IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Felimazole 2.5 mg Coated Tablets for Cats

PRODUCT SUMMARY

EU Procedure Number	IE/V/0505/002 (formerly UK/V/0198/002)
Name, Strength, Pharmaceutical Form	Felimazole 2.5 mg Coated Tablets for Cats
Active Substances(s)	Thiamazole
Applicant	Dechra Regulatory B.V., Handelsweg 25, 5531 AE Bladel, Netherlands
Legal Basis of Application	Full application (Article 12(3) of Directive No 2001/82/EC)
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.
ATC Code	QH03BB02
Date of completion of the original mutual recognition (MRP) procedure	10th March 2009 (Current procedure concluded 31st January 2018)
Date product first authorised in the Reference Member State (MRP only)	19 November 2004 (UK) 20 February 2009 (IE)
Concerned Member States for original procedure	First Use Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland (now RMS), Italy, Luxembourg, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Repeat Use Bulgaria, Croatia, Poland, Romania, Slovenia UK added via RMS change

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 indicated for the stabilisation of hyperthyroidism in cats prior to surgical thyroidectomy and for the long-term treatment of feline hyperthyroidism. The recommended starting dose rate is 5 mg per day. The daily dose should preferably divided into two and administered morning and evening. Tablets should not be split. The dose should not exceed 20 mg daily. Refer to the Summary of Characteristics (SPC) for each product for further detail.

Felimazole 2.5 mg 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 overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains the active substance thiamazole. The product also contains the following excipients:

Tablet core: lactose monohydrate, povidone, sodium starch glycolate
Magnesium stearate.

Coating: Sucrose, povidone K30, macrogol 4000, purified talc, white beeswax, carnauba wax, shellac, titanium dioxide (E171) and sodium methyl parahydroxybenzoate (E219).

The container/closure system is a white polypropylene tub with white low density polyethylene tamper evident lid containing 100 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.

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 thiamazole is an established substance described in the European Pharmacopoeia.

The active substance specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with these specifications have been provided. The excipients are produced in line with specifications.

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

A Format 2 declaration concerning the TSE status of the product states that lactose monohydrate is the only ingredient manufactured using starting materials of bovine, ovine or caprine origin. The supplier has given an appropriate declaration of compliance.

E. Control on intermediate products

Adequate controls are applied to tablet cores, which are monitored for appearance, diameter, mean weight, uniformity of mass, disintegration time and friability during the compression stage. The analytical methods employed are those of the finished product specification.

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

Thiamazole is demonstrated to be a stable entity, vulnerable only to degradation under strongly acid and oxidising 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. A retest interval of 5 years for material stored in the specified containers is justified.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Special precautions for storage

Do not store above 25ºC.

Keep the container tightly closed in order to protect from moisture.
Keep the container in the outer carton.
Blister: Keep the blister strips in the carton.

Shelf life
Tub: Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Blister: Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Pharmacological Studies
Pharmacodynamics
Thiamazole is shown to be an inhibitor of an iodide peroxidase isolated from thyroid tissue. Thiamazole exerts its action on the thyroid by inhibiting the peroxidase-catalysed oxidation of iodide leading to reduced intrathyroidal formation of iodotyrosines and iodothyronines.

The effect of thiamazole in the treatment of Grave's disease has been investigated in human patients. Thiamazole has a direct action on immunoregulation in Grave's disease that is mediated by a direct inhibitory effect on thyrocytes. There is a marked change in the proportions of activated
T-helper-like and T-suppressor cells in favour of the suppressor cells. This changed balance reflects in part the functional suppression of autoantibody production observed in thiamazole treated patients.

