**Patient Selection and Monitoring for Diabetic Cats**

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

**IMPORTANT SAFETY INFORMATION:**
- Once newly diagnosed with diabetes, your patient may be considered eligible for Bexacat™ – the **FIRST and ONLY non-insulin oral treatment** specifically indicated to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.
- Before using this product, it is important to read the entire product insert, including the boxed warning. See accompanying package insert for full prescribing 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.

### START HERE

**Can your patient be treated with Bexacat?**

#### Patient History and Physical Exam
- Any previous insulin therapy?
- Anorexia, lethargy or dehydration at diagnosis?
- Any history of pancreatitis?
- Has been diagnosed with diabetic ketoacidosis (DKA)?

**Did you answer YES to ANY of the above questions?**

Your patient is **NOT A CANDIDATE** for Bexacat.

**Did you answer NO to ALL of the above questions?**

Your patient is **CANDIDATE** for Bexacat. Initiate treatment and monitoring.

If your patient has a urinary tract infection, institute antibiotic therapy and begin Bexacat treatment.

Do not use Bexacat concurrently with insulin.

### Baseline Bloodwork Results

- Any evidence of DKA?
- Evidence of liver disease?
- Evidence of significant renal disease (IRIS stage III or higher)?
- Are beta-hydroxybutyrate (BHBA) levels > 37 mg/dL (3.6 mmol/L)?
  - BHBA levels > 25 mg/dL (2.4 mmol/L) if the patient has a history of renal disease or metabolic acidosis?
- Evidence suggesting pancreatitis, including clinical signs, diagnostic imaging or feline pancreatic lipase (fPL) > 5.3 mcg/L?

**Did you answer YES to ANY of the above questions?**

Your patient is **NOT A CANDIDATE** for Bexacat.

**Did you answer NO to ALL of the above questions?**

Your patient is **CANDIDATE** for Bexacat. Initiate treatment and monitoring.

If your patient has a urinary tract infection, institute antibiotic therapy and begin Bexacat treatment.

Do not use Bexacat concurrently with insulin.
### Treatment Monitoring Guidelines

<table>
<thead>
<tr>
<th>Time After Treatment</th>
<th>Recommended Monitoring</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–5 days</td>
<td>Physical exam, including weight, BHBA level</td>
<td>- <strong>Continue Bexacat</strong> unless cat is losing weight or BHBA is not decreasing, then discontinue Bexacat and transition to insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- <strong>Recheck at the 2-week time point</strong></td>
</tr>
<tr>
<td>2 weeks</td>
<td>Physical exam, including weight, BHBA level</td>
<td>- <strong>Continue Bexacat</strong> unless cat is losing weight or if BHBA is rising, then discontinue Bexacat and transition to insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If average blood glucose (BG) from an 8-hour curve $\geq 250\text{mg/dL}$ and/or serum fructosamine is above reference range, monitor closely</td>
</tr>
<tr>
<td></td>
<td>Physical exam, including weight, BHBA level</td>
<td>- <strong>Recheck in 2 weeks</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>Physical exam, including weight, BHBA level</td>
<td>- <strong>Continue Bexacat</strong> unless cat is losing weight or if BHBA is rising, then discontinue Bexacat and transition to insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If average BG from an 8-hour curve $\geq 250\text{mg/dL}$ and/or serum fructosamine is above reference range, monitor closely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- <strong>Recheck in 4 weeks</strong></td>
</tr>
<tr>
<td></td>
<td>Physical exam, including weight, BHBA level</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 weeks</td>
<td>Physical exam, including weight, BHBA level</td>
<td>- <strong>Continue Bexacat</strong> unless cat is losing weight or if BHBA is rising, then discontinue Bexacat and transition to insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If average BG from an 8-hour curve $\geq 250\text{mg/dL}$ and/or serum fructosamine is above reference range, transition to insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- <strong>Recheck every 90 days or as medically indicated</strong></td>
</tr>
<tr>
<td></td>
<td>Physical exam, including weight, BHBA level</td>
<td></td>
</tr>
</tbody>
</table>

**Discontinue Bexacat if the following occur:**
- Development of diarrhea unresponsive to conventional therapy
- During times of decreased caloric intake such as surgery

**Assess for DKA/euglycemic DKA** (eDKA, diabetic ketoacidosis with normal blood sugar) if any of the following occur:
- Anorexia, lethargy, dehydration, weight loss
- Poor or worsening glycemic control by week 8 or after week 8
- Increasing fructosamine or no decrease in initial levels
- Increasing BHBA or no decrease in initial levels
- Persistent or progressive hypertriglyceridemia and/or hypercholesterolemia

