VARENZIN-CA1- molidustat oral suspension
Elanco US Inc.

Elanco$_{TM}$

Varenzin™-CA1

(molidustat oral suspension)

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

25 mg/mL

For oral use in cats only

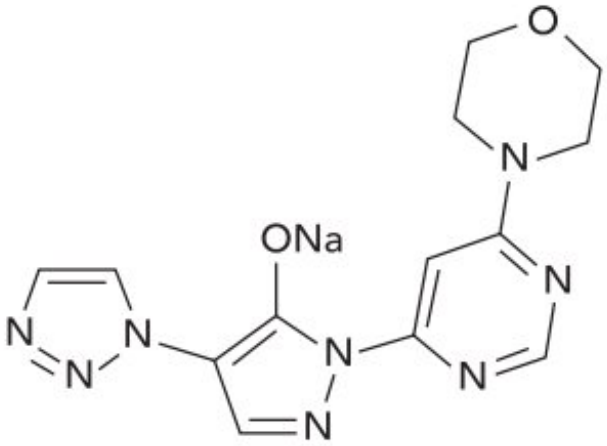
Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-571. It is a violation of Federal law to use this product other than as directed in the labeling.

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 each treatment cycle.

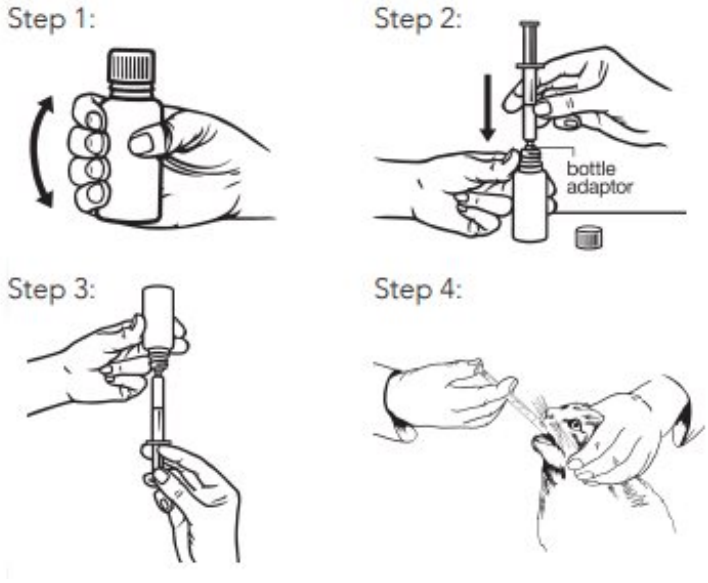
Table 1. Dosing Chart

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:



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 14^{th} 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.
Indianapolis, IN 46221 USA
Product of Germany

Revision date - 05/2025

PA513312X

Elanco™

Principal Display Panel – Varenzin-CA1 25 mg/mL

27 mL

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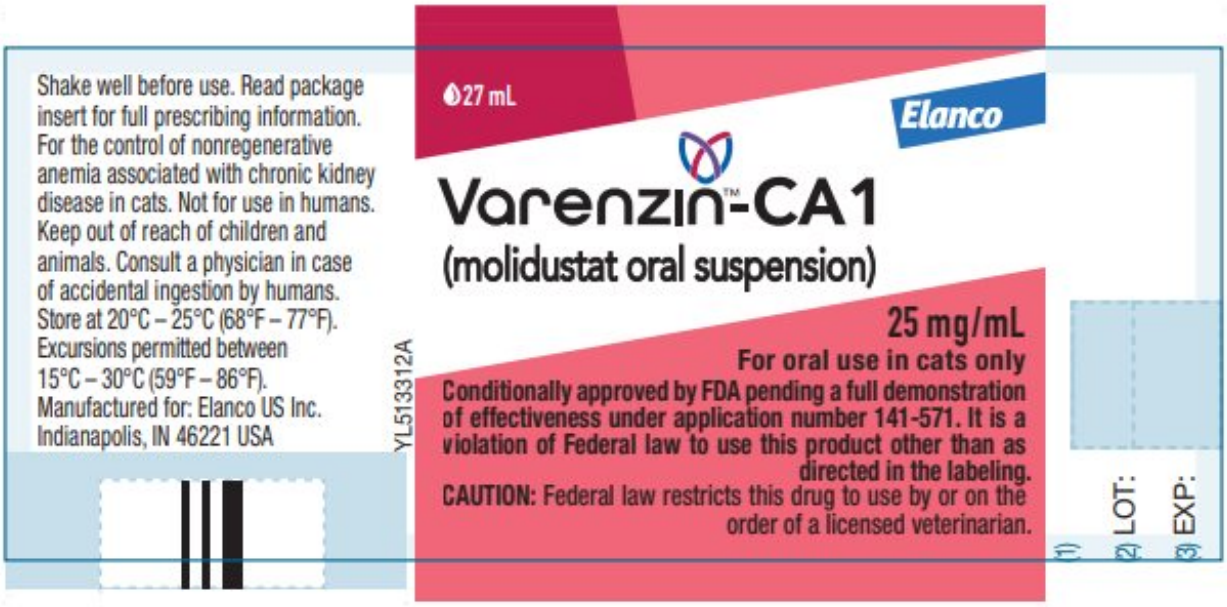

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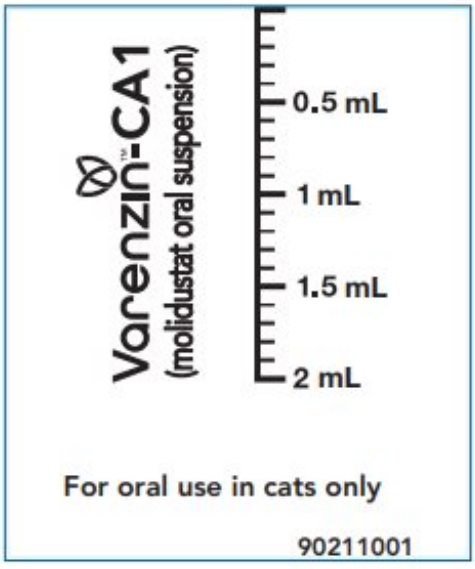

VARENZIN-CA1

molidustat oral suspension

Product Information			
Product Type	PRESCRIPTION ANIMAL DRUG	**Item Code (Source)**	NDC:58198-3697
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MOLIDUSTAT SODIUM (UNII: CI0NE7C96T) (MOLIDUSTAT - UNII:9JH486CZ13)	MOLIDUSTAT SODIUM	25 mg in 1 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:58198-3697-1	1 in 1 CARTON		
1		27 mL in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Conditional NADA	NADA141571	05/01/2023	

Labeler - Elanco US Inc. (966985624)

Revised: 7/2025 Elanco US Inc.