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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Eluracat (EMEA/V/C/005948/0000)

INN: capromorelin

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant Elanco GmbH submitted on 25 November 2021 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Eluracat 20 mg/ml oral solution for cats, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 12 May 2021 as Eluracat 20 mg/ml oral solution for cats contains an active substance (capromorelin tartrate) which is not yet authorised as a veterinary medicinal product in the Union.

At the time of submission, the applicant applied for the following indication: For body weight gain in cats experiencing poor appetite or unintended weight loss resulting from chronic medical conditions.

The active substance of Eluracat 20 mg/ml oral solution for cats is capromorelin tartrate, which selectively binds to ghrelin receptors in the hypothalamus to stimulate appetite and in the pituitary gland to stimulate secretion of growth hormone (GH). Eluracat contains 20 mg/ml capromorelin tartrate and is presented in bottles containing 10 or 15 ml. The target species is cats.

The rapporteur appointed is Ricardo Carapeto García and the co-rapporteur is Jeremiah Gabriel Beechinor.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC – full application.

On 16 May 2023, the CVMP adopted an opinion and CVMP assessment report.

On 29 June 2023, the European Commission adopted a Commission Decision granting the marketing authorisation for Eluracat.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (v3 – October 2018) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the dosage form takes place outside the EEA at two different sites. Good Manufacturing Practice (GMP) certification, which confirms the date of the last inspection and shows that the sites are authorised for the manufacture of such veterinary dosage form, has been provided. As there is a mutual recognition agreement in place for GMP between the EU and the inspecting authorities, the sites were considered appropriately certified as complying with GMP requirements.

Batch release within the EU takes place at Elanco France S.A.S, Huningue (France).

A GMP compliance declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on a remote audit by the manufacturing site responsible for batch release. Distant assessment is considered acceptable by CVMP in accordance with the guidance from the European Commission *'Notice to stakeholders: Questions and answers on regulatory expectations for medicinal products for veterinary use during the COVID-19 pandemic'.*

The remote audit took into consideration the GMP certificates available for the active substance site issued by two Competent Authorities from outside the EEA (both inspections conducted in December 2016).The QP declaration covers the manufacturers of the intermediates.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of the finished product and active substance manufacturing sites has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as a multidose oral solution containing 20 mg/ml of capromorelin tartrate as active substance.

Other ingredients are sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, sodium chloride, citric acid, sucralose, vanillin, povidone, glycerol, maltitol, liquid, Magnasweet 110 and purified water.

The product is available in HDPE bottles. Each bottle is closed with an LDPE plug-in adapter and tamper proof child resistant closure and is provided together with an oral syringe.

Containers

The primary packaging is HDPE bottles filled with 10 ml and 15 ml. Confirmation has been provided that the material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system has been supported by stability data and is adequate for the intended use of the product.

The secondary packaging is a cardboard box, each box containing 1 bottle and a graduated (per 0.1 ml) oral syringe of 1 ml. The pack sizes are consistent with the dosage regimen and duration of use.

Development pharmaceutics

Selection of the composition
Capromorelin tartrate is a new active substance in the EU.

Capromorelin tartrate is a selective ghrelin agonist and was therefore chosen as active substance to mimic the action of the naturally occurring hormone ghrelin, which stimulates appetite and can lead to

weight gain. It is a white to off-white powder which displays a pH-dependent solubility, being more soluble at acidic pH than at high pH.

The function of each excipient is discussed in the dossier. Most of the formulation development work is based on the pre-existing knowledge gained from the formulation development of a similar product marketed outside the EU for use in dogs. The list of excipients is included in section 2 of the SPC.

All excipients are well known pharmaceutical ingredients and are referenced to their corresponding Ph. Eur. Monograph, except for Magnasweet 110, a proprietary product of monoammonium glycyrrhizate in glycerine which is commonly used in oral liquids. Its components are considered to be generally recognised as safe (GRAS) by the USA's FDA. The information provided for the excipient Magnasweet 110 is considered acceptable.

Sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate were included in the composition of the veterinary medicinal product as preservatives to prevent it from microbial contamination, as the product is a non-sterile aqueous oral solution.

The formulation used during pivotal clinical studies is the same as that intended for marketing.

Selection of the container-closure system

The compatibility of the container closure system with the formulation is supported by stability studies. Compliance with Ph. Eur. monograph 3.2.2. and EU regulation 10/2011 has been confirmed. Additionally, a leachable study has been performed.

Regarding the oral syringe, dose accuracy data has been provided and compliance with specific requirements of Ph. Eur. 2.9.27 has been confirmed.

Preliminary stability studies conducted using a pilot scale batch filled into 15 mL HDPE bottles provides satisfactory results at 40°C/75% RH conditions. Freeze/thaw stabilities also support the stability of the formulation under temperature cycling.

Method of manufacture

The manufacturing process is based on the stepwise addition, dissolution and mixing of the active substance and excipients in purified water, followed by filtration and filling 10 ml and 15 ml into 15 and 20 ml high-density polyethylene bottles, respectively.

The process is considered to be a standard manufacturing process. No complex manufacturing processes have been used and no critical steps have been identified.

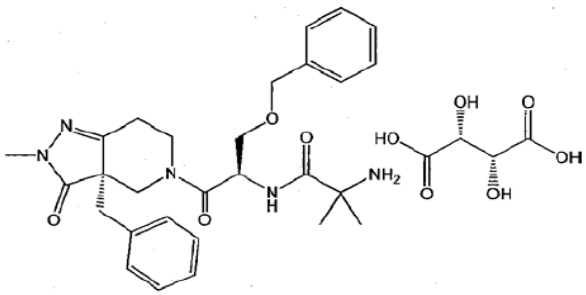
Validation data were provided for four commercial batches manufactured at one site for the 15 ml pack size (in 20 ml bottles). It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls detailed in the manufacturing description are considered adequate for this manufacturing process.

No validation data were provided for batches manufactured by the second site or for the 10 ml pack size (in 15 ml bottles). However, the applicant confirmed that manufacture at this site is currently not foreseen, and will perform the process validation on the smallest presentation and on batches manufactured at the site prior to their commercialisation.

Control of starting materials

Active substance

The chemical name of capromorelin tartrate is "Propanamide, 2-amino-N-[2-[2,3,3a,4,6,7-hexahydro -2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, [R-(R*,R*)]-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) 2-Amino-N-[(1R)-1 -[[(3aR)-3a-benzyl-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-2-(benzyloxy)ethyl]-2-methyl-propionamide L-(+)-tartrate (1:1)" and has the following structure:



The active substance is a white to off white solid freely soluble in aqueous buffers under pH 3.0. Solubility in other solvents has been also indicated.

Capromorelin tartrate exhibits stereoisomerism due to the presence of two chiral centres. The chirality in the final active substance is controlled.

Polymorphism has been observed for active substance. Since the active substance is solubilised in the product, particle size and polymorphism are not considered critical for the quality of the finished product.

Full information regarding the quality of the active substance is provided in the dossier. Capromorelin tartrate is not monographed in any pharmacopoeia.

The synthesis of capromorelin tartrate is performed outside the EU (in a 10-step synthesis process. A detailed description of the whole process including procedures, representative quantities of chemicals and reagents of each step and typical yield ranges has been provided. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been adequately presented.

The characterisation of the active substance and its impurities are in accordance with the EU 'Guideline on chemistry of new active substances'. Potential and actual impurities were discussed with regards to their origin and characterised.

The active substance specification includes tests for appearance, identity, assay, impurities, chirality, tartaric acid content, residual solvents, water content and residue on ignition.

All analytical methods have been validated and described. Results on stress conditions have been presented under acidic, alkaline, heat, oxidizing and high light conditions.

Satisfactory information regarding the reference standards used for assay, impurities testing has been presented.

Batch analysis data of 10 final batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability data on three commercial batches of active substance from the proposed manufacturer is provided, stored in the intended commercial package, during 3 years under long term conditions at

25 ºC/60% RH. Additional data is provided on process validation batches and one smaller batch for 3 years under long term conditions at 25 ºC/60% RH and for up to 1 year under accelerated conditions at 40 ºC/75% RH.

The parameters tested are the relevant stability indicating parameters in the active substance specification. The analytical methods used were the same as for the active substance specification and were stability indicating. All tested parameters were within the specification.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 3 years in the proposed container.

Excipients

The formulation contains the following excipients: methylparaben sodium, propylparaben sodium, sodium chloride, citric acid anhydrous, sucralose, vanillin, povidone K90, glycerine, maltitol solution, Magnasweet 110, and purified water.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except for Magnasweet 110, which is not monographed in any pharmacopoeia. Information provided has been completed in line the 'Guideline on excipients in the dossier for application for marketing authorisation for veterinary medicinal products (EMEA/CVMP/004/98)' declaring its qualitative composition.

There are no novel excipients used in the finished product formulation. The absence of microbiological quality control in accordance with Ph. Eur. 5.1.4. *Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use* has been justified by the Applicant for several excipients. The list of excipients is included in section 2 of the SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Valid TSE declarations from the manufacturer of the finished product and the suppliers from some excipients have been provided.

Control tests on the finished product

The specifications proposed for use at release and at the end of shelf-life are generally appropriate to control the quality of the finished product; the validation of methods for control of the active substance, degradation products and excipients comply with VICH GL1/GL2 requirements.

