Varenzin™-CA1
(molidustat oral suspension)

A REVOLUTIONARY NEW TREATMENT IN THE FIGHT AGAINST CKD-RELATED ANEMIA

The innovative, easy-to-administer oral option that safely treats non-regenerative anemia in cats with chronic kidney disease.

IMPORTANT SAFETY INFORMATION: For oral use in cats only. Keep this drug, including used syringes, out of reach of children. Wash hands immediately after use. In case of accidental ingestion, seek medical advice immediately.

Elanco™

Varenzin™-CA1 (molidustat oral suspension)

Varenzin™-CA1 (molidustat oral suspension) is the FIRST and ONLY FDA conditionally approved option for the treatment of CKD-related anemia, setting the new standard of care for cats suffering from the debilitating effects of this disease.

A first of its kind in veterinary medicine, Varenzin-CA1 stimulates a cat's body to create its own erythropoietin (EPO)*

Approved for convenient at-home treatment; no in-clinic injections needed

Reasonable expectation of efficacy with minimal side effects[1]

No costly and inconvenient extra label use of erythropoietin stimulating agents (ESAs)

ANEMIA IN CKD CATS

30-65%

of cats with CKD will develop anemia.[2]

"I do not want excessive testing or unnecessary therapeutics to compromise the patients' quality of life … managing CKD-associated anemia is one thing I can do that will really make a cat feel better, thereby improving its quality of life."

Shelly Vaden, DVM, PhD, DACVIM
Chief of Staff, Small Animal
College of Veterinary Medicine
North Carolina State University

CKD occurs in about 15-30% of feline patients over 12 years old, with anemia being a common finding in over half of all diagnosed cats, usually affecting cats in IRIS stages 3-4.[2]

Anemia develops slowly, so most cats appear to cope well with it.[3] However, they may still be suffering:

- Anemic cats experience a significantly reduced quality of life with symptoms such as lethargy, weight loss, inappetence and vomiting.
- This can take an emotional toll on veterinarians and pet owners who can feel helpless as the cat's quality of life deteriorates.

Cats with CKD-associated anemia deserve a treatment that helps support their quality of life.

There is a need for an effective, safe and convenient treatment option that can help CKD cats feel more like their feline selves.

*Versus administering with a human EPO product

IMPORTANT SAFETY INFORMATION: Women who are pregnant or may become pregnant should administer the product with caution. Varenzin-CA1 should not be administered to cats that are pregnant, lactating or intended for breeding or to cats with known hypersensitivity to molidustat.

ANEMIA TREATMENT OPTIONS CAN BE EXPENSIVE, INCONVENIENT AND FRUSTRATING

Addressing anemia is not seen as a priority

Although increasing the comfort of anemic cats is crucial for vets (less than 1/3 of anemic cats receive treatment),[4] many see targeting the progression of CKD as a much higher priority.[3]

Challenges for pet owners

A considerable share of cat owners are unwilling to treat for a number of reasons. Overall, these challenges stand in contrast to a pet owner's desire to improve their cat's quality of life[3]:

- Managing anemia can be perceived as ancillary therapy, not focused on slowing the progression of the disease.
- The costs can be high in conjunction with a specialized renal diet and other therapies.
- Injections given at the veterinarian's office or at home may be too inconvenient and time-consuming.
- CKD is more common in older cats, so anemia may be seen as an end-stage signal for euthanasia.

"I believe correcting anemia in feline CKD is often overlooked, often due to limited options for therapy. Evidence in other species strongly suggests that correcting anemia has a positive outcome on kidney health and quality of life. A targeted therapy to address anemia without the financial and logistical burden associated with darbepoetin would be a welcome development."

Jessica M. Quimby, DVM, PhD, DACVIM
Professor, Small Animal Internal Medicine
The Ohio State University

Available treatments are frustrating for vets[3]

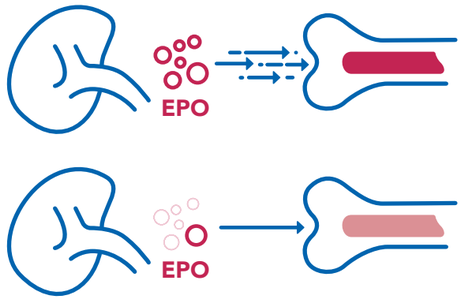
In the past, anemic cats have been treated with off-label human products. These products, while often effective, have some challenges.

Injections with darbepoetin have become the preferred treatment option for CKD-related anemia as it features a higher efficacy and safety profile. However, darbepoetin is not without its challenges:

- x Designed for human medicine, not feline medicine
- x Does not stimulate a cat's own EPO
- x High upfront cost for each vial (around $200 per 1 mL single-use vial)[5]
- x Not typically stocked in clinics
- x Requires injections given every 1-2 weeks in clinic or home

IMPORTANT SAFETY INFORMATION: Use with caution in cats with a history of seizures and in cats predisposed to thromboembolic disease. Hematocrit (HCT) or packed cell volume (PCV) levels should be monitored regularly as polycythemia may result from use of Varenzin-CA1.

