United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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Surrey KT15 3LS
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Vetoryl 10mg Hard Capsules for Dogs

PuAR correct as of 01/08/2018 when RMS was transferred to IE.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0215/004/E/001
Name, strength and pharmaceutical form	Vetoryl 10mg Hard Capsules for Dogs
Applicant	Dechra Limited Snaygill Industrial Estate Keighley Road Skipton North Yorkshire BD23 2RW United Kingdom
Active substance(s)	Trilostane
ATC Vetcode	QH02CA01
Target species	Dogs
Indication for use	For the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	13 July 2007
Date product first authorised in the Reference Member State (MRP only)	n/a
Concerned Member States for original procedure	First Use Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland. Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden Repeat Use Croatia, Slovenia

I. SCIENTIFIC OVERVIEW

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 starting dose for the product is 2 mg/kg.[2] Refer to the SPC for dosing requirements. 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 benefit/risk analysis is in favour of granting a marketing authorisation.

[1] Summary of Product Characteristics
[2] Dosage changed via variation 15th April 2014. See Module 4.

II. QUALITY ASPECTS

A. Composition

The product contains trilostane, 10 mg per capsule and excipients maize starch, lactose monohydrate and magnesium stearate. The capsule shell contains gelatin, titanium dioxide (E171), ferric oxide (yellow) (E172), ferric oxide (black) (E172). The grey ink contains titanium dioxide (E171), ferric oxide (black) (E172) and shellac glaze.

The container/closure system consists of thirty capsules (3 strips of 10) packaged in blisters made of PVDC coated polyvinyl chloride sealed with aluminium foil. The blister foil text, and colour coding on the carton are dark green to aid differentiation from the other three capsule sizes. 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; it 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.

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

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 on intermediate products

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The proposed specification is consistent with the already authorised specification for the Vetoryl 30 mg hard capsules.

The finished product specification controls the relevant parameters for the pharmaceutical form. For capsules this includes; appearance, content of active, weight, uniformity of weight, disintegration, dissolution, impurity levels and microbial purity. 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.

G. 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 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.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Shelf life: 3 years
Storage conditions: Do not store above 25°C
Keep the blister pack in the outer carton.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant cross referred to studies undertaken for Vetoryl 30 mg, 60 mg and 120 mg hard capsules which show that trilostane acts by inhibiting the synthesis of cortisol (Anricorticosterids).

The applicant referred to previously 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 cross-referred to studies undertaken for Vetoryl 30 mg, 60 mg and 120 mg hard capsules and previously provided bibliographical data which show that of low toxicity to mice, rats, rabbits and dogs when administered on a single occasion by mouth. The following descriptions of studies refer to documentation submitted for Vetoryl 30 mg, 60 mg and 120 mg hard capsules.

- 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 applicant provided 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. 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.

Observations in Humans

Trilostane has been extensively used in human medicine for over 20 years.

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[3] 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.

[3] Oedema is an excess of fluid.

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 an 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 are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
The applicant referred to published information previously provided for Vetoryl 30 mg, 60 mg and 120 mg. The data showed that the mode of action of trilostane in the rat is to act as a competitive inhibitor of the 3β-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 1000mg/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
The applicant provided a dissolution study by way of demonstrating equivalent relative bioavailability between the Vetoryl 10 mg capsule and the already existing Vetoryl 30 mg, 60 mg and 120 mg strengths. The granule used for Vetoryl 10 mg hard capsules is identical in formulation to that used for Vetoryl 30 mg hard capsules and the only difference is that the final product is 1/3rd of the capsule fill weight in a smaller capsule.

The dissolution profiles *in vitro* and therefore the rate of release *in vivo* were essentially similar in all strengths of Vetoryl capsule giving equivalent bioavailability for all strengths.

Tolerance in the Target Species of Animals

The applicant referred to a study previously submitted for Vetoryl 30 mg, 60 mg and 120 mg hard capsules. In this study, the dogs were given either a single 60mg 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 applicant referred to documentation previously provided for Vetoryl 30 mg, 60 mg and 120 mg hard capsules in which several literature references relating to the field use of trilostane were discussed along with three multi-centric clinical trials which were conducted 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[4] 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

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

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 however that this has recently been amended via a variation procedure to a starting dose of 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.

The studies provided 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.

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.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)