Batch analysis results are provided for 3 batches of 100 L size manufactured by one manufacturing site for the 10 and 15 ml pack sizes, and for 8 batches of 150 L manufactured by the second manufacturing site for the 15 ml pack size (filled in 20 ml bottles). They confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability data according to VICH guidelines are provided on batches manufactured in both proposed sites:

- Three commercial batches of finished product for the 10 and 15 ml pack sizes filled in 15 ml and 20 ml bottles, respectively.

- Eight commercial batches of finished product for the 15 ml pack sizes filled in 20 ml bottles.

For batches from the first site, 2-year long term data at 30 ºC/65% RH are available up to date and 6 months under accelerated conditions at 40 ºC/75% RH.

For batches from the second site, 6 to 12 month-long term data at 30 ºC/65% RH are available and 6 month data under accelerated conditions at 40 ºC/75% RH.

The batches of product were packed in the primary packaging proposed for marketing.

All results comply with the specifications and with no significant differences between all batches.

The applicant (Elanco) has declared that any validation batches manufactured post manufacturing changes will be placed on accelerated and long-term stability; a minimum of one commercial batch per year (if manufactured) will be placed on long-term stability; any production batches found to fall outside of the approved specifications will be withdrawn from the market, and those batches manufactured immediately before and after the batch(s) in question will be investigated.

In addition, two batches were exposed to light for a photostability study, with no significant change in any of its attributes. The study was conducted in line with VICH GL5 on photostability testing of new veterinary drug substances and medicinal products.

The freeze-thaw study was conducted on two batches manufactured. All results comply with specifications after freeze-thaw cycles. It has been concluded that no particular precaution has to be taken with regards to cold temperature.

Based on the available stability data, the proposed shelf-life of 2 years with no special storage conditions as stated in the SPC is acceptable.

Appropriate in-use data has been provided in line with VICH Guideline on in-use studies that support the proposed in-use shelf life of 3 months with no special storage conditions. Satisfactory data has been provided at the end of the study regarding the antimicrobial preservation of the formulation in accordance with Ph. Eur. 5.1.3. The applicant will carry out a new in-use stability study performed on both fresh and aged batches in 2023 and to notify the Agency in the event of unexpected trends or out of specification results.

New active substance (NAS) status

The applicant requested the active substance capromorelin tartrate contained in the veterinary medicinal product to be considered a new active substance as it is novel and has not yet been authorised in a veterinary medicinal product in the European Union. The CVMP agreed with this.

See part 4 for additional information.

Overall conclusions on quality

The finished product is presented as a multidose oral solution containing 20 mg/mL of capromorelin tartrate as active substance. Other ingredients are sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), sodium chloride, citric acid, sucralose, vanillin, povidone, glycerol, maltitol (liquid), Magnasweet 110 (glycyrrhizic acid, monoammonium glycyrrhizinate) and purified water.

The product is presented in HDPE bottles filled with 10 ml and 15 ml oral solution (i.e. 15 ml and 20 ml bottle sizes, respectively). Each bottle is closed with an LDPE plug-in adapter and tamper proof child resistant closure and is provided with an oral syringe. Confirmation has been provided regarding compliance of the materials with relevant European Pharmacopoeia (Ph. Eur.) and EU requirements.

The manufacturing process is considered a non-complex, standard manufacturing process. The process and in-process controls have been adequately described and acceptable validation data have been

provided for four commercial batches manufactured at one manufacturing site. The absence of validation data of batches manufactured by the second manufacturing site and filled in 15 ml bottles has been justified on the basis that commercial manufacture at this site is not yet performed, but that validation on the smaller presentation and on batches manufactured at this site will be provided prior to their commercialisation.

Information on the development, manufacture and control of the active substance has been presented in a satisfactory manner. Validation data provided on analytical procedures confirm compliance with VICH GL1 and GL2.The stability results on batches of active substance justify the proposed retest period of 3 years in the proposed container.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards excluding Magnasweet 110.

Appropriate data has been presented to give reassurance on TSE safety.

Information regarding the control of the finished product is considered adequate.. Batch analysis results are provided from the two proposed sites of manufacture confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Satisfactory stability data has been provided for the finished product in line with VICH Guidelines in order to support the proposed shelf-life and storage conditions as stated in the SPC.

Part 3 – Safety

The active substance of Eluracat 20 mg/ml oral solution for cats is capromorelin tartrate, a selective ghrelin receptor agonist, which has not yet been authorised as a veterinary medicinal product in the Union. A full safety file in accordance with Article 12(3)(j) of Directive 2001/82/EC has been provided.

Safety documentation

A comprehensive data package including numerous studies performed by the applicant and data from published literature has been presented by the applicant.

Pharmacodynamics

Capromorelin is an orally active pyrazolinone-piperidine growth hormone secretagogue, which acts as a selective ghrelin receptor agonist binding to ghrelin receptor 1a in the hypothalamus to stimulate appetite and in the pituitary gland to release growth hormone (and subsequently insulin-like growth factor 1). The mode of action and effects in the target species are described in Part 4.

Pharmacokinetics

A number of studies investigating the pharmacokinetics of the active substance in dogs, rats, mice, rabbits, pigs, monkeys and humans have been provided. These studies were conducted during the preclinical development of a potential human medicinal product. For studies undertaken in the target species cat, see part 4.

Absorption

Capromorelin tartrate is rapidly absorbed when administered by oral route to rats, with a T_{max} of 0.25 hours. The maximum concentration (C_{max}) when administered at 1 mg per kg body weight was

326 ng/ml. The oral bioavailability was moderate (F=65%). Similar results were obtained in dogs (F=44%) after oral administration.

In humans, absorption was also rapid after oral administration as indicated by rapid appearance of a radioactivity peak in the circulation. Plasma concentration of the parent substance peaked on average 1.1 hours after administration and plasma concentration of one metabolite (N-demethylated metabolite), peaked on average after 2.5 hours. The mean C_{max} for capromorelin and the metabolite were 28 and 1.5 ng/ml, respectively.

Distribution

Protein binding of capromorelin was found to be moderate (49% in dogs, 58% in humans, and 73% in rats) and was independent of concentration over a range of 10 ng/ml to 1000 ng/ml.

In rats, following oral administration, the highest concentrations of radioactivity were found in the contents of the gastrointestinal tract, liver, glandular tissues, and uvea between 0.5 and 1 hour after administration. Radioactivity was not measurable in the cerebellum, cerebrum, spinal cord, or any other brain tissue other than the pituitary and ocular tissues not containing melanin. By 9 hours after administration only liver, skin, uvea and the gastrointestinal tract contents had measurable concentrations of radioactivity. By 168 hours after administration radiolabelled capromorelin had been eliminated from all tissues except the uvea.

In dogs, cerebrospinal fluid concentrations of capromorelin on days 1 and day 4 were approximately 15% and 13%, respectively, of plasma concentrations, showing that the drug can penetrate the blood-brain-barrier.

In rats, dogs, pigs and monkeys, the volume of distribution was moderate after intravenous administration.

Metabolism

In vivo radiolabelled metabolism studies demonstrated that capromorelin is almost entirely metabolised by the liver in humans, monkeys, rats, mice, and dogs, predominantly through phase I metabolism. Only in mice, two minor metabolites were observed which were products of phase II metabolism.

In humans, a total of 10 metabolites in urine, 10 in plasma and 3 in faeces were detected. Most of the metabolites were due to N-dealkylation, O-debenzylation, and oxidative metabolism on the μ-methylalanyl moiety and piperidine ring. N-demethyl metabolite M3, identified in humans, mice, rats, dogs, and monkeys, showed pharmacologic activity (equivalent in potency to capromorelin) but due to the low systemic exposure (<5% of parent exposure) it was considered that it did not contribute to the in vivo activity of capromorelin.

However, biotransformation of capromorelin was also investigated in vitro using cat hepatocytes and three major metabolites were observed, M3 among them (M3 = 12.5%, M24 = 5.5% and M25 = 5.5%). It is stated that metabolite M3 is the only metabolite which shows pharmacological activity. Bearing in mind this finding, the CVMP is of the opinion that systemic exposure to the metabolite M3 should have been further evaluated in vivo in cats. Nevertheless, taking into account the results of the efficacy and safety studies performed in the target species, it can be accepted that the active metabolite M3 did not have a significant impact on the overall in vivo activity or toxicity of capromorelin in cats.

Excretion

The major route of elimination in laboratory species is via faeces. Metabolites and a small amount of the parent compound accounting for 59% in mice, 80% in rats and 62% in dogs, were recovered 168 hours after administration. In mice, most of the dose was excreted within the first 24 hours and, in rats and dogs, within the first 48 hours. This is consistent with a relatively fast absorption of capromorelin following oral administration.

In humans, the total radioactive recovery was quite high and was achieved within 240 hours, compared to 168 hours in the laboratory species. 78% of the administered dose was recovered from urine and faeces: 50% of the administered dose was excreted in the urine within the first 24 hours after administration, whereas radioactivity recovered in faeces accounted for an average of 28%. However, this value could have been impacted by the time of defecation in the human subjects.

Plasma half-life ($T_{1/2}$) values for capromorelin were generally similar between species and ranged from 0.8 to 2.1 hours.