Studies were performed using an incubation model, containing purified TPO, to investigate the mechanism of action of the thioureylene anti-thyroid drugs, including MMI. The results demonstrated that MMI is a potent inhibitor of TPO-catalysed iodination of protein and tyrosine and the potency increases as I^- decreases. MMI is also a potent inhibitor of TPO-catalysed oxidation of guaiacol. MMI is readily oxidised in the model system when iodide is present but not in the absence of iodide and this oxidation is increased by increasing the concentration of iodide. This oxidation is inhibited by relatively slight increases in MMI concentration in the model system. MMI is capable of inhibiting its own metabolism and that of propylthiouracil and *vice versa*. Inhibition of iodination is competitively antagonised by iodide at low concentrations of drug but not at higher drug concentrations. Inhibition of iodination by thiamazole may be reversible (low ratio of drug to iodide) or irreversible (higher ratio of drug to iodide). Irreversible inhibition may be transformed into reversible inhibition by increasing the concentration of enzyme or the concentration of iodide.

Pharmacokinetics
The metabolism of a single dose of S-methimazole was studied over a ten-hour period in the thyroid, plasma and liver from both a control group of rats and a group treated with phenobarbital for 4 days. In the thyroid, there was a marked increase in the accumulation of total S-radioactivity accompanied by a significant

increase in the oxidation of thiamazole in the group receiving phenobarbital. Decreased total S half-lives in the plasma and liver together with decreased proportions of unmetabolised thiamazole were observed. The changes in thiamazole metabolism in the thyroid could possibly be due to a TSH effect mediated by phenobarbital induced changes in peripheral thyroxine turnover; thyroidal microsomal enzyme induction could also be a contributory mechanism. The changes observed in the plasma and liver could result from induction of the liver microsomal enzymes responsible for thiamazole metabolism. An enhanced biliary flow is also considered as an additional mechanism.

The effect of phenobarbital and/or thyroxine on the thyroidal accumulation and oxidation of S-methimazole and serum TSH levels were studied in rats. Phenobarbital treatment increased the accumulation of thiamazole and the serum TSH levels but concurrent administration of T_4 reversed these effects. It was concluded that increased TSH secretion in phenobarbital treated animals was likely to be the major mechanism involved in the increased thiamazole accumulation. Phenobarbital also increased the intrathyroidal oxidation of thiamazole to sulphate. In contrast to the phenobarbital effect on accumulation, T_4 administration only partially reversed the effect on oxidation. The results suggest that the increased oxidation of thiamazole in phenobarbital treated animals was due to a direct effect of phenobarbital or possibly a combination of this direct effect and the indirect TSH effect. Possible mechanisms postulated for a direct effect were thyroidal microsomal enzyme induction and/or changes in thyroidal protein binding of thiamazole.

The pharmacokinetics of thiamazole have been investigated in the cat following oral and intravenous administration. There was no significant difference between mean serum thiamazole concentrations 30 minutes after oral and i.v. administration, indicating rapid and complete absorption of the drug. The bioavailability of thiamazole varied from 27-100 %, mean serum

elimination half-life was 6.6±2.0h with a range of 1.9 to 15.1 hours. Repeat administration did not significantly alter the mean serum concentration.

The thiamazole levels following administration of carbimazole and thiamazole to healthy cats was investigated. This study compares the disposition of thiamazole in the cat following oral administration of either carbimazole or thiamazole. The serum concentration following oral administration of thiamazole reached a peak of 1.37mg/ml after 30 minutes.

Toxicological Studies

Single Dose Toxicity

The applicant provided peer-reviewed published literature in support of the single-dose toxicity of thiamazole. The study was conducted on dogs, rats and mice. In the dog study, one animal vomited 6 hours post-dosing. Slight changes in ALP, AST and ALT were observed 2 days post-dosing in the dog but these values had returned to normal by day 10. The increased enzyme levels were still within the historical ranges for dogs. In the rat study, olfactory mucosal degeneration occurred at doses of 25mg/kg and above i.p., and at an oral dose of 50mg/kg. An i.p. dose of 300mg/kg resulted in almost 100 % olfactory mucosal loss in level 3 nasal cavity sections. In the mouse study, the only sign of toxicity observed was olfactory mucosal degeneration.