THE ESSENTIAL ROLE OF ERYTHROPOIETIN (EPO) IN CATS



EPO is a hormone released from the kidneys that signals bone marrow to make red blood cells.

Anemia is caused by several factors related to kidney disease, primarily a reduction of EPO produced by the renal erythropoietin-producing (REP) cells found in both the medulla and cortex of the kidney.[2]

EPO PRODUCTION IN HEALTHY VS. FAILING KIDNEYS

HYPOXIA
Lower blood oxygen conditions

EPO production is regulated by the protein hypoxia inducible factor (HIF). HIF is made of two key components, HIF_α and HIF_β, that work together to regulate blood cell production.[6]

In low blood oxygen conditions in the microenvironment of REP cells, HIF_α and HIF_β join (dimerize) to induce genetic transcription for EPO production.

NORMOXIA
Higher blood oxygen conditions

With higher oxygen conditions in the kidney, HIF_α is degraded by prolyl hydroxylase (PH) which stops dimerization, preventing excess EPO production in the body.[6]

In some CKD cats, this check-and-balance system becomes disrupted. While this is not fully understood, this may be caused by the higher level of oxygen present in the microenvironment of the REP cells of the kidney in more advanced CKD.[7,8]

- This is likely due to progressing inflammatory changes caused by CKD.[7,9]
- A higher relative oxygen level around the REP cells "fools" the HIF-PH system, and inappropriately low EPO production ensues.[7,8]

IMPORTANT SAFETY INFORMATION: Varenzin-CA1 has not been evaluated in cats less than 1 year of age. The most common adverse reactions included vomiting, increases in systolic blood pressure and mild transient increase in serum potassium.

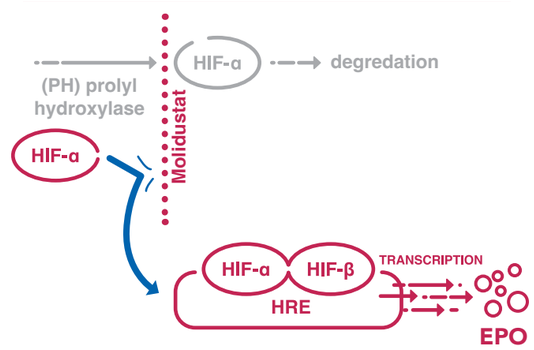
A PARADIGM SHIFT IN CKD-RELATED ANEMIA TREATMENT

Developed exclusively for cats, Varenzin-CA1 works by inhibiting PH, the enzyme responsible for initiating the breakdown of HIF_α.

By preventing HIF_α from being degraded, HIF_α can dimerize with HIF_β and code for EPO.[1]

- This mode of action induces the genetic transcription of EPO, increasing both EPO and red blood cell production in the body.[1]
- As EPO increases, red blood cell production and the oxygen-carrying ability of the blood both increase.[7,8]
- By stimulating the cat's body to produce its own natural EPO, this prevents the need to use human EPO products.

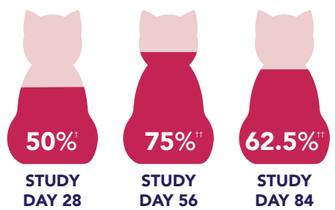
How Varenzin-CA1 works



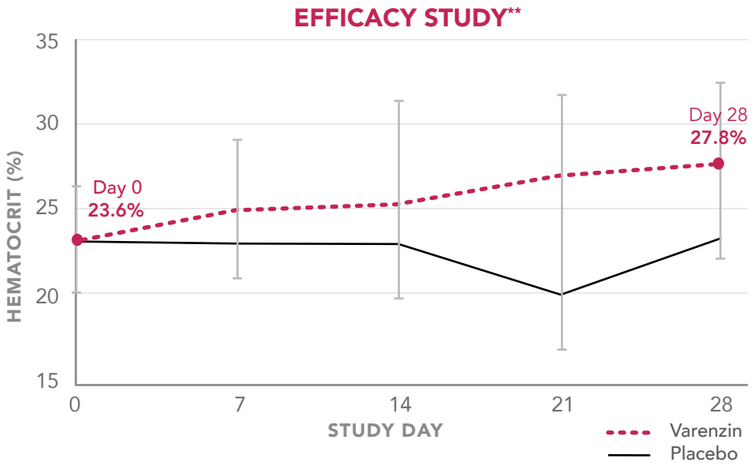
EMPOWERED WITH EFFICACY

In a series of multicenter studies,[1] Varenzin-CA1 was shown to have a reasonable expectation of efficacy managing anemia in CKD cats.

PERCENTAGE OF CATS WITH INCREASED HEMATOCRIT*



EFFICACY STUDY**



TREAT CONFIDENTLY WITH PROVEN SAFETY

The safety of Varenzin-CA1 was established in laboratory studies and field safety and effectiveness studies. There were minimal side effects with vomiting being the most frequently reported adverse effect.[1]

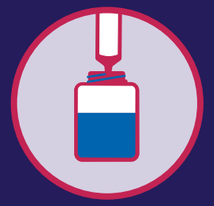
*Relative increase in HCT of >25% above baseline or an absolute increase in HCT of ≥4% above baseline
**28-day pilot field study
†Field effectiveness and safety study, effectiveness phase
††Field effectiveness and safety study, continuation phase

BREAKTHROUGH INNOVATION MEETS AT-HOME CONVENIENCE

Varenzin™-CA1 (molidustat oral suspension) is a flavored, orally administered liquid given once daily that's convenient and simple to dose.