Toxicological studies

A number of single and repeated dose toxicological studies with capromorelin tartrate were carried out in mice, rats and dogs.

Single dose toxicity

The acute toxicity of capromorelin has been investigated in a GLP-compliant study in mice and rats. The study has not been performed in accordance with the OECD guidelines but was considered to be adequate to characterise the single dose toxicity of the active substance.

No clinical signs were observed in mice after oral administration of 100 mg capromorelin tartrate/kg bw or intravenous administration of 10 or 20 mg/kg bw. Death occurred in 4/6 mice at 500 mg/kg bw following oral administration and in 2/3 mice at 50 mg/kg bw when administered intravenously.

In rats, clinical signs were observed at all doses after oral administration (50, 100, 500, and 1000 mg/kg bw); no clinical signs appeared after intravenous administration of the lowest dose (5 mg/kg bw). Death (2/3 females) occurred in rats dosed orally with the highest dose (1000 mg/kg bw). All rats injected with 250 mg/kg bw died within seconds.

A non GLP-compliant exploratory study in dogs following oral administration has also been provided; however, no toxicological endpoints have been identified. Mild clinical signs were observed in the 40 mg/kg bw dose group with a slight increase of liver enzymes in both treated and control groups. However, due to the low number of animals included in this study, limited conclusions may be drawn.

From the information provided it can be concluded that capromorelin is of moderate acute toxicity.

Repeat dose toxicity

The sub-chronic and chronic toxicity of capromorelin has been investigated in different GLP-compliant studies in mice, rats and dogs. These studies date from more than 20 years ago and have not been performed in accordance with current OECD test guidelines but were considered adequate to characterise the toxicity of the active substance.

The systemic toxicity in rats following oral administration of capromorelin tartrate daily for a 1-month period was investigated in order to determine the most appropriate doses for the 6-month repeat-dose toxicity studies. Salivation, increased liver weight and increased serum triglyceride levels were observed

at the highest dose tested (75 mg capromorelin tartrate/kg bw). In all treated groups, body weight gain and increased food consumption were observed, effects which are consistent with the pharmacological activity of this substance. The dose of 15 mg/kg bw is retained as the NOAEL for this study.

In the 6-month study in rats salivation was also increased. The applicant considers this effect is a result of an adverse taste reaction to the active substance. However, it should be taken into account that the active substance was administered by oral gavage, therefore, taste does not play any role. Furthermore, hypersalivation has also been seen in toxicity studies in dogs and tolerance studies in cats. The aetiology for the increased incidence of salivation is unknown and this effect is therefore considered as adverse event and reflected as such in the product information. Hypersalivation was observed at doses ≥15 mg/kg bw. Haematological findings in all treated groups have also been reported. The applicant states that these effects are attributable to increased growth hormone secretion, which stimulates erythropoietic activity in vivo and in vitro and also produces anti-natriuretic effects, increasing sodium retention and hence, total body extracellular fluid, decreasing total red cell parameters. The explanation given by the applicant is acknowledged. However, given that these haematological findings were already noted at the lowest dose tested (1 mg/kg bw), no NOAEL could be derived from this study.

In a one-month oral toxicity study in mice, clinical pathology changes occurred in all treated females. In the 300 mg/kg female group, there was a 73% increase in total white blood cell count relative to controls reflecting a global increase in all parameters of the differential count. These values were also increased, generally to a lesser extent, in most groups given 3, 30 and 100 mg/kg bw, but statistical significance was achieved on only a few occasions. However, the applicant states that there is no evidence of treatment-related toxicity. The purpose of this study was to assess the toxicity of the active substance in order to select dose levels for a further pre-chronic toxicity study by oral gavage in mice. In this 3-month oral toxicity testing, the compound induced effects consistent with its pharmacological activity. According to the expert report, since no treatment-related adverse effects have been reported, the NOAEL can be retained at 300 mg/kg bw. However, a significant decrease in red blood cell count, haemoglobin and haematocrit values occurred in males receiving the highest dose (300 mg/kg bw). Additionally, for both of these studies in mice, significantly higher plasma concentrations of capromorelin in females compared to males was observed (at all doses except 30 mg/kg). The CVMP considers that the haematological findings are relevant and treatment-related, and a NOAEL of 100 mg/kg bw is retained.

A one-month oral toxicity study in dogs showed that, at the highest dose (40 mg/kg bw), salivation and emesis were observed. Loose stools were noted sporadically in all dose groups including controls, with the highest frequency among dogs given 40 mg/kg bw. Cholesterol and high-density lipoprotein (HDL) levels were slightly increased in the high dose group and can be attributed to the accelerated lipolysis produced by the growth hormone. In contrast to the repeat dose studies conducted in rodents, similar plasma concentrations of capromorelin were observed in males and females. The increase of liver weight in the high dose females may be a consequence of the body weight gain and the increase of ovary weight seems to correspond to the onset of normal oestrus cycling. Therefore, based on the lack of findings, a NOAEL of 7 mg/kg bw is accepted. The results of this study were used to determine the doses for a 1-year oral toxicity study in dogs, where ECG changes were noted at doses ≥0.3 mg/kg bw/day including an increased PR interval, which may indicate a first-degree heart block. Furthermore, a slight, treatment-related increase in hepatocellular cytoplasmic vacuolation was observed in all treated animals, which suggests hepatotoxicity. The vacuolation seen in this study is consistent with the increase in liver weights and thus associated with the pharmacological effect of capromorelin on growth hormone and increased body weights in these animals (Bates et al., 1964). However, it should be noted that also pharmacological effects could be adverse and non-desirable.

Whilst it is accepted that a NOAEL of 7 mg capromorelin tartrate/kg bw can be derived from the one-month oral toxicity study conducted in dogs, it is noted that electrocardiogram abnormalities were observed in one animal and hepatocellular vacuolation was observed at

≥0.3 mg capromorelin tartrate/kg bw in the 1-year oral toxicity study conducted in dogs. Consequently, a NOAEL cannot be derived from this second study.

Tolerance in the target species of animal

Hypersalivation and emesis have been observed in cats after daily oral administration. These and other signs reported such as lethargy/depression were of limited duration and resolved without treatment.

The details of these studies as well as other details on tolerance in the target animal species are described in part 4.

Reproductive toxicity

Study of the effects on reproduction

No studies on the effects on reproduction in the target species have been provided. In the absence of studies on the effects on reproduction, a statement indicating that the safety of the veterinary medicinal product has not been established in pregnant cats or cats intended for breeding has been included in the product literature.

Study of developmental toxicity

After daily administration of 0, 1, 15 and 75 mg/kg bw/day in pregnant female rats between days 6 and 17 of gestation, a significant increase in the incidence of supernumerary ribs in foetuses has been observed in the group receiving the highest dose. According to literature, supernumerary ribs occur spontaneously in Sprague-Dawley rats and they may be associated with maternal stress. The percent of foetuses affected per litter were within the historical control range of this laboratory but the percent litter affected were higher than the historical control range. However, this change has not been considered adverse by the applicant. Based on these results and considering that the incidence of supernumerary ribs has reached significance in the high dose group, the NOAEL for teratogenicity in this study should be retained at 15 mg/kg bw.

A study of developmental toxicity in rabbits given 0, 1, 35 and 75 mg/kg bw per day of capromorelin tartrate on gestation days 7 to 19, showed no evidence of foetotoxicity or teratogenicity. Therefore, the proposed NOAEL of 75 mg/kg bw (i.e. the highest dose tested) is considered acceptable.

Genotoxicity

The genetic toxicology potential of capromorelin tartrate has been evaluated in a standard test battery in accordance with VICH guideline GL23.

In the Ames test, the active substance was negative for induction of reverse mutations in the four tested strains of *Salmonella typhimurium* and the tested strain of *E. coli*, both in the presence and absence of metabolic activation.

The test item did not induce a significant increase in chromosomal aberrations in human lymphocytes cultures in presence or absence of a rat liver metabolic activation system.

An in vitro mammalian gene mutation test using the HPRT gene conducted with and without metabolic activation has been also provided. No significant mutagenic response was observed.

In an in vivo micronucleus test in mice, no increase was seen in micronucleus formation in the bone marrow cells of male or female mice treated on three consecutive days at a maximum oral dose of 300 mg/kg bw/day.

Based on the above studies, it is accepted that capromorelin is not genotoxic.

Carcinogenicity

No carcinogenicity data have been provided. This is considered acceptable due to the lack of genotoxic potential, the lack of structural alerts, and the lack of findings relevant to neoplastic lesions in repeat dose toxicity studies.

Studies of other effects

Dermal and ocular irritation potential of capromorelin was evaluated in vivo in New Zealand White rabbits. The substance was found to be an ocular irritant, but no relevant signs of skin irritation were noted.

In a guinea pig study, following the challenge application, no evidence of delayed contact hypersensitisation was observed in any of the capromorelin-treated animals.

It should be noted that these studies have been performed with the active substance and not with the final formulation.

In clinical trials in humans, no significant increases of hyperglycaemia were observed. Glycosylated haemoglobin (HbA1c) values rose significantly at 6 months and remained high at 12 months. Significant increase in sleep disturbance in the capromorelin group at 6 months was also reported. Quantitative insulin sensitivity indexes showed significantly increased insulin resistance.

