Bexacat™
(bexagliflozin tablets)

The search for a non-insulin alternative is over.

INSULIN FREE

Give cats the once-daily tablet that provides effective glycemic control.

INDICATION Bexacat is indicated to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

IMPORTANT SAFETY INFORMATION Before using this product, it is important to read the entire product insert, including the boxed warning. See accompanying label for full prescribing information.

Elanco™

Bexacat™ (bexagliflozin tablets) is the FIRST and ONLY non-insulin oral treatment specifically designed for feline diabetes in otherwise healthy cats not previously treated with insulin.

Bexacat™
(bexagliflozin tablets)

BREAKTHROUGH SGLT2 INHIBITOR

Innovative sodium-glucose cotransporter 2 (SGLT2) inhibitor provides effective glycemic control without injections

EFFECTIVE GLYCEMIC CONTROL

On the first day of dosing, average blood glucose concentrations decreased by 67.8% in just 8 hours[1] with minimal risk of hypoglycemia

ONE TABLET ONCE A DAY

Convenient, needle-free, once-daily tablet dosed independently of patient weight ensures dosing accuracy*

*Approved for cats weighing 6.6 lbs. (3.0 kg) or greater.

IMPORTANT SAFETY INFORMATION: Cats treated with Bexacat may be at an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis, both of which may result in death. As diabetic ketoacidosis and euglycemic diabetic ketoacidosis in cats treated with Bexacat may result in death, development of these conditions should be treated promptly, including insulin administration and discontinuation of Bexacat.

IMPORTANT SAFETY INFORMATION: Do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus. The use of Bexacat in cats with insulin-dependent diabetes mellitus, or the withdrawal of insulin and initiation of Bexacat, is associated with an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis and death.

The challenge of treating feline diabetes.

Feline diabetes mellitus (DM) is a common chronic illness that requires continuing, lifelong medical care and owner education to prevent complications and ensure good quality of life.[2]

Successful treatment depends on close owner observation of clinical signs and periodic evaluation by a veterinarian.[2]

Traditionally, insulin injections have been the only way to manage diabetes in cats.

LESS THAN HALF COMPLY

Less than half of cat owners comply with proper daily insulin treatment.[1]

Potential treatment failure is high.

Pet owner compliance, costs and impact on lifestyle all contribute to potential treatment failure in diabetic cats.[3]

Unfortunately, these challenges can lead to owners electing euthanasia.

Treating feline diabetes can be frustrating for pet owners.

It can take weeks to find the optimal dosage.

Insulin requires refrigeration.

The majority of cats must be given injections twice per day.[4]

Dosing errors can occur, which can result in hypoglycemia.

On average

1 IN 10

diabetic pets are euthanized at diagnosis.[3]

Compliance presents further challenges for pet owners:

88% FIND IT INTERFERES WITH SCHEDULE

88% of pet owners find that the dosing schedule interferes with their daily routine.[1]

62% FIND IT DIFFICULT

62% of pet owners find it too difficult to administer treatment or have an uncooperative cat.[1]

An additional

1 IN 10

were euthanized within a year of treatment because of lack of success or compliance.[3]

IMPORTANT SAFETY INFORMATION: Bexacat™ (bexagliflozin tablets) should not be initiated in cats with: Anorexia, dehydration, or lethargy at the time of diagnosis of diabetes mellitus, as it may indicate the presence of other concurrent disease and increase the risk of diabetic ketoacidosis. A feline pancreatic lipase (fPL) level > 5.3 mcg/L, diagnostic imaging consistent with pancreatitis, a history of pancreatitis, or current clinical signs suggestive of pancreatitis.

Discover the needle-free diabetes treatment made for cats.

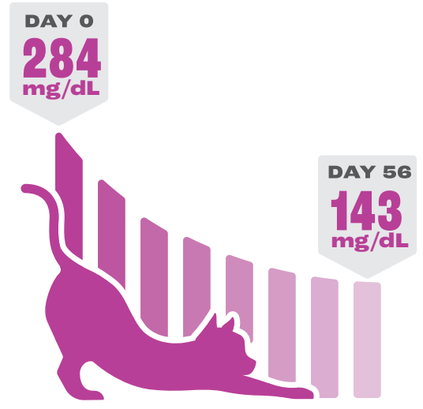
How Bexacat™ (bexagliflozin tablets) works

Bexacat is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. SGLT2 is the primary transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation.

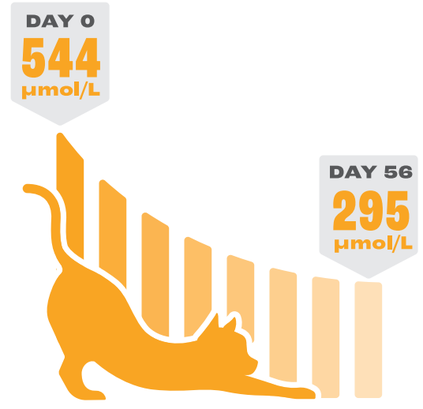
- By inhibiting SGLT2, Bexacat reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, increasing urinary glucose excretion.
- This increase in glucose excretion through the urine, in turn, lowers the plasma glucose concentration in the blood.

