Date of Approval: August 10, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-568

Senvelgo®

(velagliflozin oral solution)

Cats

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

Sponsored by:

Boehringer Ingelheim Animal Health USA, Inc.

Executive Summary

Senvelgo® (velagliflozin oral solution) is approved to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin. The oral solution is administered to cats once daily, with or without food and regardless of blood glucose level.

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

Safety and Effectiveness

The sponsor conducted a six-month field study to evaluate the safety and effectiveness of Senvelgo® in client-owned cats diagnosed with diabetes mellitus. The study included purebreds and mixed breeds of both sexes with a range of ages and weights. Enrolled cats had fasting hyperglycemia, glucosuria, and an elevated serum fructosamine in addition to at least one clinical sign of diabetes mellitus. The study did not include a control group. Starting on Day 0, all cats received Senvelgo® orally once daily at a dose of 1 mg/kg, and the dose was adjusted for body weight throughout the study.

A cat was considered a treatment success if there was an improvement in at least one blood glucose variable (mean blood glucose from a 9-hour blood glucose curve or fructosamine) and at least one clinical sign of diabetes mellitus on Day 30. Eighty-eight percent of cats were treatment successes. After Day 30, cats could continue into the extended safety period (Days 30-180) if they had an improvement in fructosamine and at least one clinical sign of diabetes mellitus.

The most common adverse reactions seen during the field study were loose stool or diarrhea, weight loss, vomiting, polyuria, polydipsia, and elevated blood urea nitrogen (BUN). A significant safety concern was the development of diabetic ketosis or diabetic ketoacidosis, including euglycemic diabetic ketoacidosis (evaluated by the emergence of ketonuria), usually within the first week of treatment. Cats previously treated with insulin were at higher risk of developing these serious conditions compared to naïve cats not previously treated with insulin.

The sponsor conducted a laboratory safety study in healthy, adult male and female cats to evaluate the margin of safety of Senvelgo® when given orally once daily at 0X, 1X, 3X, and 5X the labeled dose for 6 months. The dose was adjusted for body weight every 28 days. Senvelgo® caused soft stool and diarrhea, polydipsia, glucosuria, and increased food consumption (presumably due to caloric loss associated with glucosuria). 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 diabetic cats or diabetic cats with chronic kidney disease won't develop clinically relevant changes while on Senvelgo®.

Senvelgo® contains propylene glycol as an inactive ingredient, and cats administered the drug at the labeled dose receive 40 mg of propylene glycol/kg per day. Propylene glycol doses of greater than 80 mg/kg per day may result in increased glycogen stores in the liver and other tissues.

The results of the field study and laboratory safety study show that, when appropriate precautions are taken and the drug is used according to the labeling, Senvelgo® has an adequate margin of safety and is effective for improving glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin. Senvelgo® is contraindicated in cats with insulin-dependent diabetes mellitus and cats previously treated with insulin due to the increased risk of diabetic ketosis or ketoacidosis, including euglycemic diabetic ketoacidosis.

Although there are notable safety concerns with the use of Senvelgo®, they can be mitigated by carefully screening cats before starting the drug, close monitoring for ketonuria during the first week of treatment and during times of illness, continued diligent monitoring after the first week of treatment, and knowing how the drug works and how to promptly recognize and appropriately treat serious and life-threatening adverse reactions.

User Safety
Senvelgo® may cause mild eye irritation in people. Exposure to the drug may induce a local or systemic allergic reaction in sensitized individuals. If ingested, Senvelgo® may cause transient effects such as increased glucose excretion in the urine, increased urine volume, and hypoglycemia.

Conclusions
Based on the data submitted by the sponsor for the approval of Senvelgo®, 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 141-568

B. Sponsor

Boehringer Ingelheim Animal Health USA, Inc.
3239 Satellite Blvd.
Duluth, GA 30096

Drug Labeler Code: 000010

C. Proprietary Name

Senvelgo®

D. Drug Product Established Name

velagliflozin oral solution

E. Pharmacological Category

Sodium-glucose cotransporter 2 (SGLT2) inhibitor

F. Dosage Form

Solution

G. Amount of Active Ingredient

15 mg/mL

H. How Supplied

30 mL nominal fill volume in a 45 mL plastic bottle

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The Senvelgo® dose is 0.45 mg/lb of body weight (1 mg/kg), once daily regardless of blood glucose level. The dose may be administered directly into the mouth or with a small amount of wet food. Do not mix into food. The solution should be given at approximately the same time every day. If a dose is missed, it should be given as soon as possible on the same day. If the cat vomits within 30 minutes of dosing, the dose can be repeated.

