

[Version 8, 10/2012]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Vetoryl 30 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Active substance:

Trilostane	30 mg
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Excipients:

Titanium dioxide (E171)	1.19 mg
Yellow iron oxide (E172)	0.045 mg
Black iron oxide (E172)	0.672 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Ivory body and black cap with the capsule strength printed on the body of the capsule.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

For the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs.

4.3 Contraindications

Do not use in animals suffering from primary hepatic disease and/or renal insufficiency.

Do not use in dogs weighing less than 3 kg.

Do not use where there is suspected hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

An accurate diagnosis of hyperadrenocorticism is essential.

Where there is no apparent response to treatment, the diagnosis should be re-evaluated. Dose increases may be necessary.

Veterinarians should be aware that dogs with hyperadrenocorticism are at increased risk of pancreatitis. This risk may not diminish following treatment with trilostane.

4.5 Special precautions for use

Special precautions for use in animals

As the majority of cases of hyperadrenocorticism are diagnosed in dogs between the ages of 10-15 years, other pathological processes are frequently present. It is particularly important to

screen cases for primary hepatic disease and renal insufficiency as the product is contraindicated in these cases.

Subsequent close monitoring during treatment should be carried out. Particular attention should be paid to liver enzymes, electrolytes, urea and creatinine.

The presence of diabetes mellitus and hyperadrenocorticism together requires specific monitoring.

If a dog has previously been treated with mitotane, its adrenal function will have been reduced. Experience in the field suggests that an interval of at least a month should elapse between cessation of mitotane and the introduction of trilostane. Close monitoring of adrenal function is advised, as dogs may be more susceptible to the effects of trilostane.

The product should be used with extreme caution in dogs with pre-existing anaemia as further reductions in packed-cell volume and haemoglobin may occur. Regular monitoring should be undertaken.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Trilostane may decrease testosterone synthesis and has anti-progesterone properties. Women who are pregnant or are intending to become pregnant should avoid handling the capsules.

Wash hands with soap and water following accidental exposure and after use.

The content of the capsules may cause skin and eye irritation and sensitisation. Do not divide or open capsules: in the event of accidental breakage of the capsules and contact of the granules with eyes or skin, wash immediately with plenty of water. If irritation persists, seek medical advice.

People with known hypersensitivity to trilostane or any of the excipients should avoid contact with the product.

In the event of accidental ingestion, seek medical advice immediately and show the package leaflet or carton to the physician.

4.6 Adverse reactions (frequency and seriousness)

Corticosteroid withdrawal syndrome or hypocortisolaemia should be distinguished from hypoadrenocorticism by evaluation of serum electrolytes.

Signs associated with iatrogenic hypoadrenocorticism, including weakness, lethargy, anorexia, vomiting and diarrhoea may occur, particularly if monitoring is not adequate (see 4.9). Signs are generally reversible within a variable period following withdrawal of treatment. Acute Addisonian crisis (collapse) may also occur (see 4.10). Lethargy, vomiting, diarrhoea and anorexia have been seen in dogs treated with trilostane in the absence of evidence of hypoadrenocorticism.

There have been occasional isolated reports of adrenal necrosis in treated dogs which may result in hypoadrenocorticism.

Subclinical renal dysfunction may be unmasked by treatment with the product.

Treatment may unmask arthritis due to a reduction in endogenous corticosteroid levels.

A small number of reports have been received of sudden death during treatment.

Other mild, rare, adverse effects include ataxia, hypersalivation, bloating, muscle tremors and skin changes.

4.7 Use during pregnancy, lactation or lay

Do not use in pregnant or lactating bitches or in any animals intended for breeding.

4.8 Interaction with other medicinal products and other forms of interaction

The possibility of interactions with other medicinal products has not been specifically studied. Given that hyperadrenocorticism tends to occur in older dogs, many will be receiving concurrent medication. In clinical studies, no interactions were observed.

The risk of hyperkalaemia developing should be considered if trilostane is used in conjunction with potassium-sparing diuretics or ACE inhibitors. The concurrent use of such drugs should be subject to a risk-benefit analysis by the veterinary surgeon, as there have been a few reports of deaths (including sudden death) in dogs when treated concurrently with trilostane and an ACE inhibitor.

4.9 Amounts to be administered and administration route

Administer orally, once daily, with food.

The starting dose for treatment is approximately 2 mg/kg, based on available combinations of capsule sizes.

Titrate the dose according to individual response, as determined by monitoring (see below).

If a dose increase is required, use combinations of capsule sizes to slowly increase the once daily dose. A wide range of capsule sizes enables optimum dosing for the individual dog.

