Managing appetite disorders and weight loss in patients with chronic conditions

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Derived from: "Intake and outcome: When and why to reach for an appetite stimulant," "Evolving the clinical management of chronic inappetence in dogs (and cats)" and "Addressing anorexia: A case-based review," presented at VMX 2021.

Practice implications: In patients with chronic conditions, practicing nutritional management and prescribing appropriate therapeutics can help stimulate appetite in dogs and promote weight management in cats.

Physiology of appetite regulation

The hypothalamus receives messages from 2 neuronal populations that impact food intake in the body:

Anorexigenic inputs

- Activate the satiety center
- Increase energy expenditure

Orexigenic inputs

- Activate the hunger center
- Decrease energy use to conserve resources

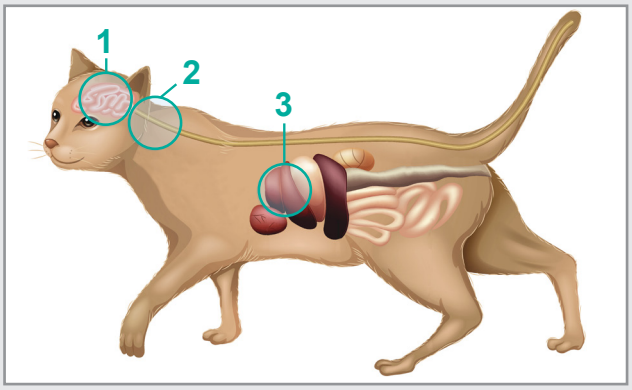
Food intake and weight management

Ghrelin, the "hunger hormone," drives food intake and promotes growth hormone release.

- Has a significant effect on weight and muscle mass
  - Activates orexigenic neurons
  - Growth hormone stimulates the production of insulin-like growth factor 1 (IGF-1)
- Decreases the production of pro-inflammatory cytokines and increases the production of anti-inflammatory cytokines
  - Counters protein degradation, which is associated with decreased muscle mass

Ghrelin mechanism of action

1. Ghrelin binds to receptors in the hypothalamus, to stimulate appetite
2. Ghrelin stimulates the release of GH from the pituitary gland
3. Growth hormones and IGF-1 bind to receptors in the liver to promote weight gain and muscle growth.



Clinical importance of inappetence in dogs

Common sign in dogs with underlying conditions

- Often the first or only sign of a chronic condition in dogs
- Frequently the cause for calls or visits to the vet

Appetite is the key indicator of a pet's quality of life.[1]
Loss of appetite is caused by a disruption of the neuroendocrine systems that regulate appetite.

- Often the first or only sign of illness in dogs
- Key consideration in a client's end-of-life decision
- Associated with higher risk of mortality if unaddressed

Common causes of inappetence		Common consequences of inappetence
• Metabolic complications • Medication side effects • Changes to GI tract	• Inflammation • Anxiety and stress	• Significant weight loss in dogs with chronic conditions • Increased mortality

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Clinical impact of weight loss in patients with chronic conditions

Chronic kidney disease (CKD) in cats	A study of 2460 cats (1230 control; 1230 with CKD) identified risk factors, including[2]: • Thin body condition score (BCS) • Anesthesia within previous year • Appetite loss Probability of disease is influenced by several variables, including weight loss.
Congestive heart failure	In a study of 108 dogs with heart failure, survival differed between dogs of different body weights[3]: • Dogs that gained weight during the study had the longest survival times
Cancer	A study of 270 dogs with lymphoma over 10 years found[4]: • Shorter survival times were identified in patients underweight at diagnosis
Renal disease	In a study of 100 dogs diagnosed with CKD[5]: • Higher BCS at the time of diagnosis was associated with longer survival
Hospitalization	Study of 467 dogs found that food intake was directly correlated to intake and survival[6]: • 93% of patients with voluntary intake were discharged • 38.4% of those with zero intake were discharged

Entyce™ (capromorelin oral solution)

FDA-approved ghrelin receptor agonist for appetite stimulation in dogs.

