Date of Approval: December 8, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-566

Bexacat™

(bexagliflozin tablets)

Cats

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

Sponsored by:

INCREVET INC

Executive Summary

Bexacat™ (bexagliflozin tablets) is approved to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin. The oral tablets are administered to cats weighing 3.0 kg or greater once daily, with or without food and regardless of blood glucose level.

Bexagliflozin is a sodium-glucose cotransporter 2 inhibitor and its pharmacodynamic effect is to induce glucosuria. The drug works by reducing reabsorption of filtered glucose in the kidneys, resulting in increased urinary glucose excretion.

Safety and Effectiveness

The sponsor conducted an 8-week pilot field study with a 4-month extended safety evaluation, a 6-month field study, and an extended use field study to evaluate the safety and effectiveness of Bexacat™ in client-owned cats diagnosed with diabetes mellitus. In all three studies, enrolled cats had hyperglycemia, glucosuria, and an elevated serum fructosamine in addition to at least one clinical sign associated with diabetes mellitus. The studies included purebreds and mixed breeds of both sexes with a range of ages and weights. There were no control groups in any of the studies. Starting on Day 0, all cats received one 15 mg tablet of Bexacat™ orally once daily. The dose was not adjusted for body weight, glycemic control, or clinical signs.

For the pilot and 6-month field studies, a cat was considered a treatment success if there was an improvement in at least one blood glucose variable (mean 8-hour blood glucose curve or fructosamine) and one clinical sign of diabetes mellitus on Day 56. In both studies, over 80% of cats were treatment successes and demonstrated improved glycemic control. Mean 8-hour blood glucose curves improved in over 84% of cats and mean fructosamine improved in over 77% of cats. Polyuria improved in over 68% of cats, polydipsia improved in over 70% of cats, and polyphagia improved in over half of the cats. The most common adverse reactions included elevated blood urea nitrogen; vomiting; elevated urine specific gravity, mainly due to dehydration and/or glucosuria; elevated serum feline pancreas-specific lipase; diarrhea or loose stool; hyporexia or anorexia; lethargy; and dehydration.

The pilot field study identified significant safety concerns related to treatment with bexagliflozin. Due to these serious adverse reactions, including death and euthanasia, several safety mitigation measures were implemented to improve the safe use of the drug, including more stringent screening for pancreatitis and diabetic ketoacidosis, and confirming cats had a consistently good appetite in the week leading up to the initiation of bexagliflozin.

The safety mitigation measures developed and implemented during the pilot study were incorporated into the second field study and improved the overall safety profile of Bexacat™. There were half as many deaths observed in this field study (3 deaths) than in the pilot study (6 deaths). The most significant safety concerns with the use of Bexacat™ are diabetic ketoacidosis and euglycemic diabetic ketoacidosis. Insulin-dependent cats may be at an increased risk of these conditions when treated with Bexacat™.

Cats enrolled in the extended use study had completed prior field studies and were either re-started on Bexacat™ or continued uninterrupted on the drug. Cats were

enrolled in the study for a range of 7 to 1064 days, with a mean of 329 days. Treatment success was considered a secondary variable and determined by a single-point blood glucose concentration or fructosamine at each study visit. Over 85% of the cats included in the effectiveness assessment met the treatment success criteria. The most common adverse reactions were similar to those noted above for the previous field studies.

Multiple serious adverse reactions associated with Bexacat™ administration occurred during the extended use study, all resulting in death or euthanasia. The study showed that cats can develop diabetic ketoacidosis or euglycemic diabetic ketoacidosis, regardless of how long they are on Bexacat™ and despite a history of having improved glycemic control on the drug. The risk of these conditions may be due to a gradual progression toward insulin-dependent diabetes mellitus in some cats.

The sponsor conducted a laboratory safety study in healthy adult cats to evaluate the toxicity of Bexacat™ when given orally at 0X, 1X, 3X, and 5X the labeled dose for 26 weeks. A cat weighing 3 kg (the minimum body weight for Bexacat™ treatment) and given a 15 mg tablet would receive 5.0 mg/kg. Therefore, the 1X dose was 5.0 mg/kg once daily.

Bexacat™ caused loose stool and diarrhea, polyuria, glucosuria, increased food consumption (presumably due to caloric loss associated with glucosuria), and ketonuria. These findings are consistent with the drug's mechanism of action. There were no clinically relevant changes in the clinical pathology and urinalysis results. However, the absence of clinically relevant changes in healthy cats doesn't mean that cats with diabetes mellitus won't develop clinically relevant changes while on Bexacat™.

The safety and effectiveness of Bexacat™ was also evaluated in a small pilot study in client-owned cats with diabetes mellitus that were being managed with insulin therapy at the time of enrollment. The study was conducted in two phases. In the first phase, cats were administered insulin. During the second phase, insulin therapy was discontinued, and cats were then administered Bexacat™. The study was terminated because of the number and severity of adverse reactions that occurred only during the Bexacat™ phase of the study.

Taken together, the studies show that Bexacat™ is effective for improving glycemic control in cats with diabetes mellitus and has an adequate safety profile when appropriate precautions are taken, and the drug is used according to the labeling. Although there are notable safety concerns with the use of Bexacat™, they can be mitigated by carefully screening cats before starting the drug, continued diligent monitoring regardless of the duration of or response to treatment, and knowing how the drug works and how to promptly recognize and appropriately treat serious and life-threatening adverse reactions.