HOW TO ADMINISTER VARENZIN-CA1

STEP 1
Shake well before use. Remove screw cap.



STEP 2
Place the enclosed syringe nozzle firmly into the opening of the bottle.

STEP 3
Turn the bottle upside down and withdraw necessary volume. Turn the bottle upright before removing syringe.

STEP 4
Administer directly into the cat's mouth.

IMPORTANT SAFETY INFORMATION: For oral use in cats only. Keep this drug, including used syringes, out of reach of children. Wash hands immediately after use. In case of accidental ingestion, seek medical advice immediately.

DOSING CHART*

The dosage of Varenzin-CA1 is 2.3 mg/lb (5 mg/kg) body weight (BW) administered orally once daily for up to 28 consecutive days. Treatment may be repeated after a minimum seven-day pause.

*The syringe included with the Varenzin-CA1 product cannot be used to accurately dose cats weighing under 3.4 lb. Cats greater than 13.2 lb BW should be treated with a dose of 2.3 mg/lb BW rounded up to the nearest 0.1 mL.

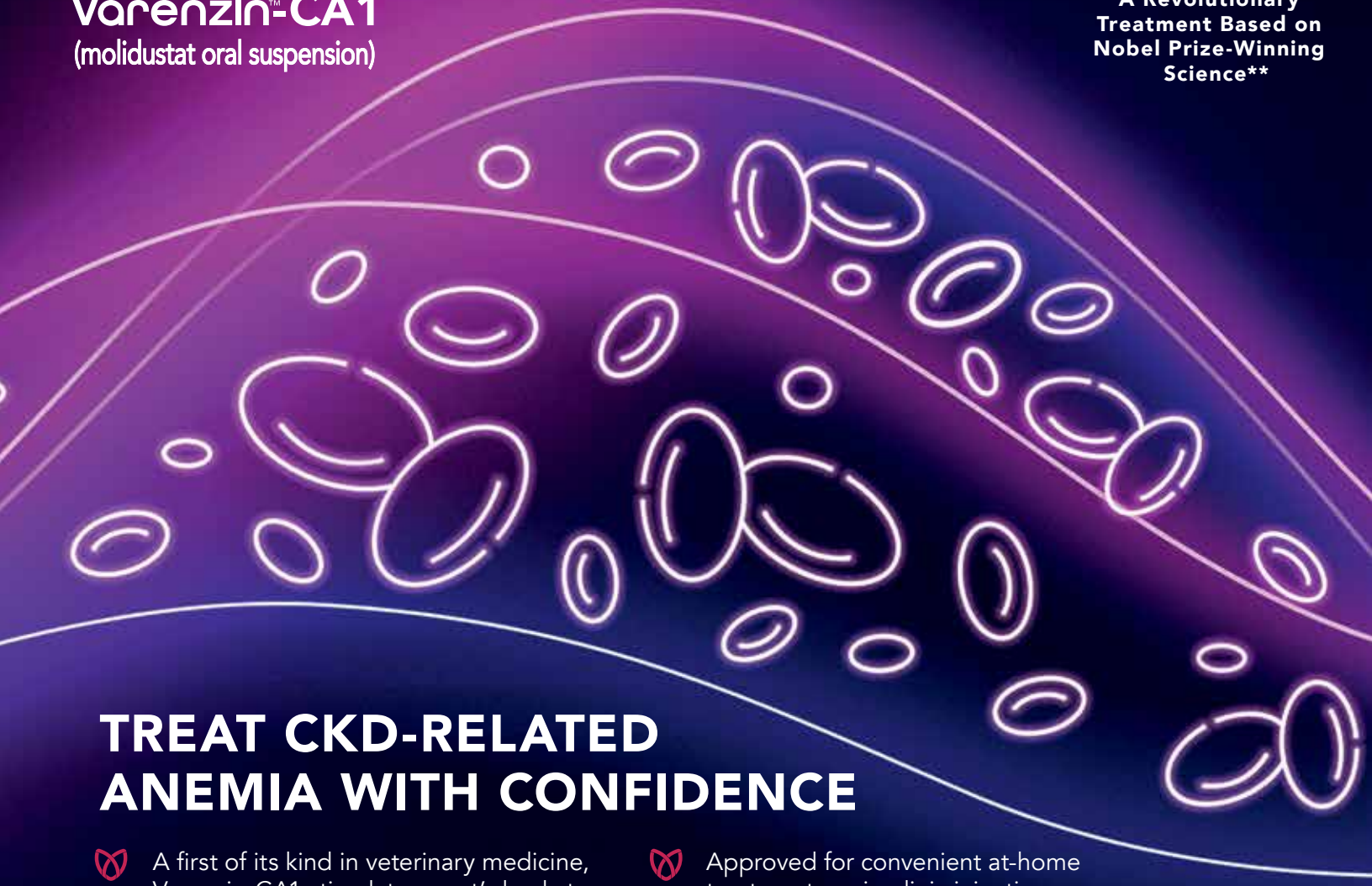
Weight Range in Pounds	Volume of Varenzin-CA1 (mL)
3.4 to 4.4	0.4
4.5 to 5.5	0.5
5.6 to 6.6	0.6
6.7 to 7.7	0.7
7.8 to 8.8	0.8
8.9 to 9.9	0.9
10 to 11	1
11.1 to 12.1	1.1
12.2 to 13.2	1.2

