have demonstrated hypersensitivity to trilostane.

Do not use VETORYL Capsules in animals with primary hepatic disease or renal insufficiency.

Do not use in pregnant dogs. Studies conducted with trilostane in laboratory animals have shown teratogenic effects and early pregnancy loss.

**WARNINGS:**

In case of overdosage, symptomatic treatment of hypoadrenocorticism with corticosteroids, mineralocorticoids and intravenous fluids may be required.

Angiotensin converting enzyme (ACE) inhibitors should be used with caution with VETORYL Capsules, as both drugs have aldosterone-lowering effects which may be additive, impairing the patient's ability to maintain normal electrolytes, blood volume and renal perfusion. Potassium sparing diuretics (e.g. spironolactone) should not be used with VETORYL Capsules as both drugs have the potential to inhibit aldosterone, increasing the likelihood of hyperkalemia.

**HUMAN WARNINGS:**

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.

**PRECAUTIONS:**

Hypoadrenocorticism can develop at any dose of VETORYL Capsules. In some cases, it may take months for adrenal function to return and some dogs never regain adequate adrenal function.

A small percentage of dogs may develop corticosteroid withdrawal syndrome within 10 days of starting treatment. This phenomenon results from acute withdrawal of circulating glucocorticoids; clinical signs include weakness, lethargy, anorexia, and weight loss<sup>1</sup>. These clinical signs should be differentiated from an early hypoadrenocortical crisis by measurement of serum electrolyte concentrations and performance of an ACTH stimulation test. Corticosteroid withdrawal syndrome should respond to cessation of VETORYL Capsules (duration of discontinuation based on the severity of the clinical signs) and restarting at a lower dose.

Mitotane (o,p'-DDD) treatment will reduce adrenal function. Experience in foreign markets suggests that when mitotane therapy is stopped, an interval of at least one month should elapse before the introduction of VETORYL Capsules. It is important to wait for both the recurrence of clinical signs consistent with hyperadrenocorticism, and a post-ACTH cortisol level of > 9.1 µg/dL (> 250 nmol/L) before treatment with VETORYL Capsules is initiated. Close monitoring of adrenal function is advised, as dogs previously treated with mitotane may be more responsive to the effects of VETORYL Capsules.

The use of VETORYL Capsules will not affect the adrenal tumor itself. Adrenalectomy should be considered as an option for cases that are good surgical candidates.

The safe use of this drug has not been evaluated in lactating dogs and males intended for breeding.



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#### ADVERSE REACTIONS:

The most common adverse reactions reported are poor/reduced appetite, vomiting, lethargy/dullness, diarrhea, and weakness. Occasionally, more serious reactions, including severe depression, hemorrhagic diarrhea, collapse, hypoadrenocortical crisis or adrenal necrosis/rupture may occur, and may result in death.

In a US field study with 107 dogs, adrenal necrosis/rupture (two dogs) and hypoadrenocorticism (two dogs) were the most severe adverse reactions in the study. One dog died suddenly of adrenal necrosis, approximately one week after starting trilostane therapy. One dog developed an adrenal rupture, believed to be secondary to adrenal necrosis, approximately six 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) (8 dogs).

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

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.

In a long term follow-up study of dogs in the US effectiveness study, 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, three 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.

In two UK field studies with 75 dogs, the most common adverse reactions seen were vomiting, lethargy, diarrhea/loose stools, and anorexia. Other adverse reactions included: nocturia, corneal ulcer, cough, persistent estrus, vaginal discharge and vulvar swelling in spayed female, hypoadrenocorticism, electrolyte imbalance (elevated potassium with or without decreased sodium), collapse and seizure, shaking, muscle tremors, constipation, scratching, weight gain, and weight loss. One dog died of congestive heart failure and another died of pulmonary thromboembolism. Three dogs were euthanized during the study. Two dogs had renal failure and another had worsening arthritis and deterioration of appetite.