- Proven to safely and effectively stimulate appetite to help improve food consumption
- Recommended part of early intervention plan to combat inappetence
  - Should be used at first sign of decreased food intake
  - Routinely used for prolonged periods in dogs with chronic conditions*

*The effectiveness of Entyce has not been evaluated beyond 4 days of treatment in the clinical field study.

Elura™ (capromorelin oral solution)

FDA-approved ghrelin receptor agonist for management of weight loss in cats with CKD.

- Was well tolerated in a clinical study of 176 cats, showing a 6.8% difference in weight between Elura and control groups after 56 days of treatment[7]
- Treatment is recommended as soon as unintended weight loss is detected
- Safe and effective for long-term use[7]

Key takeaways

Appetite is a key indicator of a pet's quality of life. Sudden decreased appetite in pets should be a cause for concern by pet owners.

If left unaddressed, decreased appetite may precede weight loss and could eventually lead to decreased survival in patients with chronic conditions.

A combination of early intervention and appropriate therapeutics are key to effectively treating inappetence in dogs and promoting weight management in cats with CKD.

Entyce Indication: Entyce (capromorelin oral solution) is indicated for appetite stimulation in dogs.

Entyce Important Safety Information: For use in dogs only. Do not use in dogs that have a hypersensitivity to capromorelin. Use with caution in dogs with hepatic dysfunction or renal insufficiency. The safe use of Entyce has not been evaluated in breeding, pregnant or lactating dogs. The most common adverse reactions included diarrhea, vomiting, elevated blood urea nitrogen, polydipsia, and hypersalivation.

Elura Indication: Elura is indicated for the management of weight loss in cats with chronic kidney disease.

Elura Important Safety Information: For oral use in cats only. Do not use in cats that have a hypersensitivity to capromorelin, or in cats with hypersomatotropism (acromegaly). Elura may increase serum glucose for several hours after dosing; use in cats with current or historical diabetes mellitus has not been evaluated and may not be appropriate. Use with caution in cats that may have cardiac disease, severe dehydration, or hepatic dysfunction. Elura has not been evaluated in cats younger than 5 months of age, or in breeding, pregnant or lactating cats. The most common adverse reactions included vomiting, hypersalivation, inappetence, behavior change and lethargy.

References: 1. Williams J, et al. *Animals* 2017;7(3):18. **2.** Greene JP, et al. *JAVMA* 2014;244(3):320–327. **3.** Slupe JL, et al. *J Vet Intern Med* 2008;22(3):561–565. **4.** Romano FR, et al. *J Vet Intern Med* 2016;30(4):1179–1186. **5.** Parker VJ, et al. *J Vet Intern Med* 2011;25(6):1306–1311. **6.** Brunetto MA, et al. *J Vet Emerg Crit Care* 2010;20:224–231. **7.** Elura Freedom of Information Summary. NADA 141–536. 2020.

Elanco™

Entyce™
(capromorelin oral solution)

30 mg/mL

For oral use in dogs only

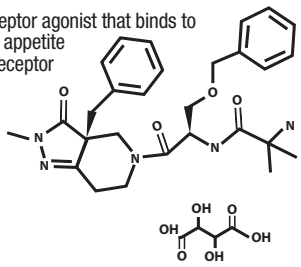
Appetite Stimulant

Caution:

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:

ENTYCE (capromorelin oral solution) is a selective ghrelin receptor agonist that binds to receptors and affects signaling in the hypothalamus to cause appetite stimulation and binds to the growth hormone secretagogue receptor in the pituitary gland to increase growth hormone secretion. The empirical formula is $C_{28}H_{35}N_5O_4 \cdot C_4H_6O_6$ and the molecular weight 655.70.
The chemical name is 2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1R-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartrate.



The chemical structure of capromorelin tartrate is:

Indication:

ENTYCE (capromorelin oral solution) is indicated for appetite stimulation in dogs.