K. Route of Administration

Oral

L. Species/Class

Cats

M. Indication

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

II. EFFECTIVENESS

A. Dosage Characterization

A dose of 0.45 mg velagliflozin/lb (1.0 mg velagliflozin/kg) body weight once daily was selected as the recommended therapeutic dose to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin The recommended dose is based on the pharmacokinetic, pharmacodynamic, and clinical results from preliminary laboratory and field studies using non-final formulations.

The laboratory studies investigated velagliflozin in both healthy, lean cats and obese, insulin-resistant cats in order to characterize the pharmacokinetics (drug exposure) and pharmacodynamic effect (induction of glucosuria) after single and repeated once daily administration within a dose range of 0.01 – 1.0 mg velagliflozin/kg body weight.

The laboratory studies confirmed the targeted pharmacodynamic effect, induction of glucosuria, of velagliflozin in cats. The observed increase in glucosuria was dose dependent at doses ≥ 0.1 mg velagliflozin/kg body weight, which is consistent with the observed dose dependent increase in plasma exposure in those doses ≥ 0.1 mg velagliflozin/kg body weight once daily.

The laboratory studies supported a dose range of > 0.1 – 1.0 mg velagliflozin/kg body weight once daily for further evaluation in cats with diabetes mellitus. The dose range was further narrowed down to 0.5 – 1.0 mg velagliflozin/kg body weight once daily in a pilot field study in diabetic cats, which confirmed a reliable improvement in glycemic laboratory parameters, including reduction of blood glucose and serum fructosamine, and clinical signs, for both the 0.5 and 1.0 mg velagliflozin/kg body weight once daily doses. Although both dose groups demonstrated acceptable improvement, the 1.0 mg velagliflozin/kg body weight once daily dose was selected based on earlier improvement in clinical signs in cats dosed at 1.0 velagliflozin/kg body weight once daily, compared with the cats dosed at 0.5 mg velagliflozin/kg body weight once daily.

Therefore, based on the earlier improvement in clinical signs and sufficient plasma exposure for glucose lowering effects, the dose of 1.0 mg velagliflozin/kg body weight once daily was selected for further evaluation in cats with diabetes mellitus.

B. Substantial Evidence

The effectiveness of Senvelgo® (velagliflozin oral solution) to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin was evaluated in a field effectiveness study (Study No. 2017088) in cats diagnosed with diabetes mellitus. The study demonstrated that Senvelgo®, 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.

1. Clinical Field Study

   Title: A Clinical Field Study to Evaluate the Efficacy and Safety of Velagliflozin for the Reduction of Hyperglycemia and Hyperglycemia-associated Clinical Signs in Diabetic Cats (Phase 1). Extended-use Phase to Evaluate the Safety of Velagliflozin in Diabetic Cats (Phase 2). (Study No. 2017088)

   Study Dates: August 2018 to December 2021

   Study Locations:

   Orange, CA
   Plymouth, MN
   Stamford, CT
   Tulsa, OK
   Williston, VT
   Riverside, CA
   Chicago, IL
   Albuquerque, NM
   New Preston CT
   Largo, FL
   Columbus, OH
   Beaverton, OR*
   Philadelphia, PA
   Decatur, IL
   Fort Collins, CO
   Jackson, MS
   Athens, GA
   Dallas, TX
   Overland Park, KS
   Riverside, MO
   Seattle, WA

   *Cats from this site were not used in the effectiveness analysis because of Good Clinical Practice (GCP) violations at the site.

   Study Design:

   Objective: To evaluate the safety and effectiveness of Senvelgo® to improve glycemic control in otherwise healthy cats with diabetes mellitus.

Study Animals: The study enrolled 252 client-owned cats diagnosed with diabetes mellitus. Of the 252 cats enrolled, there were 176 neutered males and 76 spayed females. The cats ranged in age from 4 to 18 years and in weight from 5.7 to 26.5 lbs. The cats represented both pure and mixed breeds. All 252 cats were evaluated for safety and 198 cats were evaluated for effectiveness.

