Elura™
(capromorelin oral solution)

Elanco

Elura helps cats with CKD maintain or gain weight to keep them

feline fabulous

PM-US-20-2833

Indication

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

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. See accompanying product label for full prescribing information.

Indication

For the management of weight loss in cats with chronic kidney d

Important Safety Information

For oral use in cats only. Do not use in cats that have a hyperser
cats with hypersomatotropism (acromegaly). ELURA may increa
hours after dosing; use in cats with current or historical diabetes
evaluated and may not be appropriate. Use with caution in cats
disease, severe dehydration, or hepatic dysfunction. ELURA has
younger than 5 months of age, or in breeding, pregnant or lactat
adverse reactions included vomiting, hypersalivation, inappeten
lethargy. See accompanying product label for full prescribing inf

IT'S HARD TO WATCH CATS WITH CKD WASTE AWAY

Chronic kidney disease (CKD) leads to ongoing, progressive weight loss, which is associated with shorter survival[1]

CKD has been reported to affect 80% of older cats and 1–3% of cats overall[1,2]

Weight loss has already started in most cats by the time of diagnosis, and accelerates as disease progresses[1]

Weight loss in cats with CKD is associated with shorter survival[1]

Weight loss may lead pet owners to consider euthanasia[1]

IT'S HARD TO WATCH CATS WITH CKD WASTE AWAY

Chronic kidney disease (CKD) leads to ongoing, progressive weight loss, which is associated with shorter survival[1]

