Date of Approval: October 16, 2020

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-536

Elura™

capromorelin oral solution

Cats

For management of weight loss in cats with chronic kidney disease

Sponsored by:

Elanco US Inc.

Executive Summary

Elura™ (capromorelin oral solution) is approved for the management of weight loss in cats with chronic kidney disease. Elura™ mimics the action of the naturally-occurring hormone ghrelin and increases growth hormone levels, leading to increased food intake and weight gain. Because ghrelin receptors are found in many tissues, the drug may affect numerous body systems, including the central nervous system, gastrointestinal tract, and cardiovascular system, and energy homeostasis.

Proprietary Name	Established Name	Application Type and Number	Sponsor
Elura™	Capromorelin oral solution	New Animal Drug Application (NADA) 141-536	Elanco US Inc.

Safety and Effectiveness

The sponsor conducted a 56-day field effectiveness study comparing Elura™ to a vehicle control in client-owned cats. Female spayed and male neutered cats were enrolled, representing various breeds and a range of weights. Most cats were older, with a mean age of 15 years. All cats had a documented, unintended weight loss of ≥ 5% and a history of chronic kidney disease (CKD). Although enrolled cats were in stable clinical condition, they had a variety of comorbidities, including hyperthyroidism and hypertension that were managed with medications. At the end of the study, cats in the Elura™ group had gained weight while cats in the vehicle control group had lost weight.

The most common adverse reactions were vomiting and hypersalivation. Additional adverse reactions included inappetence, behavioral changes, lethargy, anemia, progression of kidney disease, development of diabetes mellitus, and development of congestive heart failure. Given the progressive nature of CKD, the many preexisting comorbidities in these cats, and the drug's varied systemic effects, many of the observed adverse reactions were expected. More cats in the Elura™ group had a decreased heart rate (≤120 beats per minute) and decreased body temperature (<99.5°F) on at least one study visit compared to cats in the vehicle control group.

The sponsor conducted a 6-month safety study in healthy, intact domestic shorthair cats. The cats were dosed with Elura™ at 0X, 1X, 3X, or 5X the labeled dose of 2 mg/kg once daily for 6 months (180 days). A fed/fasted pharmacokinetic study showed that systemic exposure to capromorelin was higher in fasted cats compared to fed cats; therefore, the cats in the safety study were fasted before dosing.

Elura™ caused weight gain in all treatment groups and increased food intake in the 3X and 5X groups. There were dose-dependent increases in salivation and intermittent vomiting that were more frequent in males. One cat in the 5X group was euthanized on Day 50 due to diabetic ketoacidosis.

The following findings were seen more frequently in cats administered Elura™: increased mean corpuscular volume, increased triglycerides, and soft feces.

The following findings were observed only in cats administered Elura™: decreased lymphocyte, count, decreased hematopoietic cellularity of the bone marrow, focal necrosis of the bone marrow, and mononuclear cell infiltration of the liver.

The following findings were observed as trends in cats administered Elura™, although individual values remained within the reference ranges: decreased mean erythrocyte count, decreased mean hemoglobin concentration, and decreased mean hematocrit.

The sponsor also conducted a 32-day laboratory study in 8 healthy juvenile male neutered cats to provide information on the drug's effects on the cardiovascular system, and blood glucose. Cats had an implantable telemetry device for continuous monitoring of cardiovascular variables and blood glucose. They were administered vehicle control once daily for 3 days followed by the labeled dose of Elura™ (2 mg/kg) once daily for 28 days. Elura™ administration resulted in transient decreases in both heart rate and direct blood pressure (systolic, diastolic, and mean arterial), and transient increases in blood glucose.

Conclusions
Based on the data submitted by the sponsor for the approval of Elura™, FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

NADA 141-536

B. Sponsor

Elanco US Inc.,
2500 Innovation Way,
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Elura™

D. Drug Product Established Name

Capromorelin oral solution

E. Pharmacological Category

Ghrelin receptor agonist

F. Dosage Form

Oral solution

G. Amount of Active Ingredient

20 mg/mL flavored oral solution

H. How Supplied

15 mL bottle with an oral dosing syringe

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

2 mg/kg once daily

K. Route of Administration

Oral

L. Species/Class

Cats

M. Indication

For management of weight loss in cats with chronic kidney disease.

II. EFFECTIVENESS

The effectiveness of Elura™ (capromorelin oral solution) for the management of weight loss in cats with chronic kidney disease (CKD) was demonstrated in a field effectiveness study in client-owned cats (Study No. AT002-FCL-16-004). The most common adverse reactions were vomiting and hypersalivation.

