IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Vetoryl

PRODUCT SUMMARY

EU Procedure number	IE/V/0514/005/DX/001
Name, strength and pharmaceutical form	Vetoryl 5 mg hard capsules for dogs
Active substance(s)	Trilostane
Applicant	Dechra Regulatory B.V. Handelsweg 25 5531 AE Bladel The Netherlands
Legal basis of application	Extension application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of procedure	18th November 2020
Target species	Dogs
Indication for use	In dogs: For the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome).
ATC vet code	QH02CA01
Concerned Member States	AT, BE, CZ, DE, DK, EL, ES, FI, FR, HU, HR, IT, LU, NL, NO, PL, PT, SE, SI, SK, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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

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.
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.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains 5 mg of the active substance trilostane and the excipients lactose monohydrate, maize starch, magnesium stearate, capsule shells (containing yellow iron oxide, black iron oxide titanium dioxide and gelatin) and capsule inks.
The container/closure system is PVC-PVDC / aluminium blisters of 10 tablets in cartons of 30 capsules.

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 at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is Trilostane, an established active 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 has been provided.

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

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.

D. Control on Intermediate Products

Not applicable.

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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has 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 has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing
Pharmacological Studies
The applicant cross referred to previous studies and published literature provided in support of Vetoryl 10 mg, 30 mg, 60 mg and 120 mg hard capsules which show that trilostane acts by inhibiting the synthesis of cortisol, corticosterone and aldosterone (adrenocorticosteriods) and selectively and reversibly inhibiting the enzyme system 3 beta hydroxysteroid isomerase. 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

This application is for the addition of a new lower strength 5 mg product to the already authorised 10 mg, 30 mg, 60 mg and 120 mg strength hard capsules.

Given that the 5 mg strength capsule contains the same active ingredient and excipients as the higher strength products (Vetoryl 10 mg, 30 mg 60 mg and 120 mg), albeit in different quantities, it can be accepted that the toxicological aspects of the formulation have previously been assessed and considered acceptable within the context of the application for marketing authorisation for the higher strength products. Consequently, no new toxicity data is considered necessary for the purpose of this application. Warnings and precautions as listed on the product literature are the same as those of the higher strength products and are adequate to ensure safety of the product to users and the environment.

User Safety

A user safety assessment in compliance with the relevant guideline was provided and showed that the product will not present an unacceptable risk to the user when handled, used, stored and disposed of in accordance with the recommendations included in the product literature.

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, the child 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 considered adequate to ensure safety to users of the product.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines. The product will only be used in non-food animals and as a result, environmental exposure will be low and assessment may stop in Phase I. A Phase II ERA was not required. No additional risk to the environment is expected when compared with the already authorised higher strength products. It may be concluded that the product will not present an unacceptable risk to the environment when stored, handled, administered and disposed of in accordance with the recommendations included in the SPC.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

As this is a line extension application for the addition of a new lower strength 5 mg product, reference was made to pharmacodynamic information available for the higher strength products (Vetoryl 10 mg, 30 mg, 60 mg and 120 mg hard capsules).

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 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

In order to demonstrate an essential similarity in the bioavailability between the lower strength 5 mg product and the higher strength products, the applicant conducted a dose proportionality study comparing all five strengths of the capsules (5 mg, 10

mg, 30 mg, 60 mg and 120 mg). The study demonstrated a dose-response effect in an approximately proportional manner suggesting approximate linearity of absorption of all five capsule strengths and thereby supported dose-proportionality. The clinical relevance of these findings were further supported by clinical safety and efficacy data.

Tolerance in the Target Species of Animals

As this is a line extension application for the addition of a new lower strength 5 mg product, the applicant makes reference to target animal safety information previously provided in support of the higher strength propducts (Vetoryl 10 mg, 30 mg, 60 mg and 120 mg hard capsules). In addition, two clinical studies were conducted specifically with trilostane 5 mg capsules in which safety was assessed in the target species. Based on the findings from these studies, an acceptable level of tolerance following administration of the 5 mg capsule strength was suitably demonstrated.

IV.B Clinical Studies

In support of safety and efficacy of the 5 mg hard capsule, two clinical studies were conducted, a retrospective study of the safety and efficacy in dogs of down-titrating from a 10 mg Vetoryl capsule to a 5 mg capsule and a prospective clinical study to compare the clinical outcome of exchanging one Vetoryl 10 mg capsule for two 5 mg capsules in dogs with hyperadrenocorticism. The results of these studies overall were considered to adequately support the results from the dose proportionality study and the safety and efficacy of the 5 mg strength hard capsule when administered for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in 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.