Single ascending doses of 20, 50 and then 100 mg of capromorelin tartrate were administered at least 1-week apart in a phase-I safety trial in humans. Abdominal pain, lethargy, light-headedness, palpitations, low back pain and increased perspiration were reported but considered minor and transient effects.

Capromorelin was originally developed as a growth hormone secretagogue for the treatment of human frailty in the elderly. The Food and Drug Administration in the United States approved it for veterinary use, but the clinical trials in older men and women were discontinued after approximately 12 months due to a lack of efficacy for an increase in percent lean body mass.

Excipients

Toxicological information on each of the excipients included in the formulation has been submitted. The excipients citric acid anhydrous and Magnasweet 110 can cause skin and/or eye irritation. Parahydroxybenzoates and their esters may cause allergic reactions (possibly delayed) as indicated in the SPC. Also, povidone (K-90) has been reported in scientific literature to cause sensitisation.

User safety

The applicant has presented a user safety risk assessment broadly in accordance with CVMP guideline EMEA/CVMP/543/03-Rev.1.

The main potential routes of accidental contact with the product are those of dermal, ocular and, in children, oral exposure.

As stated in the 'excipients' section, in the absence of toxicological studies using the final formulation and based on the possibility of skin irritation and sensitisation potentially associated with some excipients, appropriate risk mitigation measures should be put in place.

Regarding quantitative risk assessment, the applicant has calculated a MOE for dermal and oral exposure based on the clinical signs observed in humans after exposure to doses administered in clinical trials. It

should be noted that clinical trials are not designed to characterize toxicological effects and are hence not appropriate to obtain a relevant toxicological reference value. The minor adverse events observed, which appeared even at the lowest dose administered (0.33 mg/kg), have been included in the SPC.

Also at this dose, an increase in hepatocellular cytoplasmic vacuolation and electrocardiogram abnormalities were seen in the 1-year repeated dose toxicity study in dogs. Considering these findings, the calculated margin of exposure of 11 after oral or dermal exposure is only acceptable in view of the following considerations: none of these effects appeared in the 1-month toxicity study in dogs, indicating that they are possibly associated with a chronic exposure. Since accidental user exposure is occasional and a 100% dermal absorption is assumed as a worst-case, the risk following dermal exposure can be considered acceptable in this case. Similarly, any incidental hand to mouth exposure in adults is expected to be lower than the dermal exposure.

However, an unacceptable risk for children exists following accidental oral exposure even when the NOAEL of 7 mg/kg bw derived from the 1-month repeated dose toxicity study in dogs is considered. The applicant acknowledges this risk and proposes to pack the product in childproof packaging and include warnings to keep the product out of reach of children. A child resistant packaging certificate has been provided.

The advisory statements proposed by the applicant are considered appropriate. They include risk mitigation measures regarding potential hypersensitivity. The following wording was accepted for inclusion in the product information:

- Ingestion by children may cause mild and reversible signs of abdominal pain, lethargy, light-headedness, palpitation, low back pain, feeling warm and increased perspiration. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- This veterinary medicinal product contains parabens and povidone, which may cause allergic reactions. People with known hypersensitivity to these substances administer the veterinary medicinal product with caution.
- This veterinary medicinal product may cause eye and skin irritation. Contact with the eyes, skin and mucous membranes should be avoided. Wash hands after use. In case of accidental eye or skin contact, rinse the affected area immediately with plenty of fresh water. If irritation persists, seek medical advice and show the package leaflet or the label to the physician.

Environmental risk assessment

The applicant has submitted an Environmental Risk Assessment (ERA) performed according to the VICH GL6 guideline on environmental impact assessment for veterinary medicinal products - Phase I (CVMP/VICH/592/98-FINAL) as well as the guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL 38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

VICH GL6 decision tree was followed until question 3. The veterinary medicinal product will only be used in non-food animals. Therefore, no phase II assessment is necessary.

The very limited exposure of the environment is considered to be negligible.

Eluracat 20 mg/ml oral solution for cats is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

Not applicable

Overall conclusions on the safety documentation

Pharmacology

Capromorelin is rapidly absorbed after oral administration with a mean oral bioavailability ranging from <5% to 65%. Plasma half-life values were generally similar between species and ranged from 0.8 to 2.1 hours.

Binding to serum proteins was moderate in dogs (49%), humans (58%) and rats (73%).

Capromorelin appears to be extensively metabolised and excreted via faeces and urine, with phase I metabolism playing a major role in its elimination.

It is stated that metabolite M3 is the only metabolite which shows pharmacological activity (equivalent in potency to capromorelin), but due to the low systemic exposure (<5% of parent exposure) it was considered that it did not contribute to the in vivo activity of capromorelin. However, biotransformation of capromorelin was also investigated in vitro using cat hepatocytes and three major metabolites were observed, M3 among them (M3 = 12.5%, M24 = 5.5% and M25 = 5.5%). Bearing in mind this finding, the CVMP is of the opinion that systemic exposure of the metabolite M3 should have been further evaluated in vivo in cats.

Nevertheless, taking into account the results of the efficacy and safety studies performed in the target species, it can be accepted that the contribution of the active metabolite M3 did not have a significant impact on the overall in vivo activity or toxicity of capromorelin in cats.

Overview of toxicity findings:

Results of pivotal toxicity studies			
Study type	**Tested species/test system**	**Results***	**Comments**
Single toxicity	Mice	Oral 500 mg/kg. IV 50 mg/kg.	Moderate acute toxicity
	Rats	Oral 1000 mg/kg (females); >1000 mg/kg (males) IV 250 mg/kg	
Repeat dose toxicity	Mice	-----	1 month
		NOAEL 100 mg/kg bw**	3 months
	Rats	NOAEL 15 mg/kg bw	1 month
		No NOAEL**	6 months
	Dogs	NOAEL 7 mg/kg bw	1 month
		No NOAEL**	1 year
Developmental toxicity	Rats	NOAEL 15 mg/kg bw**	16 days

Results of pivotal toxicity studies			
Genotoxicity & Carcinogenicity	Bacterial reverse mutation test *In vitro* Mammalian Chromosomal Aberration Test *In vitro* Mammalian Cell Gene Mutation Test Mouse micronucleus assay	Non mutagenic	No carcinogenicity data provided due to the lack of genotoxic potential, the lack of structural alerts, and the lack of findings relevant to neoplastic lesions in repeat dose toxicity studies.
Other effects	Rabbits	No skin irritant Ocular irritant No sensitizer	Moderate reddening of the palpebral conjunctiva and slight chemosis

*Doses are stated as capromorelin tartrate.

** Different values were proposed by the applicant, see assessment report

User Safety

The applicant has presented a user safety risk assessment broadly in accordance with CVMP guideline EMEA/CVMP/543/03-Rev.1. A risk for children following accidental oral exposure has been identified; however, the product is presented in childproof packaging and the product information includes appropriate additional user safety warnings. Based on the assessment of all the data presented, the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Regarding the excipients, in the absence of toxicological studies using the final formulation and based on the possibility of skin irritation and sensitisation potentially associated with some of them, appropriate risk mitigation measures have been put in place.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used in accordance with the SPC.

Part 4 – Efficacy

This application is for a solution for oral administration, containing 20 mg/ml capromorelin tartrate (equivalent to 15.4 mg/ml of capromorelin) as the active substance. The proposed indication is for body weight gain in cats experiencing poor appetite or unintended weight loss resulting from chronic medical conditions.

Pharmacodynamics

Capromorelin is a pyrazolinone-piperidine growth hormone secretagogue (GHS) that functions**,** like ghrelin, as a selective ghrelin receptor agonist (GRA). Ghrelin and GHSs activate the growth hormone secretagogue receptor (GHS-R).

The endogenous ligand for the GHS-R is the peptide hormone ghrelin, which is produced in the stomach in response to fasting. It is secreted and binds to GHS-Rs in the hypothalamus and pituitary to stimulate appetite and to enhance the release of growth hormone (GH) from the pituitary gland.

Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor 1a (GHS-R1a). In literature it is stated that two GHS-Rs types exist: type 1a and type 1b, and it was established that GHS-R1a is stimulated by GHSs, but not GHS-R1b. It was concluded that the pharmacological profile of GHS binding to cloned human and swine type 1a GHS-RS correlates with their biological activities in vivo. Type 1a GHS-R may thus contribute to the control of pulsatile GH release, presumably under the influence of an unidentified endogenous ligand.

Feline ghrelin was purified and its possible physiological role in cats examined. Four isoforms of ghrelin with multiple types of acylation were isolated from feline stomach. All feline ghrelin and its multiple isoforms were biologically active in an assay using cells expressing rat GHS-R. In cats, synthetic rat ghrelin stimulated the release of GH and plasma active ghrelin levels increased after fasting. The study concluded that there are many similarities in pathophysiology between humans and cats and that the studies of the physiological functions of ghrelin in cats, including effects on GH release and feeding behaviour, will help us to understand the role of ghrelin in human pathophysiology.

The information in section 4.2 ('Pharmacodynamics') of the SPC is consistent to the information included in the scientific bibliography.

Effect of capromorelin

Effect of increased Growth Hormone (GH): Unlike most other pituitary hormones, GH does not have a single target tissue but stimulates effects in the liver, muscle, fat and cartilage. It is a major metabolic hormone and acts by optimising body composition and physical function, as well as by regulating energy and substrate metabolism (e.g. increasing protein synthesis, increasing lipolysis, decreasing carbohydrate breakdown while increasing plasma glucose), as well as stimulating epiphyseal growth.

