Beta Hydroxybutyrate Blood Testing: Precise Ketone Testing for Monitoring Feline Diabetes

Why test for ketones?

- Routinely testing for ketones is critical to the health of cats taking SGLT2 inhibitors like Bexacat™ (bexagliflozin tablets) in order to detect ketone levels that could signal the risk for or onset of Diabetic Ketoacidosis (DKA) as quickly as possible.
- Elevations in ketone levels are associated with increased fat metabolism, which can be due to inadequate glucose utilization secondary to insufficient endogenous insulin production.
- Left unchecked, increasing ketone levels can lead to DKA.
- Prompt detection and intervention can reverse ketosis and prevent DKA.

What is beta-hydroxybutyrate (BHBA)?

- When glucose is not available for energy, fat is metabolized. Fat is broken down into three main ketone bodies: Betahydroxybuterate (BHBA), acetoacetate (AcAc) and acetone.
- Ketone production in DKA patients consists of 78% BHBA, 20% AcAc and 2% acetone.
- In human medicine, urine ketone testing has been widely superseded by point-of-care BHBA blood ketone tests. These blood tests are considered the standard for ketone measurement, especially for patients taking sodium-glucose cotransporter 2 (SGLT2) inhibitors.

Limitations of urine ketone testing using standard urine test strips

- **Only tests for acetoacetate**: Urine ketone testing only detects acetoacetate. Unfortunately, acetoacetate is not the predominant ketone produced in ketosis and DKA.
- **Time lag**: Blood testing more accurately measures current ketone levels. Urine testing can lag behind blood testing, potentially missing the earliest stages of DKA, and continue to yield positive readings after the resolution of DKA due to the longer half-life of AcAc.
  - The elimination half-life of AcAc ranges from 8–14 hrs, compared to only 0.8 – 3.1 hrs for Beta-hydroxybutyrate.
- **Semi-quantitative results**: Which can introduce user variability in the interpretation of color change. BHBA testing is quantitative and an exact number is provided.
- **False negatives and false positives**: Can occur due to urine concentration differences. Dilute urine, common in diabetic patients, can cause false negative AcAc values. Concentrated urine can cause false positives.
Two ways to test for BHBA

• Point-of-care test with a handheld ketone meter can be used in the hospital with a drop of blood. Results can be received in as little as 10 seconds, very similar to glucose testing with a handheld glucometer.1
  - The Precision Xtra® meter is the only handheld ketone meter that has been validated for use in diabetic cats.4
• IDEXX™ can perform this test with a turnaround time of 1-3 days
  - Note that BHBA levels are reported in mmol/L when using most handheld monitors, and in mg/dL when reported from IDEXX. To convert from mg/dL to mmol/L, divide by 10.3.

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 Bexacat, you must read the entire package insert, including the boxed warning. Call 1-888-545-5973 or visit https://www.elancolabels.com/us/bexacat for complete 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. Development of these conditions should be treated promptly, including insulin administration and discontinuation of Bexacat. 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. Sudden onset of hyporexia/anorexia, lethargy, dehydration, diarrhea that is unresponsive to conventional therapy, or weight loss in cats receiving Bexacat should prompt immediate discontinuation of Bexacat and assessment for diabetic ketoacidosis, regardless of blood glucose level. Bexacat should not be initiated in cats with pancreatitis, 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. Due to risk of severe adverse reactions, do not use Bexacat in cats with evidence of hepatic disease or reduced renal function. Consult a physician in case of accidental ingestion by humans.

