VETORYL 

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 5 sizes (5, 10, 30, 60 and 120 mg) for oral administration based on body weight. Trilostane (4α,5α-epoxy-17β-hydroxy-5a-androstane-3α-carboxylic acid) is an orally active synthetic steroidal analogue that selectively inhibits 3β-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.

DOSAGE AND ADMINISTRATION: 

Always provide the Client Information Sheet with prescription (see INFORMATION FOR DOG OWNERS).

1. Starting dose 

The starting dose for the treatment of hyperadrenocorticism in dogs is 1.3 mg/kg (2.6-6.7 mg/kg) once a day. Start with the lowest possible dose based on body weight and available combinations of capsule sizes. VETORYL Capsules should be administered with food.

2. Action at 10-14 day evaluation (Table 1) 

If the ACTH stimulation test was not conducted, then re-examine the dog and conduct a 4-6 hour post-dosing ACTH stimulation test and serum biochemical tests (with particular attention to electrolytes, and renal and hepatic function). If physical examination is acceptable, take action according to Table 1.

 Owners should be instructed to stop therapy and contact their veterinarian immediately in the event of adverse reactions such as vomiting, diarrhea, lethargy, poor/reduced appetite, weakness, collapse or any other unusual developments. If these clinical signs are observed, conduct an ACTH stimulation test and serum biochemical tests (with particular attention to electrolytes, and renal and hepatic function).

Table 1: Action at 10-14 day evaluation

<table>
<thead>
<tr>
<th>Post-ACTH serum cortisol</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.45 µg/dL (&lt; 40 nmol/L)</td>
<td>Stop treatment. Re-start at a decreased dose</td>
</tr>
<tr>
<td>1.45 to 5.4</td>
<td>Continue on same dose</td>
</tr>
<tr>
<td>&gt; 5.4</td>
<td>OR: Increase dose if clinical signs of hyperadrenocorticism are still evident</td>
</tr>
<tr>
<td>&gt; 9.1</td>
<td>OR: Increase initial dose</td>
</tr>
</tbody>
</table>

Table 2: Precautions and 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, homonadric diarrhea, collapse, hyperadrenocortical crisis or adrenal necrosis/rupture may occur, and may result in death.

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, homonadric diarrhea, collapse, hyperadrenocortical crisis or adrenal necrosis/rupture may occur, and may result in death.

In a U.S. field study with 107 dogs, adrenal necrosis/rupture (2 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 hyperadrenocorticism during the study. These two dogs had clinical signs consistent with hyperadrenocorticism (lethargy, anorexia, collapse) and post-ACTH cortisol levels ≥ 0.3 μg/dL. Both dogs responded to trilostane discontinuation and supportive care, and one dog required continued treatment for hyperadrenocorticism (glycosidic and mineralocorticoid) after the acute presentation.

Additional adverse reactions were observed in 93 dogs. The most common of these included diarrhea (51 dogs), lethargy (50 dogs), inappetence/anorexia (27 dogs), vomiting (28 dogs), muscular skeletal signs (lethargy, worsening of degenerative joint disease) (25 dogs), urinary tract infection (UTI) (17 dogs), shaking/shivering (10 dogs), ophthalmic signs (rash, conjunctivitis) (7 dogs), and skin/cutaneous signs (vesicles, 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 pituitary-dependent hyperadrenocorticism (ie, early adrenal failure, one 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/nephropathy and the two dogs with hyperadrenocorticism, 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 RBCs), but the mean values remained within the normal range. Additionally, approximately 10% of the dogs had elevated BUN values (≥ 40 mg/dL) in the absence of concurrent neoplastic conditions. 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 cardiospecific signs, inappropriate antidiuretic hormone, urinary tract infections or peritonitis, 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 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, diarrheal/loose stools, and anorexia. Other adverse reactions included: nocturia, corneal ulcer, cough, persistent estrus, vaginal discharge and vulvar swelling in a spayed female, hyperadrenocorticism, electrolyte imbalance (elevated potassium with or without decreased sodium), collapse and seizure, shaking, muscle tremors, constipation, scratching, weight gain, and weight loss. One dog had collapse with convulsion 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: hyperadrenocortical episode (including syncope, tremor, weakness, and vomiting), hyperadrenocortical crisis or renal failure (including azotemia, vomiting, dehydration, and collapse, chronic intermittent vaginal discharge, hemorrhagic diarrhea, occasional vomiting, and distal limb edema). Signs of hyperadrenocorticism were usually reversible after withdrawal of the drug, but may be permanent. One dog discontinued VETORYL Capsules and continued to have hyperadrenocorticism 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, hyperadrenocortical 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, hyperadrenocorticism (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, autonomic hypertensive crisis, vomiting, diarrhea, anorexia, skin reactions ( Rash, erythematous skin eruptions), hirudin paralysis, seizures, neurological signs from growth of macrocrineomas, oral ulceration, and muscle tremors.

POST-APPROVAL EXPERIENCE:

As of June 2013, the following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported by FDA-CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data. The following adverse events are listed in decreasing order of reporting frequency: anorexia, lethargy, depression, vomiting, diarrhea, collapse, hemorrhage, dehydration, collapse, depression, agitation, and respiratory depression.

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 and compared to the control dogs. The 5X dogs had lower mean corpuscular volume than the controls. There was a dose dependent increase in thrombocytopenia and platelet aggregation. Many 5X dogs had evidence of bone marrow suppression.

In two UK field studies, abnormalities were observed in bone marrow aspirates. Arterial and venous thrombosis and platelet aggregation were observed.

Improvement in post-ACTH cortisol levels occurred in most cases within 14 days of starting VETORYL Capsules therapy. Improvement in clinical signs (decreased thirst, decreased frequency of urination, decreased panting, and improvement of appetite and activity). Serious adverse reactions associated with this drug can occur without warning and in some cases result in death (see ADVERSE REACTIONS and POST-APPROVAL EXPERIENCE).

Owners should be advised to discontinue VETORYL Capsules and contact their veterinarian immediately if signs of intolerance such as vomiting, diarrheal/loose stools, lethargy, poor/reduced appetite, weakness, or collapse 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 accummulation 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 33.0 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 somnolence. One of the dogs showed hypothermia, hyperthermia, and azotemia, consistent with hypoadrenocorticism. Post-mortem findings included epithelial necrosis or cystic dilation of duodenal mucosal crypts, gastric mucosal or thymic hemorrhage, atrial thrombosis, pyelitis and cysitis, 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 ACTH. They had 60% to 90% of the other groups. The 3X and 5X dogs had lower weight gain than the other groups. The 3X and 5X dogs had lower serum sodium, albumin, total protein, and cholesterol compared to the control dogs. The 5X dogs had lower mean creatinine volume than the controls. There was a dose dependent increase in amylase. Post-mortem findings included dose dependent adrenal cortical hyperplasia.

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 5 mg NDC 17033-105-30
VETORYL Capsules 10 mg NDC 17033-110-30
VETORYL Capsules 25 mg NDC 17033-130-30
VETORYL Capsules 60 mg NDC 17033-160-30
VETORYL Capsules 120 mg NDC 17033-132-30

Take time to observe label directions.

NDA 141,291. Approved by FDA.
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