IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Vetoryl 30 mg hard capsules

PRODUCT SUMMARY

EU Procedure Number	IE/V/0514/002 (formerly UK/V/0215/001)
Name, Strength, Pharmaceutical Form	Vetoryl 30 mg hard capsules
Active Substances(s)	Trilostane
Applicant	Dechra Regulatory B.V., Handelsweg 25, 5531 AE Bladel, Netherlands
Legal Basis of Application	Full application (Article 12(3) of Directive No 2001/82/EC)
Target Species	Dogs
Indication For Use	For the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs.
ATC Code	QH02CA01
Date of completion of the original mutual recognition procedure	23 November 2005
Date product first authorised in the Reference Member State (MRP only)	08 December 2017 01 October 2010 (IE)
Concerned Member States for original procedure	First Use Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland (now RMS), Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Repeat Use Croatia, Slovenia UK added via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability

is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

Vetoryl Capsules contain the active substance trilostane and are intended for use in the treatment of pituitary-dependent and adrenal-dependent Cushing's syndrome in dogs. Cushing's syndrome is caused by excessive production of steroid hormones by the cortex (outer part) of the adrenal glands, hence its other name, hyperadrenocorticism.

The hormones in question (cortisol, corticosterone and aldosterone) play a vital role in:

- promoting the synthesis and storage of glucose, suppressing inflammation and regulating the distribution of fat in the body;
- preventing excessive loss of salt and water through the kidneys and maintaining a balance between sodium and potassium, which is important for muscle activity.

From these functions, it can be seen that an over-production of these hormones results in retention of salt and water, obesity, high blood pressure, weakening of bone and connective tissue and sometimes diabetes mellitus.

Because the production of adrenal hormones is controlled by a hormone known as ACTH which is produced by the pituitary gland, it follows that Cushing's disease may originate from a problem in either the pituitary or the adrenal glands. It is therefore said to be pituitary-dependent or adrenal-dependent.

The active substance of Vetoryl, trilostane, is itself a steroid, and it acts by reversibly inhibiting an enzyme system (3 β-hydroxysteroid isomerase) which is important in the synthesis of the adrenal hormones mentioned above, thus blocking the production of these hormones.

The aim of treatment is to correct the body's imbalance and since this varies considerably between individuals, the dose needs to be tailored to each patient. An average starting dose of 2 mg/kg of body weight administered once daily is recommended. Depending on the response of the individual dog to treatment the

dose rate may need to be changed. For most dogs the daily dose is usually between 2 and 10 mg/kg of body weight.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC[1].
The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains Trilostane in 30mg, 60mg and 120mg quantities depending on the strength of the capsule. It also contains the excipients Maize starch, lactose monohydrate and magnesium stearate. The capsule shell contains gelatin, titanium dioxide (E171), yellow iron oxide (E172) and black iron oxide (E172).

The products are in the form of hard gelatin capsules containing the active substance trilostane. Three strengths of the capsule are authorised (30, 60 and 120 mg), so that accurate and convenient dosing can be achieved in dogs of various sizes.

All three capsule strengths have ivory coloured bodies and black caps. They can be differentiated from each other because the strengths are printed on the capsule shells, but in order to further aid differentiation, the blister strips and cartons are colour coded.

The three different strengths of capsule are based on a similar formulation involving the same excipients: maize starch, lactose monohydrate and magnesium stearate. The 30 mg and 60 mg capsules use the same size of gelatin capsule shell whilst the 120 mg capsule uses a larger gelatin capsule shell. The capsule shells contain the following colorants: titanium dioxide (E171), yellow iron oxide (E172) and black iron oxide (E172). The ink used to print the name and strength on the capsule shells is suitable for use on foods.

The development of the product has been explained by the company, and both the formulation and method of manufacture of the capsules are largely based on a human medicinal product authorised in the UK. The method of manufacture includes steps designed to ensure that acceptable amounts of the trilostane are absorbed despite the low solubility of this substance. A test is applied to each batch

of capsules to measure the amount of trilostane that is released from the capsules into a water based medium. The three different strengths of capsule perform very similarly in this test.
The container/closure system consists of thirty capsules (3 strips of 10) packaged in blisters made of opaque white PVDC-coated polyvinyl chloride sealed with aluminium foil. The particulars of the containers and controls performed are provided and conform to the regulation.
The choice of the formulation is justified.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is Trilostane, a novel established substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.
The detailed method of manufacture and the controls performed during manufacture have been described. The method of manufacture was modified slightly in 2003 in order to avoid the use of undesirable solvents in the final stages of synthesis. Apart from residual solvents, no significant difference in quality was observed for trilostane manufactured by the earlier process and that manufactured by the current process.