Conclusions
Based on the data submitted by the sponsor for the approval of Bexacat™, FDA determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 141-566

B. Sponsor

INCREVET INC
200 Portland Street, Floor 3
Boston, MA 02114

Drug Labeler Code: 086079

C. Proprietary Name

Bexacat™

D. Drug Product Established Name

bexagliflozin tablets

E. Pharmacological Category

Sodium-glucose cotransporter 2 (SGLT2) inhibitor

F. Dosage Form

Tablet

G. Amount of Active Ingredient

15 mg

H. How Supplied

30 or 90 tablets per bottle

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

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.

K. Route of Administration

Oral

L. Species/Class

Cats

M. Indication

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

II. EFFECTIVENESS

The effectiveness of Bexacat™ (bexagliflozin tablets) to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin was evaluated in two field effectiveness studies (THR-1442-N-511 and INV-1442-N-010) and an extended use field study (INV-1442-N-002) in cats diagnosed with diabetes mellitus. The studies demonstrated that Bexacat™, with appropriate precautions and when used according to the labeling, is effective and has an adequate safety profile to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

A. Dosage Characterization

A dose of 15 mg bexagliflozin per cat, administered orally once daily as a fixed strength tablet, was selected as the recommended therapeutic dose to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin based on the results of laboratory pharmacokinetic and pharmacodynamic (PK/PD) studies and an oral tolerability study in healthy cats.

In a laboratory dose determination PK/PD study, single doses of bexagliflozin in non-final formulation capsules were administered orally at doses of 0.1, 0.3, 1.0, 3.0, and 10.0 mg/kg body weight to four healthy adult cats, with a washout period between doses. The pharmacodynamic effect (induction of glucosuria) was assessed by the measurement of urinary glucose excretion. Maximum urinary glucose excretion was observed at the 3 mg/kg dose. Variability in urinary glucose excretion at the 10 mg/kg dose was consistent with a plateau effect at approximately 3 mg/kg.

In an oral tolerability laboratory study evaluating a non-final capsule formulation, four healthy cats received a dose of bexagliflozin of 15 mg/kg every 12 hours for 21 days. Loose stools and/or diarrhea and weight loss were observed in all cats throughout the dosing period. Loose stools and diarrhea resolved with dosing termination and the mean body weight returned to pre-dosing level at the end of the two-week recovery period.

In another laboratory dose determination PK/PD study, four cats were administered non-final formulation fixed strength tablets of bexagliflozin, with no adjustment for body weight, at doses of 2.5, 5, 10, and 30 mg once daily for four days. The pharmacokinetic effect (drug exposure) was assessed by the measurement of bexagliflozin plasma levels. The pharmacodynamic effect (induction of glucosuria) was assessed by measurement of urinary glucose excretion and urine glucose to creatinine ratio. The drug exposure was proportional to the dose over the entire dose range. Bexagliflozin tablets produced greater urinary glucose excretion than comparable doses in the capsule

formulation. The study supports the use of a single size dose tablet with no adjustment for body weight.

A target dose range of 1.5 to 5 mg/kg body weight per day was selected to provide a balance between effectiveness and tolerability in cats with diabetes mellitus. A single, 15 mg fixed strength tablet, dosed once daily, with no adjustment for body weight, was chosen for further evaluation

B. Substantial Evidence

1. Pilot Field Study

Title: An 8-Week Pilot Study to Evaluate the Effectiveness of Bexagliflozin for the Management of Diabetes Mellitus in Cats Recently Diagnosed with Disease. (Study No. THR-1442-N-511)

Study Dates: June 2017 to June 2021

Study Locations:

Franklin, In	Waltham, MA
Quakertown, PA	Bartlesville, OK
Catonsville, MD	Wyoming, RI
Madison, WI	Cherryville, NC
Nixa, MO	Springfield, MO
Orange, CA	Lake Worth, FL
Veneta, OR	Raleigh, NC
Liverpool, NY	Overland Park, KS
Allentown, PA	Twinsburg, OH
Harrisburg, PA	Ancaster, ON, Canada
Horsham, PA	

Study Design: This was an open-label, prospective, unmasked, single arm, multicenter field study.

Objective: To evaluate the safety and effectiveness of bexagliflozin when administered once daily to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

Study Animals: The study enrolled 89 client-owned cats diagnosed with diabetes mellitus and presenting with at least one associated clinical sign. Enrolled cats included purebred and mixed breeds, ranging from 3 to 17 years of age, and weighing between 6.4 to 22.9 lbs (2.9 to 10.4 kg). There were 52 castrated males and 37 spayed females enrolled in the study.

Experimental Design: No concurrent control group was included in this study. All cats received one 15 mg tablet of bexagliflozin once daily for up to 6 months. The study was conducted in accordance with Good Clinical Practice.

Inclusion criteria: Cats were enrolled at the initiation of the study based on a diagnosis of diabetes mellitus according to the following criteria:

- Two separate blood glucose measurements > 250 mg/dL following a fast of ≥ 6 hours,
- Glucosuria,
- Serum fructosamine concentration > 450 µmol/L (this level was changed to > 360 µmol/L during the study due to a change in the laboratory analysis method and associated reference range), and
- At least one of the following clinical signs associated with diabetes mellitus: polyuria, polydipsia, polyphagia, or weight loss.

Following the observation of serious adverse events, including death or euthanasia, the following inclusion criterion was added: Cats with a consistently good appetite in the week leading up to initiation of bexagliflozin treatment.

