MINISTERIO DE SANIDAD
agencia española de medicamentos y productos sanitarios

DEPARTAMENTO DE MEDICAMENTOS VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

THIAMACARE 10 mg/ml Oral Solution For Cats

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0343/001/ DC
Name, strength and pharmaceutical form	Thiamacare 10 mg/ml oral solution for cats
Applicant	Ecuphar NV, Legeweg 157-i B-8020 Oostkamp Belgium
Active substance(s)	Thiamazole
ATC Vetcode	QH03BB02.
Target species	Cats
Indication for use	For the stabilisation of hyperthyroidism in cats prior to surgical thyroidectomy. For the long-term treatment of feline hyperthyroidism

MODULE 2

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

"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."

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	05/02/2020
Date product first authorised in the ReferenceMemberState (MRP only)	
Concerned Member States for original procedure	AT, BE, CY, CZ, DK, FI, FR, DE, EL, HU, IT, LU, MT, NL, PL, PT, RO, SK, SE, UK

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. Qualitative and quantitative particulars

The product contains 10 mg/ml of thiamazole as active substance and glycerol, sorbitol liquid (70%) and vanillin.

The container/closure system is a 30 ml type III amber glass vial closed with a polypropylene syringe adaptor and further closed with a child-proof white polypropylene screw cap. A 1 ml polypropylene syringe is supplied with the medicinal product provided as dosing device

B. Method of Preparation of the Product

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance is thiamazole an established substance 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. Batch analytical data demonstrating compliance with this specification have been provided.

Satisfactory TSE information has been provided in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

D. Control on intermediate products pharmaceuticals

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 proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance<s> 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.

The claim of a 3 months stability after first opening the immediate packaging is based on the demonstration of stability.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is an hybrid application according to Article 13.3 and the product contains the same active substance as the reference product but differ in the excipient composition, the pharmaceutical form and the strength, the applicant is required to provide toxicological and pharmacological data relevant to the user and to present an User Risk Assessment (URA).

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

Thiamazole acts by blocking the biosynthesis of thyroid hormone in vivo. The primary action is to inhibit binding of iodide to the enzyme thyroid peroxidase, thereby preventing the catalysed iodination of thyroglobulin and T3 and T4 synthesis.

Pharmacokinetics

Following oral dosing in healthy cats, thiamazole is rapidly and completely absorbed with a bioavailability of >75 %. However, there is a considerable variation between animals. Elimination of the drug from cat plasma is rapid with a half-life of 2.6-7.1 hours. Peak plasma levels occur within a maximum of 1 hour after dosing. Cmax is 1.6 ± 0.4 µg/ml.

In rats thiamazole has been shown to be poorly bound to plasma protein (5 %); 40 % was bound to red blood cells. The metabolism of thiamazole in cats has not been investigated, however, in rats thiamazole is rapidly metabolized. For man and rats, it is known that the drug can cross the placenta and concentrates in the foetal thyroid gland. There is also a high rate of transfer into breast milk.

Toxicological Studies

The applicant provided bibliographical data.

- Single Dose Toxicity
  LD_{50} values were provided for the mouse, for thiamazole given intraperitoneally 500 mg/kg), orally (860 mg/kg) and subcutaneously (345 mg/kg).

- Repeated Dose Toxicity
  Oral administration of thiamazole daily for 28 consecutive days to marmosets at 10 and 30 mg /kg and to rats during 21 days at 30, 100, 300 and 1000 ppm (mg/kg) showed significant decrease in serum T3 and T4 levels. Other adverse effects included increase in thyroid follicular-cell proliferation, in thyroid stimulating hormone (TSH), and in thyroid weight.

In addition, an adverse effect on the olfactory system of rats given a single intraperitoneal dose of ≥ 25 mg/kg, or an oral dose of ≥ 50 mg/kg bodyweight thiamazole was noted.

- Reproductive Toxicity, including Teratogenicity:
  Studies showed that thiamazole may cause adverse effects on the fetus development and parturition in laboratory animals and humans. Reduced pup weights at birth as well as developmental deficits and perinatal hypothyroidism was affected in the offspring of rats given thiamazole orally at 0.1 g/L from day 17 of gestation to post-natal day 10. The SPC carries suitable warning with regard to use of the product by women of child-bearing age. Refer to 'User Safety' below.

- Mutagenicity:
  From referenced studies, no adverse effects with regard to mutagenicity were noted.

- Carcinogenicity:
  Thiamazole is not classifiable as to its carcinogenicity to humans on the basis that the clinical significance to humans of the carcinomas developed in rodents was unclear.

Other Studies

Thiamazole has been associated with agranulocytosis and hepatotoxicity. The SPC carries warnings with regard to common, possible adverse reactions caused by use of the product.

Observations in Humans

The side effects of thiamazole use are dose related. These include cutaneous reactions, headache, arthralgia, fever, joint pain, itching, decrease in blood cells and platelets and gastrointestinal upset.

User Safety

A user risk assessment was provided. Reasonable worst case exposure estimates were calculated and comparisons made with NOAELs derived from laboratory animals studies to calculate MOEs. Dermal exposure during administration as well as accidental ingestion and subsequent hand to mouth exposure for children were considered the scenarios of most concern.

The estimated MOEs showed that risk mitigation measures were necessary to ensure safety to users of the product.

The following warnings and precautions are listed on the product literature:

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Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity (allergy) to thiamazole, or one of the excipients, should avoid contact with the veterinary medicinal product. If allergic symptoms develop, such as a skin rash, swelling of the face, lips or eyes or difficulty in breathing, you should seek medical attention immediately and show the package leaflet or label to the doctor.

Thiamazole may cause gastrointestinal disturbances, headache, fever, joint pain, pruritus (itching) and pancytopaenia (decrease in blood cells and platelets).

The product may also cause skin irritation.

Avoid dermal and oral exposure, including hand-to-mouth contact.

Do not eat, drink or smoke while handling the product or used litter.

Wash hands with soap and water after administration and handling of the product and cleaning the vomit of, or litter used by, treated animals. Wash any spillages or splatter from skin immediately.

Following administration of the product any residual product remaining on the tip of the dosing syringe should be wiped clean with a tissue. The contaminated tissue should be immediately disposed of.

The used syringe should be stored with the product in the original carton.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

This product may cause eye irritation.

Avoid eye contact including hand to eye contact.

In case of accidental eye contact, rinse eyes immediately with clean running water. If irritation develops, seek medical advice.

As thiamazole is a suspected human teratogen, women of child-bearing age must wear non-permeable single use gloves when administering the product or handling the litter/vomit of treated cats.

If you are pregnant, think you may be pregnant or are attempting to conceive, you should not administer the product or handle the litter/vomit of treated cats**.**

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided. 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.

The product will not pose an unacceptable risk for the environment when used in accordance with the proposed SPC.

IV. CLINICAL ASSESSMENT (EFFICACY)

For generics, insert in the relevant sections as appropriate:

As this is a generic application according to Article 13, 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.

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 veterinary Heads of 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