IMPORTANT SAFETY INFORMATION: Women who are pregnant or may become pregnant should administer the product with caution. Varenzin-CA1 should not be administered to cats that are pregnant, lactating or intended for breeding or to cats with known hypersensitivity to molidustat or to any of the inactive ingredients.

REFERENCES
[1]Varenzin Freedom of Information Summary, NADA 141-571.
[2]Chalhoub S, et al. Anemia of renal disease: what it is, what to do and what's new. J Feline Med Surg. 2011;13(9):629-40.
[3]Elanco Animal Health. Data on file.
[4]Boyd LM, et al. Survival in cats with naturally occurring chronic kidney disease (2000-2002). J Vet Intern Med. 2008;22:1111-17.
[5]GoodRx [Internet]. Darbepoetin alfa; [cited 2023 May 8]; Available from: https://www.goodrx.com/darbepoetin-alfa.
[6]Gupta N, Wish J. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients with CKD. Am J Kidney Dis. 2017;69(6):815-26.
[7]Flamme I, Oehme F, Ellinghaus P, et al. Mimicking hypoxia to treat anemia: HIF-stabilizer BAY 85-3934 (Molidustat) stimulates erythropoietin production without hypertensive effects. PLoS One. 2014;9(11):e111838.
[8]Dahl SL, Bapst AM, Khodo SN, et al. Fount, fate, features, and function of renal erythropoietin-producing cells. Pflugers Arch. 2022;474(8):783-97.
[9]Nolan KA, Wenger RH. Source and microenvironmental regulation of erythropoietin in the kidney. Curr Opin Nephrol Hypertens. 2018;27(4):277-85.

Varenzin™-CA1
(molidustat oral suspension)

A Revolutionary Treatment Based on Nobel Prize-Winning Science**



TREAT CKD-RELATED ANEMIA WITH CONFIDENCE

- A first of its kind in veterinary medicine, Varenzin-CA1 stimulates a cat's body to create its own EPO*
- Reasonable expectation of efficacy with minimal side effects[1]
- Approved for convenient at-home treatment; no in-clinic injections needed
- No costly and inconvenient extra label use of ESAs

Contact your Elanco sales representative or visit www.VarenzinVet.com

*Versus administering with a human EPO product.

**The mechanism of how cells sense oxygen and regulate EPO, the HIF-PH pathway, was uncovered by three scientists who won the Nobel Prize in 2019 for this groundbreaking discovery. Varenzin CA-1 works along this pathway to increase EPO and therefore PCV in cats.

IMPORTANT SAFETY INFORMATION: Varenzin-CA1 should not be administered to cats that are pregnant, lactating or intended for breeding or to cats with known hypersensitivity to molidustat.
Use with caution in cats with a history of seizures and in cats predisposed to thromboembolic disease.

Empower your clinic's CKD protocols with Elura® (capromorelin oral solution)
Elura increases appetite in CKD cats to help them maintain or gain weight.

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. Please see attached Elura label for product safety information.

Elanco™

Elanco

Varenzin™-CA1

(molidustat oral suspension)

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor

25 mg/mL

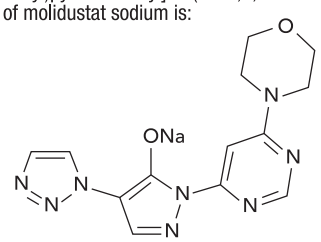
For oral use in cats only

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-571. It is a violation of Federal law to use this product other than as directed in the labeling.

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

DESCRIPTION

Varenzin-CA1 (molidustat oral suspension) is a white to yellow-white oily suspension. Each mL of Varenzin-CA1 contains 25 mg of molidustat sodium. The inactive ingredients are glycerol dibehenate, fish oil, sunflower oil, butylhydroxytoluene, and sorbic acid. The empirical formula is $C_{13}H_{13}N_8O_2Na$ and the molecular weight is 336.28. The chemical name is Sodium 1-[6-(morpholin-4-yl)pyrimidin-4-yl]-4-(1H-1,2,3-triazol-1-yl)-1H-pyrazol-5-olate. The chemical structure of molidustat sodium is:



INDICATION

Varenzin-CA1 is indicated for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats.

DOSAGE AND ADMINISTRATION

Shake well before use.