Exclusion Criteria: The study was initiated with the following exclusion criteria:

a. Cats that were pregnant, lactating, in estrus, or intended for breeding.
b. Cats presenting with a history or diagnosis of heart failure, end-stage chronic kidney disease (IRIS III/IV), hyperthyroidism (based on elevated total T4 serum levels), neoplasia, feline idiopathic cystitis, major infectious processes (other than treatable acute urinary tract infections), or any other conditions that would, in the opinion of the Veterinarian, interfere with the collection or analysis of blood samples, the administration of bexagliflozin treatment, or the assessment of effectiveness.
c. Cats not expected to survive at least 56 days.
d. Cats with clinical pathology findings considered abnormal and clinically significant, apart from findings consistent with diabetes mellitus or previously identified stable chronic conditions.
e. Cats with a baseline alkaline phosphatase or alanine aminotransferase level three times the upper limit of normal.
f. Cats with a presumptive diagnosis of acromegaly based on elevated serum IGF-1 concentrations determined at screening, unless deemed acceptable for the study at the discretion of the Veterinarian and Owner.
g. Cats with a history of urinary tract surgery or planned elective surgeries requiring general anesthesia during the study period. Dental surgery and other surgeries were allowed on a case-by-case basis.
h. Cats treated with corticosteroids (topical and systemic), progestogens, insulin, or oral antihyperglycemic agents.

Following the observation of serious adverse events, including death or euthanasia, the following exclusion criteria were added:

a. Cats with an abnormal SNAP® fPL™[1] test result. This criterion was later modified to exclude cats with an abnormal SNAP® fPL™ result unless the cat was stable enough to wait for the results of a Spec fPL®[2] test.

[1] Semi-quantitative, in-house, *in vitro* test for the determination of pancreas-specific lipase level in feline serum.
[2] Quantitative *in vitro* test performed in a reference laboratory for the determination of pancreas-specific lipase level in feline serum.

Initially, if the SNAP® fPL™ test was abnormal AND the Spec fPL® result was > 10.0 µg/L, the cat was excluded. After continued adverse reactions related to pancreatitis were observed, the Spec fPL® exclusion criterion was lowered to 5.3 µg/L.

b. Cats with diabetic ketoacidosis. Initially, ketoacidosis was defined by assessment of serum anion gap, bicarbonate, and beta-hydroxybutyrate (BHBA) levels. Cats with serum BHBA concentrations > 25.0 mg/dL were excluded. The BHBA criterion was later modified to allow inclusion of cats with BHBA levels < 37.0 mg/dL if they had no history of renal disease or metabolic acidosis.

Owners of cats completing the 56-day effectiveness portion of the study were given the option of enrolling in the extended safety evaluation period for an additional four months, for a combined study duration of 180 days.

Drug Administration: Dosing started on Day 0. Cats received one tablet containing 15 mg bexagliflozin once daily at approximately 24-hour intervals. No adjustments were made for body weight, glycemic control, or clinical signs.

Measurements and Observations: On Days 0, 14, 28, and 56, Investigators performed physical examinations, obtained body weights, and performed an 8-hour (h) blood glucose curve for all cats. At screening and on Days 14, 28, and 56, samples were collected for serum fructosamine, urinalysis, hematology, and serum chemistry analyses. On Day 56, owners evaluated the improvement or worsening of their cat's observed polyuria, polydipsia, and polyphagia, compared to their Day 0 assessments.

During the four-month extended safety evaluation, at each monthly visit through Day 180, Investigators performed physical examinations, obtained body weights, and conducted analysis of serum fructosamine, urinalysis, hematology, and serum chemistry. On Day 180, an 8-hour blood glucose curve was performed for all cats remaining in the study.

Due to the observation of serious adverse events, including death or euthanasia, at approximately six months after study initiation, the following mitigations were instituted to improve the safe use of bexagliflozin:

- SNAP® fPL™ and Spec fPL® testing were conducted for all newly screened cats and a Spec fPL® analysis was added for subsequent clinical pathology assessments for all enrolled cats, including those cats continuing in the extended safety evaluation.
- Evaluation of symmetrical dimethyl arginine (SDMA) concentration was added to the clinical pathology assessments at each visit.
- To identify cats with diabetic ketoacidosis, BHBA levels were added to the clinical pathology assessment at each visit.

The primary effectiveness variable was the percentage of cats that were considered to have treatment success on Day 56. Treatment success was defined as improvement in at least one blood glucose variable [mean blood glucose (8-hour curve) < 250 mg/dL or fructosamine < 358 µmol/L] and in at least one clinical sign (polyuria, polydipsia, polyphagia, or body weight).

Statistical Method: A statistical analysis was not conducted.

Results: Of the 72 cats included in the effectiveness analysis population, 58 (80.6%) were considered a treatment success on Day 56. Mean values for blood glucose curve mean, fructosamine, and body weight are summarized in Table II.1.

Table II.1. Mean Blood Glucose Variables and Body Weight (n = 72)

Day	Glucose Curve Mean (mg/dL)	Fructosamine* (%ULN)	Weight (kg)
Screening/Day 0	447	192	5.5
14	178	119	5.6
28	156	102	5.7
56	148	94	5.8

*A change in measurement methodology at the central laboratory resulted in a shift in the upper limit of normal (ULN) from 356 µmol/L to 275 µmol/L thereafter. Data were harmonized by expression as a percentage of the ULN.
†The values included are the screening visit values for mean blood glucose and fructosamine levels, and Day 0 values for mean body weight.

Table II.2 summarizes the percentage of cats achieving improvement in each effectiveness variable at Day 56.

Table II.2. Number and Percentage of Cats Improved in Each Variable at Day 56 (n = 72)

Variable	Number	Percentage (%)
Mean blood glucose (8 h curve)	62	86.1
Fructosamine	58	80.6
Improvement in Polyuria	52	72.2
Improvement in Polydipsia	51	70.8
Improvement in Polyphagia	37	51.4
Weight gain or no weight loss	48	66.7

Adverse Reactions: Field safety was evaluated in 89 cats treated with at least one dose of bexagliflozin. Sixty of the 89 enrolled cats completed the 6-month study.