Experimental Design: No concurrent control group was included in this study. All cats received Senvelgo® once daily for up to 6 months. The effects of Senvelgo® were compared with historically derived data that represented the expected progression of diabetes mellitus in cats. The study was conducted in accordance with GCP.

The study was conducted in two phases. To be enrolled in Phase 1 of the study, each cat was required to meet the following inclusion criteria:

- Age ≥ 2 years of any sex and domesticated breed
- Otherwise healthy cat with diabetes mellitus (included naïve cats that had not been previously treated for more than 4 days with insulin and cats previously treated with insulin)
- At least one of the following clinical signs consistent with diabetes mellitus: polyuria, polydipsia, or unintentional weight loss despite a good appetite
- Fasting (minimum of six hours) blood glucose > 270 mg/dL
- Glucosuria
- Serum fructosamine > 400 µmol/L

Cats with the following conditions or previous treatments were excluded:

- History of decreased appetite, vomiting, or diarrhea within two weeks of screening
- Clinical suspicion of pancreatitis within the previous month or confirmed pancreatitis based on clinical signs and either ultrasonographic changes consistent with pancreatitis or feline pancreas-specific lipase (fPL) > 12 µg/L
- Ongoing, progressive, or serious concurrent illness (i.e., symptomatic or confirmed pancreatitis, hyperthyroidism (defined as total thyroxine (TT4) level > 4.3 µg/dL) or other known conditions which might interfere with interpretation of study results)
- Serum creatinine > 2.0 mg/dL or serum bilirubin > 0.5 mg/dL
- Clinical or laboratory signs of diabetic ketosis or ketoacidosis requiring hospitalization and treatment with regular insulin
- Diet change within two weeks of the screening visit
- Treatment with systemic, topical, ocular, or inhaled steroids within 30 days, long-acting steroids within 90 days, or diuretics within 30 days
- Pregnant or lactating cats, or cats intended for breeding

Dosing was started on Day 0 and urine was tested for the presence of ketones (ketonuria) on Day 2 or 3 and again on Day 7. Cats developing ketonuria after starting Senvelgo® were removed from the study and started on insulin, even if the cat was not hyperglycemic or showing signs of illness. At the end of Phase 1 (Day 30), cats could enter Phase 2, the extended safety period (Days 30-180), if

they had improvement in at least one clinical sign (polyuria, polydipsia, unintentional weight loss, polyphagia, or diabetic neuropathy) and fructosamine (≤ 550 µmol/L and decreased from baseline).

Drug Administration: The dose was 0.45 mg/lb (1 mg/kg) given orally once daily in the morning regardless of blood glucose level. Dose adjustments were based on body weight measurements at regularly scheduled and unscheduled visits.

Measurements and Observations:

Baseline (Day -7 to -2) demographics, physical examination, clinical signs of diabetes mellitus, fasting blood glucose, serum fructosamine, and clinical pathology panels (complete blood counts, serum chemistry, and urinalysis with culture and sensitivity) were obtained and compared to Day 30 measurements to assess safety and effectiveness. After Day 30, cats that had not improved were allowed to withdraw from the study.

Primary laboratory variables for effectiveness consisted of baseline fasted blood glucose values and serum fructosamine values. Baseline clinical signs consisted of at least one clinical sign of diabetes: polyuria, polydipsia, unintentional weight loss, polyphagia, or diabetic neuropathy. Fructosamine and a blood glucose curve to determine a mean blood glucose were evaluated on Day 30 and compared to baseline.

Safety was evaluated throughout the study via physical examinations (including body weight monitoring and assessment of hydration status), owner observations, and laboratory or diagnostic testing. At regularly scheduled visits on Days 2/3 and 7, physical examinations, clinical signs of diabetes, and urine (dipstick evaluation for evidence of ketonuria and specific gravity) were evaluated. Complete blood count including blood smears for Heinz bodies, and serum chemistry were evaluated on Days 7, 30, 60, 120, and 180. Urinalysis was evaluated on Days 30 and 120, and urine culture and sensitivity were evaluated on Days 30 and 180. A blood glucose curve was evaluated on Day 60 and single blood glucose values 3-9 hours after dosing were evaluated on Days 90, 120, 150, and 180. Fructosamine was evaluated on Days 60, 120, and 180.