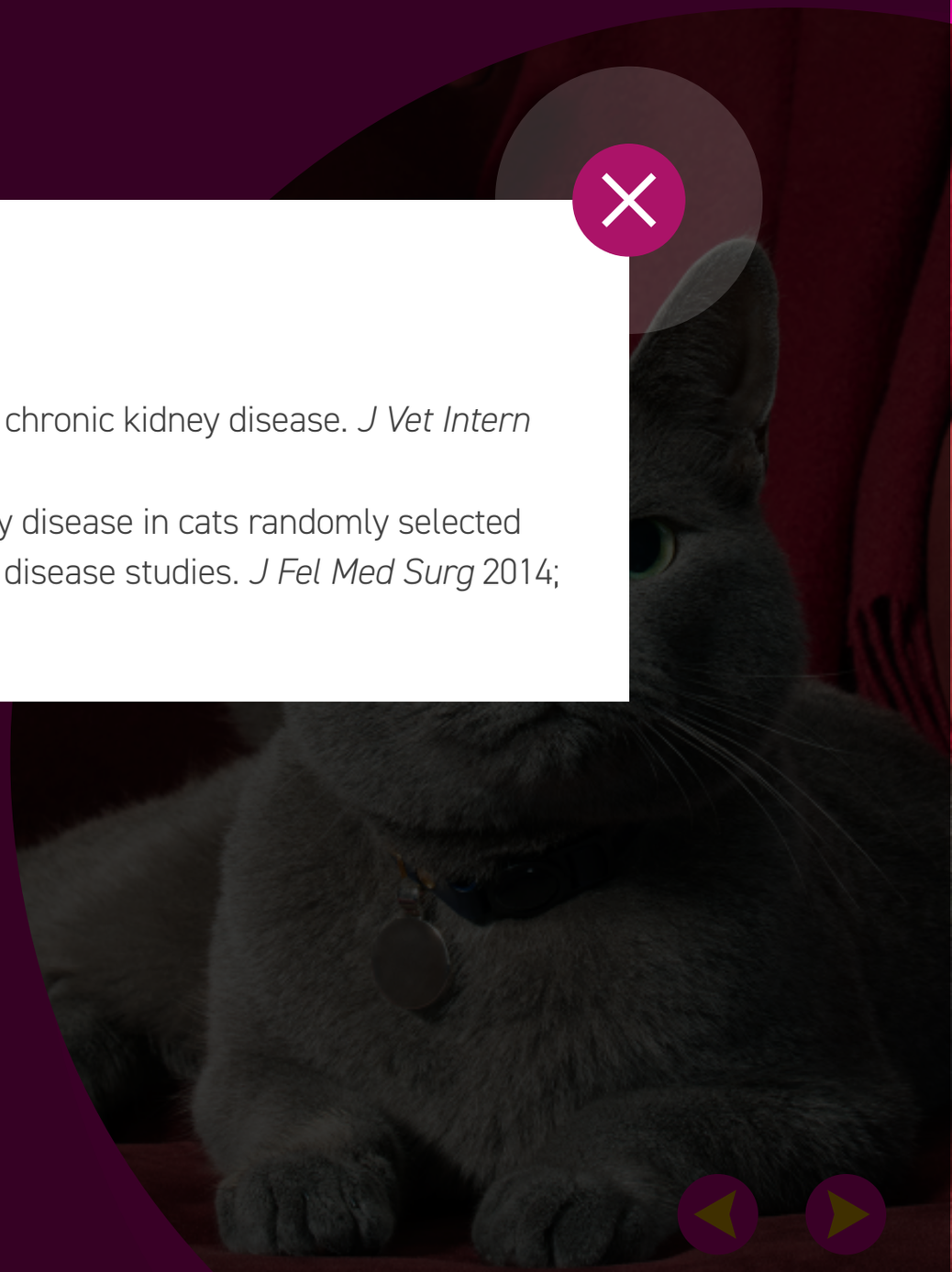
CKD has been rep… 80% … 1…

References

1. Freeman LM *et al*. Evaluation of weight loss over time in cats with chronic kidney disease. *J Vet Intern Med* 2016; 30: 1661–1666.
2. Marino CL *et al.* The prevalence and classification of chronic kidney disease in cats randomly selected within four age groups and in cats recruited for degenerative joint disease studies. *J Fel Med Surg* 2014; 16(6): 465–472.

Weight loss in cats with CKD is associated with shorter survival[1]

Weight loss may lead pet owners to consider euthanasia[1]



ELURA IS DESIGNED TO MANAGE WEIGHT LOSS IN CATS WITH CKD FROM THE FIRST SIGNS

- **Elura is an oral, flavored liquid designed specifically for cats**
  - Formulation developed to appeal to cats
  - Low dosing volume
  - Dosing syringe included for convenience