Give cats the once-daily tablet alternative that provides effective glycemic control

Mean Blood Glucose Curve



Fructosamine Levels



Treatment Success

83.1% (64/77) OF CATS WERE CONSIDERED TREATMENT SUCCESSES AT DAY 56*

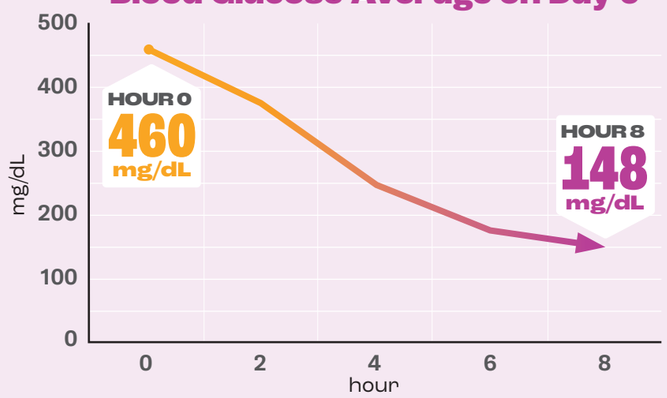
>85% OF CATS WERE CONSIDERED TREATMENT SUCCESSES AT DAY 728**

Treatment success was defined as improvement in at least one blood glucose variable and improvement in at least one clinical sign of diabetes mellitus.

Backed by efficacy.

In a series of multicenter field studies, Bexacat was proven to be effective at improving glycemic control in cats.

Blood Glucose Average on Day 0



Percentage of cats with improvements in clinical signs by Day 56*

68.0% CATS IMPROVED IN POLYURIA

74.0% CATS IMPROVED IN POLYDIPSIA

57.1% CATS IMPROVED IN POLYPHAGIA

54.6% CATS IMPROVED IN BODY WEIGHT

*In a 180-day multicenter field effectiveness and safety study.
**In an extended use study of cats previously treated with bexagliflozin.

IMPORTANT SAFETY INFORMATION: Sudden onset of hyporexia/anorexia, lethargy, dehydration, or weight loss in cats receiving Bexacat should prompt immediate discontinuation of Bexacat and assessment for diabetic ketoacidosis, regardless of blood glucose level.

IMPORTANT SAFETY INFORMATION: Persistent plasma bexaglifozin blood levels, increased serum calcium, and the long-term use of Bexacat may increase the risk of urothelial carcinoma.

Target Animal Safety Study

In a well-controlled laboratory margin of safety study of healthy, non-diabetic cats, Bexacat™ (bexagliflozin tablets) was administered orally to 28 fasted, lean, intact adult cats at doses of at least 1X (eight cats), 3X (eight cats) and 5X (12 cats) the maximum exposure dose (5 mg/kg) once daily for 26 weeks.

Polyuria, glucosuria (with a corresponding increase in food consumption), loose stools, diarrhea and ketonuria were reported more frequently in cats that received Bexacat than in control cats.

There were drug-related clinically insignificant increases in calcium, magnesium and cholesterol levels as well as decreases in creatinine and amylase levels, blood pressure and heart rate values.

Gross necropsy demonstrated treatment-related observations of mild, diffuse zonal patterns in the liver in the 5X group.

There were no clinically relevant drug-related effects on hematology and coagulation parameters and organ weight values.

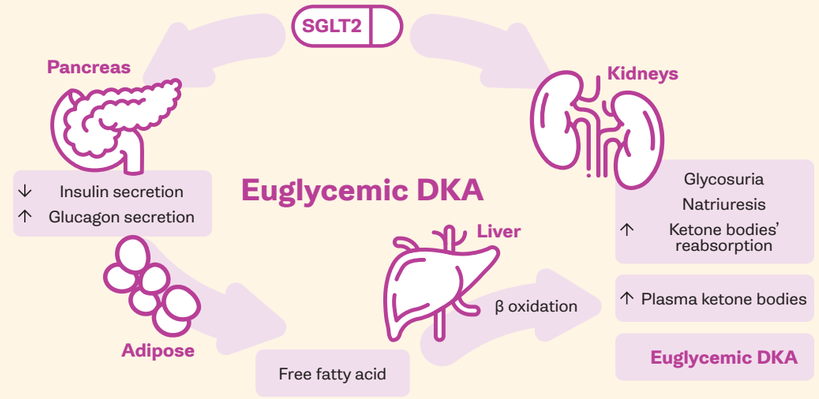
Scan to watch the Bexacat Mode of Action video.

The potential for diabetic ketoacidosis (DKA) and euglycemic diabetic ketoacidosis (eDKA)

Cats treated with Bexacat may be at an increased risk of developing DKA or eDKA, which can be life-threatening if not treated appropriately.

eDKA is DKA that occurs with a normal blood glucose concentration:

- eDKA occurs almost exclusively in patients treated with an SGLT2 inhibitor
- It is unlikely to have been seen in practice previously
- Insulin administration is critical to these patients, despite normoglycemia



How to respond to DKA and eDKA diagnosis

If cats are anorexic, lethargic, dehydrated or losing weight, measure beta-hydroxybutyrate (BHBA).
If DKA or eDKA is discovered:

- Discontinue Bexacat treatment immediately.
- Treat with insulin (even if euglycemic).
- Supplement with intravenous dextrose.
- Provide nutritional support to prevent or treat hepatic lipidosis.