The specification for trilostane includes relevant parameters, including particle size. It is in accordance with current VICH guidelines and pharmacopoeial requirements. Batch analysis data from each site of manufacture confirm that the specification can be met routinely.

The methods used to test trilostane include a liquid chromatographic (LC) method for assaying the active substance and any impurities, and a gas chromatographic (GC) method for the control of residual solvents. These methods have been shown to be valid.

Each of the non-active substances used to manufacture the granules that are filled into the capsule shells, comply with monographs in the European Pharmacopoeia. Magnesium stearate is of vegetable origin.

Information on the composition of both sizes of capsule shell has been presented, together with information on the grade of each of the substances present. This information confirms their suitability. The gelatin used to produce the capsule shells is of bovine origin but its method of preparation ensures its safety.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification.
The specification for each capsule strength has been provided. This controls appropriate parameters, which for capsules include: appearance, content of active, weight and uniformity of weight, disintegration, dissolution, impurity levels and microbial purity.

The LC method for determination of active substance content and the level of impurities has been shown to be valid, and the analytical method used in the dissolution test has been shown to be suitable for this purpose.

Batch analysis data have been provided by the company for three production scale batches of each strength of capsule. They demonstrate the consistency of the manufacturing process and the batches comply with the specifications in force at the time of their manufacture. A comparison of the level of impurities present in the active substance before and after its incorporation into the finished product suggests that no significant degradation occurs during manufacture.

F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data have been provided for batches of the active substance as supplied by each manufacturer. These include data for three batches from each manufacturer produced according to the current method of manufacture. The data confirm that a 2-year re-test period is appropriate for trilostane.

Stability data have also been presented for one batch of trilostane in the form it is used in the product, and these data are sufficient to confirm the suitability of the 12-month retest interval applied to it. Stability studies on further batches of this form of trilostane are also planned.
Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.
Stability data have also been presented for at least two batches of each strength of capsule. The capsules were stored in the blister packs used for marketing. The studies were conducted in accordance with VICH guidelines. The data extend to at least 2 years. The data revealed that under accelerated conditions for certain batches, a softening of the capsule shells occurred, together with a significant slowing of the dissolution time. However, under real time conditions, or following shorter periods of storage under accelerated conditions, no changes were observed. Therefore, when stored in the EU, no adverse changes are expected to occur. Whilst the content of the active substance in the capsule showed some variability, it remained satisfactory and did not show any time- or temperature-related trend. In addition, no accumulation of impurities was observed. Despite this, as a precaution, it is recommended that the product is stored below 25°C. The stability data confirm that the 2-year shelf-life for the capsules is appropriate [1]. (Shelf–life now 3 years, see footnote).

G. Conclusions on Quality

The supporting quality data demonstrate that the capsules are suitably formulated and controlled and that their quality remains acceptable over their authorised shelf-life.

[1] The shelf-life was changed from 2 years to 3 years by way of variation procedures. See Module 4.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has conducted studies and has provided bibliographical data which show that trilostane acts by inhibiting the synthesis of cortisol (Anricorticosterids).

The applicant has provided bibliographical data which show that 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.

Toxicological Studies

The applicant has conducted laboratory studies and provided bibliographical data which show that of low toxicity to mice, rats, rabbits and dogs when administered on a single occasion by mouth.

Single and Repeat Dose Toxicity

Several studies, published and unpublished, have been conducted on the effects of trilostane when administered daily by mouth to rats, monkeys, and dogs for periods of time up to 18 months. The major effects observed were on the adrenal gland, with the weight of this gland being increased in all studies. In an 18-month study in rats, the effect on the adrenal gland was in the form of an increased incidence of adrenal adenomas (tumours) in animals given 250 mg/kg bodyweight. Another effect found in some studies was that the ability of the animals to metabolise other drugs was found to increase in the presence of high levels of trilostane. The highest dose at which no adverse effects were observed was 10 mg/kg bodyweight/day.