A. Dosage Characterization

Laboratory Dose Selection Studies
Two studies were conducted in healthy laboratory cats to investigate the effectiveness of capromorelin (non-final formulation) to stimulate food intake and weight gain. In one study, 30 cats were administered capromorelin oral solution at a dose of 0, 1, 2, 3, or 4 mg/kg once daily for 10 days. In the second study, 32 cats were administered capromorelin oral solution at a dose of 0, 1, 2, or 3 mg/kg once daily for 21 days. Food consumption and body weight were measured in both studies for evaluation of effectiveness. Cats administered capromorelin had an increased appetite and gained weight compared to control cats. Based on the results of the studies, a dose of 2 mg/kg was chosen to further evaluate for weight gain in cats.

While activation of the ghrelin receptor has many effects, stimulation of growth hormone (GH) release, which in turn stimulates release of insulin-like growth factor 1 (IGF-1), can be used to evaluate bioactivity of one ghrelin-regulated pathway. Thus, serum IGF-1 was used as a pharmacodynamic endpoint for evaluating the bioactivity of capromorelin. During the 10 day study, serum IGF-1 levels were measured for each cat at 0, 0.5, 1, 1.5, 2, 4, and 8 hours post-dose on Day 1 and Day 10. During the 21 day study, serum IGF-1 levels were collected from each cat at 0 and 8 hours post-dose on Days 1, 14, and 21. In both studies, all capromorelin groups exhibited a numerically larger increase of IGF-1 after dose administration when compared to the control group. On the last day of both studies (Day 10 and Day 21 respectively), the pre-dose values for IGF-1 were increased in the capromorelin groups compared to the pre-dose baseline values on the first day of the study.

Pilot Field Study
This was a multicenter, prospective, randomized, masked, vehicle-controlled pilot field study to evaluate capromorelin (non-final formulation) for management of weight loss in cats with CKD. Forty-one client-owned cats presenting with a history of CKD and a history of weight loss were enrolled and administered capromorelin oral solution (20 cats) at a dose of 2 mg/kg or a vehicle control (21 cats) orally once daily for 90 days. Cats administered capromorelin gained weight compared to control cats. Hypersalivation was reported more commonly in the capromorelin-treated cats as compared to the control cats. Serum IGF-1 was increased in the capromorelin group on Days 30, 60 and 90 when compared to the study start baseline values. Based on the results of the study, a dose of 2 mg/kg was chosen for evaluation in the clinical field study to confirm the effectiveness of Elura™ for the management of weight loss in cats with CKD.

B. Substantial Evidence

Title: Pivotal Clinical Field Study to Evaluate the Safety and Effectiveness of Capromorelin on Weight Management in Cats with Chronic Kidney Disease (Study No. AT002-FCL-16-004)

Study Dates: December 2016-December 2019

Study Locations: Twenty veterinary clinics from the following locations participated in this study.

Fort Collins, Colorado	Liverpool, New York
Bristol, Connecticut	Getzville, New York
Altamonte Springs, Florida	Mechanicsburg, Pennsylvania
Duluth, Georgia	Quakertown, Pennsylvania
Dixon, Illinois	Harrisburg, Pennsylvania
Chicago, Illinois	Fort Washington, Pennsylvania
Franklin, Indiana	Downingtown, Pennsylvania
Uxbridge, Massachusetts	Dallas, Texas
Grand Rapids, Michigan	Mercer Island, Washington
Liberty, Missouri	Madison, Wisconsin

Study Design: This was a multicenter, prospective, masked, randomized, vehicle-controlled field study.

Objective: To evaluate the safety and effectiveness of Elura™ for management of weight loss in cats with chronic kidney disease under field conditions. The study was conducted in accordance with Good Clinical Practice.

Study Animals: The study enrolled 176 client-owned cats (96 female, 80 male) of various breeds, 4.4 - 22.1 years old, and weighing 1.81 - 6.76 kg (3.98 - 14.87 lbs.), with ≥5% unintended weight loss and a history of CKD. CKD stage was determined for each cat based on serum creatinine levels according to the International Renal Interest Society (IRIS) 2015 guidelines. At enrollment, 11.4% of the cats were in Stage 1 CKD, 66.5% were in Stage 2, 21.0% were in Stage 3, and 1.1% were in Stage 4. Cats enrolled in the study had a variety of comorbid conditions including: dental disease (88.1%), moderate or severe muscle loss (43.2%), heart murmur (28.4%), history of vomiting and gastrointestinal disease (28.4%), hyperthyroidism (13.6%), and hypertension (9.7%). Cats diagnosed with hyperthyroidism were receiving methimazole and cats with hypertension were receiving amlodipine and/or enalapril prior to enrollment in the study.