The dosage of Varenzin-CA1 is 2.3 mg/lb (5 mg/kg) body weight (bw) administered orally once daily for up to 28 consecutive days. Treatment may be repeated after a minimum 7-day pause (see **Monitoring and Repeating Treatment**). Varenzin-CA1 should be administered using the dosing syringe provided in the package. The dosing syringe is marked in increments of 0.1 mL. The dose should be rounded up to the nearest 0.1 mL.

Dosing Information

To ensure the correct dose is administered, body weight should be determined prior to starting treatment.

Table 1. Dosing Chart

Weight Range in pounds (lb)	Volume of Varenzin-CA1 (mL)
3.4 to 4.4	0.4
4.5 to 5.5	0.5
5.6 to 6.6	0.6
6.7 to 7.7	0.7
7.8 to 8.8	0.8
8.9 to 9.9	0.9
10 to 11	1
11.1 to 12.1	1.1
12.2 to 13.2	1.2

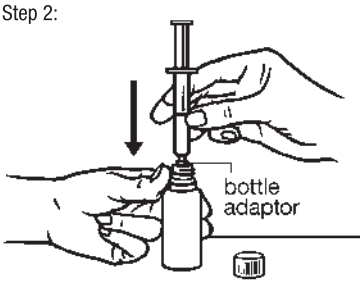
Note: The syringe included with the Varenzin-CA1 product cannot be used to accurately dose cats weighing under 3.4 pounds. Cats greater than 13.2 lb bw should be treated with a dose of 2.3 mg/lb bw rounded up to the nearest 0.1 mL.

Administration

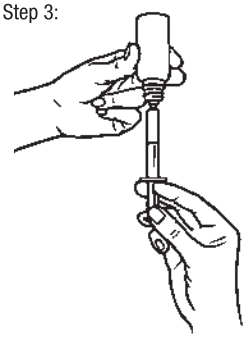
Shake well before use. Remove screw cap. Use the enclosed syringe for each treatment. Place the syringe nozzle firmly into the opening of the bottle. Turn the bottle upside down and withdraw the necessary volume. Turn the bottle back into an upright position before removing the syringe. The product should be administered with the syringe into the cat's mouth. See illustrations 1 through 4 below for administration steps:

Step 1:

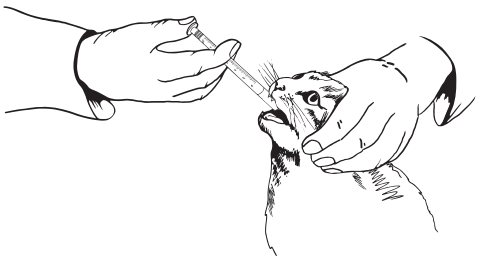
Step 2:



Step 3:



Step 4:



After administration, close bottle tightly with cap and store syringe in the carton together with the product. Do not disassemble or wash the syringe.

The product should be given once daily for up to 28 consecutive days. If the cat vomits after consuming any portion of the dose, the cat should not be re-dosed and should be considered as dosed for the day.

Monitoring and Repeating Treatment

Treated cats should initially have their hematocrit (HCT) or packed cell volume (PCV) levels monitored weekly beginning about the 14th day of the 28-day treatment cycle to ensure HCT or PCV does not exceed the upper limit of the reference range. Discontinue Varenzin-CA1 if HCT or PCV exceeds the upper limit of the reference range.

After treatment cessation the hematocrit level should be periodically checked (for example, weekly, every 2 weeks or monthly). When the HCT or PCV level declines below the lower limit of the reference range, a new treatment cycle should be started. The interval between treatment cycles will vary between cats and may change over time for an individual cat but should be at least 7 days.

If a cat does not respond to treatment after 3 weeks (see **REASONABLE EXPECTATION OF EFFECTIVENESS**), it is recommended to re-examine the animal for any other underlying condition that may contribute to anemia, such as iron deficiency, inflammatory diseases or blood loss. It is advised to treat the underlying condition before restarting treatment with Varenzin-CA1.

CONTRAINDICATIONS

Varenzin-CA1 should not be administered to cats with known hypersensitivity to molidustat or to any of the inactive ingredients.

Varenzin-CA1 should not be administered to cats that are pregnant, lactating, or intended for breeding. In an embryo-fetal-developmental toxicity study in rats, an increase incidence of ocular malformations such as flat eye rudiments and microphthalmia were observed at doses of 30 mg/kg bw per day. These effects may be due to an increase in oxygen availability, caused by molidustat-induced polycythemia. Localized hypoxia is an important factor in normal eye development. Developmental toxicity studies have not been conducted in cats. Available animal data have shown excretion of other HIF-PH inhibitors into milk. It is unknown whether molidustat is excreted into the milk of lactating cats.

WARNINGS

User Safety Warnings

Not for use in humans.

Keep this drug, including used syringes, out of reach of children. Wash hands immediately after use and/or spillage.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Symptoms of exposure to molidustat may include the following: gastrointestinal effects (nausea, vomiting, diarrhea), blood and clotting effects (increases in reticulocytes, erythropoietin, and hemoglobin), dizziness, fainting, hypertension, changes in cardiac output and cardiac index, and increases in heart rate.

Symptoms may not occur immediately; therefore, the exposed individual should be monitored. People with known hypersensitivity to molidustat sodium should avoid direct contact with this product and should administer the product with caution.