ELURA IS APPROVED FOR LONG-TERM USE

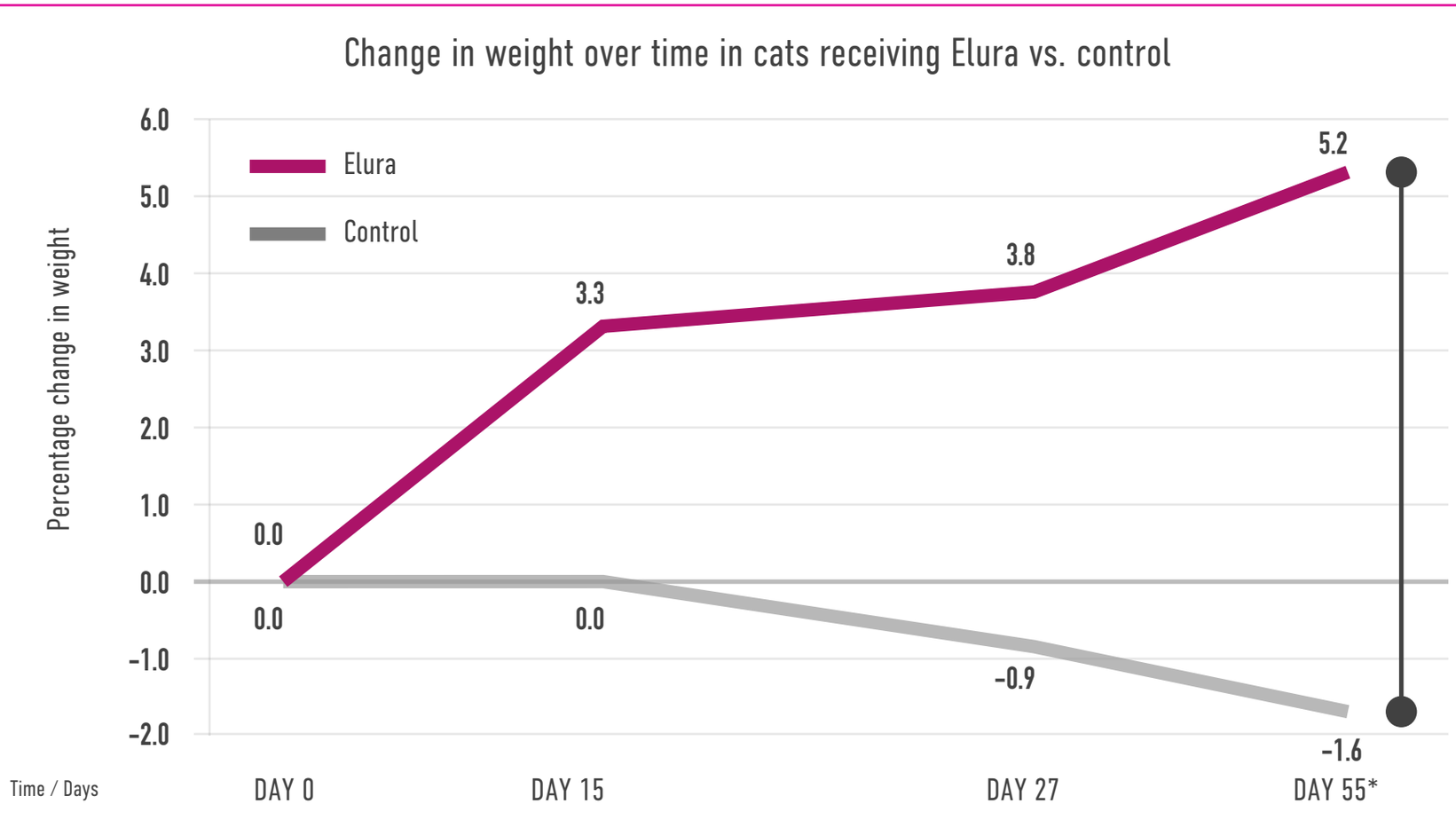
FORMULATED EXCLUSIVELY FOR CATS

SPECIFICALLY APPROVED FOR USE IN CATS WITH CKD

ELURA HELPS CATS WITH CKD GAIN WEIGHT

In a multi-center, placebo-controlled, randomized and masked field study involving 176 cats with CKD and at least 5% unintended loss of body weight:*

- **8/10 cats prescribed Elura gained weight[1†]**
- **Weight gain was observed at the earliest time point measured (day 15) and continued throughout the study[1]**



At day 55*, there was a 6.8% difference in weight for Elura vs. control cats

Cats without treatment continued to lose weight

*Primary endpoint

Elura is approved for long-term use and is safe to use daily

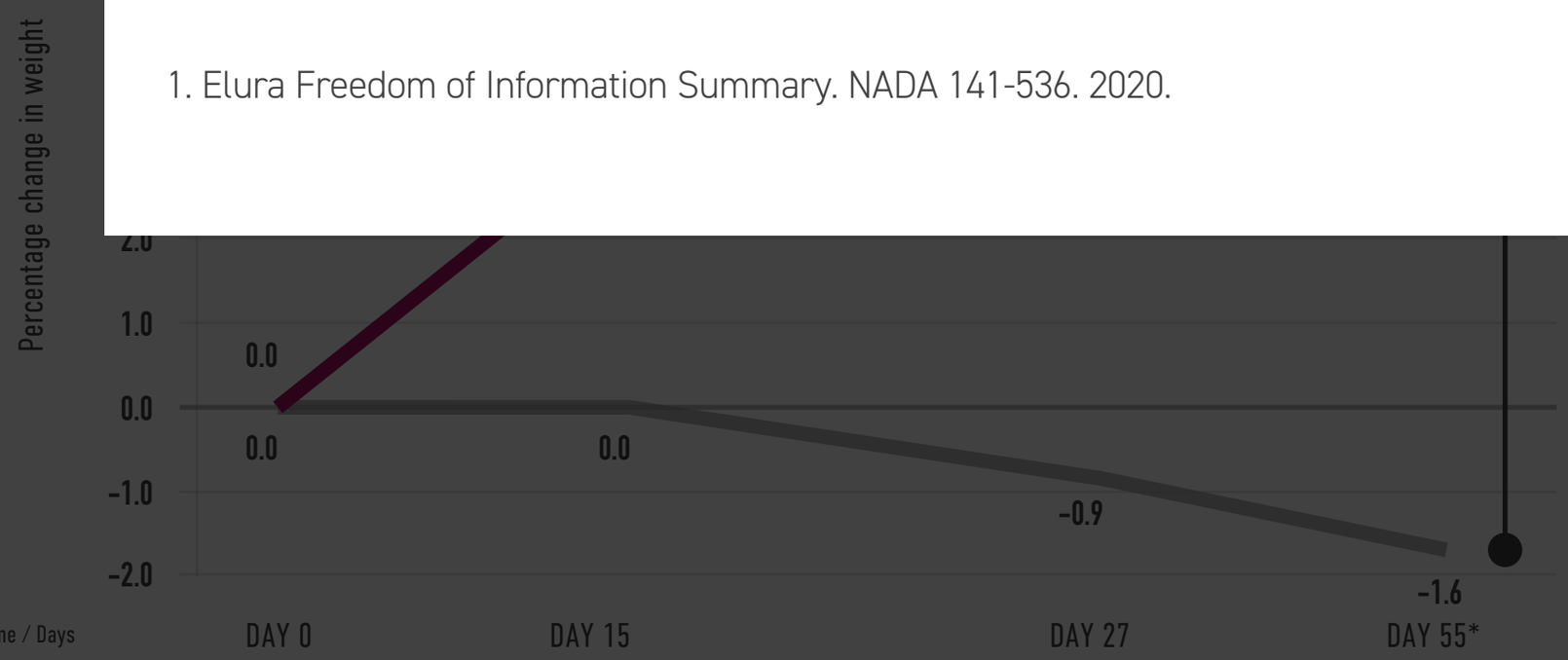
*5% as compared to the highest weight in the medical records for the 3 years preceding enrollment. Study period was 56 days (Day 0 – Day 55). † 4/10 control cats gained weight.