Dosage and Administration:

Administer ENTYCE orally at a dose of 3 mg/kg (1.4 mg/lb) body weight once daily.

To administer ENTYCE, gently shake the bottle, and then withdraw the appropriate amount of solution using the provided syringe.

Rinse syringe between treatment doses.

The effectiveness of ENTYCE has not been evaluated beyond 4 days of treatment in the clinical field study (See Effectiveness).

Contraindications:

ENTYCE should not be used in dogs that have a hypersensitivity to capromorelin.

Warnings:

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 dogs only**

Precautions:

Use with caution in dogs with hepatic dysfunction. ENTYCE is metabolized by CYP3A4 and CYP3A5 enzymes (See Clinical Pharmacology).

Use with caution in dogs with renal insufficiency. ENTYCE is excreted approximately 37% in urine and 62% in feces (See Adverse Reactions and Clinical Pharmacology).

The safe use of ENTYCE has not been evaluated in dogs used for breeding or pregnant or lactating bitches.

Adverse Reactions:

In a controlled field study, 244 dogs were evaluated for safety when administered either ENTYCE or a vehicle control (solution minus capromorelin) at a dose of 3 mg/kg once daily for 4 days. Enrolled dogs had a reduced or absent appetite for a minimum of 2 days prior to day 0 and had various medical conditions: arthritis (40); gastrointestinal disease (24); allergy (22); dental disease (22); cardiovascular disease (16); renal disease (13); and others. Some dogs may have experienced more than one of the adverse reactions during the study.

The following adverse reactions were observed:

Table 1: Adverse Reactions reported in dogs administered ENTYCE oral solution compared to vehicle control

Adverse Reactions	ENTYCE (n = 171) n (%)	Vehicle Control (n = 73) n (%)
GASTROINTESTINAL		
Diarrhea	12 (7.0 %)	5 (6.8 %)
Vomiting	11 (6.4 %)	4 (5.5 %)
Hypersalivation	4 (2.3 %)	0 (0.0 %)
Abdominal discomfort	2 (1.2 %)	0 (0.0 %)
Flatulence	2 (1.2 %)	0 (0.0 %)
Nausea	2 (1.2 %)	0 (0.0 %)
CLINICAL PATHOLOGY		
Elevated blood urea nitrogen	7 (4.1 %)	2 (2.7 %)
Elevated phosphorus	4 (2.3 %)	1 (1.4 %)
Elevated creatinine	1 (0.6 %)	1 (1.4 %)
OTHER		
Polydipsia	7 (4.1 %)	1 (1.4 %)
Lethargy/depression	2 (1.2 %)	0 (0.0 %)

The following adverse reactions were reported in < 1% of dogs administered ENTYCE: hyperactivity, increase fecal volume, increase gut sounds, and polyuria.

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US Inc. at 1-888-545-5973. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

Clinical Pharmacology:

Following oral administration of ENTYCE at a dose of 3 mg/kg to 12 Beagle dogs, absorption of capromorelin was rapid with the maximum concentration (C_{max}) reached within 0.83 hr (T_{max}). After C_{max}, the plasma concentrations declined mono-exponentially with a short terminal half-life ($T_{½}$) of approximately 1.19 hrs. There were no gender differences in capromorelin pharmacokinetics. The exposure (C_{max} and AUC) of capromorelin increased with dose, but the increases were not dose proportional following single and repeat once daily administrations of capromorelin. There was no drug accumulation following repeat oral administration.

