IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Normazole 5 mg/ml Oral Solution for Cats

PRODUCT SUMMARY

EU Procedure number	IE/V/0604/001 (formerly UK/V/0572/001)
Name, strength and pharmaceutical form	Normazole 5 mg/ml Oral Solution for Cats
Active substances(s)	Thiamazole
Applicant	VIRBAC 1ère avenue 2065 M LID 06516 Carros France
Legal basis of application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Date of Authorisation	30 March 2016 (UK) 30 November 2018 (IE)
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.
ATCvet code	QH03BB02
Concerned Member States	PL, RO, UK (NI)

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

This was a generic hybrid application submitted under Article 13 (3) of Directive 2001/82/EC, as amended. The product contains the same content of active substance as the reference product, but differs with regard to pharmaceutical form. The product is indicated for the stabilisation of hyperthyroidism in cats prior to surgical thyroidectomy, and for the long-term treatment of hyperthyroidism. The reference product is Felimazole 5 mg Coated Tablets for Cats, marketed in the UK since January 2002.

The recommended starting dose is 5mg per day. The dose is divided in two and administered morning and evening. If, for reasons of compliance, once daily dosing is preferable, then this is acceptable, although a 2.5 mg dose (0.5 ml of the product) given twice daily may be more efficacious in the short term. The product should not be administered in food, and the same dosing schedule relative to the feeding routine should be adhered to. T4 levels should be regularly monitored and adjusted accordingly by the veterinary surgeon, as advised in the Summary of Product Characteristics (SPC). If more than 10 mg per day is required animals should be monitored carefully. The dose administered should not exceed 20 mg per day. For long-term treatment of hyperthyroidism, the animal should be treated for life.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species. Any 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

II.A. Composition

The product contains 5 mg/ml thiamazole and the excipients sodium benzoate (E211), glycerol, povidone K30, xanthan gum, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, citric acid anhydrous, honey flavour, simethicone emulsion and purified water.
The container/closure system consists of 30 ml and 100 ml presentations, filled into amber polyethylene terephthalate (PET) screw bottles with HDPE/LDPE child resistant caps. The product is supplied with a 1 ml polyethylene/polypropylene measuring syringe. The syringe is graduated in 0.25 ml increments up to 1 ml. The particulars of the containers and controls performed are provided and conform to the required regulations.
The choice of the formulation and the presence of preservative are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a standard sequential addition of active substance and excipients, with appropriate quality control tests in place.

II.C. Control of Starting Materials

The active substance is thiamazole, an established substance described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice, and is sourced in accordance with a Certificate of Suitability.

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.

All excipients with the exception of honey flavour are monographed in the Ph. Eur. The honey flavour is prepared in accordance with an in-house specification, for which acceptable Certificates of Analysis were received.

II.C.4. Substances of Biological Origin

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

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. Control tests on the finished product include those for appearance, identification of the active substance, substances related to the active substance, pH, sodium benzoate, viscosity, uniformity of mass of delivered doses, microbiological quality (infrequent), and fill volume.

II.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 approved conditions. No adverse changes were noted when the product was stored under long-term conditions, (25°C/60% RH 60 months), or accelerated conditions, (40°C/75% RH 6 months). Ttherefore, the retest period was set at 5 years.

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

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the container: 6 months.
Keep the container tightly closed.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

The active substance is concentrated at the thyroid gland, and the primary effect is the inhibition of thyroid hormone synthesis via the interference of thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin. This retards the synthesis of the key thyroid products thyroxine (T4) and triiodothyronine (T3), resulting in the resolution of the signs of hyperthyroidism.

Pharmacokinetics

Thiamazole is quickly absorbed from the gastro-intestinal tract. The major route of metabolism is glucuronidation. The active substance is excreted mainly in the urine, with a half-life for urinary excretion of 5-7 hours.

Toxicological Studies

The applicant provided bibliographical data.

- Single Dose Toxicity

LD_{50}[1] values were provided for the mouse, for thiamazole given intraperitoneally (500mg/kg), orally (860 mg/kg and subcutaneously (345 mg/kg).

- Repeated Dose Toxicity

Note: Reduction in T3 and T4 is the therapeutic effect.

In one study, thiamazole was given to marmosets at oral doses of 10 or 30 mg/kg for 4 weeks. A significant adverse effect noted was hypertrophy of follicular epithelial cells. A decrease T4 concentration was noted. In another study in rats, it was observed that T4 was reduced by more than 95% following 21 days of treatment with thiamazole at oral concentrations of 30, 100, 300 and 1000 ppm (mg/kg). Reduction was also noted in T3. At 30 ppm, a 14-fold increase in thyroid follicular-cell proliferation, a 5.6-fold increase in thyroid stimulating hormone (TSH), and a 2-fold increase in thyroid weight were observed. Increase in thyroid weight and the quantity of follicular-cells was directly correlated with increase in levels of TSH.