ELURA HELPS CATS WITH CKD GAIN WEIGHT

In a multi-center, placebo-controlled, randomized and masked field study involving 176 cats with CKD and at least 5% unintended loss of body weight:*

- **8/10 cats prescribed Elura gained weight[1†]**
- **Weight gain was observed at the earliest time point measured (day 15) and continued throughout the study[1]**

Change in weight over time in cats receiving Elura vs. control



was a weight ol cats

Cats without treatment continued to lose weight

*Primary endpoint

Reference

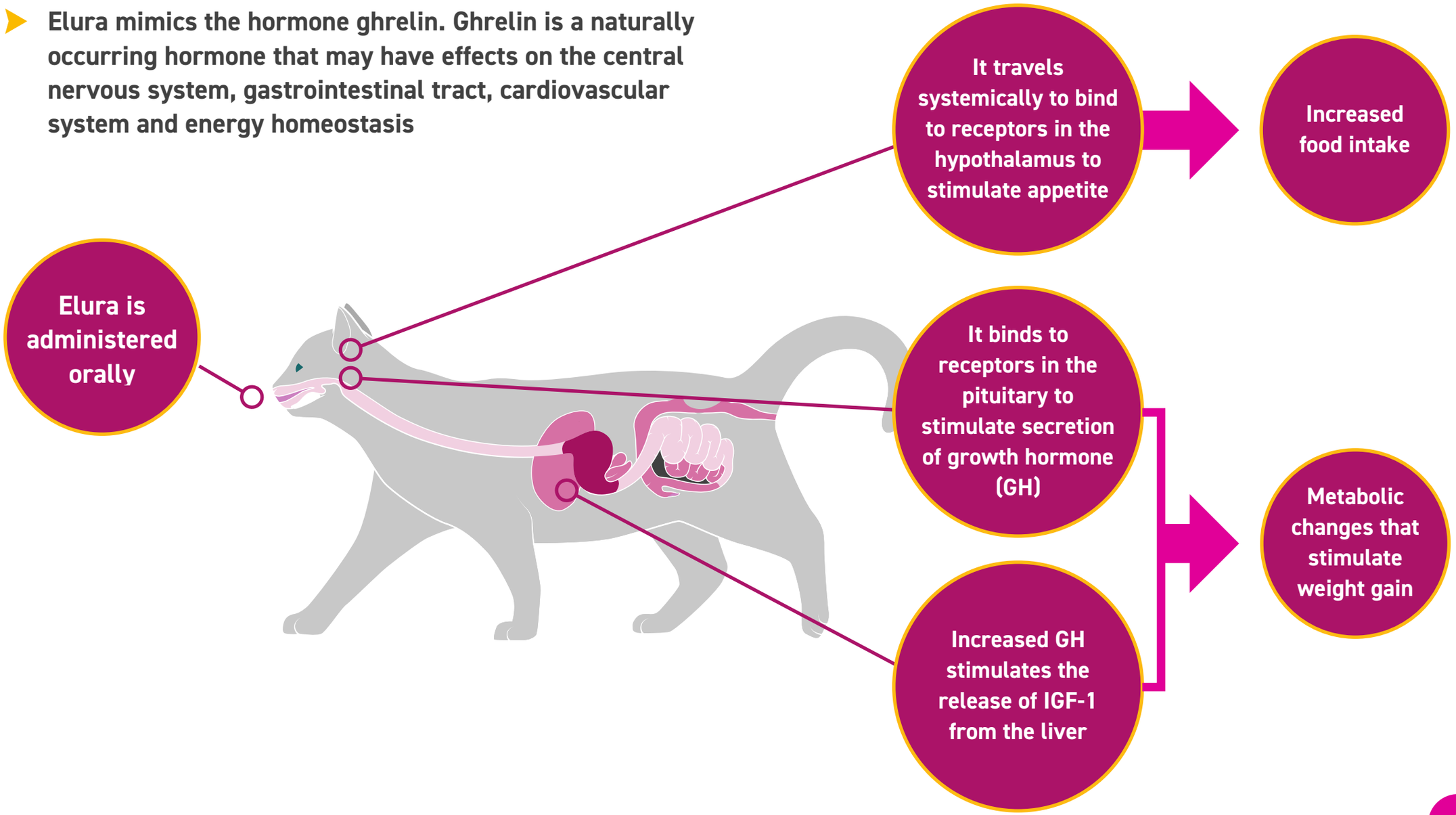
1. Elura Freedom of Information Summary. NADA 141-536. 2020.

Elura is approved for long-term use and is safe to use daily

*5% as compared to the highest weight in the medical records for the 3 years preceding enrollment. Study period was 56 days (Day 0 – Day 55). † 4/10 control cats gained weight.

WEIGHT GAIN IN CATS TAKING ELURA IS THOUGHT TO BE DUE TO A COMBINATION OF INCREASED FOOD INTAKE AND METABOLIC CHANGES

- Elura mimics the hormone ghrelin. Ghrelin is a naturally occurring hormone that may have effects on the central nervous system, gastrointestinal tract, cardiovascular system and energy homeostasis



IGF-1, Insulin-like growth factor 1.