Presence of ketonuria was evaluated by urine dipstick on Days 2/3, 7, 60, 90, 150, and by full urinalysis on Days 30 and 120. Presence of ketonuria was evaluated at any unscheduled visit prior to Day 7, and at any unscheduled visit where the cat had clinical signs such as lethargy, inappetence, or vomiting.

The primary effectiveness variable was the percentage of cats that were considered to have treatment success on Day 30. Treatment success was defined as improvement in at least one blood glucose variable [mean blood glucose (from a 9-hour curve) ≤ 300 mg/dL and below screening blood glucose, or fructosamine ≤ 450 µmol/L and below screening serum fructosamine] and in at least one clinical sign (polyuria, polydipsia, polyphagia, body weight, or peripheral neuropathy).

Statistical Methods: The experimental unit was the individual cat. Senvelgo® was considered effective if the lower bound of the 90% confidence interval for

percentage of cats achieving treatment success was ≥ 60%. The analysis utilized the GLIMMIX procedure in SAS 9.4 with binomial distribution and logit link. The model was a generalized linear mixed model with site as a random effect. The percent of treatment success and the lower 90% confidence limit was calculated using the inverse link option in the LSMEANS statement.

Results:

A total of 252 cats were enrolled in the study and received at least one dose of Senvelgo®. A total of 29 cats were excluded from the effectiveness analysis due to removal from the study due to presence of ketonuria (16) or diabetic ketoacidosis (13), as determined by the study veterinarian on or before Day 7. An additional 25 cats were removed due to adverse events unrelated or unlikely related to Senvelgo® administration or non-compliance issues.

Of the remaining 198 cats included in the effectiveness analysis, 175 (88.4%) were considered a treatment success on Day 30. The lower bound of the two-sided 90% confidence interval was 84% which met the criterion for demonstrating effectiveness of Senvelgo®.

Table II.1 summarizes mean blood glucose concentration, fructosamine, and body weight.

Table II.1. Mean Blood Glucose Variables and Body Weight (n = 198)

Day	Glucose Curve Mean (mg/dL)	Fructosamine (µmol/L)	Weight (lb)
Screening	446.4*	551.4	12.1
7	193.8	NA†	12.0
30‡	169.8	332.0	12.2

*Screening blood glucose was a single fasted reading, not from glucose curve mean.
†Not applicable as Day 7 was not a scheduled visit for fructosamine measurement.
‡Excludes five cats that were removed before Day 30 as treatment failures (n=193).

Table II.2 shows the percentage of cats achieving improvement in each effectiveness variable at Day 30.

Table II.2. Number and Percentage of Cats Improved at Day 30

Variable	Number	Total cats*	Percentage (%)
Mean blood glucose (9 h curve)	179	198	90.4
Fructosamine	175	198	88.4
Improvement in Polyuria	125	177	70.6
Improvement in Polydipsia	128	176	72.7
Improvement in Polyphagia	33	80	41.3
Weight gain or no weight loss	133	167	79.6
Neuropathy	7	30	23.3

*The total numbers of cats for polyuria, polydipsia, weight loss, polyphagia, and neuropathy were not 198 because not all cats had those clinical signs present at enrollment.

Adverse Reactions:

In the field study, 252 cats received at least one dose of Senvelgo®. The most common adverse reactions were diarrhea or loose stool, weight loss, vomiting, polyuria, polydipsia, and elevated blood urea nitrogen (BUN).

The following table summarizes the adverse reactions reported in the study.