In a long term follow-up of dogs included in the UK field studies, the following adverse reactions were seen: hypoadrenocortical episode (including syncope, tremor, weakness, and vomiting), hypoadrenocortical crisis or renal failure (including azotemia, vomiting, dehydration, and collapse), chronic intermittent vaginal discharge, hemorrhagic diarrhea, occasional vomiting, and distal limb edema. Signs of hypoadrenocorticism were usually reversible after withdrawal of the drug, but may be permanent. One dog discontinued VETORYL Capsules and continued to have hypoadrenocorticism when evaluated a year later. Included in the follow-up were reports of deaths, at least 5 of which were possibly related to use of VETORYL Capsules. These included dogs that died or were euthanized because of renal failure, hypoadrenocortical crisis, hemorrhagic diarrhea, and hemorrhagic gastroenteritis.

Foreign Market Experience: The following events were reported voluntarily during post-approval use of VETORYL Capsules in foreign markets. The most serious adverse events were death, adrenal necrosis, hypoadrenocorticism (electrolyte alterations, weakness, collapse, anorexia, lethargy, vomiting, diarrhea, and azotemia), and corticosteroid withdrawal syndrome (weakness, lethargy, anorexia, and weight loss). Additional adverse events included: renal failure, diabetes mellitus, pancreatitis, autoimmune hemolytic anemia, vomiting, diarrhea, anorexia, skin reactions (rash, erythematous skin eruptions), hind limb paresis, seizures, neurological signs from growth of macroadenomas, oral ulceration, and muscle tremors.

For a copy of the Material Safety Data Sheet (MSDS), or to report adverse reactions, call Dechra Veterinary Products at (866) 933-2472.

#### INFORMATION FOR DOG OWNERS:

Owners should be aware that the most common adverse reactions may include: an unexpected decrease in appetite, vomiting, diarrhea, or lethargy and should receive the Client Information Sheet with the prescription. Owners should be informed that control of hyperadrenocorticism should result in resolution of polyphagia, polyuria and polydipsia. **Serious adverse reactions associated with this drug can occur without warning and in rare situations result in death (see ADVERSE REACTIONS).** Owners should be advised to discontinue VETORYL Capsules and contact their veterinarian immediately if signs of intolerance are observed. Owners should be advised of the importance of periodic follow-up for all dogs during administration of VETORYL Capsules.

#### CLINICAL PHARMACOLOGY:

Trilostane absorption is enhanced by administration with food. In healthy dogs, maximal plasma levels of trilostane occur within 1.5 hours, returning to baseline levels within twelve hours, although large inter-dog variation occurs. There is no accumulation of trilostane or its metabolites over time.

#### EFFECTIVENESS:

Eighty-three dogs with hyperadrenocorticism were enrolled in a multi-center US field study. Additionally, 30 dogs with hyperadrenocorticism were enrolled in two UK field studies. Results from these studies demonstrated that treatment with VETORYL Capsules resulted in an improvement in clinical signs (decreased thirst, decreased frequency of urination, decreased panting, and improvement of appetite and activity). Improvement in post-ACTH cortisol levels occurred in most cases within 14 days of starting VETORYL Capsules therapy.

In these three studies, there were a total of 10 dogs diagnosed with hyperadrenocorticism due to an adrenal tumor or due to concurrent pituitary and adrenal tumors. Evaluation of these cases failed to demonstrate a difference in clinical, endocrine, or biochemical response when compared to cases of pituitary-dependent hyperadrenocorticism.

#### ANIMAL SAFETY:

In a laboratory study, VETORYL Capsules were administered to 8 healthy 6 month old Beagles per group at 0X (empty capsules), 1X, 3X, and 5X the maximum starting dose of 6.7 mg/kg twice daily for 90 days. Three animals in the 3X group (receiving 20.1 mg/kg twice daily) and five animals in the 5X group (receiving 33.5 mg/kg twice daily) died between Days 23 and 46. 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, consistent with hypoadrenocortical crisis. Post-mortem findings included epithelial necrosis or cystic dilation of duodenal mucosal crypts, gastric mucosal or thymic hemorrhage, atrial thrombosis, pyelitis and cystitis, and inflammation of the lungs.