PRESCRIBE ELURA WITH CONFIDENCE

In 174 client-owned cats with CKD, Elura was well tolerated over a 56 day study[1]

Elura was tested in healthy cats at up to 5x the labeled dose for 6 months supporting the margin of safety at the label dose[1]

In a 32-day telemetry study in 8 healthy cats Elura was well tolerated, supporting the safety profile[1]

- Multi-center, placebo-controlled, randomized and masked field study
- Elura administered at 2 mg/kg once daily
- The most common adverse reactions were vomiting, hypersalivation, inappetence, behavior change and lethargy

CKD, chronic kidney disease; CV, cardiovascular.

PRESCRIBE ELURA WITH CONFIDENCE

In 174 client-owned cats with CKD, Elura was well tolerated over a 56 day study[1]

Elura was tested in healthy cats at up to 5x the labeled dose for 6 months supporting the margin of safety at the label dose[1]

In a 32-day telemetry study in 8 healthy cats Elura was well tolerated, supporting the safety profile[1]

- Randomized, placebo-controlled laboratory study in 32 intact cats aged approximately 11 months
- Elura administered at 1X, 3X or 5X label dose
- Observations included dose-dependent increases in salivation and intermittent vomiting. Decreased lymphocyte count was observed only in cats administered Elura; increased mean corpuscular volume (MCV) and increased triglycerides were more common in cats receiving Elura

CKD, chronic kidney disease; CV, cardiovascular.

PRESCRIBE ELURA WITH CONFIDENCE

In 174 client-owned cats with CKD, Elura was well tolerated over a 56 day study[1]

Elura was tested in healthy cats at up to 5x the labeled dose for 6 months supporting the margin of safety at the label dose[1]

In a 32-day telemetry study in 8 healthy cats Elura was well tolerated, supporting the safety profile[1]

- A telemetry device was implanted for continuous monitoring of CV variables and blood glucose
- Vehicle control administered once daily for 3 days followed by Elura 2 mg/kg once daily for 28 days
- Observations included transient decreases in heart rate and direct blood pressure (systolic, diastolic and mean arterial), which reversed when they were handled. Transient increases in blood glucose were observed

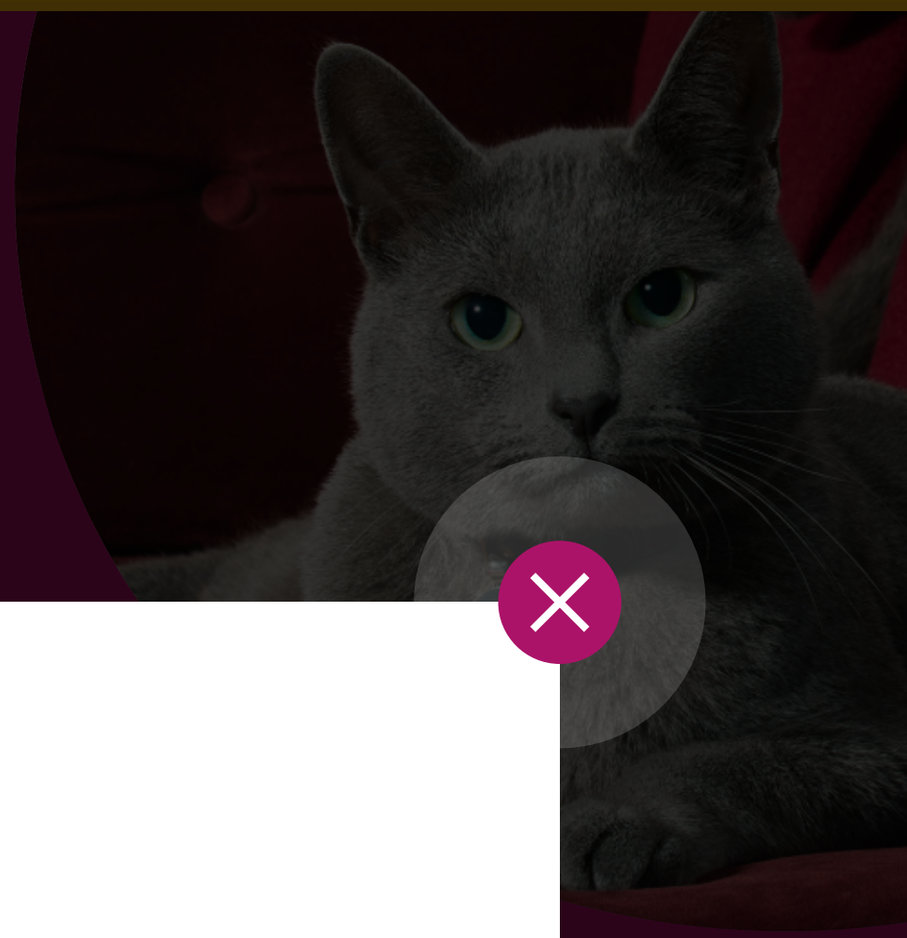
CKD, chronic kidney disease; CV, cardiovascular.