Table 2. Plasma PK parameters following oral administration of 3 mg/kg of ENTYCE

Parameter	Mean	SD
T_{max} (hr)	0.83	0.58
C_{max} (ng/mL)	330	143
AUC_t (ng*hr/mL)	655	276
AUC_{inf} (ng*hr/mL)	695	262
$T_{½}$ (hr)	1.19	0.17

The mean absolute oral bioavailability of capromorelin was 44%. The mean total plasma clearance and volume of distribution was 18.9 mL/min/kg and 2.0 L/kg, respectively. Capromorelin was not highly bound (unbound fraction 51%) to plasma protein. The protein binding was concentration-independent over the range of 10 to 1000 ng/mL. *In vitro* (human liver microsomes) and *in vivo* (rats) metabolism studies suggest that capromorelin is metabolized by hepatic enzymes, mainly CYP3A4 and CYP3A5. Therefore, drugs that inhibit CYP3A4 and CYP3A5 activity may affect capromorelin metabolism. Following oral administration of radio-labelled capromorelin to dogs, capromorelin was excreted in urine (37%) and in feces (62%) within 72 hours.

Effectiveness:

Laboratory Effectiveness Study: Twenty four healthy Beagle dogs (6 dogs per sex in each group) with normal appetite were randomized into two groups and dosed daily with ENTYCE (capromorelin oral solution) at 3 mg/kg/day or vehicle control (solution minus capromorelin) to compare food intake over a 4-day period. The dogs were 13 months of age and weighed between 6.5 and 12.5 kg at the time of randomization. Six dogs administered ENTYCE repeatedly exhibited salivation post dosing and two dogs administered vehicle control exhibited salivation only one time on study day 0. Emesis was observed in one dog administered ENTYCE on study day 1. Dogs administered ENTYCE at a dose of 3 mg/kg/day for 4 consecutive days had statistically significantly increased food consumption compared to the vehicle control group ($p < 0.001$).

Clinical Field Study: Effectiveness was evaluated in 177 dogs (121 dogs in the ENTYCE group and 56 dogs in the vehicle control group) in a double-masked, vehicle controlled field study. Dogs with a reduced appetite or no appetite, with various medical conditions, for a minimum of 2 days prior to day 0 were enrolled in the study. The dogs ranged in age from 4 months to 18 years. Dogs were randomized to treatment group and dosed once daily for 4 days with ENTYCE at 3 mg/kg or vehicle control. Dogs were assessed for appetite by owners on day 0 and day 3 ± 1 using an "increased", "no change" or "decreased" scoring system. Dogs were classified as a treatment success if the owner scored their dog's appetite as "increased" on day 3 ± 1. The success rates of the two groups were significantly different ($p = 0.0078$); 68.6% (n = 83) of dogs administered ENTYCE were successes, compared to 44.6% (n = 25) of the dogs in the vehicle control group.

Animal Safety:

In a 12-month laboratory safety study, 32 healthy Beagle dogs (4 dogs per sex per group) approximately 11-12 months of age and weighing 9-13.6 kg were dosed orally with capromorelin in deionized water daily at 0X (placebo), 0.3 (0.13X), 7 (3.07X), and 40 (17.5X) mg/kg/day. Administration of capromorelin was associated with increased salivation and reddening/swollen paws, increased liver weights and hepatocellular cytoplasmic vacuolation. Treatment related decreases were seen in red blood cell count, hemoglobin and hematocrit in the 40 mg/kg group. Pale skin, pale gums, and decreased red blood cell count, hemoglobin and hematocrit were observed in one dog administered 40 mg/kg/day. Increases were seen in cholesterol, high density lipoproteins, and the liver specific isozyme of serum alkaline phosphatase in the 40 mg/kg group. Growth hormone and insulin-like growth factor 1 plasma levels were increased in all groups administered capromorelin. There were no effects noted on gross necropsy. Capromorelin levels were similar in plasma collected on days 90, 181, and 349 indicating no accumulation of drug.