ACTH stimulated cortisol release was reduced in all dogs treated with VETORYL Capsules. The dogs in the 3X and 5X groups had decreased activity. The 5X dogs had less weight gain than the other groups. The 3X and 5X dogs had lower sodium, albumin, total protein, and cholesterol compared to the control dogs. The 5X dogs had lower mean corpuscular volume than the controls. There was a dose dependent increase in amylase. Post-mortem findings included dose dependent adrenal cortical hypertrophy.

#### STORAGE INFORMATION:

Store at controlled room temperature 25°C (77°F) with excursions between 15°-30°C (59°-86°F) permitted.

#### HOW SUPPLIED:

VETORYL Capsules are available in 30 and 60 mg strengths, packaged in aluminum foil blister cards of 10 capsules, with 3 cards per carton.

#### NADA 141-291, Approved by FDA.

Distributed by:  
Dechra Veterinary Products  
7015 College Boulevard  
Suite 525  
Overland Park, KS 66211

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\*Greco DS, Behrend EN (1995) Corticosteroid withdrawal syndrome. In: Kirk's Current Veterinary Therapy XII; Bonagura, J. (ed); WB Saunders, Philadelphia PA; pp 413-5.

PM PLT228

TAKE  
TIME



OBSERVE LABEL  
DIRECTIONS

Dechra

N-141291-M-0003  
Dog Owner Information

160mm

190mm

Dog Owner Information About



**VETORYL<sup>®</sup> (trilostane) CAPSULES**

VETORYL (pronounced "vet-or-ill") Capsules  
Generic name: trilostane ("try-low-stain")

This summary contains important information about VETORYL Capsules. You should read this information before you start giving your dog VETORYL Capsules and review it each time the prescription is refilled. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about VETORYL Capsules.

**What are VETORYL Capsules?**

VETORYL Capsules contain an adrenosuppressant drug that is used to treat hyperadrenocorticism in dogs. VETORYL Capsules are a prescription drug for dogs.

**Hyperadrenocorticism** (also known as Cushing's disease) is a condition in which excess levels of the hormone cortisol are produced. Cortisol is normally released from the adrenal gland into the bloodstream at times of stress. In dogs with hyperadrenocorticism, the level of cortisol produced is excessive and, if left untreated, becomes incapacitating.

Characteristic signs are:

- Passing large quantities of urine
- Frequent urination and possible incontinence
- Excessive drinking
- Ravenous appetite
- Lethargy or decreased activity
- Excessive panting
- Pot belly
- Thin skin
- Hair loss or recurrent skin diseases
- Muscle wasting

Your dog may not necessarily display all of these signs.

**What kind of results can I expect when my dog is on VETORYL Capsules?**

Although VETORYL Capsules **ARE NOT A CURE** for hyperadrenocorticism, the product can control the clinical signs:

- Response varies from dog to dog.
- Improvement can be seen in most dogs within a few weeks.
- If VETORYL Capsules are discontinued or not given as directed, excess cortisol production can resume and the signs of hyperadrenocorticism can return.

**Which dogs should not take VETORYL Capsules?**

Your dog should not be given VETORYL Capsules if he/she:

- Has kidney or liver disease.
- Takes certain medications. VETORYL Capsules should be used with caution with several medications used to treat heart disease (some diuretics and ACE inhibitors).
- Is pregnant.

Tell your veterinarian about all medicines you have given your dog in the past, and any medicines that you are planning to give with VETORYL Capsules. This should include other medicines that you can get without a prescription. Your veterinarian may want to check that all of your dog's medicines can be given together.

