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

Thyforon flavoured 600 microgram tablets for dogs (UK, IE)
Forthyron flavoured 600 microgram tablets for dogs (BE, BG, CY, CZ, EL, HR, HU, LU, NL, PL, RO, SI, SK)
Forthyron Flavour 600 microgram tablets for dogs (AT, DE, EE, LT, LV)
Forthyron flavoured vet., 600 microgram tablets for dogs (DK)
Forthyron Smak vet, 600 microgram tablets for dogs (FI, SE)
Forthyron vet., 600 microgram tablets for dogs (NO)
Canitroid Sabor, 600 microgram tablets for dogs (ES)
Canitroid flavoured 600 microgram tablets for dogs (PT, IT)

Thyforon flavoured 800 microgram tablets for dogs (UK, IE)
Forthyron flavoured 800 microgram tablets for dogs (BE, BG, CY, CZ, EL, HR, HU, LU, NL, PL, RO, SI, SK)
Forthyron Flavour 800 microgram tablets for dogs (AT, DE, EE, LT, LV)
Forthyron flavoured vet., 800 microgram tablets for dogs (DK)
Forthyron Smak vet, 800 microgram tablets for dogs (FI, SE)
Forthyron F XL tablets for dogs (FR)
Forthyron vet., 800 microgram tablets for dogs (NO)
Canitroid Sabor, 800 microgram tablets for dogs (ES)
Canitroid flavoured 800 microgram tablets for dogs (PT, IT)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0286/003/DC NL/V/0286/004/DC
Name, strength and pharmaceutical form	Forthyron Flavoured 600 Microgram Tablets for Dogs Forthyron Flavoured 800 Microgram Tablets for Dogs
Applicant	Eurovet Animal Health BV Handelsweg 25 Bladel The Netherlands
Active substance(s)	Levo-thyroxine sodium
ATC Vetcode	QH03AA01
Target species	Dogs
Indication for use	For the treatment of hypothyroidism in dogs.

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	Generic hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	26th October 2011.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	First Use Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden. Repeat Use Bulgaria, Croatia, Cyprus, Estonia, Latvia, Lithuania, Romania

I. SCIENTIFIC OVERVIEW

These were generic hybrid applications under Article 13 (3) of Directive 2001/82/EC as amended, where bioequivalence was appropriately established with suitable reference products. The reference products were Forthyron 200 Microgram Tablet and Forthyron 400 Microgram Tablet. Forthyron Flavoured 600 Microgram Tablets for Dogs and Forthyron Flavoured 800 Microgram tablets for Dogs are indicated for use in dogs with hypothyroidism, and the dose rate is 10 µg/kg levothyroxine sodium given orally every 12 hours. The dosage may need to be adjusted prior to a complete clinical response, with the initial dose and frequency of administration being given as a starting point. Therapy needs to be tailored to the animal, and when administering the product to dogs weighing less than 5 kg, a quarter of a 200 µg tablet is administered once daily. The administration of food may affect the absorption of the product, so timing of treatment should be related to feeding. Trough and peak T4 levels need to be monitored during treatment, and when the optimum replacement dose has been established, clinical and biochemical monitoring may be performed every 6-12 months.

The products are 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 products can be safely used in the target species, the slight reactions observed are indicated in the SPC[1]. The products are 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 products 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. Composition

The products contain levothyroxine sodium (600 or 800 mg per tablet) and excipients calcium hydrogen phosphate dehydrate, cellulose, microcrystalline, sodium starch glycolate (type A), magnesium stearate and natural meat flavour.

The container system consists of 10 tablets per blister, 5 or 25 blisters per carton, 50 or 250 tablets per carton, with tablets packaged in blisters formed from white, 20 µm aluminium. The particulars of the containers and controls performed are provided and conform to the regulation. The absence of preservative is justified.

The products are 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 products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The tituration procedure takes place with a portion of microcrystalline cellulose mixed with thyroxine sodium. Other excipients are mixed, and the portion containing the active substance added. After the creation of a final blend powder, the tablets are formed and placed into the blister packs.

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 levothyroxine sodium an established active substance described in the European Pharmacopoeia (Ph. Eur). 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. All excipients are monographed in the Ph.

[1] SPC – Summary of Product Characteristics.

Eur, apart from the natural meat flavour, which complies with the appropriate Guideline for a flavouring preparation.

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

A Format Three declaration was 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

Not applicable.

F. 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 site have been provided demonstrating compliance with the specification. Tests include those for appearance, identification of active substance, friability, resistance to crushing, uniformity of dose, microbiological quality and dissolution rate.

G. 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. The shelf-life of the products as packaged for sale is 2 years.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life of remaining tablet parts: 4 days.

Do not store above 25°C.
Return any divided tablet to the opened blister and use within 4 days.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As these were generic applications according to Article 13 (1), and bioequivalence with the reference products has been demonstrated, results of pharmacological and toxicological studies are not required. Appropriate studies were performed in support of the bioequivalence claim. No further data was required for this section.

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

III.A Safety Testing

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. 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 further assessment was required. A suitable, revised Phase I environmental risk assessment report was subsequently submitted.

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)

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for these products are equivalent to those of the reference products. Appropriate studies as indicated by the current bioequivalence guideline supported the claims for these products. These studies were acceptable for these applications.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

As bioequivalence was successfully claimed between these applications and the reference products, no data were required in this section.

IV.B Clinical Studies

Laboratory Trials

As bioequivalence was successfully claimed between these applications and the reference products, no data were required in this section.

Dose confirmation studies

As bioequivalence was successfully claimed between these applications and the reference products, no data were required in this section.

Field Trials

As bioequivalence was successfully claimed between these applications and the reference products, no data were required in this section.

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 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.

•	30 August 2018	Change in RMS from UK to NL.
•	17 July 2018	Repeat use MRP to add 7 CMS
•	26 January 2017	Renewal – UK as RMS
•	12 April 2016	Submission of 2 updated certificates of suitability.
•	31 October 2014	Change in a test procedure for the finished product.
•	10 April 2014	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product.
•	10 April 2014	Change to importer, batch release arrangements and quality control testing of the finished product.
•	10 April 2014	Change in the manufacturing process of the finished product.
•	18 April 2013	Change in specification limit of an excipient.