Experimental Design: The cats were randomized to receive EluraTM or a vehicle control at a 2:1 ratio (118 in the Elura™ group and 58 in the vehicle control group).

Table II.1. Treatment Groups

Treatment Group	Dose	Number of Cats [a]
Elura™	2 mg/kg (0.1mL/kg) orally once daily	118
Vehicle control [b]	0.1 mL/kg orally once daily	58

[a] Cats that received at least one dose of Elura™ or vehicle control were included in the safety analysis.
[b] The control was the solution without capromorelin (vehicle control).

Inclusion: Cats of any age and breed with a diagnosis of IRIS Stage 1-4 CKD at least 30 days prior to Day 0; documented unintended decrease of ≥5% body weight on Day 0 compared to the highest weight in the previous 3 years of medical records; with stable clinical condition and treatment regimen; and signed owner consent.

Exclusion: Pregnant, lactating, or intended for breeding; major diet change within 30 days of Day 0; dental disease severe enough to impair food intake; uncontrolled hyperthyroidism; uncontrolled inflammatory bowel disease; congestive heart failure; neoplasia; diabetes; receiving prohibited medications including appetite stimulants; participated in any other clinical trial within 90 days preceding Day 0 or a clinical trial for a weight management treatment at any time; in crisis, moribund state, and/or potentially too sick to survive the 56-day study; or owned by an employee of the veterinary hospital.

Drug Administration: The first dose was administered by the owner in the veterinary clinic. Cats were administered Elura™ at 2 mg/kg or a matched volume of vehicle control once daily by mouth for 56 days. The dose volume remained the same throughout study and the owner administered the solution directly into the cat's mouth with the dosing syringe. The owners were instructed to maintain their cat's normal feeding schedule and if a meal was routinely offered, to offer the meal approximately 30 minutes after dose administration. If the cat vomited within 15 minutes of dosing, or if only a partial dose was administered, the owner was instructed to attempt to re-dose the cat.

Measurements and Observations: Body condition score, muscle condition score, total T4, and fecal examination were obtained only at the screening visit. Body weight, physical examination, hematology, serum chemistry, urinalysis, and diet history were obtained on Day 0, 15±2, 27±3, and 55±4 study visits. Owners were called on Day 6±2 and 41±2 for a health status update on the cat. The owner confirmed dosing compliance at study visits and during phone calls. Administration of parenteral fluids was not permitted within approximately 12 hours prior to a scheduled study visit. It was preferred that cats were weighed with an empty bladder. At weighing, bladder fullness (full, empty, or could not be palpated) was assessed and documented along with the cat's body weight. Body weights were collected on a scale that was calibrated by a professional vendor within 60 days of the first cat enrollment at each site. Scales were recalibrated at least every 6 months for the duration of the study. Safety was monitored during

the study by clinical observations, clinical pathology, physical examinations, and documentation of adverse events.

Statistical Methods: The effectiveness analyses were conducted on per protocol populations comprised of cats with body weights recorded at Day 0 and the necessary subsequent study visits and without major protocol deviations.

Percent change in body weight from Day 0 to Day 55 was the primary effectiveness variable. Percent change in body weight from Day 0 to Day 15 and from Day 0 to Day 27 were secondary variables. The treatment effect was evaluated using analysis of variance modeling with treatment as a fixed effect and site and treatment by site interaction as random effects. The least squares means of the percent change in body weight and standard error were reported by treatment group.

Weight was also evaluated as a binary outcome variable (success/failure). Success was defined as weight gain or no weight loss from Day 0 to Day 55. Failure was defined as weight loss from Day 0 to Day 55.

Results: The primary effectiveness variable was evaluated for 112 cats (71 Elura™ and 41 vehicle control cats). There was a statistically significant difference for the percent change in body weight from Day 0 to Day 55 ($p<0.0001$). The least squares mean percent change in body weight was +5.2% for the Elura™ group and -1.6% for the vehicle control group.

Table II.2 Primary Effectiveness Variable Evaluation of Percent Weight Change at Day 55

Treatment Group	**Number of Cats**	**LSM Percent Change (SE) from Day 0 to Day 55[a]**	**Difference (Elura™- Vehicle Control)**	**p-value**
Elura™	71	+5.2% (0.8)	+6.8%	<0.0001
Vehicle control	41	-1.6% (1.0)	n/a	n/a

[a] LSM=least squares mean; SE=standard error

The evaluation of weight change at the Day 15 and Day 27 visit demonstrated weight gain for the Elura™ group on both Day 15 and Day 27. The vehicle control group had lost weight by Day 27.