The most common adverse reactions included elevated blood urea nitrogen (BUN), elevated urine specific gravity (USG), elevated serum feline pancreas-specific lipase (fPL), vomiting, diarrhea/loose stool, hyporexia/anorexia, lethargy, and elevated serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST). The adverse reactions are summarized in Table II.3.

Table II.3 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 (4.5)
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 elevations (9X and 6X upper limit of normal, respectively) on Day 28. Following discontinuation of bexagliflozin, the values decreased within 24 hours and returned to within reference range in 10 days.
** Observations included hiding, hyperactivity, irritability, 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 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 5 doses of bexagliflozin administration (range 1 to 5 doses). Four cats were euthanized due to further deterioration of their clinical condition despite supportive treatment. One cat died despite supportive treatment.

Five deaths occurred prior to the implementation of the revised exclusion criteria that included SNAP® fPL™, Spec fPL®, and BHBA parameters. After implementation of the revised exclusion criteria, one death occurred.

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)
- Persistent polyuria and polydipsia and quality of life concerns (1).

Three of the 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)
- Euglycemic diabetic ketoacidosis with concurrent pancreatitis and hepatopathy (1)

Two of the cats listed above with serious adverse reactions had persistent plasma bexagliflozin concentrations, characterized by prolonged plasma elimination half-lives, following discontinuation of bexagliflozin:
- One cat was euthanized due to a continued decline in clinical condition despite treatment for euglycemic diabetic ketoacidosis and severe hepatic lipidosis. The cat had serum renal function and liver enzyme values within the reference range at screening.
- One cat with IRIS stage 2 renal disease and liver enzyme values within the reference range at screening developed acute hepatocellular injury on Day 28, characterized by marked liver enzyme elevations. The cat recovered following supportive treatment and discontinuation of bexagliflozin.

Conclusions: This study supports the effectiveness of bexagliflozin to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

Significant safety concerns were identified during the conduct of this pilot study. Safety mitigation measures (see Inclusion and Exclusion Criteria, above) were implemented during the study to address serious adverse events, including death or euthanasia. These measures improved the safety profile of bexagliflozin. Five deaths with a possible causal relationship to bexagliflozin occurred prior to the implementation of the safety mitigation measures. After implementation of the expanded exclusion criteria, one death with a possible causal relationship to bexagliflozin occurred.

With appropriate screening for risk factors prior to bexagliflozin initiation and regular monitoring during bexagliflozin administration, bexagliflozin has an adequate safety profile in cats with diabetes mellitus.

2. Field Study

Title: A 6 Month Pivotal Study to Evaluate the Safety and Effectiveness of Bexagliflozin for the Management of Diabetes Mellitus in Cats Recently Diagnosed with Disease. (Study No. INV-1442-N-010)

Study Dates: July 2019 to December 2021

Study Locations:

Franklin, IN	Overland Park, KS
Quakertown, PA	Ancaster, ON, Canada
Madison, WI	Ottawa, ON, Canada
Veneta, OR	Mounds View, MN
Liverpool, NY	Portland, ME
Harrisburg, PA	San Diego, CA
Cherryville, NC	Cumberland, ME
Springfield, MO	
Rochester, NY	
Virginia Beach, VA	

Study Design: This was an open-label, prospective, historical-controlled, single-arm, multicenter field study.

Objective: To evaluate the safety and effectiveness of Bexacat™ when administered once daily to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

Study Animals: The study enrolled 84 client-owned cats diagnosed with diabetes mellitus and presenting with at least one associated clinical sign. Enrolled cats included purebred and mixed breeds, ranging from 3 to 18.5 years of age, and weighing between 7.3 and 24.3 lbs (3.3 to 11.3 kg). There were 43 males and 41 females.

Experimental Design: No concurrent control group was included in this study. All cats received one 15 mg tablet of Bexacat™ once daily for up to 6 months. The effects of Bexacat™ were compared with historically derived data that represented the expected progression of diabetes mellitus in cats. The study was conducted in accordance with Good Clinical Practice.

Inclusion Criteria: Cats were enrolled in the study based on a diagnosis of diabetes mellitus according to the following criteria:

- Two separate blood glucose measurements > 250 mg/dL following a fast of ≥ 6 hours
- Glucosuria
- Serum fructosamine concentration > 358 µmol/L

- At least one of the following clinical signs associated with diabetes mellitus: polyuria, polydipsia, polyphagia, or weight loss

Exclusion Criteria: Cats were excluded from the study if they met any of the following criteria:

- Pregnant, lactating, in estrus, or intended for breeding
- Concurrent illness, including, but not limited to heart failure, end-stage chronic kidney disease (IRIS III/IV), hyperthyroidism (elevated Total T4 serum levels), uncontrolled elevated blood pressure, neoplasia, a history of feline idiopathic cystitis, or major infection processes (other than treatable acute urinary tract infections).
- Not expected to survive at least 56 days from the start of the study
- The presence of abnormal, clinically significant clinical pathology values including:
  - A baseline serum alkaline phosphatase and/or alanine aminotransferase level three times the upper reference range
  - A Spec® fPL (feline pancreas-specific lipase test) > 5.3 mg/L
  - A serum BHBA ≥ 37.0 mg/dL. Cats with BHBA > 25.0 mg/dL but < 37.0 mg/dL were only enrolled in the study if they had no history of either renal disease or acidosis.
- A history of urinary tract surgery or any planned elective surgeries; dental surgery was allowed after Visit 5, Day 56 (+3).
- Treated with insulin within 3 months prior to enrollment.
- Treatment with systemic corticosteroids within 2 weeks (short acting) or 8 weeks (long acting), or progestogens prior to enrollment.
- Cats with a history of inappetence during the week prior to presentation.

