IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Leventa 1 mg/ml oral solution for dogs

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0182/001
Name, strength and pharmaceutical form	Leventa 1 mg/ml oral solution for dogs
Active substances(s)	Levothyroxine sodium (as multihydrate) equivalent to 0.97 milligram levothyroxine
Applicant	Intervet Ireland Limited Magna Drive Magna Business Park, Citywest Road Dublin 24 Ireland
Legal basis of application	Well-established use application (Article 13a of Directive No 2001/82/EC)
Date of completion of procedure	28 March 2007
Target species	Dogs
Indication for use	Treatment of hypothyroidism.
ATCvet code	QH03AA01
Concerned Member States	AT, BE, CZ, DE, DK, EL, ES, FI, FR, HU, IT, LT, LU, NL, NO, PL, PT, SE, UK

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 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; any potential adverse effects are detailed in the SPC.

The product is safe for the user, the consumer of foodstuffs from treated animals 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
Active substance
Levothyroxine sodium (1 mg/ml)

Excipients
Hydroxypropyl betadex
Ethanol
Sodiun hydrogen carbonate
Sodium Hydroxide
Hydrochloric acid
Purified water

The container/closure system consists of 30 ml amber type III glass bottle with polyethylene child resistant screw cap containing a polyethylene insert.
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.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is levothyroxine sodiuman established 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 have been provided.
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.

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.

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 approvedconditions.
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.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics:
The active substance, L-thyroxine sodium, is produced synthetically. L-thyroxine is identical in structure and activity to the endogenous thyroid hormone thyroxine (T4). T4 is de-iodinated in peripheral tissues to form tri-iodothyronine (T3). The numerous effects of T4 and T3 include:

- metabolic effects: stimulation of cellular oxygen consumption and basal metabolism, promotion of growth and maturation, regulation of lipid and carbohydrate metabolism
- catabolic effects: on muscle and fat
- essential for normal growth and development: neurological and skeletal systems
- stimulation of heart rate, cardiac output and blood flow, stimulation of erythropoiesis.

Pharmacokinetics:
The applicant has presented a selection of publications describing the pharmacokinetic properties of T4 in a variety of species.In addition, several pharmacokinetic studies have been conducted using Leventa in dogs. Based on the data provided, the pharmacokinetics of oral L-thyroxine in the dog can be summarised as follows:

There is considerable variation in the pharmacokinetics between individual dogs. After oral administration of the productto euthyroid, fasted dogs, t_{max}occurred at approximately 2.5hours. The serum half-life of L-thyroxine was approximately 7 hours. Bioavailability was approximately 22%. After repeated oral administration over 14 consecutive days at a dose rate of 40 microgram/kg/day, there was no accumulation of L-thyroxine in serum. Concomitant administration of food with the product delays absorption and reduces the extent of absorption of L-thyroxine from the gastrointestinal tract by approximately 50%. L-thyroxine is highly protein bound.

The major site of T4 metabolism is the liver. The main pathway for the metabolism of T4 is its conversion, by de-iodination, to the active metabolite T3. Further de-iodination of T4 and T3 leads to production of inactive compounds. Excretion is mainly observed via biliary and, to a lesser extent, urinary routes.

Toxicological Studies

Toxicological data is presented by way of bibliography. As L-thyroxine sodium is an endogenous mammalian hormone, signs of acute and chronic toxicity correspond with the physiological and pharmacological effects

and are identical to those occurring in spontaneous or iatrogenic hyperthyroidism, which are well documented and include metabolic, cardiac, dermatological, muscular, skeletal and neuro-psychiatric signs.

During pregnancy, maternal thyroid hormone requirements increase. An appropriate statement advising of this effect is included in the SPC.

Information relating to tolerance in the target species is provided in Part IV of this report.

User Safety

Based on the user safety assessment provided, no specific risk management is deemed necessary for either non-professional or professional users other than the relevant risk communication. Restricting distribution of the product to 'prescription only' will limit access by non-professional users. The likelihood of exposure is very low if the product is stored correctly.The packaging will also limit access to the contents by children and the presence of an insert in the bottle neck limits both the risk of splashing and, if occurring, the splashed volume. The following warnings are included in the SPC:

- Wash hands after use.
- In the case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Note: This product contains a high concentration of L-thyroxine sodium and may present a risk to humans if ingested.
- In case of eye contact, flush immediately with water.

User safety is acceptable, and the agreed SPC statements are considered appropriate.

Environmental Risk Assessment
The product is intended for use in companion animals only and as such, it is not expected to present a hazard to the environment under normal conditions of use.