Table II.3 Secondary Effectiveness Evaluation of Percent Weight Change at Day 15 and Day 27

Treatment Group	Number of Cats at Day 15[b]	LSM Percent Change (SE) from Day 0 to Day 15[a]	Number of Cats at Day 27[b]	LSM Percent Change (SE) from Day 0 to Day 27
Elura™	83	+3.3% (0.4)	78	+3.8% (0.6)
Vehicle control	42	+0.0% (0.5)	41	-0.9% (0.7)

[a] LSM=least squares mean; SE=standard error
[b] The number of cats reflects cats withdrawn during the course of the study

When the weight change was assessed as a binary variable (success/failure), the Elura™ group had 83.1% cats considered a success and the vehicle control group had 41.5% cats considered a success.

Physical Examination: Decreased body temperature (<99.5°Fahrenheit, range was 93.2-99.4°F) was documented on at least one study visit for 16/118 (13.6%) cats in the Elura™ group and 6/58 (10.3%) cats in the vehicle control group. Decreased heart rate (≤ 120 beats per minute) was documented during a study visit for 3 cats (2.5%) in the Elura™ group and 0 cats in the vehicle control group.

Concomitant Treatments: Medications which cats were receiving prior to enrollment were continued throughout the study. The most common treatments administered during the study were (in decreasing frequency): parenteral fluids, methimazole, amlodipine, antibiotics, laxatives, antiparasitics, and antiemetics.

Adverse Reactions: Safety was evaluated in 174 cats (118 Elura™, 58 vehicle control) that received at least one dose of study drug.

Table II.4 Adverse Reactions in the Field Effectiveness Study

Adverse Reaction	Elura™ (n=118)	Vehicle Control (n=58)
Vomiting	35 (29.6%)	13 (22.4%)
Hypersalivation	25 (21.2%)	0 (0%)
Inappetence	22 (18.6%)	7 (12.0%)
Behavior change [a]	17 (14.4%)	3 (5.2%)
Lethargy	16 (13.6%)	6 (10.3%)
Anemia	11 (9.3%)	1 (1.7%)
Dehydration	11 (9.3%)	2 (3.4%)
Stage of CKD Increased [b]	10 (8.5%)	3 (5.2%)

Adverse Reaction	**Elura™ (n=118)**	**Vehicle Control (n=58)**
Diarrhea	9 (7.6%)	2 (3.4%)
Urinary Tract Infection	8 (6.8%)	2 (3.4%)
Hyperglycemia [c]	8 (6.8%)	2 (3.4%)
Upper Respiratory Infection	7 (5.9%)	1 (1.7%)
Hypercalcemia	7 (5.9%)	0 (0.0%)
Facial Skin Lesion	6 (5.1%)	3 (5.2%)
Hyperkalemia	5 (4.2%)	0 (0.0%)
Ataxia	4 (3.4%)	0 (0.0%)
Diabetes Mellitus	1 (0.8%)	0 (0.0%)
Congestive Heart Failure	1 (0.8%)	0 (0.0%)

Note: If an animal experienced the same event more than once, only the first occurrence was tabulated.
[a] Behavior change included hiding from the owner (8 Elura™, 1 vehicle control); owner reported difficulty administering medication (7 Elura™, 1 vehicle control); and redirected aggression to another household cat (2 Elura™, 1 vehicle control).
[b] Two Elura™ and 1 vehicle control cat increased by 2 CKD stages; 8 Elura™ and 2 vehicle control cats increased 1 CKD stage. It could not be determined if the progressive renal disease was the natural course of the pre-existing disease or treatment related.
[c] Hyperglycemia is defined as >175 mg/dL. Other than the one cat that developed diabetes mellitus, blood glucose did not exceed 283 mg/dL for any cat during the study.

Hypersalivation was generally associated with dosing and resolved within a few minutes.

Nine cats (8 Elura™ and 1 vehicle control) either died or were euthanized during or shortly after the study. Six cats in the Elura™ group were euthanized or died from decompensated CKD. One Elura™ cat was euthanized after withdrawal on Day 33 for declining quality of life and recent identification of a new mass along the right ribcage. One cat in the Elura™ group acutely declined and was euthanized for findings of nodules in both kidneys and diagnosis of sarcoma via aspirate with cytology. The cat in the vehicle control group was euthanized for acute onset of right hindlimb paresis and suspected embolic event.

