# Veterinary Medicines Directorate

Woodham Lane, New Haw, Addlestone, Surrey KT15 3LS
Telephone (01932) 336911 Fax (01932) 336618
Website: www.vmd.gov.uk


**(Reference Member State)**

**MUTUAL RECOGNITION PROCEDURE**

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT**

**Forthyron 200 and 400**

**PuAR correct as of 28/08/2018 when RMS was transferred to DE.**
**Please contact the RMS for future updates.**

# MODULE 1

## PRODUCT SUMMARY

| | |
|---|---|
| EU Procedure number | UK/V/0217/001 |
| Name, strength and pharmaceutical form | Forthyron 200 and 400 microgram tablet |
| Applicant | Eurovet Animal Health BV<br>Handelsweg 2555<br>31 AE Bladel<br>The Netherlands |
| Active substance(s) | Levothyroxine |
| ATC Vetcode | QH03A A01 |
| Target species | Dogs |
| Indication for use | For the treatment of hypothyroidism |

# MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the veterinary Heads of Agencies website (www.HEVRA.org).

# MODULE 3

## PUBLIC ASSESSMENT REPORT

| | |
|---|---|
| Legal basis of original application | Application for marketing authorisation in accordance with Article 13.1(a)(ii) of Directive 2001/82/EC as amended. |
| Date of completion of the original mutual recognition procedure | 1 March 2006 |
| Date product first authorised in the Reference Member State (MRP only) | 13 April 2005 |
| Concerned Member States for original procedure | Austria<br>Belgium<br>Czech Republic<br>Denmark<br>Finland<br>France<br>Germany<br>Greece<br>Hungary<br>Ireland<br>Leichtenstein<br>Luxembourg<br>Netherlands<br>Poland<br>Slovakia<br>Slovenia<br>Sweden |

# 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 200 or 400 µg levothyroxine sodium and calcium hydrogen phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate and magnesium stearate. The tablets are packed in aluminium foil/white PVC/PE/PVDC foil blister packs of 10 tablets. 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 levothyroxine, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Certificates of suitability have been provided.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

### *E. Control on intermediate products*

There are no intermediate products.

### *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.

### *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.

## III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

### *III.A Safety Testing*

### *Pharmacological Studies*

The applicant has provided bibliographical data which show that levothyroxine acts in exactly the same way as the natural hormone. Thus it has effects on many different cellular processes. It is intended to rectify a deficiency in the natural hormone.

The applicant has also provided bibliographical data which show that levothyroxine (T4) is absorbed relatively slowly after oral administration, with maximum levels occurring in the blood between 1 and 5 hours after administration. There is considerable variation in the rate of absorption between individual animals. Once absorbed, levothyroxine is converted to tri-iodothyronine (T3) which is a more active form of the hormone. There may then be further changes to the substance, including the removal of iodine atoms or the addition of glucuronides and sulphates, and these changes result in a loss of biological activity. The liver plays an important part in this process. Excretion may be in the urine and the faeces. Like absorption, all these processes vary considerably between individuals.

### *Toxicological Studies*

Because levothyroxine is identical to a naturally occurring hormone, there have been relatively few conventional toxicity studies. Any adverse effects resulting from exposure to levothyroxine are predicted to be a result of its intended physiological effect. For example, levothyroxine had few adverse effects when dogs or children have accidentally consumed large quantities of tablets intended for another patient. Adult humans are slightly more susceptible to the effects of the substance but nevertheless can tolerate substantial amounts without serious effects. The type of effects observed are similar to the symptoms of hyperthyroidism, i.e. polydipsia, polyuria, nervousness, panting, increased appetite, weight loss, increased heart rate, increased pulse pressure. Repeated dose studies in animals show that levothyroxine can also reduce bone mineral density.