Due to the risk of developing DKA or eDKA, do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus.

IMPORTANT SAFETY INFORMATION: See Animal Safety Warnings and Precautions for other important criteria and screening tests prior to initiating treatment with Bexacat. Discontinue Bexacat and contact a veterinarian immediately if the cat develops anorexia, lethargy, vomiting, diarrhea, or weakness.

Improve compliance with convenience.

Bexacat™ (bexagliflozin tablets) is a convenient, needle-free, once-daily flavored tablet dosed independently of patient weight that helps ensure dosing accuracy.*

No dose titration needed

Can be given with food for convenient administration

No refrigeration required

*Approved for cats weighing 6.6 lbs. (3.0 kg) or greater.

Patient Selection

Once newly diagnosed with DM, a patient may be considered eligible for Bexacat provided:

Cat is clinically well

- Normal hydration
- Not lethargic
- Eating well

No significant disease

Baseline blood work shows no significant renal or hepatic disease, DKA or pancreatitis.

- BHBA ≤ 3.6 mmol/L (37 mg/dL) or ≤ 2.4 mmol/L (25 mg/dL) with history of renal disease or metabolic acidosis
- No other lab values consistent with DKA
- No evidence suggesting pancreatitis, including clinical signs, diagnostic imaging or feline pancreas-specific lipase (fPL) > 5.3 mcg/L

Has not been treated with insulin previously

Bexacat should not be initiated in cats with:

- Laboratory values consistent with diabetic ketoacidosis, including elevated urine or serum ketones, and metabolic acidosis (high anion gap, or decreased bicarbonate, pH, or partial pressure carbon dioxide [PaCO2] levels).
- A BHBA > 3.6 mmol/L (37 mg/dL) or > 2.4 mmol/L (25 mg/dL) and the cat history of renal disease or metabolic acidosis.

IMPORTANT SAFETY INFORMATION: Cats treated with Bexacat may be at an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis, both of which may result in death.

What is beta-hydroxybutyrate (BHBA)?

BHBA is a ketone body produced by fat metabolism and is the predominant ketone body at the onset of DKA.

Because of this, it is essential to monitor cats for BHBA during patient selection and throughout treatment with Bexacat™ (bexagliflozin tablets):

Serum ketone levels increase before urine ketone levels, so serum BHBA is a sensitive indicator of DKA.

- Urine dipsticks do not detect the presence of BHBA; therefore, equipment that can measure serum BHBA is necessary for accurate monitoring.

Two ways to measure BHBA

Portable, handheld ketone monitors that measure for serum BHBA are recommended. The Abbott® Precision Xtra has been validated for BHBA detection in diabetic cats.5

Send blood samples to reference laboratories such as IDEXX.

A note about BHBA levels

There are no established normal values for BHBA in diabetic cats. Because BHBA levels can vary from cat to cat and at various time points, it is critical to measure this value before initializing Bexacat to establish a baseline value for your patients. Monitoring this value throughout treatment is also an essential part of evaluating cats during treatment.

Beta-hydroxybutyrate (BHBA) Unit Conversion Chart

mmol/L	0.1	0.3	0.5	0.7	0.9	1.1	1.3	1.5	1.7	1.8	2.0	2.2
mg/dL	1.0	3.0	5.0	7.0	9.0	11.0	13.0	15.0	17.0	19.0	21.0	23.0
mmol/dL	2.4	2.6	2.8	3.0	3.2	3.4						
mg/L	25.0	27.0	29.0	31.0	33.0	35.0						
mmol/L	3.6	3.8	4.0	4.2								
mg/dL	37.0	39.0	31.0	43.0								

BHBA values appropriate for beginning Bexacat

BHBA values appropriate for beginning Bexacat if no history of renal disease or metabolic acidosis

Bexacat should not be initiated

Monitoring Guidelines

Time After Start of Treatment	Recommended Monitoring	Action
3-5 days	• Physical exam, including weight • BHBA level	• **Continue Bexacat** unless cat is losing weight or BHBA is not decreasing, then discontinue Bexacat and transition to insulin • **Recheck at the two-week time point**
2 weeks	• Physical exam, including weight • BHBA level • Glucose curve and fructosamine	• **Continue Bexacat** unless cat is losing weight or if BHBA is rising, then discontinue Bexacat and transition to insulin • If average blood glucose (BG) from an 8-hour curve ≥ 250mg/dL and/or serum fructosamine is above reference range, monitor closely • **Recheck in two weeks**
4 weeks	• Physical exam, including weight • BHBA level • Glucose curve and fructosamine	• **Continue Bexacat** unless cat is losing weight or if BHBA is rising, then discontinue Bexacat and transition to insulin • If average BG from an 8-hour curve ≥ 250mg/dL and/or serum fructosamine is above reference range, monitor closely • **Recheck in four weeks**
8 weeks	• Physical exam, including weight • BHBA level • Glucose curve and fructosamine	• **Continue Bexacat** unless cat is losing weight or if BHBA is rising, then discontinue Bexacat and transition to insulin • If average BG from an 8-hour curve ≥ 250mg/dL and/or serum fructosamine is above reference range, transition to insulin • **Recheck every 90 days or as medically indicated**

IMPORTANT SAFETY INFORMATION: See Animal Safety Warnings and Precautions for other important criteria and screening tests prior to initiating treatment with Bexacat. Discontinue Bexacat and contact a veterinarian immediately if the cat develops anorexia, lethargy, vomiting, diarrhea, or weakness.