Cats with elevated IGF-1 serum concentrations determined at screening were allowed to continue enrollment in the study at the discretion of the investigator and owner.

Drug Administration: Dosing started on Day 0. Cats received one tablet containing 15 mg of Bexacat™ once daily at approximately 24-hour intervals. No adjustments were made for body weight, glycemic control, or clinical signs.

Measurements and Observations: On Days 0, 14, 28, 56, 84, 112, 140, and 180, Investigators performed physical examinations, obtained body weights, and performed an 8-hour (h) blood glucose curve for all cats. At the screening visit and on Days 14, 28, 56, 84, 112, 140, and 180, serum fructosamine, urinalysis, complete blood count, and serum chemistry analyses were conducted. On Day 56, owners evaluated the improvement or worsening of their cat's observed polyuria, polydipsia, and polyphagia, compared to their assessments made on Day 0.

The primary effectiveness variable was the percentage of cats that were considered to have treatment success on Day 56. Treatment success was defined as improvement in at least one blood glucose variable [mean blood glucose curve (8-hour curve) < 250 mg/dL or fructosamine < 358 µmol/L] and in at least one clinical sign (polyuria, polydipsia, polyphagia, or body weight).

Statistical Method: The experimental unit was the individual cat. The primary effectiveness variable was treatment success. A Clopper-Pearson exact test was conducted to calculate the 90% confidence interval for the proportion of treatment successes. The analysis was performed using the SAS FREQ procedure (SAS Institute, Cary NC; version 9.4). Effectiveness was demonstrated if the lower bound of the confidence interval was > 66%.

Results: Of the 77 cats included in the effectiveness analysis population, 64 (83.1%) were considered a treatment success on Day 56. The lower bound of the two-sided 90% confidence interval (CI) was 74.5% which met the criterion for demonstrating effectiveness of Bexacat™. Mean results for blood glucose curve mean, fructosamine, and body weight values are summarized in Table II.4.

Table II.4. Mean Blood Glucose Variables and Body Weight (n = 77)

Day	Glucose Curve Mean (mg/dL)	Fructosamine* (µmol/L)	Weight (kg)
Screening/Day 0	284	544	5.6
14	159	353	5.6
28	152	313	5.6
56	143	295	5.6
84	132	Lab 1 (N = 62): 279 Lab 2 (N = 7): 257	5.7
112	131	Lab 1 (N = 54): 277 Lab 2 (N = 14): 260	5.7
140	132	Lab 1 (N = 50): 278 Lab 2 (N = 17): 265	5.8
180	131	Lab 1 (N = 42): 295 Lab 2 (N = 25): 259	5.8

* Samples collected after November 17, 2020, were analyzed by Lab 2, which resulted in a shift in the upper limit of normal (ULN) from 275 µmol/L to 349 µmol/L. All samples analyzed through Day 56 were performed by Lab 1.
† The values included are the screening visit values for mean blood glucose and fructosamine levels, and Day 0 values for mean body weight.

Table II.5 summarizes the percentage of cats achieving improvement in each effectiveness variable at Day 56.

Table II.5: Number and Percentage of Cats Improved at Day 56 (n = 77)

Variable	Number	Percentage (%)
Mean blood glucose (8 h curve)	65	84.4
Fructosamine	60	77.9
Improvement in Polyuria	53	68.8
Improvement in Polydipsia	57	74.0
Improvement in Polyphagia	44	57.1
Weight gain or no weight loss	42	54.6

Adverse Reactions: Field safety was evaluated in 84 cats treated with at least one dose of Bexacat™. Seventy-two of the 84 enrolled cats completed the 6-month study.

The most common adverse reactions included elevated blood urea nitrogen (BUN), vomiting, elevated urine specific gravity (USG), elevated serum feline pancreas-specific lipase (fPL), diarrhea, anorexia, lethargy, and dehydration. The adverse reactions are summarized in Table II.6.

Table II.6. 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)
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.

No clinical signs of hypoglycemia were observed, and dosing was not adjusted in any cat due to hypoglycemia.

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 was euthanized due to further deterioration of its clinical condition despite supportive treatment. One cat was euthanized without treatment. One cat died on Day 77 despite supportive care and additional diagnostics. Six of the nine cats had serious adverse reactions that did not result in death or euthanasia.

Three deaths were associated with the following conditions (number of cats):
- Euglycemic diabetic ketoacidosis and hepatic lipidosis (1)
- Lack of effectiveness, anemia, hepatic lipidosis (1)
- Anorexia, lethargy, dehydration, azotemia, hypokalemia (1)

Six serious adverse reactions did not result in death or euthanasia. Five cats were treated for their clinical condition 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 enzymes (1)
- Diabetic ketoacidosis (1)
- Diabetic ketoacidosis and pyelonephritis (1)
- Lack of effectiveness, weight loss, dehydration (1)

One cat with constipation and pancreatitis was treated and remained on Bexacat™.

Conclusions: Bexacat™ is effective to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin. With appropriate precautions and when used according to the labeling, the study demonstrated an adequate safety profile in cats with diabetes mellitus not previously treated with insulin.

The safety mitigation strategies developed during the pilot field study (THR-1442-N-511) improved the overall safety profile of Bexacat™. There were half as many deaths observed in this field study (INV-1442-N-010) than were observed in the pilot field study (THR-1442-N-511). Six of nine cats with serious adverse reactions, predominantly diabetic ketoacidosis or euglycemic ketoacidosis, survived after treatment of the serious adverse reaction and transition to insulin in cats with diabetic ketoacidosis or euglycemic ketoacidosis. The most significant safety concerns with the use of Bexacat™ are diabetic ketoacidosis and euglycemic diabetic ketoacidosis. Insulin dependent cats may be at an increased risk of developing these conditions when treated with Bexacat™.