GH also exerts its anabolic effect (after the post-natal period) indirectly, via the stimulation of insulin-like growth factor-1 (IGF-1). The liver is the predominant source of IGF-1 but it is also synthesized in many other tissues, where it acts in an autocrine/paracrine manner.

Effect of increased insulin-like growth factor-1 (IGF-1): The stimulation of IGF-1 provides complimentary protein synthesis and epiphyseal growth to GH. However, conversely to GH, lipolysis is decreased with IGF-1 and the effects on carbohydrate metabolism are insulin-like: increased glucose uptake in extra-hepatic tissues, decreased hepatic glucose output and decreasing plasma glucose.

Circulating IGF-1 levels have been found to parallel those of GH; however, IGF-1 has a delayed onset in comparison to GH, which has a short half-life and exhibits a pulsatile secretory profile. The half-life of IGF-1 is prolonged by complex formations with high affinity proteins (a group of six IGF binding proteins have been described) which help to modulate availability, with some species variation. For this reason, IGF-1 levels are measured in place of GH.

The CVMP agreed that the measurement of the IGF-1 levels can be used as an indirect parameter to study the action of capromorelin in cats.

Regulation of effects: The effect of ghrelin and GHSs is regulated by a complex interplay of feedback as well as the balancing effect of GH and IGF-1, in relation to carbohydrate metabolism and lipolysis.

Somatostatin is the endogenous inhibitor of growth hormone (antagonistic to growth hormone–releasing hormone at the level of the pituitary) and its action is complemented by the negative feedback of GH and IGF-1, also at the level of the pituitary gland. Additionally, regulation is aided by GH and IGF binding proteins.

As a consequence of this regulation, the administration of GHSs such as capromorelin at the recommended dose does not result in supraphysiological GH concentrations, and the treatment effect is not comparable to the condition of hypersomatotropism (acromegaly), where a GH-secreting tumour raises levels that are beyond the physiological feedback mechanisms. However, a warning relating to the use of the product in acromegalic cats is included in the product information.

Pharmacodynamic studies

In addition to a number of references from published literature, the applicant also provided twelve pilot studies investigating the effect of capromorelin in cats.

All these pilot studies were carried out in 2002 in the USA (Veterinary Medicine Pharmaceutical Discovery, Pfizer Inc., Groton, CT) following the same design. Even though some deficiencies regarding the method of analysis of the plasma samples and the certificate of analysis of the active substance were detected, it has to be taken into account that these were exploratory studies. In addition, it should be noted that the formulation used was not the final one, and different doses were tested although the differences in composition did not affect the bioavailability of the active substance.

Considering the tested doses in those studies, the following conclusions are observed:

The results of these studies demonstrate that capromorelin increases appetite and body weight in healthy cats. Usually, it was observed that the mean food intake at six hours post dose was significantly increased from baseline measurements. However, the mean food intake at 24 hours post dose also tended to be increased from baseline measurements, but not always significantly. This points out that the effect of capromorelin was reduced twenty-four hours post dose.

Dosages over the range 0.1 to 15 mg/kg bw of capromorelin were tested in early studies with treatment duration between 4 and 10 days. In one study capromorelin at a dosage of 3 mg/kg body weight for 6 days did not increase appetite in cats treated with oral cyclophosphamide (50 mg/m^2). However, it is likely that this chemotherapy model of inappetence was too severe and/or acute to demonstrate efficacy relevant to the proposed use in this application.

Additionally, four studies investigated the effects of capromorelin in neutered/spayed cats at different doses (approximately 1, 2, or 4 mg/kg body weight, oral), and the effects of capromorelin as an appetite stimulant in intact cats, at 0.5, 1 and 2 mg/kg body weight in one further study. In order to rule out a possible bias due to this condition (neutered/spayed and intact cats), the applicant provided the available data from these studies for which reproductive status could be confirmed. Although no statistical comparison was performed, the results seem comparable.

In addition, the applicant submitted bibliographic references, some of which addressed the secondary pharmacodynamic effects. Effects on glucose homeostasis, cardiovascular effects, as well as long term effects were described.

The potential for cardiovascular effects resulting from the administration of capromorelin to cats has been investigated and is discussed further in the target animal safety part. In section 3.5. ('Special precaution for use') of the SPC, warnings related to the use in cats with diabetes mellitus or hypotension are included.

Pharmacokinetics

The applicant included a summary to explain the pharmacokinetics of the active substance. This summary includes bibliographic references and a large number of studies from non-target and target species.

Pharmacokinetics in non-target species

The studies conducted in rats, monkeys and pigs demonstrated rapid oral absorption after administration. The systemic clearance was moderate in monkeys and moderate to high in pigs. The volume of distribution was considered as moderate for both species and the half-life short. See part 3.

Pharmacokinetics in target species

The applicant has provided a large number of studies (13) in order to characterise the pharmacokinetics of capromorelin in cats.

The study design in most of these studies was similar. A capromorelin formulation was orally administered, and food intake and weight gain in treated cats was measured; and capromorelin and IGF-1 serum concentrations were measured. These studies were conducted in order to study different issues like dose, duration, pharmaceutical form, influence of the sex or the prandial state. This approach is acceptable since this kind of active substance is regulated by a complex process in which several substances can be involved.

Nevertheless, it is noted that these studies included different, non-final formulations of capromorelin. In vitro dissolution studies are not appropriate for Eluracat 20 mg/ml oral solution for cats, since it is a true solution, and no formal bioequivalence studies have been conducted. The applicant considered however that it can be assumed that the oral bioavailability should be similar for the various solutions. This approach was accepted by CVMP.

Bioavailability was studied in a pilot study which tested capromorelin formulations (non-final) that allowed enough active substance in the blood circulation to achieve an appetite stimulating response in cats, and define a capromorelin PK profile in the serum of cats. Capromorelin tartrate was administered via intravenous (0.75 mg/kg bw) injection and via oral gavage (3 mg/kg bw).

Following the intravenous (IV) injection of capromorelin, clearance was rapid (~30 ml/minute/kg body weight). The volume of distribution was large (>1 l/kg) indicating high tissue affinity. The terminal half-life was short (0.9 hours) due to the rapid clearance.

The oral bioavailability and mean absorption time could not be determined individually (since different cats received IV and oral administrations). However, based on the mean area under curve (AUC) and mean residence time (MRT), the estimated oral bioavailability was estimated as 34% and estimated absorption was 1.53 hours. This information is included in section 4.3 'Pharmacodynamics' of the SPC.

Metabolism and Excretion of capromorelin was studied in healthy rats, mice, dogs, monkeys and humans, treated in the fasted state following the administration of a single, radiolabelled dose, orally (see part 3).

The protein binding of capromorelin in cat plasma was studied by equilibrium dialysis (ELAVV200123). Capromorelin was evaluated over a concentration range of 1-100 ng/ml for six hours at 37°C. Quantification of capromorelin was via an LC-MS/MS method over a range of 0.3 to 600 ng/ml. Capromorelin showed moderate plasma protein binding in cats with the fraction bound ranging from 56.1% to 64.3%. The results did not indicate concentration dependent binding for the range evaluated in this study. The CVMP agrees with this conclusion. It is noted that this information is stated in the SPC of the product.

Repeated dose study

This study was intended to define an appropriate dose of a capromorelin oral solution (non-final formulation, PRT3-99 I A) that provides the desired profile of IGF-1 (<1000 ng/ml on Day 10) and cortisol levels to support the positive effects of treatment (increased appetite and muscle mass).

Five groups of 6 cats each were included. Four groups were treated once daily, in the fasted state, for 10 consecutive days at different doses (1, 2, 3, and 4 mg capromorelin tartrate/kg bw via oral syringe) and group 1 was the non-treated placebo group.

Maximum serum concentrations of capromorelin generally occurred at 30 or 60 minutes after administration. In general, concentrations declined to very low levels within 8 hours (h). There was no evidence of capromorelin accumulation in serum. A dose-dependent increase in the serum capromorelin profile was observed. According to the applicant, although no formal dose-response relation analysis was attempted, visual inspection of the data indicates that serum concentrations of capromorelin increased approximately linear to dosage. The CVMP agrees.

The applicant also stated that since capromorelin is being proposed at a single dosage (2 mg capromorelin tartrate /kg bw) and there is no dose range, detailed knowledge of dose linearity is not essential for the proposed clinical use of capromorelin. This conclusion can be accepted since a fixed dose is proposed.

Regarding serum IGF-1 levels, in the placebo group levels remained at baseline when comparing study day 10 to study day 1. Serum IGF-1 levels increased in all capromorelin groups and on study day 10, each group exhibited a sustained increase of IGF-1 over a 24-hour period. This is consistent with previous studies and supportive of achieving the intended therapeutic effect. Regarding this point, it is noted that in some of the studies conducted, an IGF-1 value <1000 ng/ml on Day 10 was considered as objective. The desired level of IGF-1 (<1000 ng/ml) is based on normal values for IGF-1 levels reported in the literature for cats (Norman and Mooney 2000, Tschuor et al 2012). Normal values for GH are also based on literature reports for GH levels in cats (Norman and Mooney 2000, Peterson 1990).