Bexacat™
(bexagliflozin tablets)

Sudden onset of hyporexia/anorexia, lethargy, dehydration or weight loss in cats receiving Bexacat™ (bexagliflozin tablets) should prompt immediate discontinuation of Bexacat and assessment for diabetic ketoacidosis, regardless of blood glucose level.

Cats demonstrating poor glycemic control, including weight loss, an average blood glucose concentration from an 8-hour blood glucose curve ≥ 250 mg/dL and/or a fructosamine above reference range should be closely monitored. If poor glycemic control exists by Week 8, discontinue Bexacat and initiate insulin.

FEAR FREE
Taking the pet out of petrified.

Focused on Fear Free® experiences

Elanco is proud to be the exclusive Diabetes Category sponsor of Fear Free® because it's the right thing to do for pets and the people who care for them. Our products help veterinary professionals provide Fear Free® experiences — and we support them with Fear Free® content like podcasts, blogs and conference calls.

Interested in Fear Free® certification?

We're happy to help you with savings.

Learn more at fearfreepets.com.

[1]Elanco Animal Health. Data on file.

[2]Aptekmann K, Armstrong J, Coradini M, et al. Owner experiences in treating dogs and cats diagnosed with diabetes mellitus in the United States. J Am Anim Hosp Assoc. 2014. 2014;50(4):247-253.

[3]Niessen S, Hazuchova K, Powney S, et al. The big pet diabetes survey: perceived frequency and triggers for euthanasia. Vet Sci. 2017;4(27):1-13.

[4]Behrend E, Holford A, Lathan P, et al. 2018 AAHA diabetes management guidelines for dogs and cats. J Am Anim Hosp Assoc. 2022. Accessed online https://www.aaha.org/aaha-guidelines/diabetes-management/diabetes-management-home/November 6, 2022.

[5]Zeugswetter FK, Rebuzzi L. Point-of-care β-hydroxybutyrate measurement for the diagnosis of feline diabetic ketoacidaemia. J Small Anim Pract. 2012 Jun;53(6):328-31.

The search for a non-insulin alternative is over.

Bexacat™
(bexagliflozin tablets)

Provides effective glycemic control without injections

Minimal risk of hypoglycemia and no dosage changes during treatment

Convenient, needle-free, once-daily tablet dosed independently of patient weight ensures dosing accuracy*

*Approved for cats weighing 6.6 lbs. (3.0 kg) or greater.

Elanco™

Bexacat™
(bexagliflozin tablets)

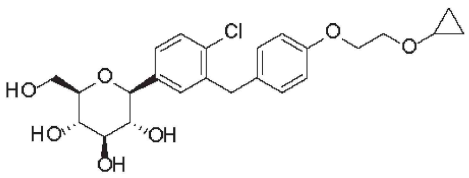
Elanco™

15 mg flavored tablets
For oral use in cats only
Sodium-glucose cotransporter 2 (SGLT2) inhibitor

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

WARNING: DIABETIC KETOACIDOSIS/EUGLYCEMIC DIABETIC KETOACIDOSIS
- **Cats treated with Bexacat may be at an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis (see Adverse Reactions). As diabetic ketoacidosis and euglycemic diabetic ketoacidosis in cats treated with Bexacat may result in death, development of these conditions should be treated promptly, including insulin administration and discontinuation of Bexacat (see Monitoring).**
- **Due to the risk of developing diabetic ketoacidosis or euglycemic diabetic ketoacidosis, do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus (see Contraindications).**
- **Bexacat should not be initiated in cats with anorexia, dehydration or lethargy at the time of diagnosis of diabetes mellitus or without appropriate screening tests (see Animal Safety Warnings).**

DESCRIPTION
Bexacat (bexagliflozin tablets) are flavored pentagonal, 10 mm, speckled white, brown, or tan biconvex with a characteristic odor. The empirical formula is $C_{24}H_{29}ClO_7$ and the molecular weight is 464.94 g/mol. The chemical name is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.
The chemical structure of bexagliflozin is:



INDICATION
Bexacat is indicated to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

DOSAGE AND ADMINISTRATION
Always provide the Client Information Sheet with the prescription.

Dosing Instructions
Administer one tablet by mouth to cats weighing 6.6 lbs (3.0 kg) or greater once daily, at approximately the same time each day, with or without food, and regardless of blood glucose level.