The results of the study demonstrate notable safety concerns that require careful screening of cats prior to initiation of Bexacat™, continued diligent monitoring, knowledge of how SGLT2 inhibitors work, and knowledge of how to promptly recognize and appropriately treat serious and life-threatening adverse reactions that may develop in cats treated with Bexacat™.

3. Extended Use Study

Title: An Extended Use Field and Effectiveness Study to Evaluate Bexagliflozin for the Management of Diabetes Mellitus in Cats (Study No. INV-1442-N-002)

Study Dates: June 2018 to December 2021. An Interim Study Report was generated with a data cutoff date of June 30, 2021

Study Locations:

Franklin, IN	Allentown, PA
Quakertown, PA	Raleigh, NC
Madison, WI	Overland Park, KS
Veneta, OR	Twinsburg, OH
Liverpool, NY	Ancaster, ON, Canada
Harrisburg, PA	Ottawa, ON, Canada
Waltham, MA	Mounds View, MN
Bartlesville, OK	Portland, ME
Wyoming, RI	Sand Diego, CA
Cherryville, NC	Cumberland, ME
Springfield, MO	Catonsville, MD
Rochester, NY	Nixa, MO
Virginia Beach, VA	Horsham, PA
Indianapolis, IN	

Study Design: This was an open-label, prospective, single-arm, multicenter field study.

Objective: To assess the safety and effectiveness of the extended use of Bexacat™ when administered once daily to improve glycemic control in otherwise healthy cats with diabetes mellitus that received Bexacat™ in prior field studies.

Study Animals: As of the data cutoff date of June 30, 2021, the study enrolled 125 cats diagnosed with diabetes mellitus that received Bexacat™ in prior field studies. Enrolled cats included purebred and mixed breeds, ranging from 4 to 19 years of age, and weighing between 6.2 and 22.7 lbs (2.8 to 10.3 kg). There were 70 males and 55 females.

Experimental Design: No concurrent control group was included in this study. All cats received one 15 mg tablet of Bexacat™ once daily. The study was conducted in accordance with Good Clinical Practice.

Inclusion Criteria: Cats previously diagnosed with diabetes mellitus that completed a previous field study for Bexacat™ and exhibited a consistently good appetite the week prior to Day 0 were enrolled in the study.

Exclusion Criteria: The exclusion criteria were the same as Study INV-1442-N-010 (field study), except cats that had uninterrupted Bexacat™ treatment after completion of a field study for Bexacat™ were exempt from the clinical pathology exclusion criteria.

Drug Administration: Dosing started (or continued from the previous study) on Day 0. Cats received one tablet containing 15 mg of Bexacat™ once daily at approximately 24-hour intervals. No adjustments were made for body weight, glycemic control, or clinical signs.

Measurements and Observations: At the screening visit and on Days 7, 56, and continuing at 56-day intervals, Investigators performed physical examinations, obtained body weights, collected samples for serum fructosamine, urinalysis, complete blood count, serum chemistry analyses and an in-clinic, single point, blood glucose measurement.

Treatment success was a secondary variable and was evaluated at each visit. Treatment success was defined as a single-point blood glucose concentration between 80 and 252 mg/dL or serum fructosamine measurement less than or equal to the laboratory reference range lower limit corresponding to good glycemic control.

Statistical Method: A statistical analysis was not conducted.

Results: Cats were enrolled in the study for a range of 7 to 1064 days, with a mean of 329 days. At each study visit, > 85% of the cats included in the effectiveness assessment met the treatment success criteria. Table II.7 summarizes the number of cats included in the effectiveness assessment by day.

Table II.7. Number of Cats in the Effectiveness Assessment by Day

Day	Number of Cats	Day	Number of Cats	Day	Number of Cats
0	121	336	46	728	7
7	117	392	38	784	5
56	112	448	31	840	1
112	103	504	25	896	1
168	83	560	20	952	1
224	69	616	15	1008	1
280	60	672	11	1064	1

Adverse Reactions: Field safety was evaluated in 125 cats treated with at least one dose of Bexacat™. 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 loss to follow up.

The most common adverse reactions were similar to those noted in previous field studies and included elevated USG, vomiting, elevated fPL, anorexia, diarrhea, urinary tract infections, lethargy, and death. The adverse reactions are summarized in Table II.8.

Table II.8. Adverse Reactions (n = 125)

Adverse Reaction	Number (%)
Elevated USG*	44 (35.2)
Vomiting	34 (27.2)
Elevated fPL†	33 (26.4)
Anorexia	30 (24.0)
Diarrhea	28 (22.4)
Urinary tract infection	22 (17.6)
Lethargy	21 (16.8)
Death	20 (16.0)
Elevated BUN‡	14 (11.2)
Dehydration	14 (11.2)
Weight loss	13 (10.4)
Inappropriate urination	12 (9.6)
Hypercalcemia	10 (8.0)
Elevated symmetrical dimethylarginine (SDMA)	9 (7.2)
Euglycemic diabetic ketoacidosis	8 (6.4)
Elevated ALT and/or AST§	8 (6.4)
Elevated total bilirubin	7 (5.6)
Pancreatitis	6 (4.8)
Elevated creatinine	6 (4.8)
Behavioral changes**	6 (4.8)
Hepatic lipidosis	5 (4.0)
Diabetic ketoacidosis	4 (3.2)
Proteinuria	4 (3.2)
Elevated creatine kinase††	4 (3.2)
Elevated alkaline phosphatase	3 (2.4)
Urothelial carcinoma	2 (1.6)
Cystic calculi [calcium hydrogen phosphate dihydrate calculi (brushite)]	1 (1.1)

* 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 cats had elevations < 1.5X the upper limit of normal (ULN).
§ Of the five cats with elevations ≥ 1.5X ULN, 3 cats developed diabetic ketoacidosis and hepatic lipidosis resulting in death or euthanasia. Two cats were withdrawn from the study.
** Observations included hiding and aggression
†† ≥ 3X ULN

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. Owner permission to conduct necropsy was not granted in all cases.

