Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Eluracat 20 mg/ml Oral Solution for Cats

Date Created: September 2024

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Eluracat 20 mg/ml Oral Solution for Cats
Applicant	Elanco GmbH, Heinz-Lohmann Strasse 4, Groden, Cuxhaven, D-27472, Germany
Active substance	Capromorelin tartrate
ATC Vetcode	QH01AX90
Target species	Cats
Indication for use	For body weight gain in cats experiencing poor appetite or unintended weight loss resulting from chronic medical conditions

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	Full application in accordance with Article 8 of VMRs 2013 (Schedule 1, Part 1) as amended.
Date of conclusion of the procedure	26/06/2024

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, any reactions observed are indicated in the SPC.[1] 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 [2] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains Capromorelin tartrate 20 mg (equivalent to 15.4 mg capromorelin) and the excipients Sodium methyl parahydroxybenzoate (E 219), Sodium propyl parahydroxybenzoate (E 217), Sodium chloride, Citric acid, Sucralose, Vanillin, Povidone (K-90), Glycerol, Maltitol, liquid, Magnasweet 110 (glycyrrhizic acid, monoammonium glycyrrhizinate) and Purified water.
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The container/closure system consists of HDPE bottles filled with: 10 ml and 15 ml. Each bottle is closed with an LDPE plug-in adapter and tamper proof child resistant closure. It is also supplied with 1 oral ml scale syringe. The particulars of the containers and controls performed are provided and conform to the regulation.

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.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

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: synthesis, heating, mixing and cooling.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

II.C. Control of Starting Materials

The active substance is capromorelin tartrate, 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.

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

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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, density, viscosity, pH, identification of active substance, assay, degradation of products, preservative concentration, microbial limit and residual solvents.

II.F. 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 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.

G. Other Information

Shelf life: 2 years
Shelf life after first opening the immediate packaging: 3 months
Do not store above 30 ºC.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Studies have been Bibliographical data has been provided which show that Capromorelin tartrate acts by binding to ghrelin receptors in the hypothalamus to stimulate appetite and in the pituitary to stimulate secretion of growth hormone. The applicant has also has provided bibliographical data which show that After oral administration, capromorelin was rapidly absorbed in cats with a T_{max} of 0.35 hours (without food). The mean half-life of capromorelin in serum following intravenous and oral administration is 0.9 and 1.1 hours.

Toxicological Studies

The applicant has conducted laboratory studies for single dose, repeated dose, reproductive toxicity, mutagenicity and carcinogenicity.

Single dose toxicity
Two single dose studies were conducted, one in rats and mice and the other in dogs. In the study which had rats and mice a single dose of capromorelin was given either via orally through oesophageal intubation or intravenously. Clinical signes were then observed for 14 days. The results of this study showed that the approximate LD_{50} values provided, toxicity was lower following oral administration compared to intravenously for both species. The LD_{50} for rats was >1000 mg/kg whilst the greatest toxicity was observed in mice following intravenous administration which gave a range of LD_{50} 20 mg/kg - 50 mg/kg.
The study with the dogs, 2 dogs were treated with 40 mg/kg capromorelin once daily for 2 consecutive days and 1 dog was treated with a single 60 mg/kg dose of capromorelin. Blood samples were taken at intervals after dosing. This showed no clinical signs highest dose, mild elevations in liver enzymes were recorded. This shows that capromorelin is of relatively low toxicity when administered orally.

Repeated Dose Toxicity
Six repeat-dose toxicity studies were conducted in rats, mice and dogs, in all these studies capromorelin was given orally. In the mice study it was seen that capromorelin did not induce toxicity in mice. In the two repeat dose rat studies the NOAL value for the one-month study was 15mg/kg and the six month was 75mg/kg. the one-month repeated dose study in dogs the NOAEL was observed to be 40mg/kg/day and no adverse effects were observed at 7mg/kg. however in the one year study,at 7 mg/kg there were multiple adverse effects observed.

Reproductive Toxicity, including Teratogenicity
Reproductive studies were conducted in rats and rabbits. In the rat study, doses of capromorelin was given orally over 12 days. It was concluded from both of these studies that there was no dose-response relationship was established. Therefore, a NOAEL of 75 mg/kg was reported. In the rabbit study capromorelin was given orally for a period of time. It was seen in these studies it was seen that there were increases in gestational and foetal bodyweights were attributed to the pharmacological activity of capromorelin. The NOEL should be considered to be the lowest dose due to the findings in rabbits.