The study concludes that the effective dose for cats appears to be between 2 mg/kg and 4 mg/kg bw of capromorelin tartrate. It should be noted that the final formulation was not used.

Gender

Influence of gender was specifically addressed in five other studies.

In one study a total of 12 cats were randomly allocated to one of two treatment groups, after an acclimation period of seven days. All cats were treated once daily, in the fasted state, for 10 consecutive days (study days 1 - 10). Group 1 received a target dose of 3 mg/kg bw of an oral formulation containing 30 mg/ml of capromorelin as tartrate salt. Group 2 received a target dose of 4 mg/kg of the same formulation. Male cats were observed with moderate increases of food intake while female cats were observed with higher increases of food intake. Males in groups 1 and 2 were observed with similar food intake while food intake by females in group 1 was considerably higher than females in group 2. In another study, males in groups 1 and 2 showed a similar food intake while females in group 1 had a considerably higher food intake compared to females in group 2.

Although in some of these studies, differences were noted for some of the groups, no clear conclusions could be drawn. The applicant concluded therefore that no biologically relevant differences in pharmacokinetics of capromorelin were detected between male and female cats. This conclusion is accepted.

Effect of feeding (healthy cats)

The effect of feeding on the pharmacokinetics of capromorelin in cats was studied in three studies. The final formulation of the proposed product was used in all three studies.

The first study was a two-period crossover study to determine whether prandial state impacts systemic concentrations of capromorelin attained, following oral administration. Four cats were treated with Eluracat (CF6-OPT-AET-100). Prandial state appeared to have an effect on serum concentrations of capromorelin attained, following administration of a dose of 2 mg/kg bw. Feeding appeared to greatly reduce C_{max} in all cats.

The second study was a partially blinded, randomised, two-period crossover study conducted in healthy, adult cats. It was intended to further evaluate the effect of prandial state on systemic concentrations of capromorelin, following oral administration. Both groups were orally administered a dose of 2 mg/kg bw of capromorelin tartrate. Cats were dosed on two separate days with a 14 day washout period. Notably, all cats maintained their weight during the study.

Sample analysis and, subsequently, data analysis was not performed due to a shipment failure; secondary set of samples lacked adequate volumes to support a full analysis. Samples were deemed compromised to a degree, which warranted the cancellation of bioanalysis, and, subsequently, the data analysis. Consequently, the analysis was not performed, and the study was repeated. No conclusions regarding the pharmacokinetics of capromorelin or IGF-1 could be drawn for this study.

As consequence a third GLP study was conducted, with the same study design, dose and route as for the second study.

Serum samples for capromorelin determination were processed and analysed using a validated assay for capromorelin under GLP conditions in accordance with FDA Guidance for Industry on Bioanalytical Methods Validation, May 2001. Although IGF-1 levels were determined by radioimmunoassay under non-GLP conditions, a validation report, describing specificity, sensitivity, accuracy, and precision was provided to support the assay validity for quantification of IGF-1 in feline serum.

Similar to the second study, all cats maintained their weight during the study.

For IGF-1, all cats presented quantifiable concentration in all the sampling points. For capromorelin, the pharmacokinetic analysis originally presented within the report was revised to reflect the mean values for cats whose parameter estimates could be generated. While this approximation can be accepted i.e. the inclusion only of those profiles with at least three time points with quantifiable serum concentrations, it should be noted that for some PK parameters like AUC_{tlast}, K_{elim} or half-life in the fed state only one cat was included for the calculation.

The results showed that capromorelin $AUCt_{last}$ and C_{max} values in fed group were significantly lower than $AUCt_{last}$ and C_{max} values in fasted cats.

The study concluded that the systemic exposure to capromorelin was higher when capromorelin was administered to cats under the fasted condition as compared to the fed condition. IGF-1 values were not affected by feeding state.

While it is accepted that IGF-1 has an important role in the gain of weight, the food intake seems to be influenced by capromorelin concentrations as stated in previous studies (Pearson correlation coefficient). In addition, it is noted that most of the PK studies were conducted in fasted conditions.

Pharmacokinetics in diseased animals:

The applicant provided a study in which the appetite stimulation response, pharmacokinetic profile and drug accumulation of capromorelin was assessed when administered subcutaneously and intravenously to adult cats with compromised (induced) kidney function after 14 days of treatment (i.e. cats representative of the intended target population of cats with CKD).

Capromorelin and IGF-1 concentrations were quantified. The maximum serum concentration of capromorelin reported following a single intravenous administration was lower than that reported in healthy cats, and approximately the same as in healthy cats following a single subcutaneous administration. No accumulation of capromorelin in serum was observed. However, comparable changes in IGF-1 are reported between healthy cats and those with compromised renal function.

The mean clearance after intravenous administration was 23.8 (±9.2) ml/min/kg bw in renal impaired cats compared to 31.1 (±11.6) ml/min/kg bw in healthy cats. According to the applicant, this suggests

that renal elimination does not play a major role in the clearance of capromorelin and supports the proposal not to adjust the dosage of capromorelin according to the severity of chronic kidney disease. The CVMP agrees to this conclusion.

The study concluded that the formulation was well tolerated in cats with compromised renal function but did not achieve the desired therapeutic effect (increase in food intake or body weight gain) when administered intravenously at a dose of 0.75 mg/kg bw or subcutaneously at 2 mg/kg bw since capromorelin was unable to stimulate appetite.

Other studies: In addition, further pilot studies were conducted in order to test different formulations, doses and routes of administration.

Validation of analytical methods: Studies were conducted using validated methods (compliance with the VICH GL2 (Validation Methodology).

Conclusion: The applicant has submitted a large number of pharmacokinetic studies to characterise the pharmacokinetics of capromorelin in the target species cat after oral administration (healthy cats and cats with renal impairment). Furthermore, the bioavailability and metabolism were studied. The information stated in the SPC is in accordance with these studies.

In addition, the possible influence of the repeated administration, gender, prandial state and disease was addressed in different studies.

Regurgitation/vomiting and hypersalivation were the most frequently reported adverse events in these studies.

Dose justification

The proposed dose of 2 mg capromorelin tartrate/kg bw for the product was established based on the findings of a dose determination study.

The applicant has presented their rationale for the selection of the dose and the daily administration schedule of capromorelin for body weight gain in cats experiencing poor appetite or unintended weight loss resulting from chronic medical conditions, as described below.

Reference is made to the repeated dose study (see section pharmacokinetics) in which the effective dose of capromorelin tartrate for cats appeared to be between 2 mg/kg and 4 mg/kg bw as these doses showed adequate IGF-1 levels and increased appetite and body weight.

Based on this study, 4 different pilot dose determination studies have been performed using doses of 1 – 4 mg capromorelin tartrate / kg bw.

- The first two studies were performed in USA and Germany, respectively, and results were analysed together. The objective was to evaluate the efficacy in the treatment of inappetent and anorexic cats when administered capromorelin at a dose of 1 mg/kg, 2 mg/kg bw or placebo once a day for at least 2 days. The final formulation was not used.
There were no significant differences between any treatment groups in food consumption and a wide variation in response among animals in all treatment groups.
Taking into account the small sample size, differences in days of treatment and the results, it is considered that this study has a limited value for the selection of a suitable posology.

- The third study evaluated the effectiveness of capromorelin on appetite in cats that received either a dose rate of 4 mg/kg body weight or placebo. The final formulation was not used. The study was performed in USA.

According to the results, both groups increased the appetite at study day 6 and study day 13. No statistical differences between treatment groups were noted. In addition, no statistically significant differences were found for any of the secondary variables.

The usefulness of this study is considered limited and no conclusions about the suitability of the dose can be reached.

In this study, two cats treated with capromorelin died: One cat was euthanised after 3 days treatment due to progression of pre-existing renal disease (relationship to test article unlikely). A second cat died with acute collapse after vomiting occurred within 0.5-1 hour after the first dose (relationship possible). Although fructosamine was not measured as part of the post-mortem diagnostics for this cat, no clinical signs (polyuria, polydipsia, weight loss, and increased appetite) attributable to the development of diabetes mellitus were recorded in this cat during clinical observations or veterinary examination. Given the lack of similar findings in the target animal safety study and a lack of evidence to support an association between capromorelin administration and the clinical signs noted, the CVMP did not consider this event associated with the use of capromorelin.

- The pivotal dose finding study investigated the effects of capromorelin on food consumption and weight gain in laboratory cats over a 21 day period, and determined IGF-1 serum levels over 14 and 21 days. The study was performed in the USA.

A total of 32 healthy cats were randomly treated once daily (n=8 cats/group) with placebo, or doses of 1 mg/kg, 2 mg/kg, and 3 mg capromorelin tartrate/kg bw. The final formulation was not used, but is accepted that bioavailability is unlikely to be significantly impacted by the changes observed between the formulations. From days -10 to day 21, food consumption was determined daily and statistical analysis were performed. Body weight was measures weekly.

Most cats in Groups 2, 3 and 4 (treated groups) had an increase in appetite (as measured by consumption). Body weight decreased in the placebo group, and increased in the three treatment groups for study day 8, study day 15 and study day 22.