Monitoring
- Sudden onset of hyporexia/anorexia, lethargy, dehydration, or weight loss in cats receiving Bexacat should prompt immediate discontinuation of Bexacat and assessment for diabetic ketoacidosis, regardless of blood glucose level.
- During treatment with Bexacat, blood glucose, fructosamine, serum β-hydroxybutyrate (BHBA), serum feline pancreas-specific lipase (fPL), liver parameters, serum cholesterol and triglycerides; and body weight and clinical signs should be routinely monitored.
  - Increasing or persistently elevated feline pancreas-specific lipase or liver parameters should prompt further evaluation for pancreatitis and/or hepatic disease and consideration for discontinuing Bexacat.
  - BHBA is the predominate ketoacid in diabetic ketoacidosis. Bexacat should be discontinued if a notable reduction in BHBA is not observed after initiation of Bexacat, or if BHBA persistently rises after an initial reduction.
  - Cats with increasing or persistently elevated cholesterol and triglyceride levels may be at an increased risk for developing diabetic ketoacidosis or euglycemic diabetic ketoacidosis.
  - Bexacat should be discontinued if poor glycemic control, as described below, develops.
- During the first 8 weeks after initiation of Bexacat, assessment of glycemic control and clinical improvement should be evaluated.
  - A physical examination, an 8-hour blood glucose curve, serum fructosamine and body weight should be assessed at 2, 4 and 8 weeks.
  - Cats demonstrating poor glycemic control, including weight loss, an average blood glucose concentration from an 8-hour blood glucose curve ≥ 250 mg/dL, and/or a fructosamine indicating poor glycemic control should be closely monitored.
  - Bexacat should be discontinued, and initiation of insulin considered in cats demonstrating poor glycemic control, as described above, at 8 weeks.
- Cats may present with diabetic ketoacidosis and a normal blood glucose concentration (euglycemic diabetic ketoacidosis). Delay in recognition and treatment of diabetic ketoacidosis and euglycemic diabetic ketoacidosis may result in increased morbidity and mortality.
- Development of diabetic ketoacidosis and euglycemic diabetic ketoacidosis requires the following actions:
  - Discontinuation of Bexacat
  - Prompt initiation of insulin therapy
  - Administration of dextrose or other carbohydrate source, regardless of blood glucose concentration
  - Appropriate nutritional support should be promptly initiated to prevent or treat hepatic lipidosis.

For more information refer to **CONTRAINDICATIONS** and **WARNINGS.**

CONTRAINDICATIONS
- Do not use Bexacat in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus. The use of Bexacat in cats with insulin-dependent diabetes mellitus, or the withdrawal of insulin and initiation of Bexacat, is associated with an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis and death.
- Due to risk of severe adverse reactions, do not use Bexacat in cats with evidence of hepatic disease or reduced renal function.

WARNINGS
User Safety Warnings
Not for use in humans. Keep out of reach of children. Consult a physician in case of accidental ingestion by humans.

Animal Safety Warnings
- Bexacat should not be initiated in cats with:
  - Anorexia, dehydration, or lethargy at the time of diagnosis of diabetes mellitus, as it may indicate the presence of other concurrent disease and increase the risk of diabetic ketoacidosis.
  - An fPL level > 5.3 mcg/L, diagnostic imaging consistent with pancreatitis, a history of pancreatitis, or current clinical signs suggestive of pancreatitis.
  - Laboratory values consistent with diabetic ketoacidosis, including elevated urine or serum ketones, and metabolic acidosis (high anion gap, or decreased bicarbonate, pH, or partial pressure carbon dioxide [$PaCO_2$] levels).
  - A BHBA > 37 mg/dL, or if BHBA is > 25 mg/dL and the cat has a history of renal disease or metabolic acidosis.
- Persistent plasma bexagliflozin concentrations and reduced clearance of Bexacat, represented as the presence of plasma half-lives in excess of 24 hours, may result in prolonged clinical effects such as glucosuria and/or euglycemia despite discontinuation of Bexacat in some cats with hepatic disease and/or reduced renal function, including cats with clinically undetectable disease at the time of Bexacat initiation. Reduced clearance of Bexacat may contribute to persistent glucosuria, resulting in an osmotic diuresis and dehydration that requires appropriate hydration support. These cats may require hospitalization, which may be protracted, for sequalae such as diabetic ketoacidosis, euglycemic diabetic ketoacidosis, or hepatic lipidosis.
- Cats should be screened for urinary tract infections and treated, if indicated, when initiating Bexacat. Treatment with Bexacat may increase the risk for urinary tract infections (see **Adverse Reactions**). Cats treated with Bexacat should be monitored for urinary tract infections and treated promptly. Consider discontinuation of Bexacat in cats with recurrent urinary tract infections.
- Bexacat may cause increased serum calcium concentrations. Bexacat should be discontinued in cats with persistent increases in serum total calcium or ionized calcium because of increased risk of forming calcium containing uroliths (see **Adverse Reactions**).
- Long term use of Bexacat may increase the risk of urothelial carcinoma (see **Adverse Reactions**).
- Keep Bexacat in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS
- Bexacat should be discontinued in cats who develop diarrhea unresponsive to conventional therapy.
- Consider temporary discontinuation of Bexacat in cats during times of decreased caloric intake, such as surgery or decreased appetite, as administration of Bexacat in these cats may increase the risk of diabetic ketoacidosis or hepatic lipidosis.
- The osmotic diuretic effects of Bexacat may contribute to inappropriate urination in some cats (see **Adverse Reactions**).
- Polyphagia as a compensatory response to caloric wasting from glucosuria may persist in up to 80% of cats, despite evidence of adequate glycemic control, and may lead to progressive weight gain.
- Approximately 20-30% of cats may have persistent polyuria and/or polydipsia secondary to Bexacat-induced osmotic diuresis and may be a risk factor for dehydration-associated diabetic ketoacidosis.
- The concurrent use of volume depleting drugs in cats treated with Bexacat has not been evaluated.
- The safety of Bexacat in breeding, pregnant, and lactating cats has not been evaluated.