- Euglycemic diabetic ketoacidosis (8)
- Hepatic lipidosis: (5)
- Diabetic ketoacidosis: (4)
- 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)

Conclusions: Bexacat™ improves glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin. With appropriate precautions and when used according to the labeling, the study demonstrated an adequate safety profile in cats with diabetes mellitus.

The results of this study continue to demonstrate notable serious and life-threatening safety concerns, predominantly the development of diabetic ketoacidosis and euglycemic diabetic ketoacidosis. The study demonstrates that cats can develop diabetic ketoacidosis or euglycemic diabetic ketoacidosis, regardless of the duration of Bexacat™ administration, and despite previously documented improved glycemic control while receiving Bexacat™. The risk of these conditions may be due to a gradual progression toward insulin dependent diabetes mellitus in some cats and highlights the need for continued diligent monitoring, regardless of the duration of or response to Bexacat™ administration.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: Target Animal Safety of Bexagliflozin in Cats (Study No. INV-1442-N-009)

Study Dates: May 10, 2019 to August 31, 2020

Study Location: Stouffville, ON, Canada

Study Design:

Objective: To determine the margin of safety of Bexacat™ tablets, 15 mg, in healthy adult laboratory cats when administered once daily for 26 weeks at 0, 1, 3, and 5X the maximum drug exposure.

Study Animals: Thirty-six (18 male and 18 female) healthy, lean, intact adult domestic shorthair cats, at least one year of age, and weighing between 2.7 to 5.6 kg (5.9 to 12.3 lbs).

Experimental Design: The study was a masked, controlled, laboratory study. Cats were randomized to one of four treatment groups (see Table III.1). The proposed dosage is 15 mg per cat once daily, regardless of body weight. The minimum body weight of a cat with diabetes mellitus eligible for Bexacat™ use was considered to be approximately 3 kg. A 3 kg cat administered 15 mg would receive 5.0 mg/kg. Therefore, the maximum exposure dose (1X) for this study was 5.0 mg/kg once daily.

This study was conducted in accordance with Good Laboratory Practices (GLP) regulations.

Table III.1: Treatment Groups

Group	Minimum Daily Dose of Bexacat™ (mg/kg)	Number and Sex of Animals
Control (0X)	0 (sham dosed)	8 (4 male, 4 female)
1X	5	8 (4 male, 4 female)
3X	15	8 (4 male, 4 female)
5X	25	12 (6 male, 6 female)

Drug Administration: Cats were fasted prior to dosing. Beginning on Day 0, Bexacat™ tablets were administered orally in up to three dosing sessions per cat. Each session consisted of the administration of up to four tablets after which a 3 mL water flush was administered. After each dosing session, the cat was returned to its cage for a rest period of at least ten minutes. Control cats were sham dosed, followed by a 3 mL water flush.

Measurements and Observations: Clinical observations were performed twice daily throughout the study. Physical examinations were conducted twice during acclimation on Days -12 and -5, and on Days 8, 28, 56, 84, 112, 140, 167, and 181. Body weights were measured twice during acclimation on Days -12 and -1, and once weekly throughout the study. Systolic blood pressure was measured on Days -14, -6, 7, 27, 57, 85, 113, 141, and 168. Food consumption was measured daily throughout the study.

Samples for clinical pathology evaluations (hematology and serum chemistry including symmetric dimethylarginine [SDMA] and feline pancreas-specific lipase [spec fPL], and coagulation) were collected on Days –13, -7 (SDMA and spec fPL were not evaluated), 13, 42, 70, 99, 126, 154, and 181. Samples for urinalysis were collected once during acclimation on Days -7, -6, -5, or -2, and on Days 13 or 14, 41, 69, 98 or 99, 125 or 126 or 127, 153 or 154, and 181 or 182 or 183. Blood samples were collected on Days 0, 21, and 175 to measure plasma Bexacat™ concentrations.

Statistical Methods: The experimental unit was the individual animal. For continuous outcomes measured only once during the study, analysis of variance was used to evaluate a model containing dose, sex, and the sex-by-dose interaction as fixed effects. Pre-dose values were used as a covariate.

Continuous variables measured at multiple times were analyzed by a repeated measures analysis of covariance (RMANCOVA), with dose, sex, time, dose-by-sex, sex-by-time, dose-by-time, and dose-by-sex-by-time terms in the model as fixed effects, and animal ID as the subject in the repeated statement (MIXED procedure in SAS 9.4, SAS Institute, Cary, NC). The Kenward-Roger approximation for denominator degrees of freedom was used. No adjustment was made for multiple comparisons. All statistical tests and pairwise comparisons between treatment groups were based on a significance level of 0.10 except for three-way interactions, which were tested at a significance level of 0.05.

Results: There were no drug-related changes in routine physical examination variables including body weight and body condition score.

Polyuria was observed in more cats administered Bexacat™ than in the control cats. Glucosuria was present in all cats administered Bexacat™. Glucosuria is an expected outcome of Bexacat™ administration because its mechanism of action is to reduce reabsorption of filtered glucose in the kidney, thereby increasing urinary glucose excretion. Trace ketonuria was present in all groups, including 0X, with a higher incidence in the 5X group. Food consumption was significantly different ($p < 0.10$) and increased in the 3X and 5X groups compared to 0X cats, presumably due to caloric loss associated with glucosuria. Fasting blood glucose remained normal throughout the study in all groups, including 0X.