- Reproductive Toxicity, including Teratogenicity:

Studies have also been made, in rats and rabbits, of possible effects on reproduction. The studies in rats cover the whole range of the reproductive cycle from before mating, during pregnancy and during lactation, whilst those in rabbits cover pregnancy only. No adverse effects were observed in male or female rats when trilostane was administered prior to mating. However, there was some evidence that administration during pregnancy affected the maintenance of pregnancy and, at high doses (more than 25 mg/kg bodyweight/day) there were some changes in the development of bones.

Maintenance of pregnancy was also affected in rabbits at doses of 5 mg/kg bodyweight/day and above. This was thought to happen because trilostane interferes with the production in the body of the female hormone progesterone, which is essential for the maintenance of pregnancy. The fact that when rats were given progesterone at the same time as trilostane, the adverse effects did not occur, indicates that this explanation is correct, and it has also been reported that trilostane has been used as an aid in the induction of abortion in women because of its effects on progesterone. Studies in healthy young men showed that trilostane can also decrease the production of the male hormone testosterone.

- Mutagenicity

The company provided the reports of new studies which fully investigated the ability of trilostane to cause mutations. Two studies were conducted in cultured cells, both bacterial and mammalian. The first of these studies showed no evidence of any mutations although the second did. However, because these studies were conducted in cells cultured in the laboratory, it was not clear whether the changes that occurred would actually occur in animals or people. To investigate this, two further studies were conducted, one in mice and one in rats, in accordance with internationally agreed guidelines. Both these studies produced negative results, indicating that the mutagenic potential which had been observed in cultured cells was not realised in living animals.

- Carcinogenicity:

Studies of carcinogenic potential have been conducted in long-term studies in rats and mice. Although these studies were old, they were well-conducted and the results provided no evidence of carcinogenicity. There was evidence of some enlargement of the adrenal glands in rats but this was considered to be a result of the intended action of trilostane on these glands rather than a carcinogenic effect.

Other Studies

With regard to other possible adverse effects of trilostane, information has been provided to show that it has no effect on the central nervous system or the cardiovascular system. Trilostane has been used in human medicine for the treatment of Cushing's disease and breast cancer. Side effects in humans are rare, although high doses may cause nausea, vomiting, diarrhoea and oedema[1] of the palate. Such effects may also occur if the initial dose is increased too quickly. Overuse of trilostane can also cause the adrenal cortex to produce too few hormones (hypoadrenocorticism), and this can have serious consequences, although the effect is usually reversible if treatment is stopped. Trilostane may interfere with other drugs such as oral contraceptives and certain diuretics.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that Vetoryl is in the form of capsules and anyone administering them is therefore unlikely to come into contact with the active substance. However, because trilostane has been shown to have an effect on progesterone and the maintenance of pregnancy, it has been agreed that warnings are required to alert users of the product to these effects and to advise women who are pregnant or intending to become pregnant to avoid handling the capsules.

Another potential means of human exposure to the product would be accidental ingestion by children. This is unlikely because the capsules are provided in blister packs and these are generally considered to be child-resistant. Even if a child gained access to a capsule, it would probably not swallow the contents because of the bitter taste. If the capsules were swallowed, the most likely effect would be vomiting. However, it is recommended that medical advice should be sought to ensure no more serious outcome.

Trilostane may be irritant, and it is unclear whether it can produce allergic reactions. Therefore all users are advised not to divide or open the capsules and to wash eyes or skin in the event of accidental contact with the contents of the capsule; also to wash hands after handling the capsules. Anyone who has previously had a reaction to trilostane or any of the other substances is advised to avoid contact with the product.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that animals prescribed Vetoryl Capsules will be given the capsules by mouth on a daily basis for an extended period of time. Exposure of the environment to trilostane will occur when it is excreted in the urine and faeces of treated dogs. Only a small percentage of the total dog population will need treating for Cushing's disease; dogs are usually kept singly, resulting in small scale exposure in discrete areas. No warnings regarding the use of the product are therefore required.
Warnings and precautions as listed on the product literature for the disposal of the product are adequate to ensure safety to the environment.