Storage Conditions:

Store at or below 86° F (30° C)

How Supplied:

30 mg/mL flavored solution in 10 mL, 15 mL and 30 mL bottles with measuring syringe

Approved by FDA under NADA # 141-457

Manufactured for:
Elanco US Inc.
Greenfield, IN 46140, USA
Revised: September 2020

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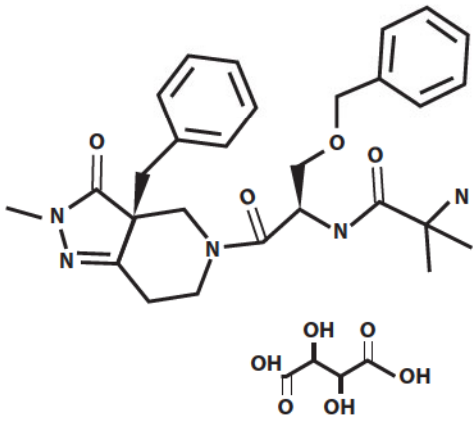
Elura™
(capromorelin oral solution)

20 mg/mL
For oral use in cats only

CAUTION:
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

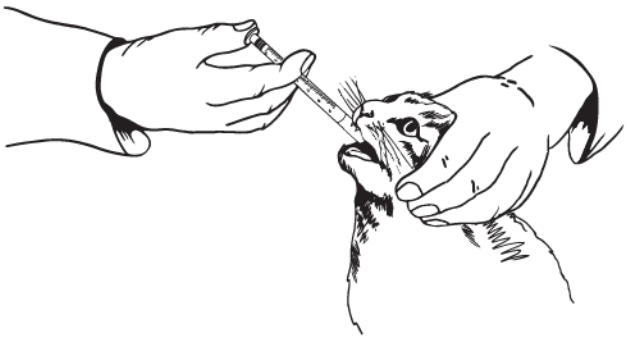
DESCRIPTION:
ELURA (capromorelin oral solution) is a colorless to yellow or orange, clear liquid. Each milliliter of ELURA contains 20 mg of capromorelin tartrate. The empirical formula is $C_{28}H_{35}N_5O_4 \cdot C_4H_6O_6$ and the molecular weight 655.70. The chemical name is 2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-yl)-1R-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartrate. The chemical structure of capromorelin tartrate is:



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

DOSAGE AND ADMINISTRATION:
Administer ELURA orally at a dose of 2 mg/kg (0.9 mg/lb) or 0.1 mL/kg (0.045 mL/lb) body weight once daily.
To administer ELURA:
- Remove the cap, insert the dosing syringe, invert the bottle, withdraw the appropriate amount of solution.
- Return the bottle to the upright position, remove syringe, replace the cap.
- Administer the solution into the cat's mouth.
- Rinse the syringe and plunger with water and leave apart to dry.

If the cat is routinely fed meals, offer food 30 minutes after administering the dose.
If the cat vomits within 15 minutes or only receives a partial dose, then the dose may be re-administered.



CONTRAINDICATIONS:
ELURA should not be used in cats that have a hypersensitivity to capromorelin.

WARNINGS:
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 oral use in cats only.
Do not use in cats with hypersomatotropism (acromegaly).
ELURA may increase serum glucose for several hours after dosing (see Animal Safety and Clinical Pharmacology). Use in cats with current or historical diabetes mellitus has not been evaluated and use may not be appropriate.

PRECAUTIONS:
Use with caution in cats that may have cardiac disease or severe dehydration. ELURA causes transient decreases in heart rate and blood pressure up to 4 hours following dose administration. Some cats may exhibit clinical signs of bradycardia or hypotension following administration of ELURA. (See Adverse Reactions and Animal Safety).
Use with caution in cats with hepatic dysfunction. Capromorelin is metabolized in the liver in humans and dogs and similar metabolism is expected in the cat.
The safe use of ELURA has not been evaluated in cats younger than 5 months old.
The safe use of ELURA has not been evaluated in cats that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS:
Safety was evaluated in a 56-day field effectiveness study in 176 client-owned cats (118 administered ELURA, 58 administered vehicle control) that received at least one dose. Cats enrolled had ≥5% unintended weight loss and a history of chronic kidney disease (CKD). Cats had a mean age of 15 years and 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: dental disease (88.1%), moderate or severe muscle loss (43.2%), heart murmur (28.4%), history of vomiting or underlying gastrointestinal disease (28.4%), hyperthyroidism (13.6%) and hypertension (9.7%).

