IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Vetoryl 30 mg chewable tablets for dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0514/007/DX/002
Name, strength and pharmaceutical form	Vetoryl 30 mg chewable tablets for dogs
Active substances(s)	Trilostane
Applicant	Dechra Regulatory B.V. Handelsweg 25 5531 AE Bladel Netherlands
Legal basis of application	Full application - known active substance (Article 8 of Regulation (EU) 2019/6)
Date of completion of procedure	02/04/2024
Target species	Dogs
Indication for use	For the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome)
ATCvet code	QH02CA01
Concerned Member States	AT, BE, CZ, DE, DK, EL, ES, FR, FI, HU, HR, IT, LU, NL, NO, PL, PT SK, SI, SE, UK(NI)

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 relevant articles of Regulation (EU) 2019/6. 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition
The product contains trilostane in 20 mg, 30 mg, 60 mg or 120 mg quantities depending on the strength of the tablet. It also contains the excipients maize starch, lactose monohydrate, cellulose microcrystalline, sodium starch glycolate (type A), chicken flavour, yeast (dried), silica colloidal hydrated and magnesium stearate.
The products are in the form of a chewable tablet containing the active substance trilostane. Four strengths of the tablet are authorised (20, 30, 60 and 120 mg), so that accurate and convenient dosing can be achieved in dogs of various sizes. The tablets contain a cross-shaped break line on one side and can be divided into 2 or 4 equal parts.
The finished product is packaged in thermofoiled and sealed blisters. Pack sizes are detailed in the SPC.

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 at 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. 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.
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 have been provided.
Batch analytical data from the production sites have been provided demonstrating compliance with the specification.

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. These include data for three batches from each manufacturer produced according to the current method of manufacture. The data confirm the shelf life detailed in the SPC.
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)

The current applications have been submitted for the addition of a new pharmaceutical form (a chewable tablet) as well as a new strength (20 mg trilostane) to the Vetoryl range, based on the approved marketing authorisation for the veterinary medicinal product Vetoryl hard capsules for dogs.
The applicant has demonstrated bioequivalence of the candidate chewable tablet formulation with the authorised hard capsule formulation of Vetoryl.
As bioequivalence with a suitable authorised comparator product has been demonstrated, results of safety and efficacy tests are not required.
The safety and efficacy aspects of this product are identical to the authorised comparator product.
Warnings and precautions as listed on the product literature are largely the same as those of the authorised comparator product and are adequate to ensure safety of the product to users and the environment.

III. SAFETY ASSESSMENT

Pharmacological Studies
The applicant conducted two (1 pilot and 1 pivotal) *in vivo* bioequivalence studies in which bioavailability of the proposed 60 mg chewable tablet formulation was compared to the authorised originator product, 'Vetoryl 60 mg hard capsules for dogs.'
The pivotal *in vivo* bioequivalence study was conducted to GLP-standard and in accordance with relevant guidance. In this four-period, two-sequence cross-over study, 60 mg of the test or reference article was administered to 36 Beagle dogs, with a washout period of 7 days between doses. The test article was well-tolerated. The evaluation of bioequivalence was based upon

validated measurement of the active substance, trilostane, in plasma. Calculated lower and upper confidence limits for the ratio of the geometric means for AUC_t fell within the pre-specified acceptance limits. However, for C_{max}, the 90% confidence intervals for the ratios of the test to reference products were outside the standard limits. The applicant provided suitable justification that deviation from the standard acceptance limits for C_{max} is not expected to be of clinical relevance (i.e., not anticipated to have significant implications in terms of either safety or efficacy).
Dissolution studies were performed in order to extrapolate *in vivo* bioequivalence to the 20 mg, 30 mg and 120 mg tablet strengths. The additional strengths were demonstrated to have similar dissolution profiles to the 60 mg chewable tablet that was used in the pivotal bioequivalence study, and therefore, bioequivalence can be accepted for all tablet strengths.

Toxicological Studies
The results of special studies demonstrate that trilostane is not a skin sensitiser, nor is it an ocular or skin irritant. Additionally, *in vitro* data were presented to demonstrate that the final tablet formulation is non-irritant to skin.

User Safety
The applicant provided a user safety assessment broadly in compliance with the relevant guideline. The proposed user safety warnings incorporate those approved for the authorised originator product, and a warning specific to the new pharmaceutical form
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product, as follows:
•Trilostane may decrease testosterone synthesis and has anti-progesterone properties. Women who are pregnant or are intending to become pregnant should avoid handling the veterinary medicinal product.
•Wash hands after use. People with known hypersensitivity to trilostane or any of the excipients should avoid contact with the veterinary medicinal product.
•To prevent children from having access to the tablets, used blister packs should be stored in the original carton out of sight and reach of children.
•In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician. Accidental ingestion may cause adverse effects including vomiting and diarrhoea.

Environmental Risk Assessment
The environmental risk assessment stopped in Phase I and no Phase II assessment is required because the candidate product will be used only in a non-food producing target animal (dogs). The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies
Tolerance in the Target Species of Animals
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies
No clinical studies were submitted with this application.
Bioequivalence with a suitable comparator product has been demonstrated for the candidate product (please see 'Pharmacological studies' above). The target species (dogs) and the product indication (for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome)) remain unchanged from that for the originator product and the product is to be administered at the same dose, by the same route of administration as that already approved for the originator product. As bioequivalence with the originator product can be accepted, the provision of clinical trial data is unnecessary as these data may be extrapolated from the originator product.

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 of the product(s) is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.