United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Thiafeline 2.5mg Film-coated Tablets for Cats (AT, BE, CZ, DE, EE, EL, ES, FR, HU, IE, IT, LT, LU, LV, PT, RO, SK, UK)
Thiafeline vet 2.5mg Film-coated Tablets for cats (FI, IS, PL, SE)
Thiafeline Vet (DK, NO)

Thiafeline 5mg Film-coated Tablets for Cats (AT, BE, CZ, DE, EE, EL, ES, FR, HU, IE, IT, LT, LU, LV, PT, RO, SK, UK)
Thiafeline vet 5mg Film-coated Tablets for cats (FI, IS, PL, SE)
Thiafeline Vet (DK, NO)

PuAR correct as of 25/03/2019 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0466/001/DC UK/V/0466/002/DC
Name, strength and pharmaceutical form	Thiafeline 2.5mg Film-coated Tablets for Cats, Thiafeline 5mg Film-coated Tablets for Cats
Applicant	Le Vet Beheer B.V. Wilgenweg 7 3421 TV Oudewater The Netherlands
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 Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	22nd August 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

This was a generic application for Thiafeline 2.5mg and 5mg Film-coated Tablets for Cats, submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended. The, reference products were Felimazole 2.5 mg Coated Tablets for Cats and Felimazole 5 mg Coated Tablets for Cats, marketed by Dechra Limited, which have been authorised in the UK since 19 November 2004 and 22 January 2002 respectively. Thiafeline 2.5mg and 5mg Film-coated Tablets for Cats are indicated for the stabilisation of hyperthyroidism in cats prior to surgical thyroidectomy and for the long term treatment of feline hyperthyroidism.

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 product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The products contain Thiamazole (2.5mg/5mg) and excipients Lactose monohydrate, povidone, sodium starch glycolate type A, colloidal anhydrous silica, magnesium stearate, hypromellose, microcrystalline cellulose, lactose monohydrate, macrogol, titanium dioxide (E171) and carmoisine (E122). The 2.5mg strength tablets contain sunset yellow (E110) and quinolone yellow WS (E104) instead of carmosine (E122).

The container/closure system consists of a cardboard carton containing aluminium/pvc strips, each holding 30 tablets. The pack sizes are 30, 60, 120, 150, and 300 tablets. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation is justified.

The products are an established pharmaceutical form and their 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.

The manufacturing process generally consisted of several stages of mixing the active and several of the excipients. Once the mixture is satisfactory and all excipients have been added, there is a compression stage and the resulting tablets are film coated. Process validation data on two batches of the product at each tablet strength, (100kg per batch equating to roughly 1,000,000 tablets), have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is thiamazole, an established active substance described in the European Veterinary 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.

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

Lactose used within the product is confirmed to be derived from milk for human consumption.

E. Control on intermediate products

There are no intermediate products formed during the manufacture of this product.

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. The tests include appearance, disintegration, tablet hardness, HPLC identification tests and microbiological quality tests, all based on principles set out in the Ph. Eur. where possible.

Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from two full scale production batches of 100kg from the proposed production site has been provided, demonstrating compliance with the specification.

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 at 25°C ± 2°C / 60% RH ± 5% for 60 months and at 40°C ± 2°C / 75% RH ± 5% for 6 months. The shelf life and storage conditions are justified.

H. Genetically Modified Organisms

Not Applicable.

J. Other Information

Shelf life of the product as packaged for sale: 3 years
Keep the blister in the outer package in order to protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological tests are not required.

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The applicant has provided bibliographical data which show that 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

When given as an oral dose in healthy cats, thiamazole is absorbed rapidly. Peak plasma levels occur approximately 0.5 – 1 hour after dosing, C_{max}[2] is between 1.1 and 2.7µg/ml and the half-life is 3.3 hours. Metabolism of thiamazole in rats shows that 64% of the administered dose is eliminated in the urine, with 7.8% being excreted in faeces.