Published literature has shown that when levothyroxine is administered to newborn rats, it caused a positive effect on early locomotor activity and time of eye opening, although body weight and thyroid weight were lower than in controls. The effect on eye opening was also reported in the young of female rats which had been treated when they themselves were newborn. However, in this case, some other developmental parameters were delayed, e.g. later vaginal opening, later first oestrus, longer cycle length and other effects on the reproductive system. Although it has been shown in guinea pigs that levothyroxine can cross the placenta, the developmental effects discussed above were not observed when levothyroxine was given to pregnant rats from day 7 – 13 of pregnancy. However, in mice, there was a small increase in the incidence of cleft palate when pregnant females were given T3 or T4 during pregnancy. In humans, exposure of pregnant women to thyroxin is associated with a slight increase in the incident of cardiac malformations.

Levothyroxine is generally accepted as belonging to a group of substances which do not have mutagenic potential. It is theoretically possible that levothyroxine could have an effect on the development of hormone-dependent cancers but the epidemiological data based on long-term use of the substance in human medicine do not show a clear trend.

### *User Safety*

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the most likely routes of human exposure are dermal contact by the person administering the product or accidental ingestion by a child of a tablet portion, as such portions are stored in opened blisters and may therefore be accessible to children. Skin contact with the product would only be a concern in the case of pregnant women because of the adverse effects that may occur if exposed to levothyroxine during pregnancy. Accidental ingestion by a child of a portion of a tablet is unlikely to result in serious adverse effects as there is evidence to show that children have tolerated much higher doses.

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, as a product used only in a small proportion of dogs at a low dose and replacing an endogenous hormone, exposure of the environment following treatment with Forthyron will not be extensive.

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*

The applicant presented a mixture of bibliographical and proprietary data to show that a starting dose of 10 µg/kg body weight twice a day is appropriate to address a thyroid deficiency but that, because of the variability between animals, this may have to be adjusted depending on each animal's response to treatment.

### *Tolerance in the Target Species of Animals*

The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species. An untreated group of

animals was used as a control. All doses were administered twice daily by the oral route for four consecutive weeks.

Parameters evaluated were clinical condition, blood levels of T4, TSH, creatinine, urea, glucose, liver enzymes, proteins and electrolytes, body weight, heart rate and body temperature.

Minimal adverse effects were seen following doses up to six times the recommended dose. It should be noted that the dogs in this study did not have hypothyroidism and it would therefore be expected that any effects observed in these euthyroid animals would be greater than those in hypothyroid patients.

Bibliographical data and post marketing information on effects in hypothyroid dogs have also been provided which confirm that Forthyron is well-tolerated.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

## *IV.B Clinical Studies*

### *Field Trials*

The applicant has provided bibliographical data which demonstrates that a starting dose of 20 µg levothyroxine/kg bodyweight per day is suitable for most dogs, with a rapid improvement in metabolic function followed by a slower improvement in dermatological signs. Therapeutic monitoring was shown to be necessary because of the variability in individual response to treatment, and dose adjustments are required in approximately half of cases.

The applicant also conducted field studies to demonstrate the efficacy of the formulated product Forthyron. Two studies were retrospective studies of dogs given 10 µg/kg twice each day to treat hypothyroidism, one study in 1990 and one in 2003. In one study, the main parameter assessed was the blood level of T4, but in the other study owners were required to assess clinical signs associated with hypothyroidism (activity, appetite, cold intolerance, skin/coat signs, libido, neural signs, muscular/locomotory signs and gastrointestinal signs). In each study the dogs responded satisfactorily to treatment although a significant number needed an increased dose.

The pivotal study was dated 2004 and was conducted in accordance with Good Clinical Practice. The efficacy of Forthyron was evaluated by comparison of the clinical (body temperature, heart rate, respiratory rate, body weight and clinical manifestations of hypothyroidism) and laboratory (T4/TSH levels plus other blood constituents indicative of hypothyroidism) investigations prior to treatment and after at least six weeks of treatment. Participating dogs served as their own controls and T4/TSH levels were compared with those of healthy dogs using data taken from literature. As in the other studies, the starting dose was 10 µg/kg; this dose had to be adjusted in around half of the dogs, based on T4/TSH levels and clinical signs. Clinical efficacy was proven by elevation of T4 levels

by at least 18 nmol/L, and confirmed by anamnesis, clinical examination and haematological/biochemistry parameters.

## 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 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)