Other studies also noted a reduction in T3 and T4. 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 post-natal neurological development 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. Reduction in T3 and T4, serum follicular-stimulating hormone and luteinizing hormone were also noted in additional studies. Testes weight and sperm production were noted to slightly increase, but a reduction in body weight was seen in rats in further studies. The SPC carries suitable warning with regard to use of the product by women of child-bearing age. The product should not be used without proper precaution. Refer to 'User Safety' below.

- Mutagenicity

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

- Carcinogenicity

In mice and rats, it was seen that thiamazole decreases thyroid peroxidase, decreasing thyroid hormone production and increasing cell proliferation via stimulation of thyroid stimulating hormone production. This is considered to be a non-genotoxic mode of carcinogenic action.

Studies of Other Effects

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 LOAELs[2] derived from human studies to calculate MOEs[3]. Accidental ingestion and dermal exposure during administration as

well as subsequent hand-to-mouth exposure were considered. Information was provided to demonstrate that dermal absorption was likely to be less than 10%. Accidental oral ingestion of product either directly or via hand-to-mouth-contact was considered the exposure of most concern and the table below details the MOEs calculated.

Exposure scenario	Exposure	LOAEL (mg/d)	MOE
Ingestion by a 10 kg child	Reasonable Worse Case Exposure = 1 ml filled syringe	7.5 mg/d	1.5
Accidental ingestion by a 60 kg female adult of childbearing age	Reasonable Worse Case Exposure = 0.1 ml of product (and in assumption of 10% hand to mouth transfer)	2.5 mg/d (teratogenicity)	50
Accidental ingestion by a 60 kg "ordinary" adult	Reasonable Worse Case Exposure = 0.1 ml of product (and in assumption of 10% hand to mouth transfer)	7.5 mg/d	150

The MOEs were below 200 (the factor needed to take account of intra-individual variation, use of LOAELs rather than NOAELs and a limited database). It was therefore considered that risk mitigation measures were necessary. The solution is provided in bottles along with a 1 ml measuring syringe. The bottles are fitted with a child-proof cap that will prevent direct access to the solution; additionally, the closure system includes a vial insert that helps prevent the free flow of solution from the bottles even when inverted or placed on their side. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- 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.
- 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 of the product and handling the vomit of or litter used by treated animals. Wash any spillages 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.
- This product may cause eye irritation.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- 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 Safety

A Phase I Environmental Risk Assessment (ERA) was carried out. The product will only be used in individual non-food animals, and as a result environmental exposure will be low. A Phase II ERA was not required. The SPC and product literature carry suitable warnings.

[1] LD_{50} - Lethal dose of an ingested substance that kills 50 percent of a test sample.
[2] LOAEL – Lowest observed effect level.
[3] MOE – Margin of exposure.

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies
Pharmacology
Pharmacodynamics

The active substance is concentrated at the thyroid gland, and the primary effect is the inhibition of thyroid hormone synthesis via the interference of thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin. This retards the synthesis of the key thyroid products thyroxine and triiodothyronine, resulting in the resolution of the signs of hyperthyroidism.

Pharmacokinetics

A staggered, two period, two treatment, two sequence cross-over in vivo bioequivalence study was performed using the proposed product and the reference product, Felimazole 5 mg Coated Tablets for Cats. This was a GLP[1]-compliant study on 7 sets of cats comprised of 3 animals in each group. The animals were assessed for good health, and relevance for the study prior to the start, and were then monitored throughout. Cats were administered the product once over a series of days before a 35 day washout period commenced, the reciprocal treatment was then provided.

The products were administered orally at a dose rate of 5 mg per animal. Blood samples were taken at appropriate time points. Feeding was not performed on the morning of administration, until 2 hours after administration of the products. Samples were appropriately stored and tested, followed by assessment of the following pharmacokinetic parameters: AUC_t (area under the concentration/time curve from time 0 to last sampling time point of the active substance), C_{max} (maximum plasma concentration of the active substance), and T_{max} (time of maximum plasma concentration of the active substance). AUC∞ (prediction of extended efficacious effect), was also assessed.

In order to compare the results of the test group to the control group, analysis of variance (ANOVA) of the parameters AUC_t and C_{max} was carried out with logarithmically transformed data, using the SAS software system (SAS Institute Inc., Cary, USA). 90% confidence intervals were calculated to determine if the articles were bioequivalent. The allowable ratios of the test mean to control mean were 0.7 - 1.43 for C_{max} and 0.8 - 1.25 for AUC_{0-t}. In the event where an animal did not provide sufficient data for both the test and control products, the data was presented but was not included in the statistical analysis.

The 90% confidence intervals for the ratio of population means (test/reference) for the pivotal parameters C_{max} and AUC_{0-t} fell within the acceptance limits of 80 to 125%. Therefore bioequivalence could be concluded.

Tolerance in the Target Species

The applicant submitted data relating to previous target animal safety studies and published information. Thiamazole is known to have a low margin of safety (reflected within the SPC), however, there were no new data suggesting that the excipients are unsafe for the target animals when the product is used as recommended.

IV.II. Clinical Documentation

Based on the nature of this application, there was no requirement to submit data for this section.

[1] GLP – Good Laboratory Practice.

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 of the product is favourable.