Repeated Dose Toxicity

The applicant provided two peer reviewed papers in support of the repeat dose toxicity of thiamazole. The study was conducted in rats at 0, 5, 30 and 180 ppm doses for the duration of 2 years. The study concluded that no adverse effects were observed in this dose group 5 ppm, the thyroid enlargement, high incidence of follicular adenomas and low incidence of follicular adenocarcinomas mostly in the thyroid was observed in rats dosed at 30 ppm. The mortality was 50% in the first year in the rates dosed at 180 ppm. The growth rate was retarded and obesity was observed in mature animals. Thyroid enlargement was also observed in rats dosed at this dose level.

Other Studies

Carcinogenicity

The carcinogenic potential of thiamazole was investigated in a two year study in mice. The animals were dosed via the drinking water with 35mg/l increasing to 500mg/l over 26 months, 500mg/l for the entire study or 250mg/l for 2 months then 500mg/l. The study evaluated the carcinogenic potential of thiamazole in animals under differing levels of iodine intake. Only those animals on the low iodine intake developed thyroid adenomas, an incidence of 9.3 % compared an incidence of 0.7 % in the controls. The thyroid weight increased in all animals receiving thiamazole, regardless of the level of iodine intake. This increased weight was time-dependent.

Immunotoxicity:

The effect of thiamazole on the activation of vitamin K-dependent coagulation factors II, VII, IX and X to induce coagulopathy in hyperthyroid cats was investigated. The daily oral doses of 5-15mg thiamazole do not induce measurable coagulopathy in most hyperthyroid cats.

The incidence of insulin autoimmune syndrome in Japanese hyperthyroid patients treated with thiamazole was investigated. In 206 patients treated with thiamazole, 13 patients demonstrated insulin autoantibodies in the serum, which peaked 2-3 months after start of treatment and then reduced spontaneously 12 months later, even when treatment was continued. It is postulated that this effect of thiamazole is due to the sulphydryl group on the molecule.

Observations in Humans

The effect of thyroid disease on the metabolism of various drugs is discussed. The plasma half-life of thiamazole was 7.9±0.4 hours in thyrotoxic patients and

increased to 11.2±1.2 hours in such patients after treatment with carbimazole. In hyperthyroid patients the half-life of thiamazole was 6 to 7.2 hours (mean 6.9±0.6 hours) and in normal subjects the mean plasma half-life was 9.3±1.4 hours. In hypothyroid patients, the half-life of thiamazole was 13.6±4.8 hours.

A report of hypothyroidism and goitre in one infant of each of two sets of twins is provided. The twins were born to mothers who were thyrotoxic during pregnancy and were treated with antithyroid drugs. Both affected infants presented with a transient though significant depression in serum free thyroxine. Both infants had transient elevation of serum thyrotropin. The results confirm the hypothesis that antithyroid drugs cause thyroid hyperplasia in the human foetus by stimulation of foetal pituitary thyrotropin. The reason for the effects of anti-thyroid drug treatment on the thyroid of only one twin are not explained although a genetic difference between dizygotic twins is suggested as the most likely cause.

Microbiological Studies

Thiamazole does not possess antimicrobial activity.

User Safety

Signs of toxicity are only observed in the studies reported at much higher doses than could be expected from handling the product during dosing of cats. The product is sugar-coated and this should reduce the possibility of contact with thiamazole during handling. The applicant has provided a number of reports of human exposure to thiamazole in human medicine, demonstrating that adverse events are rare and usually manifest after several administrations of doses much higher than that proposed for the cat.

The applicant has provided a satisfactory user safety assessment, addressing the possible routes of exposure of the user. The most likely exposure is by accidental ingestion of a tablet, especially by a child. The safety margins are expected to be satisfactory, based on the single dose studies.

The following user warnings have been included in the SPC and product literature:

- 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 antithyroid 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 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 the product is only for non-food animals so the exposure of the environment to the active substances is not considered to be extensive.