PRESCRIBE ELURA WITH CONFIDENCE

In 174 client-
with CK
well tole
56 d

Elura was tested in healthy cats

In a 32-day telemetry study in



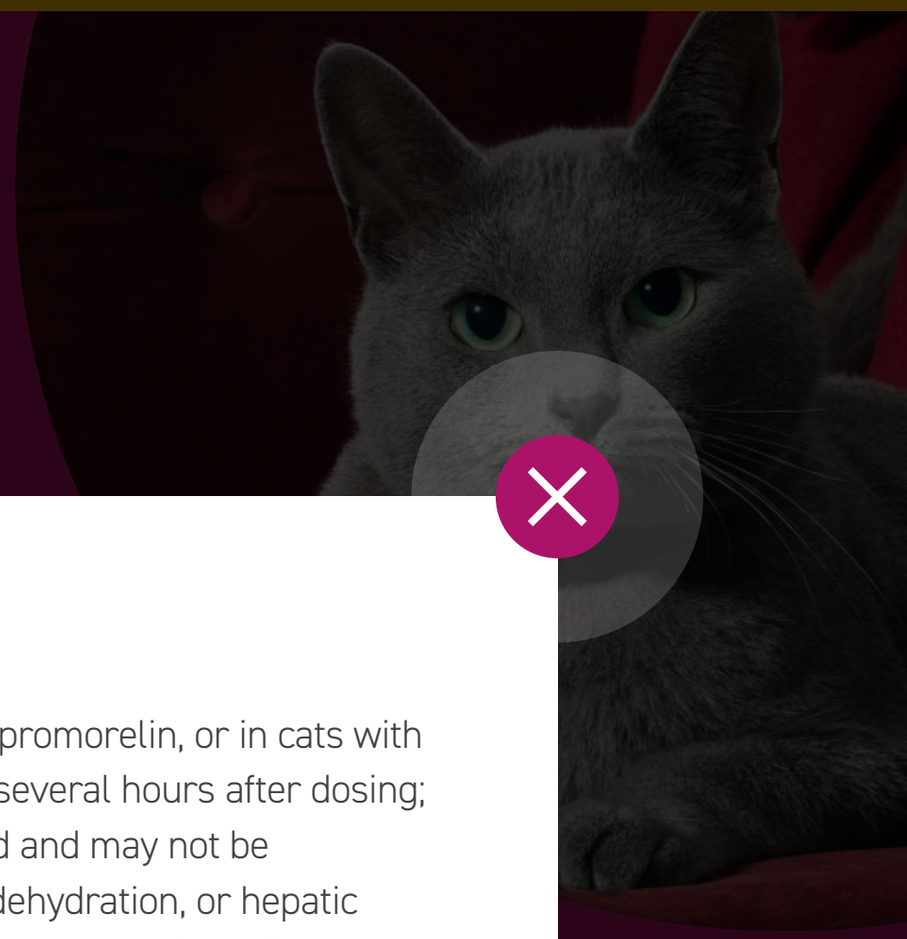
Reference

1. Elura Freedom of Information Summary. NADA 141-536. 2020.

- **A telemetry device was implanted for continuous monitoring of CV variables and blood glucose**
- **Vehicle control administered once daily for 3 days followed by Elura 2 mg/kg once daily for 28 days**
- **Observations included transient decreases in heart rate and direct blood pressure (systolic, diastolic and mean arterial), which reversed when they were handled. Transient increases in blood glucose were observed**

CKD, chronic kidney disease; CV, cardiovascular.

PRESCRIBE ELURA WITH CONFIDENCE



client-
with CK
well tol
56 d

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.

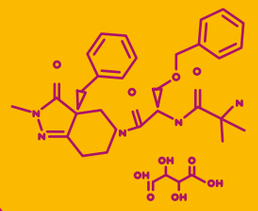
- **A te**
- **Vehicle control administered once daily for 3 days followed by Elura 2 mg/kg once daily for 28 days**
- **Observations included transient decreases in heart rate and direct blood pressure (systolic, diastolic and mean arterial), which reversed when they were handled. Transient increases in blood glucose were observed**

CKD, chronic kidney disease; CV, cardiovascular.