III.B Residues Documentation

Residue Studies
Not applicable

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology

See section IIIA

The results of pharmacokinetic studies conducted by the applicant correspond to those published in the literature, although there is considerable individual variability in pharmacokinetic parameters. This emphasises the need for adjusting the dose to achieve therapeutic effects for each individual. Absorption is reduced when administered with food, so treatment should always be given consistently with or without food in any individual. This is addressed in the SPC.

Tolerance in the Target Species of Animals

Literature
Acute accidental exposure to an overdose of L-thyroxine has been reported. Generally signs were mild and reversible, and related to the known pharmacological actions. The potential for chronic toxicity in dogs has also been discussed in the literature: suppression of TRH response and reversible histological changes in the thyroid gland may occur with doses of 32 microgram/kg/day for 8 weeks, but no changes in ECG or echocardiography parameters were seen.

Target animal tolerance study
A target animal tolerance study was conducted in healthy dogs using the final formulation. The study was conducted in accordance with relevant guidance. Based on the findings of that study, the following was concluded:

Treatment at the maximum recommended dose (40 microgram/kg/day) for a period of three months had no significant effect except a decrease in plasma cholesterol.
At 3 times and 5 times the maximum RTD, abnormalities were weight loss, hyperactivity, transient cardiac arrhythmia, soft faeces, decreased plasma cholesterol and total protein, increased plasma glucose and inorganic phosphorus. All the effects correspond to the known pharmacological effects of thyroxine.
Transient pruritus occurred in one dog: this is a known sign of thyrotoxicosis in humans. All effects were reversible within 5 weeks after stopping treatment.

IV.B Clinical Studies

Laboratory Trials

A report of the use of L-thyroxine in hypothyroid dogs provides support for the dose chosen for Leventa [Dixon et al (2002)]. Thirty-one dogs with spontaneous hypothyroidism were treated with thyroid hormone replacement therapy (THRT) and monitored for approximately three months. Good clinical and laboratory control was ultimately achieved in all cases with a mean L-thyroxine (T4) dose of 0.026 mg/kg administered once daily. After commencing treatment, 11 cases subsequently required an increase and three cases required a decrease in dose to achieve optimal clinical control. Lethargy and mental demeanour were typically the first clinical signs to improve, with significant bodyweight reduction occurring within two weeks of commencing THRT.
In that publication, the authors consider the options of once or twice daily treatment, pointing out that although many clinicians advocate dividing the dose and administering twice daily, once daily is easier for owners although it is less physiologically normal. Biological half life extends beyond the circulating half life and probably explains the success of once daily treatment, as shown in this study.
It is concluded that a recommendation for divided doses in certain cases is not necessary.

Field Trials
Efficacy data generated in two long-term field trials using Leventa were presented in the dossier. Stringent inclusion criteria were used to ensure correct diagnosis, based on up-to-date recommendations from the literature.

Field Study 1
The first of those was a multicentre non-blinded self-controlled GCP field study conducted at veterinary schools and private clinics in Belgium, France, Germany, Ireland, UK.
The treatment was effective in controlling clinical and hormonal signs of hypothyroidism in all treated dogs. Clinical condition improved and hormonal condition normalised within 4 weeks of the start of treatment in

most dogs. A single daily dose of 20 microgram/kg was effective in 79% of cases. 6% required a decrease to a minimum of 10 microgram/kg and 15% required an increase up to 30 microgram/kg.T aking changes in bodyweight into account, at the end of the study actual dose rates ranged from 20 – 42 microgram/g.
The study was well reported. A complete description of the range of clinical signs and clinical pathology for each dog, prior to and during treatment was presented.The study adequately confirms that the product is effective for long-term treatment.

Field Study 2
The Applicant conducted a small field study (limited numbers of test animals) to investigate the efficacy of Leventa for the control of hypothyroidism in dogs already controlled with L-thyroxine tablets. The study was conducted at 2 veterinary schools and 2 private clinics in Belgium, Ireland, UK.
The findings of the study demonstrated that dogs treated successfully with L-thyroxine tablets can be switched to Leventa in a dose for dose manner without any safety or efficacy issues.Switched dogs remained clinically and hormonally free from signs of hypothyroidism.

Conclusions on Part IV
The available data provide adequate support for efficacy of the product and confirm the findings of the pharmacokinetic and tolerance studies. It can be accepted, taking the entire data package into account, that the product will be effective in restoring the TT4 to the reference range and resolving clinical signs in hypothyroid 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.

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.

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.

Changes:
None