Overall, there was a positive correlation between percent change in food consumption for study day 1 - 7 and percent change in body weight on study day 8, and for the treatment period study day 8 to 14 and percentage change in body weight on study day 15. There was no correlation for the treatment interval study day 15 to 22; however, it is accepted that the lack of a correlation in the day 15 to 22 treatment interval was probably driven by the increase of the % change in food consumption in the placebo group.

IGF-1 levels increased in all cats treated with capromorelin with a sustained increase on study days 14 and 21, when compared to study day 1. In addition, IGF-1 levels were higher on study day 14 and 21 at the higher dose, 4 mg/kg bw.

Overall, when administered as a 20 mg/ml solution, the most effective dose for capromorelin was shown to be at 2 mg/kg bw based on the changes in body weight and increased feed intake.

However, IGF-1 levels on study days 14 and 21 were higher at the higher dose of capromorelin, that is, 4 mg/kg bw. This may be explained by the IGF-1 mediated negative feedback. This mechanism prevents hyperstimulation of the growth hormone/IGF-1 axis and as long as IGF-1 levels are moderately but continuously elevated, IGF-1 will then negatively feedback on the pituitary gland to inhibit release of GH keeping it within the physiologic range during long-term administration. It is assumed that this sustained increase in IGF-1 doesn't result in a development of tolerance to capromorelin during prolonged duration of treatment because IGF-1 levels remain within the normal physiologic range in cats treated with a dose of 2 mg/kg bw. On the other hand, IGF-1 levels may be raised beyond the physiological range as a result of treatment with a dose of 4 mg/kg bw.

Based on the results of this study, the CVMP agreed that the most effective dose for capromorelin was demonstrated as 2 mg capromorelin tartrate/kg bw.

Target animal tolerance

The applicant provided results of three GLP and one non-GLP target animal safety studies in order to determine the margin of safety of the investigational veterinary medicinal product (IVP). One of the GLP target animal studies was considered pivotal and the other three were considered as supportive studies. However, it is noted that some of these studies have several deviations from the guideline VICH GL 43 on target animal safety for veterinary pharmaceutical products (EMEA/CVMP/VICH/393388/2006).

The pivotal GLP-compliant target animal safety study was performed to determine safety of the test article (capromorelin oral solution 20 mg/ml, final formulation), when administered once daily via oral syringe to domestic short hair healthy cats, 10-11 months old, at 0X (control) and 2 mg/kg bw (1X RTD), 6 mg/kg bw (3X RTD), and 10 mg/kg bw (5X RTD), once daily to animals in the fasted state for 180 consecutive days. Each dose group was formed by 8 animals (4 males, 4 females) randomly assigned stratified by sex.

Two of the four male cats included in the 5x dose group (10.5 mg/kg) were euthanized/ died during the study: One cat was euthanized in extremis due to diabetic ketoacidosis (day 50), but the relationship of this death to the test article was evaluated as 'uncertain'. The other cat's death was attributed to urinary tract blockage (day 23), and was considered to be 'unrelated' to the test article.

Overall, it is concluded that treatment with 1x, 3x and 5x the recommended dose for 180 days was well tolerated. The relevant adverse events related to the test product and seen in this study have been included in the product information.

In addition, three further supportive studies were provided.

The first one, a GLP-study was performed to determine the safety of capromorelin in healthy adult mixed breed cats aged more than 6 months when administered at 5 different doses (0, 9, 15, 30 and 60 mg/kg bw) once daily for 14 consecutive days. Each of the dose groups was formed of 6 animals (3 males and 3 females). The clinical signs that were concluded to be related to treatment were confined to cats in the 30 mg/kg and 60 mg/kg bw groups and consisted of emesis, sporadic salivation and lethargy/depression. Also, sporadic elevations in serum and urine glucose were observed. In addition, increases in mean absolute and relative liver weights in treated groups compared to placebo were observed but not associated to microscopic hepatic abnormalities. In addition, adverse events such as lip smacking and head-shaking were recorded. These findings were scarce and resolved within 5 minutes after administration.
This study had several deviations from the guideline VICH GL 43. It is pointed out that the final formulation was not used. Instead of capromorelin 20 mg/ml oral solution, capromorelin in an oral capsule was used. However, these data can be taken into account as supportive to the additional studies provided to further investigate target animal safety.

The second study was a non GLP study performed to determine the safety of capromorelin administered at 6 mg/kg bw, i.e. 3X the recommended treatment dose (RTD) including a negative control for 91 days. Healthy domestic short hair cats aged between 3.0 and 7.2 years old were randomly assigned to one of the treatment groups, that is placebo (2 males and 2 females) or 3X RTD (4 males and 4 females) and treatments were administered once daily in the fasted state.

In this study, sustained elevated levels of IGF-1 were observed; however, these remained within the normal physiological range. In addition, adverse events such as lip smacking and head-shaking were recorded. These findings were scarce and resolved within 5 minutes after administration.

The last study was performed to evaluate the potential cardiovascular and glycaemic effects of test article, capromorelin oral solution (final formulation), when administered once daily via oral syringe to 8 domestic short hair neutered male cats, aged 9-9.5 months, in the fasted state. All cats received placebo on Days 1 to 3 followed by 1X the proposed dose of the capromorelin oral solution (2 mg/kg bw) on Days 4 to 31.

An increase in serum glucose for several hours after dosing and decreases in heart rate and blood pressure were observed.

The adverse events from all these studies are reflected in section 3.6. of the product information, i.e. hypersalivation at the time of dosing and resolved within a few minutes (very commonly), and vomiting, diarrhoea, dehydration, anaemia, lethargy and skin lesions on the mouth and chin (commonly). Further information regarding changes in serum glucose levels and decreases in heart rate and blood pressure has also been included under section 3.5 of the SPC (symptoms of overdose).

Clinical trials

Dose confirmation

The applicant performed one proof of concept dose-confirmation study in the USA under clinical field conditions using a dose of 0 (placebo group) or 2 mg capromorelin/kg bw administered once daily for 90 days. The study was conducted according to GCP.

A total of 41 cats diagnosed with chronic kidney disease (CKD) according to International Renal Interest Society (IRIS) criteria and a minimum 6 months history of weight loss were enrolled. Information about other underlying acute or chronic health issues is provided.

The per-protocol population 1 (PPP1) consisted of 30 cats, 17 cases in the placebo group and 13 cases in the capromorelin group. The per-protocol population 2 (PPP2) consisted of 33 cats, 18 cases in the placebo group and 15 cases in the capromorelin group.

The PPP1 was a subset of the safety population that included cats without significant protocol deviation and completed the 90 day study. A total of 11 cats were removed from the PPP1. The PPP2 was a subset of the safety population that included cats without a significant protocol deviation. For this population, it was not a requirement to have completed the study or have a body weight measurement at Day 90. A total of 8 cats were removed from the PPP2.

The test article was a flavoured oral solution but not the final formulation intended to be marketed.

The primary endpoint was the percentage gain in body weight. In addition, blood samples were collected for clinical pathology (haematology and clinical chemistry) and serum IGF-1 levels were measured on study days 0, 30, 60 and 90.

The mean (±SEM) body weight, primary effectiveness variable, was analysed in PPP1. For the treated group, statistically significant changes from Day 0 were found for Day 14 ($p = 0.0013$), Day 30 ($p = 0.0007$), Day 60 ($p = 0.0144$) and Day 90 ($p = 0.0434$). No statistically significant changes from Day 0 were found for the control group.

For the success criteria of "maintenance or gain", secondary effectiveness variable for PPP2, there were no statistically significant differences between groups.

As a result, the study confirmed the efficacy of the proposed dose of 2 mg/kg bw in client-owned cats of mixed breeds that were diagnosed with CKD stage II, III or IV (according to IRIS) and a minimum 6 months history of weight loss.

Adverse events reported in more than 10% of the overall population were inappetence, vomiting, increased salivation and diarrhoea/loose stool. There was evidence for a potential relationship to capromorelin treatment only for increased salivation and potentially vomiting. Events like inappetence, diarrhoea/loose stool could be directly related with a loss of weight and were followed in the pivotal field study.

Study protocol, protocol amendments and deviations, certificates of analysis, raw data and statistical report are reported.

Pivotal clinical trial

One pivotal multicentre, randomised, partly blinded, placebo-controlled study of 2 parallel group design, was conducted to evaluate the safety and effectiveness of capromorelin tartrate oral solution (final formulation) for management of weight loss in cats with chronic kidney disease (CKD) under field conditions at a dose of 2 mg/kg bw administered orally once daily for 56±4 days. The study was a GCP-compliant efficacy field study that was conducted according to VICH GL9 in the USA at 23 sites, using the final formulation intended to be marketed.

After enrolment, each case was randomly assigned to the capromorelin or control group in a 2:1 ratio. A total of 254 cases were screened, of which 176 were enrolled and treated. The Safety Population was defined as all cats which were randomised and which received at least one dose of study medication, consisting of 176 cats, with 118 cats in the capromorelin group and 58 cats in the control group.

Cats included in the study were diagnosed with CKD (all IRIS stages) at least 30 days prior to Day 0, and displayed an unintended decrease of body weight on Day 0 (as compared to the highest weight in the medical records within 3 years of Day 0). Exclusion criteria included cats that were pregnant, lactating or intended for breeding, as well as cats that had major diet changes within 30 days before Day 0, or were diagnosed with certain diseases such as diabetes, cancer, hyperthyroidism or other conditions/diseases.