WHEN YOU SEE WEIGHT LOSS IN A CAT WITH CKD, THINK ELURA

8/10

More than 8/10 cats gained weight*[1]



Mimics the naturally occurring hormone ghrelin

The clinical effects are thought to be due to a combination of increased food intake and metabolic changes

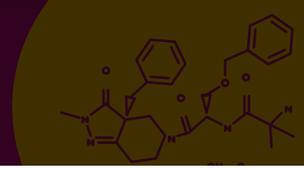
An oral solution with a low dosing volume, developed to appeal to cats

Help them stay their *fabulous* selves with Elura – safe to use daily and approved for long-term use

*compared to 4/10 control cats

WHEN YOU SEE WEIGHT LOSS IN A CAT WITH CKD, THINK ELURA

8/10



Reference

1. Elura Freedom of Information Summary. NADA 141-536. 2020.

More t… n with
gain… olume,
…ppeal
…to cats

…increased food intake
and metabolic changes

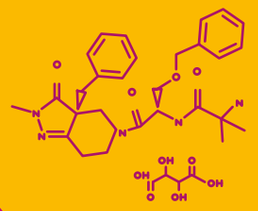
Help them stay their *fabulous* selves with Elura – safe to use daily and approved for long-term use

*compared to 4/10 control cats

WHEN YOU SEE WEIGHT LOSS IN A CAT WITH CKD, THINK ELURA

8/10

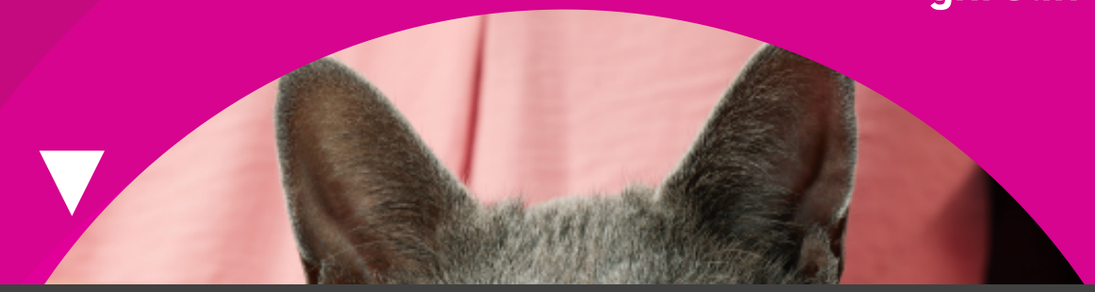
More than 8/10 cats gained weight*[1]



Mimics the naturally occurring hormone ghrelin

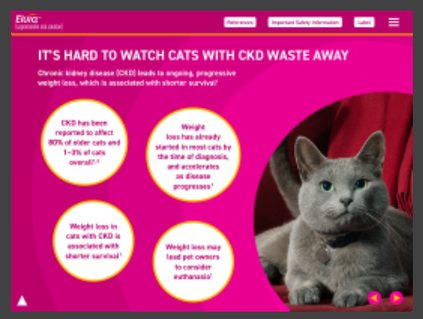
The clinical effects are thought to be due to a combination of increased food intake and metabolic changes

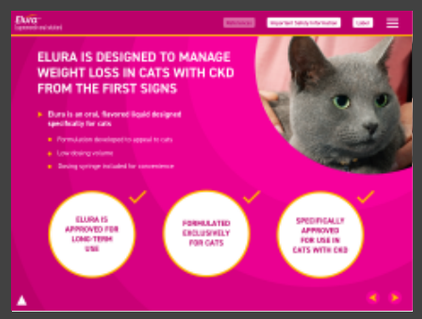
An oral solution with a low dosing volume, developed to appeal to cats

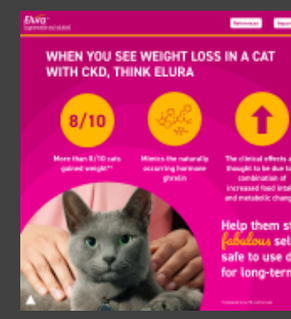


Help them stay their

Elura CKD





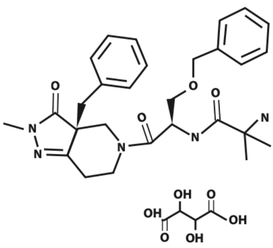


Elura™ (capromorelin oral solution)

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.

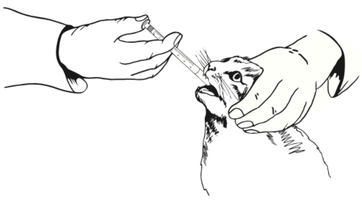
DESCRIPTION:
ELURA (capromorelin oral solution) is a colorless to yellow or orange, clear liquid. Each milliliter of ELURA contains 20 mg of capromorelin tartrate. The empirical formula is $C_{39}H_{50}N_6O_7 \cdot C_4H_6O_6$ and the molecular weight 655.70. The chemical name is 2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-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

WITH REDUCED APPETITE, THERE'S

MORE THAN MEETS THE EYE

APPETITE IS A KEY INDICATOR OF QUALITY OF LIFE

Often first and only sign pet is sick

Pet owners consider inappetence, weight loss and depression in their dog as unacceptable side effects[1]

COMMON CAUSES AND CLINICAL IMPACT OF INAPPETENCE

Chronic kidney disease

- Higher BCS at diagnosis associated with significantly improved survival[2]

Chronic gastrointestinal disease

- Malnutrition in chronic GI disease is multifactorial
  - » Nutrient loss, malabsorption, lack of intake

Congestive heart failure

- Dogs that gained body weight had longer survival times[3]

Cancer

- Nearly 40% of dogs experienced ≥ 5% weight loss[4]
  - » Dogs underweight at diagnosis with lymphoma had shorter survival times[5]

WHY INTERVENE EARLY?