ADVERSE REACTIONS
Field Study
Eighty-four cats with newly diagnosed diabetes mellitus were enrolled in a 180-day multicenter field effectiveness and safety study. Safety data were evaluated in 84 cats treated with at least one dose of Bexacat. All cats received one tablet, once daily, regardless of body weight or blood glucose level. Seventy-two of the 84 enrolled cats completed the study. The most common adverse reactions included elevated blood urea nitrogen (BUN), vomiting, elevated urine specific gravity (USG), elevated serum fPL, diarrhea, anorexia, lethargy, and dehydration. The adverse reactions seen during the field study are summarized in Table 1 below.

Table 1. Adverse Reactions (n=84)

Adverse Reaction	Number (%)
Elevated BUN*	46 (54.8)
Vomiting	42 (50.0)
Elevated USG†	33 (39.3)
Elevated fPL‡	33 (39.3)
Diarrhea	32 (38.1)
Anorexia	31 (37.0)
Lethargy	17 (20.2)
Dehydration	16 (19.0)
Elevated symmetrical dimethylarginine (SDMA)	13 (15.5)
Weight loss	13 (15.5)
Urinary tract infection	12 (14.3)

Adverse Reaction	Number (%)
Elevated ALT and/or AST§	11 (13.1)
Hypercalcemia	8 (9.5)
Behavioral changes**	6 (7.1)
Proteinuria	5 (6.0)
Elevated creatinine	4 (4.8)
Elevated creatine kinase	4 (4.8)
Inappropriate urination	4 (4.8)
Death	3 (3.6)
Diabetic ketoacidosis	3 (3.6)
Pancreatitis	3 (3.6)
Euglycemic diabetic ketoacidosis	2 (2.4)
Hepatic lipidosis	2 (2.4)
Elevated alkaline phosphatase	2 (2.4)
Elevated total bilirubin	2 (2.4)
Constipation	2 (2.4)

* Most cats had elevations < 1.5 times the upper limit of normal (ULN).
† Elevations were predominantly attributable to dehydration and/or glucosuria.
‡ Most cats had one or more isolated elevations, followed by a return to previous values.
§ Of nine cats with elevations ≥ 1.5X ULN, 2 cats developed diabetic ketoacidosis and were transitioned to insulin. One cat developed diabetic ketoacidosis and hepatic lipidosis resulting in death (euthanasia). One cat developed anemia, progressive weight loss and fPL elevations resulting in death.
** Observations included hiding, agitation, aggression, vocalization, and anxious behavior.

Nine serious adverse reactions associated with Bexacat administration occurred during the study, including three cats who died or were euthanized. Of the three cats who died or were euthanized, two cats became clinically ill within 5 doses of Bexacat administration (range 3 to 5 doses). One cat with euglycemic diabetic ketoacidosis and hepatic lipidosis was euthanized due to further deterioration of its clinical condition, despite supportive treatment. One cat demonstrating anorexia, lethargy, dehydration, azotemia, and hypokalemia was euthanized without supportive treatment. One cat, who demonstrated a lack of effectiveness, anemia and hepatic lipidosis died on Day 77 despite supportive treatment and additional diagnostics. Six of the nine cats had serious adverse reactions that did not result in death or euthanasia. Five cats were treated for their clinical conditions and transitioned to insulin. Serious adverse reactions in these cats were associated with the following conditions (number of cats): euglycemic diabetic ketoacidosis (1); lack of effectiveness, diabetic ketoacidosis, elevated liver parameters (1); diabetic ketoacidosis (1); diabetic ketoacidosis and pyelonephritis (1); and lack of effectiveness, weight loss, dehydration (1). One cat with constipation and pancreatitis received supportive treatment and remained on Bexacat (bexagliflozin tablets).

Pilot Field Study

Eighty-nine cats with newly diagnosed diabetes mellitus were enrolled in a 56-day multicenter pilot field effectiveness and safety study, with continued use for up to 180 days. All cats received one tablet, once daily, regardless of body weight or blood glucose level. Safety data were evaluated for all 89 cats treated with at least one dose of bexagliflozin. The most common adverse reactions included elevated blood urea nitrogen (BUN), elevated urine specific gravity (USG), elevated serum feline pancreas-specific lipase, vomiting, diarrhea/loose stool, hyporexia/anorexia, lethargy, elevated serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and urinary tract infections. The adverse reactions seen in the pilot study are summarized in Table 2 below.

