

## 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.



# Varenzin - CA1 (molidustat oral suspension)

Varenzin<sup>™</sup>-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<sup>1</sup>



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.<sup>2</sup>

"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.<sup>2</sup>

Anemia develops slowly, so most cats appear to cope well with it.<sup>3</sup> 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),<sup>4</sup> many see targeting the progression of CKD as a much higher priority.<sup>3</sup>

#### 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<sup>3</sup>:

- 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

## Available treatments are frustrating for vets<sup>3</sup>

The Ohio State University

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)<sup>5</sup>
- 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

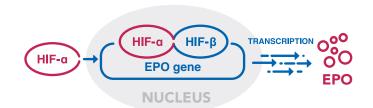


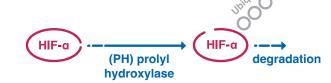
EPO is a hormone released from the kidneys that signals bone marrow to make red blood cells.



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.<sup>2</sup>

#### **EPO PRODUCTION IN HEALTHY VS. FAILING KIDNEYS**







EPO production is regulated by the protein hypoxia inducible factor (HIF). HIF is made of two key components,  $HIF_{\alpha}$  and  $HIF_{\beta}$ , that work together to regulate blood cell production.<sup>6</sup>

In low blood oxygen conditions in the microenvironment of REP cells, HIF $_{\alpha}$  and HIF $_{\beta}$  join (dimerize) to induce genetic transcription for EPO production.



With higher oxygen conditions in the kidney,  $HIF_{\alpha}$  is degraded by prolyl hydroxylase (PH) which stops dimerization, preventing excess EPO production in the body.<sup>6</sup>

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.<sup>7,8</sup>

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

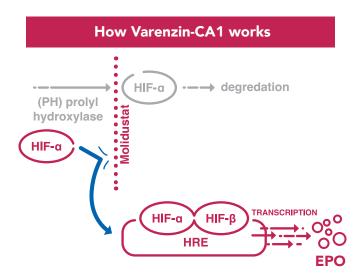
### A PARADIGM SHIFT IN CKD-RELATED ANEMIA TREATMENT



Developed exclusively for cats, Varenzin-CA1 works by inhibiting PH, the enzyme responsible for initiating the breakdown of HIF<sub>a</sub>.

By preventing HIF $_{\alpha}$  from being degraded, HIF $_{\alpha}$  can dimerize with HIF $_{\beta}$  and code for EPO.<sup>1</sup>

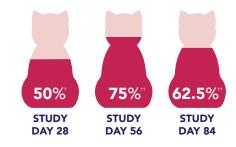
- This mode of action induces the genetic transcription of EPO, increasing both EPO and red blood cell production in the body.<sup>1</sup>
- As EPO increases, red blood cell production and the oxygen-carrying ability of the blood both increase.<sup>7,8</sup>
- By stimulating the cat's body to produce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

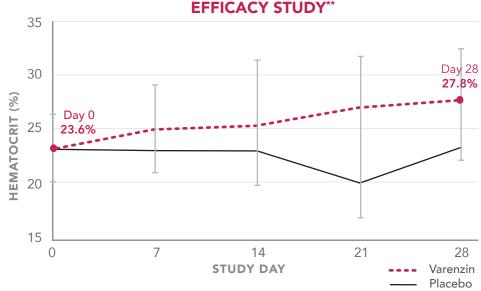


## EMPOWERED WITH EFFICACY

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

## PERCENTAGE OF CATS WITH INCREASED HEMATOCRIT\*





## 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.<sup>1</sup>

**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.

<sup>\*</sup>Relative increase in HCT of >25% above baseline or an absolute increase in HCT of ≥4% above baseline \*\*28-day pilot field study

<sup>&</sup>lt;sup>†</sup>Field effectiveness and safety study, effectiveness phase

<sup>&</sup>lt;sup>††</sup>Field effectiveness and safety study, continuation phase



## BREAKTHROUGH INNOVATION MEETS AT-HOME CONVENIENCE

Varenzin<sup>™</sup>-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**



Shake well before use. Remove screw cap.



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



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



Administer directly into the cat's mouth.

## **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



#### REFERENCES

<sup>1</sup>Varenzin Freedom of Information Summary, NADA 141-571.

<sup>2</sup>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.

<sup>3</sup>Elanco Animal Health. Data on file.

<sup>4</sup>Boyd LM, et al. Survival in cats with naturally occurring chronic kidney disease (2000-2002). J Vet Intern Med. 2008;22:1111-17.

<sup>5</sup>GoodRx [Internet]. Darbepoetin alfa; [cited 2023 May 8]; Available from: https://www.goodrx.com/darbepoetin-alfa.

<sup>6</sup>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.

<sup>7</sup>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.

<sup>8</sup>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. 
<sup>9</sup>Nolan KA, Wenger RH. Source and microenvironmental regulation of erythropoietin in the kidney. Curr Opin Nephrol Hypertens. 2018;27(4):277-85.



- 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<sup>1</sup>
- 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.