[1] Oedema is an excess of fluid.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
Published information has been provided by the company showing that the mode of action of trilostane in the rat is to act as a competitive inhibitor of the 3b-hydroxysteroid dehydrogenase-isomerase system, an enzyme system that is important in the synthesis of steroid hormones. Thus this action blocks the production of cortisol, corticosterone and aldosterone in the adrenal cortex. Studies in dogs treated with trilostane demonstrated a similar mode of action.

Studies in rats and monkeys showed that trilostane had no effect on the central nervous system or cardiovascular system. Trilostane showed no oestrogenic, progestagenic, androgenic or glucocorticoid activity. However doses of 1000 mg/kg administered to rats suggested an inhibition of gonadal (sex) hormone synthesis. Although trilostane has not shown any anti-fertility activity, it has been shown to cause abortion, especially at high doses, in the rat and rhesus monkey.

Therefore, the primary activity of trilostane has been shown to be the inhibition of adrenal steroid hormone synthesis, with some secondary effects on the production of hormones by the ovaries and testes.

Pharmacokinetics
Various publications described the absorption, distribution, metabolism and excretion of trilostane in rats, monkeys and man. Trilostane is well absorbed from the gastrointestinal tract in both rats and monkeys, although absorption may be inhibited by the presence of bile. It is distributed to the kidneys, liver and lungs, with the majority being present in the gastro-intestinal tract and liver. Trilostane accumulates in the adrenal glands of the rat.

Trilostane appears to be metabolised primarily to the active metabolite, ketotrilostane, in all species, but also to other inactive metabolites. In rats, excretion is predominantly in the faeces, but in monkeys is divided almost equally between the urine and faeces.

This published information was supplemented by reports of some studies which the company had conducted using the formulated product, Vetoryl. These studies investigated:

- the amount of trilostane reaching the bloodstream when the product was administered as a 30 mg capsule once, as a 60 mg capsule once or as a 120 mg capsule once;

- the amount of trilostane reaching the bloodstream when the product was administered as a 30 mg capsule twice a day for seven days or fifteen days, or as a 60 mg capsule once a day for seven days;
- whether there was any difference in absorption if the capsules were administered before feeding or with food.

The results of these studies showed that:

- the amount of trilostane and its major metabolite ketotrilostane reaching the bloodstream increased in proportion to the increase in the amount of trilostane administered at doses up to 120 mg;
- individual dogs varied considerably in the amount of trilostane absorbed;
- there appeared to be slightly more trilostane absorbed when the dose was given in the form of 30 mg capsules twice a day compared with one 60 mg capsule once a day;
- there appeared to be better absorption of trilostane from the gut if the capsules were given with food.

Tolerance in the Target Species of Animals

The company submitted the report of a study that had been conducted to investigate how well Vetoryl capsules were tolerated by normal Beagle dogs. In this study, the dogs were given either a single 60 mg capsule per day (i.e. the normal dose for a dog of this size), or twice or five times this dose. All animals continued treatment for 12 weeks, and all showed good tolerance to it. The only adverse effects identified were a decrease in food consumption in female dogs, a decrease in red blood cell count and associated blood parameters, and a decrease in the amount of sodium and chloride in the blood. These effects did not appear to affect the general well-being of the dogs.

This study was supported by the results of a study conducted in 1987 and by further published information. In the earlier study a different formulation of trilostane had been used. However, the results were similar to those of the newer study but, because the maximum dose given was higher, the adverse effects were more serious. An increase in the weight of the adrenal glands was also observed. The published information also included mention of an increase in the size of the adrenals, as well as other changes in the appearance of these glands. It is unclear what the exact significance of these changes might be, but it has also been reported that prolonged treatment with trilostane can cause hypoadrenocorticism (i.e. under-production of steroid hormones by the cortex of the adrenal glands), which is potentially very serious although usually reversible. Signs associated with this condition include lethargy, anorexia, vomiting, diarrhoea and ataxia. The SPC carries

a warning with regard to possible instances of pancreatitis in dogs with hyperadrenocorticism.