Women who are pregnant or may become pregnant should administer the product with caution. Molidustat administered orally to pregnant rats during the period of organogenesis was associated with adverse fetal outcomes (see **CONTRAINDICATIONS**).

Do not eat, drink, or smoke while handling this product.

Animal Safety Warnings

Keep Varenzin-CA1 in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS

Varenzin-CA1 has been associated with thromboembolic disease (see **ADVERSE REACTIONS**).

Use with caution in cats that may be predisposed to thromboembolic disease.

Use with caution in cats with a history of seizures (see **ADVERSE REACTIONS**).

Phosphate binders or other products containing multivalent cations such as calcium, iron, magnesium or aluminum have been shown to chelate with other HIF-PH inhibitors. Based on information in humans, consider staggered administration of Varenzin-CA1 and phosphate binders and iron supplements (at least 1 hour apart), if possible, to prevent potentially decreasing absorption of molidustat.

Polycythemia may result from use of Varenzin-CA1. When starting Varenzin-CA1, cats should have their hematocrit (HCT) or packed cell volume (PCV) levels monitored regularly during the treatment cycle to ensure HCT or PCV does not exceed the upper limit of the reference range (see **DOSAGE AND ADMINISTRATION**). Clinical signs associated with polycythemia found in preapproval studies in healthy cats included changes in mucous membrane color, slightly prolonged capillary refill time, heart pounding, and tachycardia (see **TARGET ANIMAL SAFETY**). Polycythemia after Varenzin-CA1 administration was also associated with increases in serum potassium, creatinine, serum phosphorus, and systolic blood pressure, which were not associated with clinical signs (see **ADVERSE REACTIONS** and **TARGET ANIMAL SAFETY**).

The use of Varenzin-CA1 administered concurrently with other erythropoiesis-stimulating agents, including recombinant erythropoietin drugs, has not been studied.

The safe use of Varenzin-CA1 has not been evaluated in cats less than 1 year of age.

ADVERSE REACTIONS

The safety of Varenzin-CA1 was evaluated in a masked, controlled 28-day field study to evaluate the effectiveness of molidustat oral suspension (not commercial formulation) for the control of nonregenerative anemia associated with CKD in cats (see **REASONABLE EXPECTATION OF EFFECTIVENESS**). Enrollment included 21 cats; 15 cats were treated with Varenzin-CA1, and 6 cats were administered a vehicle control. Eight of these cats were subsequently enrolled in an extended open-label safety study for up to 8 additional weeks. Cats were dosed daily for 28 days. Vomiting was the most frequently reported adverse event, observed in 6/15 (40%) cats in the molidustat group and no cats in the control group. Increases in systolic blood pressure and mild transient increases in serum potassium were also observed. The most serious adverse event was a cat in the molidustat group that presented, after 28 days of treatment, in lateral recumbency with a cold front leg from a suspected thromboembolism and was euthanized.

The safety of Varenzin-CA1 was evaluated in an interim analysis of data collected in an open label safety phase of an ongoing clinical field effectiveness and safety study. Varenzin-CA1 was administered for 28 consecutive days, followed by a treatment pause of at least 7 days, then treatment was repeated for up to 4 treatment cycles. The study evaluated 55 client-owned cats with nonregenerative anemia (PCV < 28%) secondary to CKD that had received at least one dose of Varenzin-CA1 at 5 mg/kg bw in the safety phase. Cats had a mean age of 13 years (range 5.2 to 23.4) and initial body weights between 2.3 to 5.9 kilograms. At baseline just prior to enrollment into the study, 31%, 47%, and 22% of cats were in International Renal Interest Society (IRIS) Stage 2, 3, and 4 CKD, respectively (to learn more about IRIS staging, visit http://www.iris-kidney.com/index.html).

Vomiting was the most frequently reported adverse event, either alone or with other events, and was reported at least once in 29/55 (52.7%) of the cats in the study. Vomiting was more frequent on treatment days than during treatment pause.

Two cats had seizures during the study. One cat had a seizure associated with severe uremia, severe anemia, and dehydration. One cat, which had a history of a seizure about 1 year prior, had a seizure during the study and severe hypertension.

Nineteen cats died or were euthanized before completion of the safety phase of the study due to worsening CKD or declining quality of life, and one cat was euthanized due to an abdominal mass.

CONTACT INFORMATION

To report suspected adverse drug reactions, 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 reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY

Mechanism of Action

Varenzin-CA1 (molidustat oral suspension) is a competitive and reversible inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PH). The inhibition of HIF-PH induces a dose-dependent increase of endogenous erythropoietin (EPO) by stabilizing HIF, resulting in increased erythropoiesis (red blood cell production).

Pharmacokinetics

The pharmacokinetic parameters of Varenzin-CA1 after a single oral dose of 2.5, 5, and 10 mg/kg bw and intravenous dose of 5 mg/kg bw were evaluated in a laboratory study in which 8 healthy, young adult cats (4 neutered males, 4 spayed females) received Varenzin-CA1 orally or molidustat sodium aqueous suspension intravenously, utilizing a crossover study design. Following oral administration, molidustat was rapidly absorbed.