Three cats (2 Elura™ and 1 vehicle control) had reports of neoplasia discovered during the study. The cat with sarcoma in the kidneys is described above. The other cat in the Elura™ group developed an unspecified soft tissue sarcoma and was euthanized after the study ended. The vehicle control cat developed mammary adenocarcinoma and completed the study.

Conclusion: Elura™ was effective and was determined to have an adequate safety profile for managing weight loss in cats with CKD when administered at a dose of 2 mg/kg orally once daily. Elura™ mimics the action of the naturally-occurring hormone ghrelin and increases growth hormone. The ghrelin receptor is found in many tissues and therefore Elura™ may have effects on the central nervous system, gastrointestinal tract, cardiovascular system, and energy homeostasis. The most common adverse reactions were vomiting and hypersalivation.

III. TARGET ANIMAL SAFETY

The safety of Elura™ (capromorelin oral solution) administered to cats was demonstrated in a 6-month laboratory study (Study No. AT002-FTX-16-002). Eight cats in each group were administered water (0X; placebo control) or Elura™ at 2.1 mg/kg (1X), 6.3 mg/kg (3X), or 10.5 mg/kg (5X) orally once daily. Administration of Elura™ resulted in increased body weight (all treated groups) and increased food consumption (6.3 and 10.5 mg/kg groups); these changes are expected because capromorelin stimulates weight gain and increased food consumption. One cat in the highest dose group (10.5 mg/kg) developed diabetic ketoacidosis and was euthanized on Day 50. Salivation and intermittent vomiting were observed in both the placebo and treated groups, more frequently in males, and increased in a dose-dependent manner. The following were observed more frequently in cats in groups administered Elura™: increased mean corpuscular volume (MCV), increased triglycerides, and soft feces. The following were observed only in cats in groups administered Elura™: decreased lymphocyte count, decreased hematopoietic cellularity of the bone marrow, focal necrosis of the bone marrow, and mononuclear cell infiltration of the liver. The following changes were observed as trends in groups administered Elura™, although individual values remained within the reference intervals: decreased mean erythrocyte counts, mean hemoglobin concentrations, and mean hematocrits. This study supports the safety of Elura™ when administered to cats at a dose of 2.0 mg/kg orally once daily for the management of weight loss in cats with chronic kidney disease.

A fed/fasted pharmacokinetic study (Study No. AT002-FPK-17-011) demonstrated that systemic exposure to capromorelin is higher in fasted cats compared to fed cats. The laboratory safety study was conducted in fasted cats.

A 32-day laboratory study provided information on the cardiovascular and glycemic effects of Elura™ in 8 healthy juvenile male cats. Cats had an implantable telemetry device for continuous monitoring of cardiovascular variables and blood glucose. Elura™ administration resulted in transient decreases in heart rate, transient decreases in direct blood pressure (systolic, diastolic and mean arterial), transient increases in blood glucose, and increases in serum IGF-1.

A. Margin of Safety Laboratory Study

Title: "AT-002: 180 Day Pivotal Target Animal Safety Study in Cats" (Study No. AT002-FTX-16-002)

Study Date: November 2016 to July 2018

Study Location: Mattawan, MI

Study Design:

Objective: The objective of this study was to evaluate the systemic safety of Elura™ at 1X, 3X, and 5X the highest clinical dose per cat when administered orally once a day.

Study Animals: Thirty-two domestic intact short-haired cats (16 males, 16 females), aged approximately 11 months and weighing 2.6-5.5 kg at first dose administration, determined to be healthy based on physical examination, clinical pathology, and fecal parasitology. Cats were individually housed during the study.

Experimental Design: Cats were randomized and stratified by gender to receive either placebo control (water) or Elura™. The study was a 6-month masked laboratory safety study conducted in accordance with the Good Laboratory Practice (GLP) regulations.

Drug Administration: Cats were administered either Elura™ or placebo control (water) once a day orally via a 1 mL syringe for 180 days. The actual dose administered to each cat was calculated and adjusted based on the most recent body weight of each cat. Cats were fasted for 8 to 10 hours prior to dosing and cats were fed 4 hours after dose administration. During hours cats were allowed food, the food was not limited in quantity. If the cat vomited within 30 minutes of dosing, the dose was administered again.