Table 2. Adverse Reactions (n=89)

Adverse Reaction	Number (%)
Elevated BUN*	51 (57.3)
Elevated USG†	43 (48.3)
Elevated fPL‡	39 (43.8)
Vomiting	39 (43.8)
Diarrhea/Loose Stool	29 (32.6)
Hyporexia/Anorexia	28 (31.4)
Lethargy	16 (18.0)
Elevated ALT and/or AST§	13 (14.6)
Urinary tract infection	13 (14.6)
Dehydration	10 (11.2)
Elevated symmetrical dimethylarginine (SDMA)	10 (11.2)
Behavioral changes**	9 (10.1)
Ketosis/Ketonuria	8 (9.0)
Weight loss	8 (9.0)
Proteinuria	8 (9.0)
Pancreatitis	7 (7.9)
Death	6 (6.7)
Anemia	6 (6.7)
Hepatopathy	6 (6.7)
Hypercalcemia	4 (4.5)
Elevated creatine kinase	4 (4.5)
Inappropriate urination	4 (4.5)
Peritonitis	3 (3.4)
Constipation	3 (3.4)
Elevated creatinine	2 (2.2)
Euglycemic diabetic ketoacidosis	2 (2.2)
Diabetic ketoacidosis	2 (2.2)
Hemolytic anemia	2 (2.2)
Elevated total bilirubin	2 (2.2)

* Most cats had elevations ≤ 1.5X upper limit of normal (ULN).
† Elevations were predominantly attributable to dehydration and/or glucosuria.
‡ Most cats had one or more isolated elevations, followed by a return to previous values.
§ Most elevations were ≤ 2X ULN. One cat had marked ALT and AST (9X and 6X upper limit of normal, respectively) elevations on Day 28. Following discontinuation of bexagliflozin, the liver enzymes decreased within 24 hours and returned to within reference range in 10 days.
** Observations included hiding, hyperactivity, vocalization, and abnormal behavior.

Twenty cats (22%) had at least one blood glucose value < 65 mg/dL recorded during 8-hour blood glucose curves. No clinical signs of hypoglycemia were observed and bexagliflozin dosing was not adjusted in any cat due to documented hypoglycemia. Nine serious adverse reactions associated with bexagliflozin administration occurred during the study, including six cats who died or were euthanized. Of the six cats who died or were euthanized, five became clinically ill within receiving 5 doses of bexagliflozin (range 1 to 5 doses). Four of the cats were euthanized due to further deterioration of their clinical condition despite supportive treatment. One cat died despite supportive treatment. Deaths were associated with the following conditions (number of cats): necrotizing pancreatitis and pancreatic abscess (1), pancreatitis and hepatic lipidosis (1), euglycemic diabetic ketoacidosis and severe hepatic lipidosis (1), pancreatitis and hepatic abscesses (1), diabetic ketoacidosis (1), and persistent polyuria and polydipsia and quality of life concerns (1).

Three of nine serious adverse reactions that did not result in death or euthanasia included the following (number of cats): acute hepatocellular injury (1), immune-mediated hemolytic anemia (1), and euglycemic diabetic ketoacidosis with concurrent pancreatitis and hepatopathy (1). Two cats with serious adverse reactions demonstrated persistent bexagliflozin blood plasma levels and elimination half-lives after discontinuation of bexagliflozin. One cat with renal and liver values within the reference range at screening was euthanized due to a continued decline in clinical condition despite treatment for euglycemic diabetic ketoacidosis and severe hepatic lipidosis. The second cat, noted to have IRIS (International Renal Interest Society) stage II renal disease and liver values within the reference range at screening, recovered following treatment for marked liver enzyme elevations above the reference range on Day 28.

Extended Use Field Study

One hundred twenty-five cats with diabetes mellitus that had previously completed a bexagliflozin field study were enrolled in a multicenter extended use field study. Cats were enrolled in the study for a range of 7 to 1064 days, with a mean of 329 days. Safety data were evaluated for all 125 cats treated with at least one dose of Bexacat (bexagliflozin tablets). All cats received one tablet, once daily, regardless of body weight or blood glucose level. Forty-nine of the 125 enrolled cats were withdrawn from the study due to adverse reactions, serious adverse reactions, death/euthanasia, lack of effectiveness, suspected diabetic remission, withdrawal of owner consent, or lost to follow up. The most common adverse reactions were similar to those noted in the previous field studies and included elevated USG (35.2%), vomiting (27.2%), elevated fPL (26.4%), anorexia (24.0%), diarrhea (22.4%), urinary tract infections (17.6%), lethargy (16.8%), and death (16.0%).

Twenty serious adverse reactions associated with Bexacat administration occurred during the study, all resulting in death or euthanasia. Clinical signs of hypoglycemia were observed in two of these cats. Deaths were associated with the following conditions (number of cats), with some cats experiencing multiple comorbidities (necropsy was not granted in all cases): euglycemic diabetic ketoacidosis (8); diabetic ketoacidosis (4); hepatic lipidosis (5); pancreatic necrosis/peripancreatic fat saponification (3); urothelial carcinoma (2); hypercalcemia, recurrent calcium containing cystic calculi (1); lack of effectiveness, weight loss, anorexia (1); lethargy, weight loss, pallor (1); chronic renal disease, glomerulonephritis (1); chronic enteropathy (1); hypoglycemia, possible pancreatitis (1).

CONTACT INFORMATION

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

INFORMATION FOR CAT OWNERS

Owners should be given the Client Information Sheet to read before Bexacat is administered. Owners should be advised to discontinue Bexacat and contact a veterinarian immediately if their cat develops anorexia, lethargy, vomiting, diarrhea, or weakness.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bexagliflozin is an inhibitor of sodium-glucose cotransporter 2 (SGLT2), the renal transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, bexagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion.