As this product is a generic in accordance with Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence has been demonstrated, the applicant is not required to submit pharmacological and toxicological data. Furthermore, as the product is for a non-food producing species, residues data is not needed.

Observations in Humans

The applicant has provided information which show that the active ingredient thiamazole is used in human medicine in the USA and EU. Human product warnings are detailed below in the User Safety section.

Agranulocytosis, leukopenia, thrombocytopenia, and aplastic anaemia (pancytopenia) are potential side effects that may occur in humans. There have been rare reports of fulminant hepatitis, hepatic necrosis, encephalopathy, and death. Thiamazole readily crosses the placental membrane and can cause goitre and, rarely, congenital effects such as aplasia cutis, as manifested by scalp defects; oesophageal atresia with tracheoesophageal fistula; and choanal atresia with absent/hypoplastic nipples.

[2] C_{max} – Maximum plasma concentration obtained.

Studies on metabolites, impurities, other substances and formulation

The excipients in the tablet formulation are commonly used in veterinary medicinal products and as such do not raise any toxological concern.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that human antithyroid drugs have side effects including agranulocytosis, leukopenia, thrombocytopenia, and aplastic anaemia (pancytopenia), as well as being potentially hazardous to unborn foetuses. However, as a human dose is 15-60mg daily, the exposure hazard a person administering the product would be subject to is minimal, and the main hazard identified is to pregnant women. The excipients are commonly used in both human and veterinary medicines, and are not considered a risk to the user.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the products. These include:-

- 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.
- Thiamazole may cause vomiting, epigastric distress, headache, fever, arthralgia, pruritus and pancytopaenia. Treatment is symptomatic.
- Wash hands with soap and water after handling litter used by treated animals.
- Do not eat, drink or smoke while handling the tablet or used litter.
- Do not handle this product if you are allergic to anti-thyroid products. 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.
- Do not break or crush tablets.
- As thiamazole is a suspected human teratogen, women of child-bearing age and pregnant women should wear gloves when handling litter of treated cats.
- Pregnant women should wear gloves when handling this 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 the active ingredient is not new and the product is not expected to pose a risk to the environment when used as recommended. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the products are 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.

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided a dissolution study as part of the bioequivalence evidence. In the study, blood plasma concentrations of thiamazole were measured for both the test product (Thiafeline 2.5mg and 5mg tablets) and reference product (Felimazole 2.5mg and 5mg Coated Tablets For Cats), in 14 cats for each product. Statistical analysis (ANOVA) was performed for the C_{max} gave a 90% confidence interval of 94.69-106.9%, and for AUC[3] the interval was 85.07-98.6%. These values are well within the stipulated 90% confidence interval boundaries, meaning the pharmacokinetics for the test and reference products are similar enough to satisfy bioequivalence criteria. This means that the bioavailability of both products is equivalent and adequate information is provided on the SPC.

In the dissolution study, all tablets reached acceptable levels of dissolution within a specified time, and such can be considered to have similar dissolution profiles. The methodology of the dissolution testing was in accordance with the guidelines and the analytical method was adequately validated.

The applicant has provided bibliographical data to justify the design and methodology of the bioequivalence study, and provide supporting evidence for the behaviour of the active ingredient *in vivo*.

Tolerance in the Target Species of Animals

As this is a generic application where bioequivalence has been proven, data for the tolerance of the active substance can be extrapolated from the reference product. However, since the excipients in the product differ from those in the reference product, the applicant has provided bibliographic data (Rowe, 2009, Handbook of Pharmaceutical Excipients) on the excipients. Since the excipients are all widely used in veterinary oral formulations, they are considered not to pose any significant risk. The risks that do apply are considered low because the small concentrations when used as recommended mean that exposure is low. Adequate warnings regarding adverse reactions are present on the SPC.

[3] AUC - Area Under the Curve

Resistance

As this is a generic product where bioequivalence has been demonstrated, evidence relating to resistance of the active substance can be extrapolated from the reference product.

Adequate warnings and precautions appear on the product literature.

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 Product Information Database of the Veterinary Medicines Directorate website.

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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.

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