Table III.1 Six-month Target Animal Safety Study for Cats administered Elura™ (20 mg/mL oral solution):

Dosage Group	Dose (mg/kg/day)	Number of Cats (Males/Females)	Dose Volume (mL/kg)
0X	Tap Water	4M, 4F	0.525
1X	2.1 mg/kg	4M, 4F	0.105
3X	6.3 mg/kg	4M, 4F	0.315
5X	10.5 mg/kg	4M, 4F	0.525

Measurements and Observations: The cats were evaluated twice a day for morbidity, mortality, injury and availability of food and water, and once a day for detailed clinical observations and food consumption measurement. The cats were evaluated by physical examination at acclimation and Days 15, 30, 60, 90, 120, 180; body weights weekly; and complete blood count (CBC), clinical chemistry, coagulation profile, and urinalysis at acclimation and on Days 30, 59, 90, 120, and 180. Fructosamine was collected on Days 59, 90, 120, and 180. At the conclusion of the study, cats were euthanized and necropsied for pathology and histopathology.

Statistical Methods: Statistical comparisons were performed for each treatment group compared to the placebo control group.

In the model analyses, the main effect treatments and two-way interactions with treatment were tested at the 10% significance level. Three-way interactions were tested at the 5% significance level.

Endpoints measured multiple times post-treatment for which there was a pre-treatment measurement (body weight, food consumption, hematology, serum chemistry, coagulation and urinalysis) were analyzed using repeated measures analysis of covariance with 'treatment', 'time', and 'sex'; the two-way interactions 'treatment by time', 'treatment by sex', and 'sex by time'; the three-way interaction 'treatment by time by sex' and a covariate all as fixed effects. The pre-treatment value closest to dosing was used as the covariate.

Endpoints measured multiple times post-treatment that did not include a pre-treatment measurement (fructosamine) were analyzed using repeated measures analysis of variance with 'treatment', 'time', and 'sex'; the two-way interactions 'treatment by time', 'treatment by sex', and 'sex by time'; and the three-way interaction 'treatment by time by sex' as fixed effects. Endpoints measured once post-treatment (organ weights) were analyzed using analysis of variance with 'treatment', 'sex', and 'treatment by sex' as fixed effects.

Results:

Mortality and Morbidity: There were two unscheduled deaths during the study.

One male in the 10.5 mg/kg group died due to complications associated with urethral obstruction on Day 23. Due to additional findings of high urine specific gravity, high urine pH, proteinuria, and crystalluria in other cats in all groups, including pre-study, a diet change was instituted on Study Day 52 for all the cats. Cats were transitioned from Lab Diet #5007 to Purina Pro Plan UR Urinary® St/Ox® dry feline diet.

One male in the 10.5 mg/kg group was euthanized due to clinical decline associated with diabetic ketoacidosis. This cat had hyperglycemia (serum glucose 415 mg/dL, normal range 52-127 mg/dL) with glucosuria (≥1000 mg/dL) and ketonuria (15 mg/dL) on Day 30. Decreased activity, soft feces, thin body condition, and increased urination were noted in the following weeks, with lateral recumbency reported on Day 49. Clinical pathology findings were consistent with diabetic ketoacidosis and included hyperglycemia (547 mg/dL), glucosuria (≥1000 mg/dL), and ketonuria (80 mg/dL). The cat was euthanized on Day 50 when his clinical condition deteriorated further. Histopathology revealed vacuolation of the pancreatic islets, hepatocytes and renal tubules, consistent with diabetes mellitus.

Clinical Observations and Examinations: Salivation and intermittent vomiting were seen in all groups, more frequently in males, and increased in a dose-dependent manner. Instances of soft feces were reported more often in the 6.3 and 10.5 mg/kg groups.

Body Weight: Body weights in cats administered Elura™ were significantly different and numerically higher compared to the placebo control cats (overall treatment effect p-value=0.0047 with p-value=0.0035, 0.0099 and 0.0008, in the 2.1 mg/kg, 6.3 mg/kg and 10.5 mg/kg Elura™ groups respectively).

Food Consumption: Food consumption in cats administered 6.3 mg/kg and 10.5 mg/kg Elura™ was significantly different and numerically higher compared to the placebo control cats (overall treatment effect p-value=0.01 with p-value=0.0651 and p=0.0022, in the 6.3 mg/kg and 10.5 mg/kg Elura™ groups respectively).