Clinically relevant loose stool and diarrhea was seen more frequently in the 3X and 5X groups, and suspected to be due to inhibition of SGLT1, which is responsible for glucose absorption from the intestinal lumen into the enterocytes. Vomiting after dosing was seen in the 5X group.

Both systolic blood pressure in the 3X group and heart rate in the 1X and 3X groups were significantly ($p < 0.10$) different and lower than in the 0X group (males only). The lowered blood pressure and heart rates remained in normal ranges and were not associated with any clinical changes.

There were statistically significant ($p < 0.10$), drug-related differences in the following clinical pathology variables. The group means remained within the reference ranges and the magnitude of the changes were not clinically relevant.

Albumin and calcium were increased in the 3X and 5X groups compared to the 0X group. Magnesium was increased in the 1X and 3X groups compared to the 0X group. Cholesterol was increased in the 1X, 3X, and 5X groups compared to the 0X group.

Creatinine was decreased in all three groups administered Bexacat™ compared to the control group on different study days. Amylase was decreased in the 3X and 5X groups compared to the 0X group. There were no drug-related changes in SDMA and feline pancreas-specific lipase (spec fPL).

There were four 5X cats with gross observations of mild diffuse zonal patterns in the liver. One cat had a corresponding histopathological observation of minimal, multifocal hepatocellular vacuolation. Another cat had a histopathological observation of minimal, multifocal necrosis which did not correspond to the gross zonal patterns. This cat had mild elevations in alanine aminotransaminase and aspartate aminotransaminase.

There were no additional abnormal findings in gross necropsy, organ weights, or histopathology attributed to Bexacat™.

Mean maximum observed plasma bexagliflozin concentration (Cmax) was approximately dose proportional over a dose range of 5 mg/kg (1X) to 25 mg/kg (5X). Mean area under the plasma concentration-time curve from time zero to 24 hours (AUC0-24h) exposure was approximately dose-proportional over a dose range of 5-15 mg/kg but was more than dose proportional from 15-25 mg/kg. An increase in exposure (AUC0-24h and Cmax), was observed in female cats compared to male cats on all evaluation days. There was no accumulation of Bexacat™ following daily dosing of 5, 15, and 25 mg/kg for 26 weeks. Median time to maximum concentration (Tmax) was 0.5 hours for all treatment groups and ranged from 0.5 to 2 hours. Mean half-life (T1/2) was similar among all groups, 5.32 ± 1.3 hours for 1X, 5.23 ± 1.4 hours for 3X, and 5.11 ± 1.6 hours for the 5X group.

Conclusions: Bexacat™ had an adequate margin of safety when administered at 5, 15, or 25 mg/kg once daily in healthy, lean adult cats for 6 months. The effects of Bexacat™ on stool consistency, polyuria, glucosuria (with a corresponding increase in food consumption), and ketonuria are consistent with its mechanism of action. The drug-related changes in the clinical pathology and urinalysis results were not clinically relevant. Absence of clinically relevant changes in clinical pathology in healthy cats does not preclude the emergence of clinically relevant changes in cats with diabetes mellitus.

B. A Pilot Study to Compare Effectiveness and Safety of Bexagliflozin with that of Optimized Insulin Therapy for the Management of Cats with Diabetes Mellitus. (Study No. INV-1442-N-008)

In a pilot study (INV-1442-N-008), the safety and effectiveness of once daily Bexacat™ administration was evaluated in 12 (8 male, 4 female) client-owned cats with diabetes mellitus that were being managed with insulin therapy at the time of enrollment. Cats had previously received intermediate or long-acting insulin products for various durations ranging from 1.5 to 84 months. The study was conducted in two phases. In the first phase, cats were administered insulin subcutaneously approximately every 12 hours for 28 days. During the second phase, insulin therapy was discontinued, and Bexacat™ was administered once daily for 56 days. Effectiveness of glycemic control, based on blood glucose (mean blood glucose < 180 mg/dL and > 70 mg/dL or fructosamine ≤ 330 µmol/L) and clinical assessments, was evaluated 28 days after insulin administration and again after 28 and 56 days of Bexacat™ administration. Two cats were withdrawn from the study after the insulin phase of the study prior to Bexacat™ administration due to suspected remission of diabetes mellitus and not included in the effectiveness evaluation. During the Bexacat™ phase of the study, one cat was withdrawn after one dose of Bexacat™ due to an inability for the

owner to dose and four cats were withdrawn after experiencing serious adverse reactions including (number of cats): diabetic ketoacidosis (3), pancreatitis (2), and hepatic lipidosis (2). Of the four withdrawn cats, two cats were euthanized, and two cats were transitioned back to insulin therapy after withdrawal from the study. Six (6) of 10 cats were considered treatment successes at the end of the insulin phase of the study. Four (4) of 10 cats were considered treatment successes after 28 days of Bexacat™ administration. Adverse reactions only occurred during the Bexacat™ phase and included (number of cats): elevated Spec fPL® (6), increased serum BHBA (5), lethargy (4), decreased appetite (4), dehydration (2), ketonuria (2), hypokalemia (2), acidosis (2), and weight loss (2).

Because of the number and severity of adverse reactions experienced in this study, the study was terminated.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Bexacat™:

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

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Bexacat™, when used according to the label, is safe and effective to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to diagnose diabetes mellitus, to properly assess the cat's clinical condition prior to initiating Bexacat™, to provide adequate instructions for post treatment care, and to monitor the safe use of the product, including treatment of adverse reactions.

B. Exclusivity

Bexacat™, as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active moiety in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.