**What should I know about giving VETORYL Capsules to my dog?**

- VETORYL Capsules should be given according to your veterinarian's instructions. Your veterinarian will tell you the number of VETORYL Capsules that is right for your dog.
- Administer capsules with food.
- Keep out of reach of children. Not for human use.
- Do not open capsules and do not attempt to split or divide capsules.
- Wash hands after use.
- Do not handle the capsules if pregnant or trying to become pregnant. Studies in laboratory animals have produced birth defects and early pregnancy loss. In the event of accidental ingestion/overdose, seek medical advice immediately and take the labeled container with you.



Dechra

160mm

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**What should I talk to my veterinarian about before giving VETORYL Capsules?**

Talk to your veterinarian about:

- What tests might be done before VETORYL Capsules are prescribed.
- How often your dog may need to be examined by your veterinarian.
- The risks and benefits of using VETORYL Capsules.

Tell your veterinarian if your dog has ever had the following medical problems:

- Liver disease
- Kidney disease

Tell your veterinarian about:

- Any other medical problems or allergies that your dog has now or has had.
- If your dog is pregnant, nursing or if you plan to breed your dog.
- Any medications your dog is taking, including over-the-counter products and nutritional supplements.

**What are the possible side effects that may occur in my dog during therapy?**

VETORYL Capsules, like other drugs, may cause some side effects. Serious, but rare side effects have been reported in dogs taking VETORYL Capsules. Serious side effects can occur with or without warning and, in rare situations, result in death.

Side effects generally involve an over suppression of the adrenal glands (hypoadrenocorticism, also known as Addison's Disease). Look for the following side effects that may indicate your dog is having a problem with VETORYL Capsules or may have another medical problem:

- Depression, lethargy or decrease in activity.
- Change in bowel movements (such as diarrhea or loose stools).
- Vomiting.
- Stops eating or loses all interest in food.

**As VETORYL Capsules control the hyperadrenocorticism, there should be a decrease in food and water consumption to normal levels.** There should also be resolution of excess urination. If, however, there is a dramatic decrease in appetite or the dog stops drinking water, it could be an indication of a side effect requiring treatment.

It is important to stop therapy and contact your veterinarian immediately if you think your dog has a medical problem or side effect from VETORYL Capsule therapy. If you have additional questions about possible side effects, talk to your veterinarian.

**What do I do in case my dog takes more than the prescribed amount of VETORYL Capsules?**

Contact your veterinarian immediately if your dog takes more than the prescribed amount of VETORYL Capsules.

**What else should I know about VETORYL Capsules?**

This sheet provides a summary of information about VETORYL Capsules. If you have any questions or concerns about VETORYL Capsules, or hyperadrenocorticism, talk to your veterinarian.

As with all prescribed medicines, VETORYL Capsules should only be given to the dog for which it was prescribed.

It is important to periodically discuss your dog's response to VETORYL Capsules at regular checkups. Your veterinarian will determine if your dog is responding as expected and if your dog should continue receiving VETORYL Capsules.

TAKE  OBSERVE LABEL  
TIME DIRECTIONS

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Dechra Veterinary Products  
7015 College Boulevard  
Suite 525  
Overland Park, KS 66211

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Dechra

N-141291-M-0003  
Blister Label (30 mg)

**VETORYL® CAPSULES**  
(trilostane) NADA 141-291, Approved by FDA.  
30 mg  
For oral use in dogs only  
See package insert for complete product information.  
Store at controlled room temperature 25°C (77°F) with excursions between 15°-30°C (59°-86°F) permitted.  
**KEEP OUT OF REACH OF CHILDREN**



Batch and Expiration

**VETORYL® CAPSULES**  
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Batch and Expiration

N-141291-M-0003  
Blister Label (60 mg)

**VETORYL<sup>®</sup> CAPSULES**  
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See package insert for complete product information.  
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Batch and Expiration



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Batch and Expiration



N-141291-M-0003  
Dispensing Container Carton Label (30 mg)