Clinical Pathology: The following changes were outside the reference range and were observed on one or more study days: Decreased lymphocyte count was only observed in the groups administered Elura™ (3 cats in the 2.1 mg/kg group, 3 cats in the 6.3 mg/kg group, and 1 cat in the 10.5 mg/kg group; the lowest value reported was 1250 lymphocytes/µL). Increased mean corpuscular volume (MCV) was observed more frequently in the groups administered Elura™ (1 cat in the placebo group, 2 cats in the 2.1 mg/kg group, 1 cat in the 6.3 mg/kg group, and 2 cats in the 10.5 mg/kg group; the highest value reported was 49.4 fL). Increased triglycerides occurred more frequently in the groups administered Elura™ than in the placebo control group. Elevated serum glucose occurred in one male cat in the 10.5 mg/kg group as described above. Elevated serum glucose in the absence of other clinical pathology changes were reported for one female in the placebo control group on Day 59 (157 mg/dL, normal range 60-154 mg/dL) and Day 181 (162 mg/dL) and one female in the 2.1 mg/kg group on Day 181 (187 mg/dL). The following changes were observed as trends in groups administered Elura™, although individual values remained within the reference intervals: decreased mean erythrocyte counts, mean hemoglobin concentrations, and mean hematocrits in males (6.3 and 10.5 mg/kg groups) and females (all Elura™ groups).

Organ Pathology/Histopathology: Histopathology findings included decreased hematopoietic cellularity in the bone marrow for the 2 male cats in the 10.5 mg/kg group who died or were euthanized during the study; focal necrosis of the bone marrow at one site for 1 female cat in the 10.5 mg/kg group; and mononuclear cell infiltration in the liver for 4 cats in the 2.1 mg/kg group, 4 cats in the 6.3 mg/kg group, and 3 cats in the 10.5 mg/kg group. There were no clinically relevant effects of Elura™ administration on organ weights.

Conclusions: This study demonstrated an acceptable margin of safety when Elura™ was administered at 2.1, 6.3, or 10.5 mg/kg orally once daily for six months. One male cat in the 10.5 mg/kg group was euthanized due to diabetic ketoacidosis. Administration of Elura™ resulted in increased body weight (all treated groups) and increased food consumption (6.3 and 10.5 mg/kg groups). There were dose-dependent increases in salivation and intermittent vomiting that was more frequent in males. The following were observed more frequently in groups administered Elura™: increased mean corpuscular volume (MCV), increased triglycerides, and soft feces. The following were observed only in groups administered Elura™: decreased lymphocyte count, decreased hematopoietic cellularity of the bone marrow, focal necrosis of the bone marrow, and mononuclear cell infiltration of the liver. The following changes were observed as trends in groups administered Elura™, although individual values

remained within the reference intervals: decreased mean erythrocyte counts, mean hemoglobin concentrations, and mean hematocrits.

B. Pharmacokinetic Study

Title: Pharmacokinetics of Capromorelin (AT-002) Following Oral Administration to Cats in the Fed and Fasted State (Study No. AT002-FPK-17-011).

Type of Study: Laboratory study conducted in accordance with Good Laboratory Practices (GLP)

Study Dates: November 2017 to August 2018

Study Location: Stouffville, Ontario, Canada

Study Design:

Objective: To compare the pharmacokinetics of capromorelin after oral administration of 2 mg/kg Elura™ to healthy cats in the fed and fasted state using a crossover design.

Study Animals: Twelve domestic short-haired cats (4 males, 8 females), aged 1.6-3.1 years and weighing 3.7-4.9 kg at first dose administration.

Experimental Design: The cats were randomly assigned to one of two groups. All cats were fasted for at least 8 hours overnight. One group was then given a meal of canned food within 30 minutes of dosing, while the other group remained fasted. Food was offered to all cats 4 hours after dosing. A 14-day washout occurred between the two dosing days.

Table III.2 Study Design and Prandial State

Group	Period 1 (Dosed on Day 0)	Period 2 (Dosed on Day 14)
1	Fasted	Fed
2	Fed	Fasted

Drug Administration: All cats were administered 2 mg/kg (0.1 mL/kg) Elura™ by mouth using a 1-mL syringe. One dose was administered for each period.

Pharmacokinetic Assessments: Blood samples were collected prior to dosing (pre-feeding) and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dosing for determination of serum capromorelin concentrations. Blood samples were collected prior to dosing (pre-feeding) and at 8, 12, and 24 hours post-dosing for determination of serum IGF-1 concentrations. Serum concentrations of capromorelin were measured using a liquid chromatography with mass spectrometry detection method and serum IGF-1 concentrations were measured using a radioimmunoassay.

Results: The maximum serum concentration (C_{max}) and the area under the curve from the time of dosing to the last quantifiable serum concentration (AUC_{last}) for capromorelin were 55% and 43% lower, respectively, when Elura™ was administered to cats in the fed state, as compared to the fasted state. However, serum IGF-1 values did not appear to be affected by the feeding state.