Table 2: Mean (± standard deviation) pharmacokinetic parameters of molidustat following a single oral or intravenous dose of 5 mg/kg in cats:

Route	Oral	Intravenous
T_{max}† (hour)	1 (0.67 – 1.5)	Not Applicable
C_{max} (µg/mL)	3.86 ± 0.495	26.0 ± 8.42††
AUC_{last} (hour*µg/mL)	13.0 ± 2.98	16.5 ± 2.97
AUC_{inf} (hour*µg/mL)	13.1 ± 2.99	16.6 ± 3.01
$T_{1/2}$ (hour)	4.68 ± 0.661	6.28 ± 4.43

† Median and range are reported for T_{max} instead of arithmetic mean and standard deviation

†† C_0 back-extrapolated concentration at time 0 by a log-linear regression of first 2 data points following intravenous administration

C_{max}: Maximum observed plasma concentration

T_{max}: Time to maximum observed plasma concentration

AUC_{last}: Area under the plasma concentration versus time curve from time of dosing to the last quantifiable concentration

AUC_{inf}: Area under the plasma concentration versus time curve from time of dosing extrapolated to infinity

$T_{1/2}$: Terminal elimination half-life

The pharmacokinetic parameters of molidustat after 6 daily oral doses of 5 mg/kg bw were evaluated in a second laboratory study using 8 healthy, young adult cats (4 neutered males, 4 spayed females). Minimal accumulation of molidustat in the plasma pharmacokinetic profile was observed in the study.

REASONABLE EXPECTATION OF EFFECTIVENESS

A reasonable expectation of effectiveness may be demonstrated based on evidence such as, but not limited to, pilot data in the target species or studies from published literature.

Varenzin-CA1 is conditionally approved pending a full demonstration of effectiveness.

Additional information for Conditional Approvals can be found at www.fda.gov/animalca.

A reasonable expectation of effectiveness for Varenzin-CA1 for the control of nonregenerative anemia associated with CKD in cats is supported by a 28-day, masked, randomized, controlled field study. The study was conducted at 23 U.S. and 10 European Union veterinary clinics. The study included 21 client-owned cats with nonregenerative anemia associated with CKD. The enrolled cats weighed 2 to 6 kg and ranged from 4 to 17 years of age. The enrolled cats were randomized to treatment with molidustat oral suspension (not commercial formulation) (n=15) or vehicle control (n=6). Cats were dosed based on body weight at a minimum dose of 5 mg molidustat/kg bw or an equivalent volume of vehicle control, administered orally once daily for 28 days. One molidustat-treated cat, which was dehydrated on Study Day 28, was excluded from the Study Day 28 effectiveness analysis because the dehydration may have affected the cat's HCT results. Treatment success was based on an absolute increase of ≥4 percentage points in HCT observed on Study Day 28 compared to Study Day 0, or a relative increase of 25% in HCT on Study Day 28 compared to Study Day 0. The treatment success rate in the molidustat-treated group was numerically superior to the vehicle control group on Study Day 28 (50% [7/14] vs. 16.7% [1/6]). Eight cats from the effectiveness phase were enrolled in a continuation phase, which lasted an additional 56 days, and received, depending on their PCV, either 2.5 mg/kg or 5 mg/kg bw of the same molidustat oral suspension formulation. The continuation phase was a multi-center, unmasked, non-randomized, uncontrolled field safety and effectiveness study. During the continuation phase of the study, PCV was evaluated weekly, and HCT was evaluated on Study Days 56 and 84 (± 2 days). Treatment success for each cat during the continuation phase was defined the same as during the 28-day study. On Study Day 56, 75% (6/8) of the cats were considered successes and on Study Day 84, 62.5% (5/8) of the cats were considered successes.

TARGET ANIMAL SAFETY

The safety of Varenzin-CA1 was established in 2 laboratory studies and 2 field safety and effectiveness studies (see **REASONABLE EXPECTATION OF EFFECTIVENESS** for details on the first field study).

Target Animal Safety Study

In a laboratory study, molidustat oral suspension (not commercial formulation) was administered orally to healthy 10 to 11-month-old male cats (6 cats per group) at doses of 2.5 mg/kg bw or 5 mg/kg bw daily for 56 or 28 consecutive days, respectively. Cats administered 2.5 mg molidustat/kg bw were euthanized on Study Day 57, and cats administered 5 mg molidustat/kg bw were euthanized on Study Day 29. Due to HCT values over the threshold of 60%, 2 cats dosed at 2.5 mg/kg bw and 1 dosed at 5 mg/kg were euthanized on Study Day 23; another cat dosed at 5 mg/kg bw was euthanized on Study Day 25. The control group (4 cats) were untreated. No clinically relevant changes related to molidustat were observed among the cats for food consumption and body weight. The most common physical exam findings included abnormal mucous membrane color, prolongation of capillary refill time (about 3 seconds), heart pounding, and tachycardia in the molidustat oral suspension groups. Polycythemia was noted in conjunction with these exam findings (all cats had HCTs greater than 50%).