Table II.3. Adverse Reactions (n = 252 cats)

Adverse Reactions	Frequency (%)
Diarrhea (including loose stool)	132 (52.3%)
Weight loss *	111 (44%)
Vomiting	92 (36.5%)
Polyuria	46 (18.3%)
Polydipsia	42 (16.7%)
BUN†	39 (15.5%)
Anorexia or hyporexia	34 (13.5%)
Hypersalivation and/or gagging	33 (13.1%)
Urine specific gravity > 1.060	29 (11.5%)
Dehydration	28 (11.1%)
Lethargy	20 (7.9%)
Polyphagia	19 (7.5%)
Urinary tract infections/cystitis	18 (7.1%)
Diabetic ketoacidosis or euglycemic diabetic ketoacidosis‡	18 (7.1%)
Hypercalcemia	16 (6.3%)
Ketonuria§	14 (5.6%)
Inappropriate urination	14 (5.6%)
Death or euthanasia	13 (5.2%)
Elevated AST and/or ALT**	12 (4.8%)
Hypertriglyceridemia††	12 (4.8%)
Hyperphosphatemia	12 (4.8%)
Elevated fPL	11 (4.4%)
Pancreatitis	10 (4.0%)
Elevated creatinine	9 (3.6%)
Hepatic lipidosis	6 (2.4%)
Urinary incontinence	3 (1.2%)

*Approximately 80 cats had weight loss during the first week of treatment, likely due to dehydration and/or caloric wasting from glucosuria.
†Most cases were ≤ 1.5X upper limit of normal (ULN).
‡All but 5 cases occurred within 2 weeks of starting Senvelgo®. Twelve of these cases had euglycemic diabetic ketoacidosis.

§These cats did not progress to diabetic ketoacidosis or euglycemic diabetic ketoacidosis. All but one of these cases developed ketonuria within a week of starting Senvelgo®. The cats discontinued Senvelgo® and transitioned to insulin.
**Four of these cats had AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase)
††These cats sometimes also had elevated cholesterol.

The following adverse reactions were seen in the study with < 1% frequency: elevated creatine kinase (> 3X ULN), hypoglycemia (blood glucose ≤ 50 mg/dL) without clinical signs, anemia, abnormal behavior, bradycardia, and dermatitis.

Ketonuria and diabetic ketoacidosis:

Due to emergence of diabetic ketoacidosis, including euglycemic diabetic ketoacidosis, leading to significant morbidity and mortality in pilot studies, urine ketone checks at Days 2/3 and 7 were included in the field study. All cats were required to return to the clinic for additional screening for ketonuria and were removed from the study and started on insulin if they were positive.

Twenty-six cats developed ketonuria, diabetic ketoacidosis, or euglycemic diabetic ketoacidosis within the first 7 days of treatment with Senvelgo®. Thirteen (13) cats developed ketonuria without further progression to diabetic ketoacidosis or euglycemic ketoacidosis. These 13 cats were removed from the study and transitioned to insulin. An additional 13 cats developed diabetic ketoacidosis or euglycemic ketoacidosis. Nine cats recovered after hospitalization and intensive treatment. Three of the 9 cats had concurrent conditions: hepatopathy (1), hepatic lipidosis (1), and pancreatitis and hepatic lipidosis (1). Four of the 13 cats were euthanized; three because the owners declined treatment and one cat was euthanized after not responding to hospitalized and intensive treatment.

Six cats developed ketonuria, diabetic ketoacidosis or euglycemic diabetic ketoacidosis after the first 7 days of treatment. One cat developed ketonuria without progression to diabetic ketoacidosis or euglycemic ketoacidosis after more than 4 months on Senvelgo®. Five cats developed diabetic ketoacidosis or euglycemic ketoacidosis. Two (one with concurrent pancreatitis and hepatic lipidosis) were treated and recovered. One with concurrent pancreatitis was treated and recovered but died several days later. Two of the five cats were euthanized; one cat was euthanized after poor response to hospitalization and intensive therapy; and one was euthanized due to declining condition unrelated to diabetic ketoacidosis.

Thirty-eight enrolled cats had been previously treated with insulin. Of those 38 cats, 12 (32%) developed ketonuria, diabetic ketoacidosis or euglycemic diabetic ketoacidosis during the first week and were removed from the study. These 12 cats are included in the 26 cases reported above and represent 46% of the cases removed in the first week of treatment due to ketonuria or ketoacidosis.