Administer the lowest dose necessary to control the clinical signs.

Ultimately, if symptoms are not adequately controlled for an entire 24 hour inter-dose period, consider increasing the total daily dose by up to 50% and dividing it equally between morning and evening doses.

Do not divide or open capsules.

A small number of animals may require doses significantly in excess of 10 mg per kg body weight per day. In these situations appropriate additional monitoring should be implemented.

Monitoring:

Samples should be taken for biochemistry (including electrolytes) and an ACTH stimulation test pre-treatment and then at 10 days, 4 weeks, 12 weeks, and thereafter every 3 months, following initial diagnosis and after each dose adjustment. It is imperative that ACTH stimulation tests are performed 4 – 6 hours post-dosing to enable accurate interpretation of results. Dosing in the morning is preferable as this will allow your veterinary surgeon to perform monitoring tests 4-6 hours following administration of the dose. Regular assessment of the clinical progress of the disease should also be made at each of the above time points.

In the event of a non-stimulatory ACTH stimulation test during monitoring, treatment should be stopped for 7 days and then re-started at a lower dose. Repeat the ACTH stimulation test after a further 14 days. If the result is still non-stimulatory, stop treatment until clinical signs of hyperadrenocorticism recur. Repeat the ACTH stimulation test one month after re-starting treatment.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Overdose may lead to signs of hypoadrenocorticism (lethargy, anorexia, vomiting, diarrhoea, cardiovascular signs, collapse). There were no mortalities following chronic administration at

36 mg/kg to healthy dogs, however mortalities may be expected if higher doses are administered to dogs with hyperadrenocorticism.

There is no specific antidote for trilostane. Treatment should be withdrawn and supportive therapy, including corticosteroids, correction of electrolyte imbalances and fluid therapy may be indicated depending on the clinical signs.

In cases of acute overdosage, induction of emesis followed by administration of activated charcoal may be beneficial.

Any iatrogenic adrenocortical insufficiency is usually quickly reversed following cessation of treatment. However in a small percentage of dogs, effects may be prolonged. Following a one week withdrawal of trilostane treatment, treatment should be reinstated at a reduced dose rate.

4.11 Withdrawal periods

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antiadrenal preparations
ATC Vet Code: QH02CA01.

5.1 Pharmacodynamic properties

Trilostane selectively and reversibly inhibits the enzyme system 3 beta hydroxysteroid isomerase, thus blocking the production of cortisol, corticosterone and aldosterone. When used to treat hyperadrenocorticism, it reduces the production of glucocorticoid and mineralocorticoid steroids in the adrenal cortex. Circulating concentrations of these steroids are thus reduced. Trilostane also antagonises the activity of exogenous adrenocorticotrophic hormone (ACTH). It has no direct effect on either the central nervous or cardiovascular systems.

5.2 Pharmacokinetic particulars

Pharmacokinetic data in dogs have demonstrated large inter-individual variability. In a pharmacokinetic study in laboratory beagles, AUC ranged from 52 to 281 micrograms/ml/min in fed dogs, and from 16 to 175 micrograms/ml/min in fasted dogs. Generally trilostane is rapidly removed from the plasma with concentrations in the plasma reaching a maximum between 0.5 to 2.5 hours and returning almost to baseline by six to twelve hours after administration. The primary active metabolite of trilostane, ketotrilostane follows a similar pattern. Furthermore, there was no evidence that trilostane or its metabolites accumulated with time. An oral bioavailability study in dogs demonstrated that trilostane was absorbed more extensively when administered with food.

Trilostane has been demonstrated to be excreted primarily in the faeces of the rat, indicating biliary excretion as the major metabolic pathway. In the monkey, trilostane is excreted in equal amounts in the faeces and urine. Results have shown that trilostane is rapidly and well absorbed from the gastrointestinal tract in both the rat and monkey and that it accumulates in the adrenal glands of the rat.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Titanium dioxide (E171)

Yellow iron oxide (E172)
Black iron oxide (E172)
Maize starch
Lactose monohydrate
Magnesium stearate
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the blister strips in the carton.

6.5 Nature and composition of immediate packaging

PVC-PVdc / aluminium foil blister packs containing 10 capsules. Each carton contains 3 blister strips.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Dechra Limited
Snaygill Industrial Estate
Keighley Road
Skipton
North Yorkshire
BD23 2RW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

UK: Vm 10434/4071
IE: VPA 10799/020/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

UK: 13/04/2005
IE: 25/06/2010

10. DATE OF REVISION OF THE TEXT

October 2014