Abnormal clinical pathology findings included a mild increase in serum potassium above baseline values in the 5 mg/kg bw group and a mild increase in serum creatinine above baseline in most cats in the molidustat groups (up to 21.6% in one 5 mg/kg bw cat). At necropsy, there was an apparent dose-dependent decrease in the mean kidney to brain ratio in the molidustat groups. Numerically lower (57.17% of control) mean thymus weight was recorded in cats administered molidustat at 5 mg/kg bw. Lower thymus weights were also noted in cats administered molidustat at 2.5 mg/kg bw. The administration of molidustat was associated with histopathological findings of congestion of the vasculature in the brain, thrombosis/hemostasis in the heart, prominent myocardial vessels, minimal edematous change of valves in the heart, and acute thrombosis of large pulmonary arteries in the lung. These findings were attributed to the pharmacologic mode of action (erythropoiesis via HIF-PH inhibition) of molidustat oral suspension.

Exploratory Pharmacokinetic and Pharmacodynamic Study

Molidustat oral suspension (not commercial formulation) was administered orally to 10 male and 12 female, healthy 22 to 24-month-old cats at doses of 5 mg/kg bw (5% oily suspension, 6 cats) or 10 mg/kg bw (10% oily suspension, 5 cats; or 10% aqueous suspension, 5 cats) daily for 24, 16, or 16 consecutive days, respectively.

The control group (6 cats) were administered an oily suspension vehicle-only control for 24 days. Study Day 0 was the first day of drug administration, and all cats remained on study for evaluation until Study Day 104. No clinically relevant changes related to molidustat were observed among the cats for food consumption, body weight, and physical examination. Molidustat oral suspension administration was associated with an apparent dose-related increase in vomiting. All cats in the 10 mg/kg bw groups showed a clinically relevant increase in serum creatinine on Study Day 12. One cat in the 10 mg/kg bw oily suspension group had an 86% increase in creatinine levels, which was just above the reference range, at Study Day 12. Similar increases in blood urea nitrogen were not found. All creatinine values in the 10 mg/kg bw groups returned to baseline by Study Day 97. A transient, mild increase in serum phosphorus was also noted on Study Day 12 (10 mg/kg bw groups) or Study Day 23 (5 mg/kg bw group). The increased values did not exceed the reference range for any cat and generally returned to baseline by Study Day 97. One cat in the 10 mg/kg bw oily suspension group showed a mild but clinically relevant increase in serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels on Study Day 12. There were no clinically relevant changes in other liver enzymes or total bilirubin. The cat also showed a concurrent 50% increase in creatinine on Study Day 12 that was at the upper end of the reference range. The rises in ALT, ALP, and creatinine on Study Day 12 values decreased by Study Day 97. There were no clinical signs related to hepatic or renal disease in this cat. The cause for the changes was not identified, but a direct drug effect or an indirect effect secondary to polycythemia could not be ruled out.

STORAGE CONDITIONS

Store at controlled room temperature 20°C – 25°C (68°F – 77°F). Excursions permitted between 15°C and 30°C (59°F – 86°F).

HOW SUPPLIED

27 mL of a 25 mg/mL oral suspension in a bottle with an oral dosing syringe.

Manufactured for:
Elanco US Inc.
Greenfield, IN 46140 USA
Product of Germany

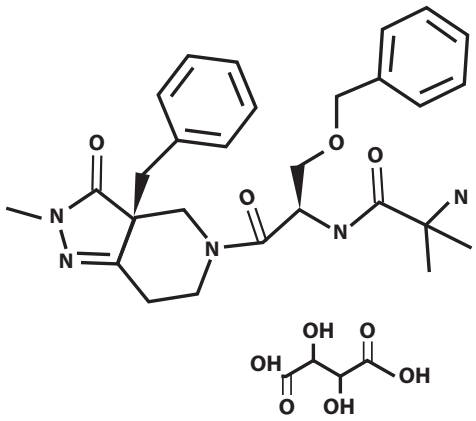
Revision date - 05/2023

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.

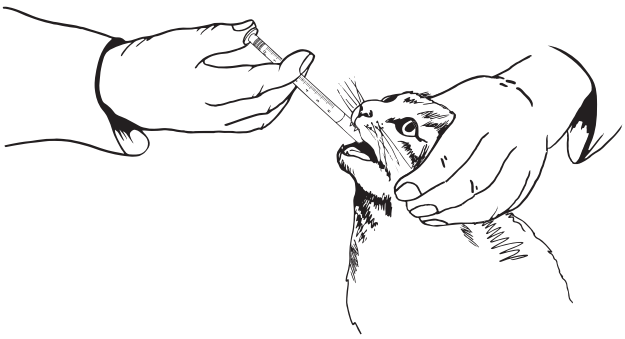
DESCRIPTION:
ELURA (capromorelin oral solution) is a colorless to yellow or orange, clear liquid. Each milliliter of ELURA contains 20 mg of capromorelin tartrate. The empirical formula is $C_{28}H_{35}N_5O_4 \cdot C_4H_6O_6$ and the molecular weight 655.70. The chemical name is 2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridi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