Table 1: 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 (0.0%)
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%)
Diarrhea	9 (7.6%)	2 (3.4%)
Urinary Tract Infection	8 (6.8%)	2 (3.4%)
Hyperglycemia	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 two CKD stages; 8 ELURA and 2 vehicle control cats increased one CKD stage. It could not be determined if the progressive renal disease was the natural course of the pre-existing disease or treatment related.
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 ELURA cats were euthanized or died from decompensated CKD. One ELURA cat was euthanized after study withdrawal on Day 33 for declining quality of life and recent identification of a new mass. One ELURA cat acutely declined and was euthanized for findings of nodules in both kidneys and diagnosis of sarcoma. The vehicle control cat was euthanized for acute onset of right hindlimb paresis and suspected embolic event. Two additional cats were diagnosed with neoplasia during the study (one ELURA cat with unspecified soft tissue sarcoma and one control cat with mammary adenocarcinoma) but completed the study.
In voluntary post-approval reporting for extra-label use of a capromorelin product for dogs, the following adverse events have been reported in cats (listed in decreasing order of reporting frequency): bradycardia, lethargy, hypersalivation, hypotension, behavior change, and vomiting.
To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US, Inc. at 1-888-545-5973.
For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

INFORMATION FOR CAT OWNERS:
Owners should be advised that ELURA mimics the action of a naturally-occurring hormone called ghrelin. Ghrelin influences many systems in the body. ELURA may also affect these systems. Owners should monitor for changes in: thirst or water intake; lethargy or weakness; digestive issues (vomiting, diarrhea, drooling, decreased appetite); or behaviors.

CLINICAL PHARMACOLOGY:
Mechanism of Action
ELURA is a selective ghrelin receptor agonist. The ghrelin receptor is found in many tissues in various species and may have effects in the central nervous system, gastrointestinal tract, cardiovascular system and energy homeostasis. ELURA binds to 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 can stimulate weight gain. IGF-1 remains elevated during administration of the drug. In humans, IGF-1 elevation may act as a negative feedback regulator of GH, but this is unknown in cats. The clinical effects of ELURA in cats are thought to be due to a combination of increased food intake and metabolic changes resulting in weight gain.
Pharmacokinetics
The pharmacokinetic parameters of capromorelin were evaluated in a cross-over study in 4 male and 8 female laboratory cats receiving a single oral dose of ELURA at 2 mg/kg in the fed or fasted state. Following 8 hours of fasting, half the cats were fed a meal of canned food 30 minutes before dosing and the others continued to be fasted until 4 hours post ELURA administration. 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. Serum concentrations of capromorelin were measured using a liquid chromatography with mass spectrometry detection method. Blood samples were collected prior to dosing (pre-feeding) and at 8, 12, and 24 h post-dosing for determination of serum IGF-1.

Table 2. Mean (Standard Deviation) Pharmacokinetic Parameters for Serum Capromorelin

Parameter	Fasted	Fed
T_{max}[a] (hr)	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 10 and 6 cats in the fasted and fed 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 for $T_{½}$
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
Capromorelin was rapidly absorbed following oral administration of ELURA to fasted cats. The C_{max} and AUC_{last} for capromorelin were 55% and 43% lower, respectively, in the fed state, as compared to the fasted state. Serum IGF-1 values did not appear to be affected by the feeding state.

EFFECTIVENESS:
Effectiveness was demonstrated in a multicenter, prospective, masked, randomized, vehicle-controlled field study. The study enrolled 176 client-owned cats with ≥5% unintended weight loss and a history of chronic kidney disease. The cats enrolled included 96 females and 80 males of various breeds, 4.4 - 22.1 years old with a mean age of 15 years and weighing 1.81 - 6.76 kg. CKD stage was determined based on creatinine at screening according to the International Renal Interest Society (IRIS) 2015 guidelines. All stages were enrolled. Cats were administered ELURA at 2 mg/kg or a matched volume of control once daily by mouth for 56 days. The control was the solution without capromorelin (vehicle control). The primary effectiveness variable was the percent change in body weight from Day 0 to Day 55. Effectiveness was evaluated in 112 cats: 71 cats administered ELURA and 41 cats administered vehicle control. There was a statistically significant difference between the percent change in weight for the ELURA group (+5.2%) compared to the vehicle control group (-1.6%) at Day 55 ($p<0.0001$). Secondary analysis for percent change in weight at Day 15 and Day 27 demonstrated cats in the ELURA group gained weight throughout the study.