Changes occur early, often before noticeable weight loss

- Decline in GI tract function
- Decreased immune response
- Impaired healing, recovery

Don't wait for weight loss.
Stimulate appetite early to treat the whole picture.

entyce®
(capromorelin oral solution)

Add ENTYCE® (capromorelin oral solution) at the first sign of decreased eating as part of your overall treatment plan.

- Proven safe for long-term use[6]
- Effectively stimulates appetite to help improve food consumption
- The ONLY FDA-approved appetite stimulant for dogs

entyce® (capromorelin oral solution)

ENTYCE treated dogs demonstrated significant increases in appetite compared to placebo treated inappetent dogs in the clinical field study[7]

Parameter	Capromorelin	Placebo	*P*-Value
Treatment success–single-question assessment %*	68.6	44.6	0.0078
Treatment success–owner appetite assessment, %**	56.2	26.8	0.0071
Percent change in owner appetite assessment, mean (±SD)	73.3 (±75.9)	37.6 (±53.9)	0.0125
Percent change in body weight, mean (±SD)	1.83 (±2.75)	0.11 (±3.61)	0.0004

*A dog was considered a treatment success if the owner answered that their dog's appetite was increased in response to the question, "Do you feel that during the study (over the 4 ± 1 days of treatment) your dog's appetite was increased, no change or decreased?"
**Treatment success was defined as an increase in total score ≥ 5 from day 0 to day 3 ± 1 (scoring scale 5-25)

Most common side effects reported by pet owners in the study include:[7]

- Diarrhea
- Vomiting
- Hypersalivation
- Excessive drinking

Convenient, once-daily oral solution for treating inappetence

Dose
3 mg/kg (1.4 mg/lb) body weight once daily

1. Williams J, Phillips C, Byrd HM. Factors Which Influence Owners When Deciding to Use Chemotherapy in Terminally Ill Pets. *Animals.* 2017;7(3):E18. 2. Parker VJ and Freeman LM. Association between body condition and survival in dogs with acquired chronic kidney disease. *J Vet Intern Med.* 2011;25(6):1306-11. 3. Slupe JL, Freeman LM, Rush JE. Association of Body Weight and Body Condition with Survival in Dogs with Heart Failure. *J Vet Intern Med.* 2008;22:561-565. 4. Michel KE, Sorenmo K, Shofer FS. Evaluation of body condition and weight loss in dogs presented to a veterinary oncology service. *J Vet Intern Med.* 2004;18(5):692-5. 5. Romano FR, Heinze CR, Barber LG, Mason JB, Freeman LM. Association between Body Condition Score and Cancer Prognosis in Dogs with Lymphoma and Osteosarcoma. *J Vet Intern Med.* 2016;30:1179–1186. 6. Zollers B, Huebner M, Armintrout G, Rausch-Derra LC, Rhodes L. Evaluation of the safety in dogs of long-term, daily oral administration of capromorelin, a novel drug for stimulation of appetite. *J Vet Pharmacol Ther.* 2017 Jun;40(3):248-255. 7. Zollers B, Wofford JA, Heinen E, Huebner M, Rhodes L. A Prospective, Randomized, Masked, Placebo-Controlled Clinical Study of Capromorelin in Dogs with Reduced Appetite. *J Vet Intern Med.* 2016;30(6):1851-1857.

IMPORTANT SAFETY INFORMATION: ENTYCE® (capromorelin oral solution) is for use in dogs only. Do not use in breeding, pregnant or lactating dogs. Use with caution in dogs with hepatic dysfunction or renal insufficiency. Adverse reactions in dogs may include diarrhea, vomiting, polydipsia, and hypersalivation. Should not be used in dogs that have a hypersensitivity to capromorelin. Please see the enclosed full Prescribing Information for more detail.

ARATANA THERAPEUTICS

entyce™

(capromorelin oral solution)

30 mg/mL

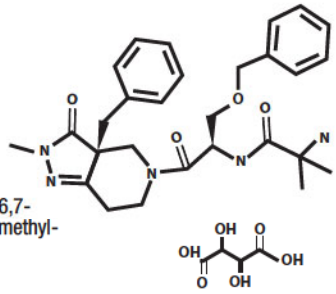
For oral use in dogs only

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 $C_{28}H_{36}N_5O_4 \cdot C_4H_6O_6$ 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: February 2020

Elanco™