College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Trilotab 10 mg chewable tablets for dogs
Trilotab 30 mg chewable tablets for dogs
Trilotab 60 mg chewable tablets for dogs
Trilotab 120 mg chewable tablets for dogs
Trilotab 150 mg chewable tablets for dogs

NL/V/0373/001-005/DC

Created: July 2023

CMS: AT, BE, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LV, PL, PT, SE, SK, UK(NI)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0373/001-005/DC
Name, strength and pharmaceutical form	Trilotab 10, 30, 60, 120 or 150 mg chewable tablets
Applicant	CP Pharma Handelsgesellschaft mbH Ostlandring 13 31303 Burgdorf Germany
Active substance(s)	Trilostane
ATC Vet code	QH02CA01
Target species	Dogs
Indication for use	For the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome).

Trilotab Flavoured	NL/V/0373/001-005/DC
CP-Pharma	DCP
	Publicly available assessment report

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Trilotab 60 mg chewable tablets for dogs: Generic application in accordance with Article 18 of Regulation (EU) 2019/6 Trilotab 10, 30, 120 and 150 mg chewable tablets for dogs: Hybrid application in accordance with Article 19(1) of Regulation (EU) 2019/6
Date of completion of the original decentralised procedure	31 May 2023
Concerned Member States for original procedure	AT, BE, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LV, PL, PT, SE, SK, UK(NI)

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.

The reference product for this generic/hybrid application is Vetoryl 60 mg, IE/V/0514/003 (previously: UK/V/0215/003).

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The tablets contain 10 mg, 30 mg, 60 mg, 120 mg and 150 mg Trilostane and the following core excipients: Lactose monohydrate, Pregelatised starch (maize), Hydroxypropylcellulose, Colloidal silica hydrated, Sodium starch glycolate (type A), Magnesium stearate and Chicken flavour.
The tablet is cross scored and meant to be broken into equal halves or quarters.
The products are packed in Al-Al blisters, each containing 10 tablets.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
A bioequivalence study demonstrated that the 60 mg chewable tablets are similar to the reference product (Vetoryl 60 mg capsules). The 10 mg, 30 mg, 120 mg and 150 mg tablets fulfil the requirements of the biowaiver for strengths.

Trilotab Flavoured	NL/V/0373/001-005/DC
CP-Pharma	DCP
	Publicly available assessment report

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.

The product is manufactured using conventional manufacturing techniques.

The tests performed during production are adequately described.

C. Control of Starting Materials

The active substance is Trilostane and is not described in the European Pharmacopoeia. 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 from the supplier. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients are in conformity with the Ph. Eur. requirements, with the exception of Chicken flavour which has been adequately specified.

The packaging is conformity with the Ph. Eur. and EU Food Directive.

Specific measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies are taken.

The Magnesium stearate is of vegetable origin. In regard to Chicken flavour, a TSE declaration and Viral Safety Evaluation are provided.

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. Relevant 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 site have been provided demonstrating compliance with the specification.

F. Stability

According to the stability data for the active substance the claimed retest period can be granted.

Stability data on the finished product has been provided in accordance with applicable European guidelines. According to the accelerated stability results provided, the claimed shelf life of 22 months and the proposed storage claim “Do not store above 25 °C” can be granted for the 10 mg, 30 mg, 60 mg and 150 mg strengths of the product packed in Alu-Alu blister. For the 120 mg strength in the container closure system, a shelf life of 34 months without any special storage condition can be granted.

G. Other Information

Not applicable.

Trilotab Flavoured	NL/V/0373/001-005/DC
CP-Pharma	DCP
	Publicly available assessment report

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 18 and a hybrid application according to Article 19(1), and bioequivalence with the reference product has been demonstrated, results of pharmacological and toxicological tests are not required.

The pharmacological and toxicological aspects of this product is/are identical to the reference product.

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

III.A Safety Testing

Pharmacological Studies

No pharmacological studies were provided.

Toxicological Studies

No toxicological studies were provided.

Observations in Humans

The applicant has provided respective data. Adverse effects associated with trilostane administration in humans included flushing, gastritis, ulcer, nausea, vomiting, diarrhoea, rhinorrhoea, and tingling and swelling of the mouth. Rashes may occur and, rarely, granulocytopenia in immunocompromised patients. Trilostane suppresses the production of progesterone.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product may decrease testosterone synthesis and has anti-progesterone properties, cause skin and eye irritation and sensitization or hypersensitivity.
Dermal exposure is foreseen every time the product is administered, but exposure is expected to be much less then the human therapeutic dose and washing hands after administration of the product will mitigate exposure. Adverse effects following oral intake cannot be excluded and therefore suitable user warnings are in place.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals.

Trilotab Flavoured	NL/V/0373/001-005/DC
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IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 18 and a hybrid application according to Article 19(1), and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

A single dose, crossover (two period), two sequence, bioequivalence study was performed, to demonstrate that Trilotab 60 mg chewable tablet and the reference product Vetoryl 60 mg capsule produced similar plasma concentrations of the active ingredient after oral administration in fed Beagle dogs, in order to conclude that the systemic effects of both products, in respect of efficacy and safety, are the same. The study was conducted in accordance with GLP. Suitable statistical analyses were performed on the samples obtained, and bioequivalence was determined based on log-transformed C_{max} and AUC. The results of this study indicate that the 90% confidence interval for the primary variables fell within pre-defined limits. As such, this study successfully demonstrated bioequivalence between the reference product Vetoryl 60 mg and the investigated product Trilotab 60 mg. On safety, it is noted that the investigated product was well tolerated, as no adverse reactions were observed after administration of both test and reference product.

The applicant has presented a report on the validation of the bioanalytical method, used in the bioequivalence study mentioned above. This validation demonstrated the suitability of the method for quantitative determination of trilostane in dog plasma.

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 risk benefit 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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

None.