REFERENCES:

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

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 IPI level > 5.3 mg/dL, 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 [PaCO2] levels).
  - A BHBA > 37 mg/dL, or if BHB 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 48 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 prolonged, for sequelae 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 IPI, 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)
<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number (%)</th>
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</thead>
<tbody>
<tr>
<td>Elevated BUN*</td>
<td>46 (54.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>42 (50.0)</td>
</tr>
<tr>
<td>Elevated USG†</td>
<td>33 (39.3)</td>
</tr>
<tr>
<td>Elevated IPI‡</td>
<td>33 (39.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (38.1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>31 (37.0)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>17 (20.2)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>16 (19.0)</td>
</tr>
<tr>
<td>Elevated symmetrical dimethylarginine (SDMA)</td>
<td>13 (15.5)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>13 (15.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 (14.3)</td>
</tr>
</tbody>
</table>

For more information refer to CONTRAINDICATIONS and WARNINGS.
Adverse Reaction | Number (%) | Number (%)
--- | --- | ---
Elevated ALT and/or AST$ | 11 (13.1) | Elevated creatine kinase | 4 (4.5)
Hypercalcemia | 8 (9.5) | Inappropriate urination | 4 (4.5)
Behavioral changes$$ | 6 (7.1) | Peritonitis | 3 (3.4)
Proteinuria | 5 (6.0) | Constipation | 3 (3.4)
Elevated creatinine | 4 (4.8) | Elevated creatinine | 2 (2.2)
Elevated creatinine kinase | 4 (4.8) | Euglycemic diabetic ketoacidosis | 2 (2.2)
Inappropriate urination | 4 (4.8) | Diabetic ketoacidosis | 2 (2.2)
Death | 3 (3.8) | Hemolytic anemia | 2 (2.2)
Diabetic ketoacidosis | 3 (3.8) | Elevated total bilirubin | 2 (2.2)
Pancreatitis | 3 (3.8) | **Most cats had elevations $\leq 1.5X$ upper limit of normal (ULN).**
Euglycemic diabetic ketoacidosis | 2 (2.4) | $^*$ Elevations were predominantly attributable to dehydration and/or glucosuria.
Hepatic lipidosis | 2 (2.4) | $^*$ Most cats had one or more isolated elevations, followed by a return to normal values.
Elevated alkaline phosphatase | 2 (2.4) | § Most elevations were $\leq 2X$ ULN. One cat had marked ALT and AST ($8X$ and $6X$ upper limit of normal, respectively) elevations on Day 28. Following discontinuation of bexalgliflozin, the liver enzymes decreased within 24 hours and returned to within range in 10 days.
Elevated total bilirubin | 2 (2.4) | **Observations included hiding, hyperactivity, vocalization, and abnormal behavior.
Constitution | 2 (2.4) | 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 bexalgliflozin dosing was not adjusted in any cat due to documented hypoglycemia. Nine serious adverse reactions associated with bexalgliflozin 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 5 days of treatment (range 1 to 5 days). Four of the six 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): acute hepato cellular injury (1), immune-mediated hemolytic anemia (1), and euglycemic diabetic ketoacidosis with concurrent pancreatitis and hepatopathy (1).

Pilot Field Study

Eight-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 at least once a day of Bexacat (bexalgliflozin 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, and other reasons follow up. The most common adverse reactions were similar to those noted in the previous field studies and included elevated UG (35.2%), vomiting (27.2%), elevated IFL (26.4%), anxiety (24.0%), diarrhea (22.4%), ur-inary 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 (necrosis was not granted in all cases): euglycemic diabetic ketoacidosis (3), diabetic ketoacidosis (4), hepatic lipidosis (5), pancreatic necrosis/peripancreatic fat necrosis (2), ulcer ophthalamic (2), hypercalce- mouria, recurrent calcium containing cystic calculi (1); lack of effectiveness, weight loss, anxiety (1); lethargy, weight loss, pallor (1); chronic renal disease, g lomerulonephritis (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-VEIS or http://www.fda.gov/reportanimalmeds.

**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**
Bexalgliflozin 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, bexalgliflozin 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 bexalgliflozin 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(last)).
In a well-controlled margin of safety study (see **Target Animal Safety**), mean $C_{\text{max}}$ 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$_{\text{max}}$ and $C_{\text{max}}$), was observed in female cats compared to male cats on all evaluation days. Median time to reach peak plasma concentration ($T_{\text{max}}$) 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 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 assumption 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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