Table 3. Least Squares Mean (Standard Error) Percent Change in Weight from Day 0

Study Day	ELURA	Vehicle Control	Difference (ELURA-Vehicle Control)
Day 15	+3.3% (0.4)	0.0% (0.5)	+3.3% (0.6)
Day 27	+3.8% (0.6)	-0.9% (0.7)	+4.7% (0.8)
Day 55[a]	+5.2% (0.8)	-1.6% (1.0)	+6.8% (1.2)

[a] Primary endpoint

ANIMAL SAFETY:
Margin of Safety Laboratory Study
In a 6-month laboratory study, 32 healthy cats (4 cats/sex/group) approximately 11 months of age were dosed orally once daily in the fasted state with placebo control (0.5 mL/kg water) or ELURA at 2.1 mg/kg (1X), 6.3 mg/kg (3X) or 10.5 mg/kg (5X). Two cats died during the study. One male in the 10.5 mg/kg group died due to urethral obstruction on Day 23; this was unrelated to ELURA administration. One male in the 10.5 mg/kg group developed hyperglycemia and glucosuria on Day 30. This cat was euthanized for clinical decline associated with diabetic ketoacidosis on Day 50. Administration of ELURA resulted in increased body weight (all groups) and increased food consumption (6.3 and 10.5 mg/kg groups). Salivation and intermittent vomiting were observed in placebo and all groups administered ELURA, more frequently in males, and increased in the groups administered ELURA in a dose-dependent manner. The following were observed more frequently in cats in the groups administered ELURA: increased mean corpuscular volume (MCV), increased triglycerides, and soft feces. The following were observed only in cats in the 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. There were no clinically relevant treatment-related effects on organ weights.
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 cats. Cats had a telemetry device implant for continuous monitoring of cardiovascular variables and blood glucose. Cats were administered vehicle control once daily for 3 days (Days 1-3) followed by ELURA at 2 mg/kg once daily for 28 days (Days 4-31). ELURA administration resulted in transient decreases in heart rate which began after dosing, reached maximal suppression at approximately 1 hour post-dose (lowest individual value was 83 bpm) and returned to baseline within 4 hours. ELURA resulted in transient decreases in direct blood pressure (systolic, diastolic and mean arterial) which began after dosing, reached maximal suppression at approximately 1 hour post-dose (lowest individual value was 72 mmHg systolic) and returned to baseline within 4 hours. The effects on blood pressure were greatest following the first dose of ELURA and decreased in magnitude and frequency, returning to baseline after the ninth dose. 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 increased blood glucose in 4 cats, with individual variability in magnitude and duration. One cat had a maximum blood glucose of 296 mg/dL recorded 19 hours after the third dose, while values in all other cats remained <160 mg/dL at all times. The effects on glucose resolved after the eighth dose. ELURA administration resulted in increased serum IGF-1, with individual cat variability. 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.

STORAGE CONDITIONS:
Store at or below 86°F (30°C)

HOW SUPPLIED:
20 mg/mL flavored oral solution in a 15 mL bottle with an oral dosing syringe.
Approved by FDA under NADA # 141-536.
Manufactured for: Elanco US Inc, Greenfield, IN 46140 USA
REV. DATE-10/2020

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PMO Approval	Kyle Thorpe Material Owner 02-Aug-2021 13:41:22 GMT+0000

Regulatory Approval	Karen Smith Regulatory 02-Aug-2021 16:40:15 GMT+0000

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