Table III.3. Mean (SD) Pharmacokinetic Parameters for Serum Capromorelin

Parameter	Fasted	Fed
T_{max} (hr) [a]	0.25 (0.25-1) (n=10)	0.75 (0.5-4) (n=6)
C_{max} (ng/mL)	59 ± 42 (n=10)	28 ± 20 (n=6)
AUC_{last} (ng*hr/mL)	83 ± 42 (n=10)	51 ± 21 (n=6)
$T_{½}$ (hr)	1.12 ± 0.16 (n=8)	NA[b]

Data were analyzed for only 6 and 10 cats in the fed and fasted groups respectively, because there was an insufficient number of quantifiable serum concentrations for analysis.
[a]Median and Range
[b]Insufficient data to calculate mean and standard deviation
T_{max} = time to maximum serum concentration
C_{max} = maximum serum concentration
AUC_{last} = area under the curve from the time of dosing to the last quantifiable serum concentration
$T_{½}$= half-life

Conclusions: The study demonstrated that systemic exposure to capromorelin was higher when Elura™ was administered to cats under the fasted condition as compared to the fed condition. Consequently, the target animal safety study was conducted in the fasted state for maximum drug exposure.

C. Laboratory Cardiovascular and Blood Glucose Safety Study

A 32-day laboratory study provided information on the cardiovascular and glycemic effects of Elura™ in 8 healthy juvenile male neutered cats. Cats had a telemetry device implanted for continuous monitoring of cardiovascular variables and blood glucose. Cats were administered vehicle control once daily for 3 days (Days 1-3) followed by 2 mg/kg Elura™ once daily for 28 days (Days 4-31). Telemetry data were recorded on Days 3 (vehicle dosing day) and 4, 5, 6, 11, 12, 18, 19, 25, 26, 31 (Elura™ dosing days).

Elura™ administration resulted in transient decreases in heart rate and direct blood pressure (systolic, diastolic and mean arterial). The depressive effects of Elura™ on heart rate and blood pressure were reversed when the cats were handled by study personnel. Elura™ administration resulted in transient increases in blood glucose and increased serum IGF-1 values.

On Day 3 (vehicle), heart rates in all cats were greater than 120 bpm. Heart rates began decreasing after dosing with Elura™, reached maximal suppression at approximately 1 hour post-dose (lowest individual value was 83 bpm), and returned to baseline within 4 hours post-dose (see Figure 1). Effects on heart rate were present on all Elura™ treatment days and the magnitude of the effect varied with the individual cat.

On Day 3 (vehicle), systolic blood pressures in all cats was greater than 90 mmHg. Blood pressure began decreasing after dosing with Elura™, reached maximal suppression at approximately 1 hour post-dose (lowest individual value was 72 mmHg systolic), and returned to baseline within 4 hours post-dose (see Figure 1). The effect on blood pressure was greatest following the first dose of Elura™ and decreased in magnitude and frequency, returning to baseline after the ninth day of dosing with Elura™.

On Day 3 (vehicle), the highest individual blood glucose value was 140 mg/dL. Blood glucose increased after administration of Elura™ in 4 cats. One individual cat had a maximum blood glucose of 296 mg/dL recorded 19 hours after the third Elura™ dose, while values in all other cats remained <160 mg/dL at all times after dose administration. The trend in increased blood glucose values after dosing had resolved after the eighth day of Elura™ dosing. There was individual variability in magnitude and duration for glucose measurements.

Serum IGF-1 was measured on Day -3; both pre-dose and 8 hours post-dose on Day 27; and on Day 32, one day after the last Elura™ dose. Group mean serum IGF-1 was increased on Day 32 compared to the Day -3 baseline. On Day 27, group mean serum IGF-1 was increased 8 hours post-dosing compared to pre-dosing on the same day.

The study supports the safe use of Elura™ when administered to cats at a dose of 2 mg/kg orally once daily for the management of weight loss in cats with chronic kidney disease.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Elura™:

"Not for use in humans. Keep this and all medications out of reach of children and pets. Consult a physician in case of accidental ingestion by humans. **For use in cats only.**"

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that Elura™, when used according to the label, is safe and effective for the management of weight loss in cats with chronic kidney disease.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to diagnose and manage chronic kidney disease in cats. Furthermore, professional expertise is required to monitor for and respond to any adverse reactions.

B. Exclusivity

Elura™, as approved, in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of Elura™.

C. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA website.