The 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

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The primary action of thiamazole is to inhibit the binding of iodide to thyroid peroxidase (TPO), the enzyme which catalyses the iodination of thyroglobulin. During this process thiamazole is principally oxidized to sulphate. The inhibition of thyroid peroxidase (TPO) is irreversible so thyroid hormone biosynthesis is inhibited until TPO is renewed by protein synthesis. At low ratios of thiamazole:iodide, iodide competes favourably with the drug, the TPO-iodide complex is readily formed and thiamazole is extensively oxidized to sulphate. At higher ratios inhibition of iodide binding to TPO is more complete and there is less drug oxidation. This explains why a decrease in dietary iodine results in decreased thiamazole metabolism.

Carbimazole has been shown to be an inactive pro-drug that was rapidly converted to thiamazole, but appeared to offer no pharmacokinetic advantage over thiamazole.

The thiamazole is metabolized by cytochrome P450 monoxygenases in rat hepatic microsomes. The metabolites of thiamazole bind covalently to hepatic macromolecules and it was postulated that this might be responsible for the centrilobular necrosis observed with administration of the drug to rats.

Pharmacokinetics

Following oral administration to healthy cats, thiamazole was rapidly absorbed with a bioavailability > 75 % and T_{max}[1] of 1-2 hours. The elimination was rapid with t½ of 4.5 – 5 hours. (For the 2.5 mg product, peak plasma levels occur approximately 1-2 hours after dosing. C_{max}[2] is approximately 0.8 µg/ml and t½ is 3.5-4.0 hours). Multiple dose studies with cats administered 2.5

mg and 5 mg thiamazole orally BID did not show evidence of accumulation. The dissolution profiles of Felimazole 5 mg and 2.5 mg tablets demonstrated that the bioavailability of both strengths was comparable in terms of speed of availability and the profile of the release of thiamazole from the tablet matrix. Hyperthyroid cats may have an accelerated elimination of thiamazole when compared to normal cats, but this was not considered to be of clinical significance.
The pharmacokinetics of thiamazole has been extensively investigated in man as the substance is used in the treatment of Graves' disease. Oral bioavailability is high and unaffected by prandial status. Tmax was 1 h in healthy humans and 1-4 h in hyperthyroid patients.
Thiamazole is taken up by the thyroid gland by two mechanisms. Saturable active uptake is associated with reversible binding to cell components. This occurs at low concentrations and is inhibited by high thiamazole concentrations. The second mechanism of accumulation is non-saturable passive diffusion, which occurs at higher concentrations of thiamazole.
Radiolabelling studies have shown that thiamazole crosses the placenta and in man concentrates in the foetal thyroid gland. There is also a high rate of transfer into breast milk.
Thiamazole is thought to undergo enterohepatic circulation. It is cleared much more rapidly from the plasma than from the thyroid indicating complex kinetics in the thyroid and allowing the relatively long duration of action. In man it is extensively metabolised in the liver and the t½ is prolonged in hepatic dysfunction. Pharmacokinetics do not change significantly once euthyroidism is achieved. After oral dosing t½ is 6-9.3 h in normal human patients and 6-7.9 h in untreated hyperthyroid patients. The main route of excretion of thiamazole and its metabolites in rats and in man is the urine.
Thiamazole can affect prostaglandin E production in vitro which could account for its immunomodulatory effect. It has also been demonstrated to accumulate in monocytes and macrophages which may induce immunosuppression.

Tolerance in the Target Species of Animals
The treatment of cats with thiamazole with doses up to 30 mg/day for 3 months was not well tolerated. Although many of the observations could be construed as toxic effects, they are consistent with hypothyroidism. It is therefore considered that some of the findings are due to the pharmacological response to the administration of thiamazole and cannot be considered as primarily toxic.
As a consequence of the findings of the applicant's tolerance study, the maximum dose is restricted to 20 mg/day.

Resistance
Thiamazole has no known antimicrobial, antiparasitic or other properties against which resistance could develop.

IV.B Clinical Studies
Laboratory Trials

Suitable studies were performed to establish the efficacy and safety of the product, when used as recommended.
[1] Tmax – Time at which the maximum blood plasma concentration of active substance is reached.
[2] C_{max} – Maximum concentration of active substance in the blood plasma.

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.