**If DKA/eDKA develops:**
- Discontinue Bexacat
- Promptly initiate insulin therapy
- Maintain dextrose infusion, as necessary, to allow for sustained insulin administration
- Promptly initiate appropriate nutritional support to prevent or treat hepatic lipidosis

**Evaluate for concurrent disease** if any of the following occur:
- Increasing Spec fPL
- Increasing liver parameters
- Persistent or progressive hypercalcemia
- Persistent or recurrent urinary tract infections
During treatment with Bexacat, blood glucose, fructosamine, serum β-hydroxybutyrate, and ketone bodies should be monitored at approximately the same time each day, with or without food, and regardless of blood glucose level. Dogs and cats that have not previously treated with insulin are at increased risk for development of diabetic ketoacidosis, regardless of blood glucose level. 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)-4-[5-(4-chloro-2-cyclopropoxybenzyloxy)benzyl[[(3S)-3-hydroxyethyl]tetrahydro-2H-pyran-3-yl]thiophene-2-carboxylic acid. The chemical structure of bexagliflozin is:

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 FPL level > 5.3 mcg/dL, 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 BHB > 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 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 prolonged, for sequelae such as diabetic ketoacidosis, euglycemic diabetic ketoacidosis, or hepatic lipodosis.
- 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 urolithic clinical disease (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 lipodosis.
- 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 15% of animals, 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 depletion 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 study and efficacy 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, death/euthanasia, lack of effectiveness, suspected diabetic remission, withdrawal of consent, and mortality.

Average number of blood glucose curves = 46 per cat. The number (%) of adverse reactions based on pilot field study data and the effectiveness population are shown in the table below:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number (%)</th>
</tr>
</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>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.
**CONTRAINDICATIONS**

- Bexacat should not be used in cats with diabetes mellitus who have previously developed glucosuria and/or glucosuria (euglycemic diabetic ketoacidosis). Delay in recognition and treatment of diabetic ketoacidosis, do not use Bexacat in cats with diabetes mellitus who have previously developed glucosuria and/or glucosuria (euglycemic diabetic ketoacidosis).

- **Prompt initiation of insulin therapy**
- **Bexacat should be discontinued if poor glycemic control, as described below, develops.**

**ADVERSE REACTIONS**

**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 were treated with at least one dose of Bexacat (bexagliflozin tablets). Of 77 cats included in the effectiveness-evaluable population:

- Anemia 6 (6.7)
- Elevated ALT and/or AST § 11 (13.1)

**Pilot Field Study**

- Dehydration 16 (19.0)
- Elevation of ALT and/or AST § 51 (57.3)
- Elevated USG† 43 (48.3)
- Elevated IFL‡ 39 (43.8)
- Vomiting 39 (43.8)
- Diarrhea/Loose Stool 29 (32.6)
- Hypoglycemia/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)

**Clinical Pharmacology**

**Mechanism of Action**

Bexagliflozin is an inhibitor of sodium-glucose cotransporter 2 (SGLT2), the renal transporter responsible for reabsorption of glucose from 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 (Cmax), and by 54% for the mean area under the plasma concentration versus time curve (AUC) from dosing (time 0) to the last quantifiable concentration (AUClast), 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_{max} 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.

**ADVERSE REACTIONS**

Table 1. Adverse Reactions (n=84)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>6</td>
<td>6.7</td>
</tr>
<tr>
<td>Behavioral changes**</td>
<td>9</td>
<td>10.1</td>
</tr>
<tr>
<td>Dehydration</td>
<td>10</td>
<td>11.2</td>
</tr>
<tr>
<td>Dehydration nephropathy</td>
<td>8</td>
<td>9.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>4.8</td>
</tr>
<tr>
<td>Elevated creatine kinase</td>
<td>4</td>
<td>4.8</td>
</tr>
<tr>
<td>Euglycemic diabetic ketoacidosis</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Hepatic lipidosis</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>4</td>
<td>4.8</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Insulin-dependent diabetes</td>
<td>3</td>
<td>3.6</td>
</tr>
<tr>
<td>Lethargy</td>
<td>16</td>
<td>18.0</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3</td>
<td>3.6</td>
</tr>
<tr>
<td>Polyuria</td>
<td>6</td>
<td>6.7</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>6</td>
<td>6.7</td>
</tr>
<tr>
<td>Polyphagia</td>
<td>6</td>
<td>6.7</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Peritonitis nephropathy</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Recurrent peritonitis</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Skin necrosis</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Skin necrosis/peripancreatic fat saponification</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Urolithiasis</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8</td>
<td>9.5</td>
</tr>
</tbody>
</table>

**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

Bexacat, Elanco and the diagonal bar logo are trademarks of Elanco or its affiliates.

© 2022 Elanco or its affiliates

September 2022