Mutagenicity
There were 4 studies where cells were tested to see if capromorelin causes a mutogenic affect. There was a study on *Salmonella typhimurium* and *Escherichia coli*, mammalian cells, human lymphocyte and mouse bone marrow cells. These studies showed that capromorelin was not found to be a bacterial mutagen nor to elicit dose-dependent mutagenicity.

Carcinogenicity
Due to negative mutagenicity results no carcinogenicity studies were carried out.

Studies of Other Effects

The applicant has provided bibliographical data which show that in rats and in guinea pigs capromorelin cause ocular and dermal toxicity. However, there were no sensitisation effects reported in guinea pigs. Therefore, it is accepted capromorelin is not likely to present a risk of sensitisation in humans.

Observations in Humans

Capromorelin is not authorised for use in humans however laboratory trails and off label use is currently being used/undertaken. There are current clinical trials to stimulate appetite in humans and also to treat Alzheimer's disease.

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:,

- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- In case of accidental eye contact, rinse eyes with water.
- Wash hands after use.

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

Capromorelin is a selective ghrelin receptor agonist. Capromorelin binds to ghrelin receptors in the hypothalamus to stimulate appetite and in the pituitary to stimulate secretion of growth hormone (GH). Increased GH stimulates release of insulin like growth factor 1 (IGF-1) from the liver, which in turn stimulates weight gain.

The clinical effects of capromorelin in cats are a combination of increased food intake and metabolic changes resulting in weight gain.

In healthy cats, capromorelin increased food consumption, body weight and serum IGF-1 concentrations. In cats with chronic kidney disease and ≥5% unintended body weight loss, capromorelin increased body weight in the per protocol population by 6.8% compared to an untreated control group after 55 days of treatment (body weight loss of 1.7% in the control group and body weight gain of 5.1% in the capromorelin group).

Pharmacokinetics

Binding of capromorelin to cat plasma proteins was moderate (61%) over the assessed concentration range of 1 ng/ml to 100 ng/ml.

After oral administration, capromorelin was rapidly absorbed in cats with a T_{max} of 0.35 hours (without food). The mean half-life of capromorelin in serum following intravenous and oral administration is 0.9 and 1.1 hours. Mean systemic clearance is 31.1 ml/min/kg body weight and mean apparent volume of distribution is 1.6 L/kg body weight. The short half-life can be attributed to the medium systemic clearance coupled with a medium volume of distribution. Administration of capromorelin with the entire daily ration compared to fasted

cats led to increases in T_{max} (1.25 versus 0.35 hours) and decreases in C_{max} (28 versus 59 ng/ml) and $AUC_{(0\text{-last})}$ (51 versus 83 ng.hour/ml). However, serum IGF-1 concentrations were increased by a similar amount when capromorelin was administered with or without food.

Serum concentrations of capromorelin increase proportionally with increasing dose over the range 1 - 4 mg/kg body weight as evidenced by an increase in mean C_{max} and AUC and did not accumulate with repeated dosing over 10 days.

Tolerance in the Target Species

The applicant has conducted controlled target animal tolerance studies using multiples of the recommended dose in the target species. An authorised reference product containing the same active substance. A placebo was used as a control. All doses were administered orally once per day for a period of 180 and 28 days respectively. There were different adverse events observed in male and female cats. Adverse effects consisting of Vomiting, anaemia, lethargy, dehydration and diarrhoea were reported commonly. Skin lesions on the mouth and chin were reported commonly and were attributed to the formulation sticking to fur were seen following 5 times the recommended dose in the target animals

IV.II. Clinical Documentation

Laboratory Trials

The applicant has conducted dose determination and confirmation studies.

Dose confirmation studies:

A dose confirmation study was completed to see the effectiveness of capromorelin on weight management in cats. In this study a dose of 2mg/kg was administered once daily for 60 days. A placebo was also used in a randomised and masked field study. There were no restrictions on age, gender, breed or weight. The exclusions were cats who were pregnant, lactating, participating in other clinical trials, crisis or moribund state; food intake contraindicated, dental disease severe enough to impair food intake documented and uncontrolled hyperthyroidism; documented and uncontrolled inflammatory bowel disease; documented congestive heart failure; documented cancer; documented diabetes. The results of this study confirm that AT-002, administered at a dose of 2 mg/kg once orally for 56 days, was safe and effective for managing weight loss in cats.

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.

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.

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