IV.B Clinical Studies

Field Trials

The company provided several literature references relating to the field use of trilostane and also conducted three multi-centric clinical trials in the UK with Vetoryl. Each of these trials was run in a similar way, the main difference being the dose of trilostane administered. All the trials complied with principles of Good Clinical Practice.

Before including each dog in the study, tests were performed to establish a diagnosis and, as far as possible, to differentiate pituitary- and adrenal-dependent hyperadrenocorticism. In fact very few of the dogs were found to be suffering from adrenal-dependent hyperadrenocorticism. As well as haematology and biochemistry, these tests included a test to see how much ACTH (see Introduction) there was in the blood, how much cortisol was produced in response to administration of ACTH (an ACTH stimulation test) and whether treatment with different doses of dexamethasone[1] affected the amount of ACTH present (dexamethasone suppression tests).

All the dogs in the studies were treated with trilostane as there is no authorised product which could have been given to some dogs for comparative purposes, and it was considered ethically unacceptable to leave any of the dogs untreated. Dogs started their treatment on one of the following dosing regimens:

- a single daily dose of around 3 mg trilostane/kg bodyweight,
- a single daily dose of around 6 mg trilostane/kg bodyweight, or
- two daily doses of around 2 mg trilostane/kg bodyweight.

All dogs were examined 9 -12 days after the start of treatment. This examination included another ACTH stimulation test 4 - 6 hours after administration of the daily trilostane dose. Haematological and biochemical tests were also repeated at this stage. The parameters of disease severity, drug efficacy and tolerance of the treatment were scored by the investigating veterinary surgeon. Dog owners reported on signs concerning the dog's activity level, appetite, thirst etc. This process was repeated at 4, 12 and 24 weeks following the start of treatment. At re-examination, the dose of trilostane was adjusted according to the results of the ACTH stimulation test and the clinical signs. The trial ended at 24 weeks. The critical factors in deciding whether treatment with trilostane had been successful were the results of the ACTH stimulation test and the health of the dogs as judged by owners and veterinarians.

There was a significant improvement in the response of dogs to the administration of ACTH by the first examination 9 – 12 days after the start of treatment, and this was maintained throughout the studies. There was a significant improvement in disease

severity in most dogs 4 weeks after the start of treatment. Changes in haematology and biochemistry parameters were consistent with the resolution of hyperadrenocorticism.
The data suggested that a dose of 6 mg/kg/day was a reliable starting dose, with most dogs being eventually stabilised on doses between 2 and 10 mg/kg/day. Note that recent studies have now established the starting dose as 2 mg/kg/day. The clinical trials and long term follow-up showed that most dogs could be adequately stabilised with once daily dosing. Published literature provided further support for once daily dosing of trilostane as this was found to produce the desired effect on cortisol levels for up to 20 hours. Moreover, it was suggested that the risk of hypoadrenocorticism developing might be reduced if cortisol levels were not suppressed for a full 24-hour period.
Suspected adverse reactions appeared to be largely consistent with the pharmacological effect of the drug, e.g. anorexia, vomiting, lethargy, and in some instances these adverse reactions were transient. It was not clear whether over-suppression of the adrenal was the cause of the reactions or not because dogs which were unresponsive in ACTH stimulation tests during treatment (suggesting over-suppression of adrenal function) often appeared clinically well controlled. However, such over-suppression is potentially serious and close monitoring is required. Three dogs were withdrawn from studies as a result of deterioration of kidney function and it was suggested that in these cases treatment may have unmasked pre-existent renal disease. It is therefore recommended that the product is not used in dogs with renal failure.

Conclusions on Efficacy

The studies provided clearly demonstrated the efficacy of Vetoryl for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism, although it is recognised that due to the infrequency of the latter disease cases were limited in number. Tolerability was adequate in relation to the severity of the clinical signs of the disease. In many instances, but not all, adverse reactions may be related to the pharmacological effects of the drug. Adequate warnings regarding monitoring are given in the SPC and, providing this advice is followed, serious adverse reactions may be averted as the effects of the drug are usually reversible on its withdrawal. The overall risk: benefit assessment is considered to be favourable.

[1] Dexamethasone is a synthetic steroid which inhibits the release of ACTH from the pituitary in normal dogs.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for

the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.