Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Felinta 10 mg Prolonged Release Tablets for Cats
Felinta 15 mg Prolonged Release Tablets for Cats

Date Created: December 2022

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Felinta 10 mg Prolonged Release Tablets for Cats Felinta 15 mg Prolonged Release Tablets for Cats
Applicant	Milstein C.V. Patroonsweg 20e Zeewolde, Flevoland 3892 DB, The Netherlands
Active substance	Carbimazole
ATC Vetcode	QH03BB01
Target species	Cats
Indication for use	Treatment of hyperthyroidism and hyperthyroidism-associated clinical signs in cats.

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 conclusion of the procedure	11/10/2022

I. SCIENTIFIC OVERVIEW

These applications are for generic products submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended. The quality / safety / efficacy aspects of these product are identical to Vidalta 10 mg Prolonged Release Tablets for Cats and Vidalta 15 mg Prolonged Release Tablets for Cats. Bioequivalence studies were conducted.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains carbimazole and the excipients: cellulose microcrystalline, Hypromellose, citric acid anhydrous, FD & C Red No. 3 and magnesium stearate.

The container/closure system consists of Alu-Alu blister packs contained in a carton box. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence 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 sifting, blending, lubrication and compression.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is carbimazole, an established active 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.

The substance is supplied in accordance with ASMF.

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 are those for: appearance, identification, water content, β dissolution, uniformity of dosage units, assays, related substances and microbial quality.

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.

G. Other Information

Felinta 10mg:
Shelf life of the veterinary medicinal product as packaged for sale: 18 months
Do not store above 25°C.
Store in the original package.

Felinta 10mg:
Shelf life of the veterinary medicinal product as packaged for sale: 24 months

Do not store above 30°C.
Store in the original package.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that carbimazole inhibits thyroid peroxidases which catalyse the iodination of tyrosine residues in thyroglobulin and the oxidative coupling of iodinated tyrosinases. The applicant has also provided bibliographical data which show that carbimazole is rapidly absorbed from the gastrointestinal tract after oral administration and is hydrolysed in the gastrointestinal tract to the active metabolite thiamazole (methimazole). Bioavailability studies were conducted.

Toxicological Studies

The applicant has provided bibliographical data on toxicological studies.

Single Dose Toxicity

Studies from published literature were submitted for the single dose toxicity of carbimazole in mice and rats. From the studies submitted, carbimazole was shown to cause olfactory toxicity following oral and intraperitoneal administration. The lowest LD_{50} (345 mg/kg) was reported for mice following subcutaneous exposure whilst one NOEL was reported for rats (100 mg/kg).

Repeated Dose Toxicity

The applicant has submitted several references addressing the repeat-dose toxicity of carbimazole and methimazole. No NOAELs (No Observed Adverse Effect Level) were identified. In mice and rats, repeat-dose studies were found to induce thyroid follicular cell adenomas. In mice and rats, repeat-dose studies were found to induce thyroid follicular cell adenomas. Increases in cell proliferation were observed alongside decreases in thyroid hormone production as a result of methimazole treatment in rats.

Reproductive Toxicity, including Teratogenicity:

The applicant has provided references from published literature in addressing the reproductive and developmental toxicity of carbimazole. Whilst some effects on the foetus were observed (reduced total serum T3 and T4 concentrations) in addition to inhibitory effects on developmental parameters, it was not possible to identify the relevant no effect levels.

Mutagenicity

The applicant has submitted several references from published literature concerning the mutagenicity of carbimazole. In vitro mutagenicity testing demonstrated that methimazole induced chromosomal aberrations, inhibited cell-to-cell communication in mice and rat cells and interfered with the normal proliferation of T lymphocytes in mice. However, no concerns were identified from in vivo mutagenicity tests.

Carcinogenicity

Studies from the published literature, identify carbimazole to be a potential carcinogen in mice and rats. Incidences of follicular adenoma, hyperplasia of thyroid glands and metastases have been reported in both species.

Studies of Other Effects

The applicant has provided bibliographical data which show that methimazole has been found to affect many different parts of the body in different ways, including inhibition of dopamine ß-hydroxylase in rats, impairment of the immune system in mice, as well as having an anti-inflammatory effect. Some studies showed that methimazole causes olfactory mucosal damage at doses of ≥25 mg/kg ip in rats (NOAEL = 2 mg/kg ip) and at doses of 50 mg/kg orally (NOAEL = 25 mg/kg po).

Observations in Humans

Bibliographical data were provided which show that in pregnancy, no differences in the rates of malformations were seen in the infants of hyperthyroid mothers who had and had not taken methimazole; however, 17 cases of aplasia cutis congenita were found in the offspring of women who had used methimazole during pregnancy. In contrast, in other studies no increase or association was found. No malignant thyroid neoplasm was found within a year of treatment.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:,

- Wash hands with soap and water after use and when handling litter used by treated animals.
- 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.
- As carbimazole is a suspected human teratogen, women of child-bearing age should wear gloves when handling litter or vomit of treated cats.
- Pregnant women should wear gloves when handling the product. Do not break or crush tablet.
- Do not eat, drink or smoke while handling the tablet or used litter.
- In the case of accidental ingestion, seek medical advice immediately and show the package or the label to the physician.
- Carbimazole, as a prodrug of thiamazole (methimazole), may cause vomiting, epigastric distress, headache, fever, arthralgia, pruritus and pancytopaenia. Treatment is symptomatic.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Not required as these applications were submitted under Article 13(1).

However, the applicant referred to information regarding the pharmacodynamics of the active substance, carbimazole. This literature indicates that carbimazole is rapidly, and almost completely, converted following ingestion to methimazole. Methimazole blocks thyroid peroxidase, hence preventing the iodination of tyrosine residues in thyroglobulin, and therefore inhibiting thyroxine (T4) and triiodothyronine (T3) production, resulting in the resolution of signs of hyperthyroidism.

A single *in vivo* bioequivalence study for both tablet strengths has been performed and bioequivalence was established between these products and the reference products.

Tolerance in the Target Species

Tolerance studies were not required because of the legal basis of the application. The applicant has performed a literature review of tolerance and safety aspects of carbimazole.

IV.II. Clinical Documentation

Not required due to the legal basis of the application.

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 products is favourable.

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.

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

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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