The primary efficacy parameter was Percent Change in body weight from Day 0 to Day 55 (PPP1); secondary efficacy parameters were Percent Change in body weight from Day 0 to Day 15 (PPP2a) and Day 0 to Day 27 (PPP2b), and "Success", i.e. body weight at Day 55 equal to or greater than the body weight at Day 0.

Based upon the results of this study, Eluracat was demonstrated to be superior to placebo for the primary and secondary efficacy parameters at each of the study time points.

Regarding the PPP analysis the difference in the least square (LS) mean percentage 'percent change in body weight' between Eluracat and placebo groups was 3.26%, 4.68% and 6.81% for study days 15, 27 and 55, respectively ($p=0.0002$, $p<0.0001$ and $p<0.0001$). The LS mean percent change in weight for the placebo group was zero at study day 15 but decreased through study days 27 and 55.

In the ITT (Intention To Treat) analysis for the primary endpoint, cats in the capromorelin group had a least square mean (LSM) that was >0% and was significantly higher than the control LSM, with a difference of 5.8% ($P=0.0003$).
Likewise, for the secondary variables capromorelin had a LSM that was >0% and was significantly higher than the control LSM, with a difference of 3.1% ($p<0.0001$) and 4.3% ($p<0.0001$), respectively.

Regarding the body weight "success", cats in the capromorelin group had a significantly higher percentage of success than cats in the control group (83.10% vs 41.46%, $p=0.0010$) for the PP dataset. In addition, the applicant presented the results for the ITT dataset joined to the confidence intervals.

It is accepted that the results of this study indicate that Eluracat is superior to placebo for the primary endpoint. In addition, statistical significant differences were observed in the percentage change between

Eluracat and placebo groups for body weight "success" between intermediate days, that is, days 15 and 27.

In addition, the applicant provided results comparing the intermediate days. These comparisons showed the cats in the capromorelin group had a LSM >0% but were not significantly higher than the control LSM for day 15 to day 27 or for day 27 to day 55. These results can be explained because once the hormone levels are restored to the normal physiological levels it is expected that weight gain will slow due to physiological feedback mechanisms and the fact that GH/IGF-1 are not in the supraphysiologic range.

The clinical trial was carried out for 56±4 days. No information about the post-administration period has been found and therefore the change of weight in cats after the treatment stopped is not known. These data would have been relevant in order to support the necessity to administer the treatment for a long duration.

Besides, safety was assessed through the occurrence of adverse events (AEs), physical examination, serum chemistry, haematology and urinalysis parameters. The most commonly reported adverse events such as hypersalivation, vomiting, anaemia, lethargy, dehydration and diarrhoea have been included in the product information.

It is noted that concomitant treatments administered to the treated group included mirtazapine, vitamin B12, gabapentin and dexamethasone. It was concluded that these concomitant treatments did not impact in the results. Mirtazapine treated cats were excluded from the final assessment and study report.

Study protocol, protocol amendments and deviations, certificates of analysis, raw data and statistical report are provided.

A warning regarding the minimal weight and age of the cats has been included in the section 3.4 and 3.5 of the product information.

According to these results, the applicant concluded that product could be used for body weight gain in cats experiencing poor appetite or unintended weight lost resulting from chronic medical conditions.

Given the mode of action of the active substance, it can be accepted that the effects observed on appetite and body weight would not be isolated to cases of CKD.

The pivotal studies provided predominantly evaluated efficacy in cats with chronic kidney disease (CKD), Nevertheless, it is noted that in the pivotal field trial, 92.4% of cats administered the IVP were also diagnosed with other on-going pre-existing conditions, such as dental disease, heart murmurs, vomiting, hyperthyroidism, arthritis, hypertension, anaemia and gastritis.

Therefore, the CVMP considers it reasonable to conclude that the animals included in the pivotal field trial are suitably representative of a feline population in which chronic disease, manifesting as weight loss, has been diagnosed, thus supporting the indication proposed by the applicant. In addition, the PI reflects the safety findings derived from these studies and also takes into consideration that the product will not be suitable for use in all cases of chronic disease.

Bearing in mind these considerations, the CVMP accepts the indication as proposed by the applicant.

New active substance (NAS) status

The applicant argued that capromorelin mimics the action of the naturally-occurring hormone ghrelin which increases growth hormone levels and leads to increased food intake and body weight in sample populations of cats.

In November 2021, the WHO ATCvet Working Group classified capromorelin according to the mechanism of action as 'QH01AX' - Other anterior pituitary lobe hormones and analogues considering the wide

mechanism of action and taking into account the complex physiological actions of ghrelins in general. The ATCvet code (QH01AX90) was implemented in the ATCvet Index of January 2022.

Overall conclusion on efficacy

This application is for a solution for oral administration, containing 20 mg/ml of capromorelin tartrate (equivalent to 15.4 mg /ml capromorelin). The proposed indication is for body weight gain in cats experiencing poor appetite or unintended weight loss resulting from chronic medical conditions.

Pharmacodynamics:

Capromorelin is an orally active pyrazolinone-piperidine growth hormone secretagogue (GHS) that functions**,** like ghrelin, as a selective ghrelin receptor agonist (GRA). Ghrelin and GHSs activate the growth hormone secretagogue receptor (GHS-R). Increased GH stimulates release of insulin like growth factor 1 (IGF-1) from the liver, which in turn stimulates weight gain.

The mode of action has been sufficiently described. The main clinical effects of capromorelin are an increase appetite and body weight in cats.

Pharmacokinetics:

The pharmacodynamic and pharmacokinetic characteristics of capromorelin are generally well documented and have been satisfactorily evaluated in cats.

The estimated oral bioavailability was estimated as 34% at a dose of 3 mg/kg bw with non-final formulation. 31.1 ml/min/kg and mean apparent volume of distribution is 1.6 l/kg. The mean half-life of capromorelin in serum following intravenous and oral administration is 0.9 and 1.0 hours. The primary elimination route is the faecal route.

Capromorelin showed moderate plasma protein binding in cats with the fraction bound ranging from 56.1% to 64.3%. The results did not indicate concentration dependent binding for the range evaluated in this study.

Dose determination:

The dose of 2 mg/kg bw was established based on a number of dose finding studies using placebo, 1, 2 and 3 mg capromorelin/kg bw, and supported by one dose confirmation study performed under field conditions.

Tolerance:

Capromorelin was well-tolerated in a clinical field study at the recommended dose of 2 mg/kg bw. In the pivotal target animal safety study, capromorelin was well-tolerated in doses up to 5X the recommended dose. The main adverse events are hypersalivation, vomiting, dehydration, diarrhoea, anaemia, lethargy and skin lesions (on the mouth and chin).

Efficacy:

The results from the pivotal clinical field trial showed that the product is effective for body weight gain at the proposed dose of 2 mg/kg bw in cats diagnosed with CKD (all IRIS stages) and various co-morbidities that had an unintended decrease of body weight.

Part 5 – Benefit-risk assessment

Introduction

Eluracat is an oral solution for cats containing 20 mg/ml capromorelin tartrate as the active substance and is presented in bottles containing 10 or 15 ml. Capromorelin is a selective ghrelin receptor agonist, which 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. In humans, IGF-1 remains elevated and acts as a negative feedback regulator of GH. The clinical effects of capromorelin in cats are a combination of increased food intake and metabolic changes resulting in weight gain.

The product is intended to result in body weight gain in cats experiencing poor appetite or unintended weight loss resulting from chronic medical conditions.

The dossier has been submitted in line with the requirements for submissions under Article 31 of Regulation (EC) No 726/2004 of 31 March 2004; and in accordance with Article 3(2)a, as the product contains an active substance, which was not authorised in the Community as a veterinary medicinal product prior to the date of entry into force of the Regulation.

Benefit assessment

Direct therapeutic benefit

The benefit of capromorelin is its efficacy in body weight gain in cats diagnosed with poor appetite or unintended decrease of body weight resulting from a chronic medical condition.

The efficacy of a once-daily oral dose of 2 mg capromorelin tartrate / kg bw (i.e., 0.1 ml of Eluracat / kg bw) was demonstrated in a large number of well-designed laboratory and field studies conducted in cats with Chronic Kidney Disease (CKD, all IRIS stages) and various co-morbidities to an acceptable standard.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Administration of Eluracat in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include hypersalivation at the time of dosing (resolved within a few minutes), diarrhoea, vomiting, anaemia, skin lesions (on mouth and chin), dehydration and lethargy.

Risk for the user:

The risk for the user of this veterinary medicinal product is considered acceptable when used according to the SPC recommendations. Appropriate safety advice has been included in the product literature.

Risk for the environment:

Eluracat is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, and environment and to provide advice on how to prevent or reduce these risks.

User safety:

An unacceptable risk for children following accidental oral exposure has been identified. This risk is mitigated by the presentation of the product in child-resistant packaging and inclusion of safety warnings in the SPC. Risk mitigation measures regarding potential hypersensitivity associated with the excipients have also been included.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: "For body weight gain in cats experiencing poor appetite or unintended weight loss resulting from chronic medical conditions."

The product has been shown to be efficacious for these indications, and the CVMP accepted the indications as proposed by the applicant.

Based on the data presented, the overall benefit-risk balance is considered positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Eluracat 20mg/ml oral solution for cats is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.