Pharmacokinetics

In a laboratory pilot study conducted to determine the prandial state of maximum exposure, systemic exposure for bexagliflozin was greater in the fasted state than in the fed state by 82% for the mean maximum observed plasma concentration (C_{max}), and by 54% for the mean area under the plasma concentration versus time curve (AUC) from dosing (time 0) to the last quantifiable concentration ($AUC_{0\text{-last}}$), respectively.

In a well-controlled margin of safety study (see **Target Animal Safety**), mean C_{max} was approximately dose-proportional over a dosage range of 5 mg/kg (1X) to 25 mg/kg (5X). Mean AUC from time 0 to 24 hours exposure was approximately dose-proportional over a dosage range of 5 to 15 mg/kg, but more than dose-proportional at 15 to 25 mg/kg. An increase in exposure (AUC_{0-24} and C_{max}), was observed in female cats compared to male cats on all evaluation days. Median time to reach peak plasma concentration (T_{max}) was approximately 0.5 hours (range 0.5 to 2 hours) and mean half-life ($T_{1/2}$) was approximately 5 hours across all dose groups. There was no accumulation of bexagliflozin following daily dosing of 5, 15, and 25 mg/kg in healthy non-diabetic cats. However, field studies showed that some diabetic cats had persistent bexagliflozin blood levels after discontinuation of the drug, which may be related to a decrease in liver function in some cats (see **Animal Safety Warnings**).

EFFECTIVENESS

Field Study

Eighty-four cats diagnosed with diabetes mellitus were enrolled in a 180-day multicenter field effectiveness and safety study. Enrolled cats included purebreds and mixed breeds, ranging in age from 3 to 19 years, and weighing between 7.3 to 24.3 lbs (3.3 to 11.3 kg). Cats received one tablet, once daily, regardless of body weight or blood glucose level. Treatment success was defined as improvement in at least one blood glucose variable (blood glucose curve mean or fructosamine) and improvement in at least one clinical sign of diabetes mellitus (polyuria, polydipsia, polyphagia, or body weight [weight gain or no weight loss]).

Of 77 cats included in the effectiveness-evaluable population:

- 64 cats (83.1%) were considered a treatment success on Day 56.
- The lower bound two-sided 90% confidence interval was 74.5%. Effectiveness was demonstrated if the lower bound of the confidence interval was > 66%.
- Mean blood glucose curve mean decreased from 284 mg/dL on Day 0 to 143 mg/dL on Day 56.
- Mean fructosamine levels decreased from 544 µmol/L prior to Day 0 to 295 µmol/L on Day 56.
- Improvements in the clinical signs of polyuria, polydipsia, polyphagia, and body weight on Day 56 were observed in 53 (68.8%), 57 (74.0%), 44 (57.1%), and 42 (54.6%) cats, respectively.
- 66 cats (85.7%) completed the 180-day study.

Pilot Field Study

Eighty-nine cats diagnosed with diabetes mellitus were enrolled in a 56-day, multicenter pilot field effectiveness and safety study with continued use for up to 180 days. Enrolled cats included purebreds and mixed breeds, ranging in age from 3 to 17 years and weighing 6.4 to 22.9 lbs (2.9 to 10.4 kg). Cats received one tablet, once daily, regardless of weight. Treatment success was defined as improvement in at least one blood glucose variable (blood glucose curve mean or fructosamine) and improvement in at least one clinical sign of diabetes mellitus (polyuria, polydipsia, polyphagia, or body weight [weight gain or no weight loss]). Of the 72 cats included in the effectiveness-evaluable population, 58 (80.6%) were considered treatment successes on Day 56.

TARGET ANIMAL SAFETY

In a well-controlled laboratory margin of safety study, Bexacat was administered orally to 28 fasted, healthy, lean, intact adult cats at doses of at least 1X (8 cats), 3X (8 cats), and 5X (12 cats) the maximum exposure dose (5 mg/kg) once daily for 26 weeks. The control group (8 cats) was sham dosed. The maximum exposure dose (5 mg/kg) was based on the assessment that the minimum weight of an eligible cat with diabetes mellitus is approximately 3 kg. Polyuria, glucosuria (with a corresponding increase in food consumption), loose stools and diarrhea, and ketonuria were reported more frequently in cats that received Bexacat than in control cats. There were drug-related clinically insignificant increases in calcium, magnesium, and cholesterol levels, and decreases in creatinine and amylase levels, and blood pressure and heart rate values. Gross necropsy demonstrated treatment-related observations of mild, diffuse zonal patterns in the liver. One cat with the observed zonal pattern had mild elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and a histopathological observation of minimal, multifocal necrosis in the liver. The histopathological finding did not correspond to the zonal patterns observed grossly. There were no clinically relevant, drug-related effects on hematology and coagulation parameters and organ weight values.

STORAGE CONDITIONS Bexacat should be stored at room temperature 68 to 77 ˚F (20 to 25 °C).

HOW SUPPLIED

Flavored tablet each containing 15 mg bexagliflozin; 30 or 90 tablets per bottle.

Approved by FDA under NADA # 141-566
Manufactured for: Elanco US Inc, Greenfield, IN 46140

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