Deaths or euthanasia: Nineteen cats, including 7 cases described above, died (3) or were euthanized (16) during the study or shortly following removal from the study, thirteen possibly related to Senvelgo® use or declining glycemic control. In addition to the 6 cases with ketoacidosis described above, euthanasia was associated with the following conditions (number of cats): acute renal failure within a week of starting Senvelgo® (1), worsening or emergent urinary incontinence associated with poor glycemic control (2), worsening polyuria/polydipsia and inappropriate urination (1) progressive signs of diabetes mellitus (1), declining condition and suspected pancreatitis (1), azotemia and lack of effect within a week of starting Senvelgo® and possible concurrent hypersomatotropism (1).

Conclusions:

Treatment with Senvelgo® 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.

A significant safety concern is development of diabetic ketosis or diabetic ketoacidosis usually within the first week of treatment with Senvelgo®. This necessitates close monitoring for ketonuria during the first week of dosing beginning at Days 2 to 3 after initiation of dosing. Twenty-six cats developed ketonuria or diabetic ketoacidosis within the first 7 days of treatment and were removed from the study. However, despite careful monitoring for ketonuria and discontinuation of Senvelgo® beginning within a few days of dosing, some cats progressed to clinical diabetic ketoacidosis requiring intensive treatment, including hospitalization.

Cats previously treated with insulin are at higher risk of developing ketonuria and/or diabetic ketoacidosis, including euglycemic diabetic ketoacidosis than naïve cats not previously treated with insulin. Thus, the use of Senvelgo® in cats previously treated with insulin is contraindicated. Insulin dependent cats may be at increased risk of developing diabetic ketoacidosis, including euglycemic diabetic ketoacidosis, when treated with Senvelgo®.

The results of the study demonstrate notable safety concerns that require careful screening of cats prior to initiation of Senvelgo®. In addition, treatment with Senvelgo® requires monitoring for ketonuria during the first week of treatment and during times of illness, continued diligent monitoring after the first week, 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.

III. TARGET ANIMAL SAFETY

The safety of Senvelgo® (velagliflozin oral solution) to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin was demonstrated in a laboratory study.

A. Margin of Safety Study

Title: Evaluation of the Margin of Safety of Velagliflozin Oral Solution Following Once Daily Oral Administration for 6 Months in Healthy Male and Female Cats. (Study No. 2017072)

Study Dates: August 20, 2020, to February 10, 2022

Study Location: Walsrode, Germany

Study Design:

Objective: To evaluate the margin of safety of Senvelgo® in healthy adult, laboratory cats when administered once daily at 0X, 1X, 3X, and 5X of the recommended point dose (1 mg/kg) for 6 months.

Study Animals: Thirty-two (16 male, 16 female) domestic shorthair (DSH) cats, aged 8-9 months old, were included in the study. Body weight ranges at acclimation were 3.0-4.6 kg for male cats and 2.7-3.6 kg for female cats.

Experimental Design: The study was a masked, randomized, controlled laboratory study. Thirty-two cats were randomly assigned to treatment group (see Table III.1), paired housing, cage, and necropsy order after stratification by sex (sex ratio of 1:1).

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

Table III.1: Treatment Groups

Group	Dose (mg/kg)	Volume (mL/kg)*	Number and Sex of Animals
0X	0 (Saline)	0.33	4 males 4 females
1X	1	0.067	4 males 4 females
3X	3	0.2	4 males 4 females
5X	5	0.33	4 males 4 females

*Doses for individual cats were rounded up to the closest 0.1 mL.

Drug Administration: Cats were fasted overnight for at least 8 hours prior to dosing. Cats were dosed with Senvelgo® at 1, 3, or 5 mg/kg once daily in the morning. Control group cats were dosed with sterile saline (0.9% NaCl). Food was offered at least four hours after dosing with Senvelgo® or sterile saline. Individual doses were based on the most recent body weight and the dose was adjusted every 28 days.

Measurement and Observations: General health observations, food and water consumption, and evaluation of fecal consistency were conducted once daily. Cage side observations were performed twice daily. Veterinary physical examinations were performed twice during acclimation and bi-weekly during the treatment phase. Ophthalmic examinations were conducted twice during acclimation and on Days 84 and 182 (prior to necropsy). Indirect systolic blood pressure (SBP) was measured three times during acclimation and then every 4 weeks through study end (Day 182). Clinical pathology (hematology, serum chemistry, urinalysis, coagulation times, and symmetric dimethylarginine [SDMA]) were evaluated twice during acclimation and then every 4 weeks through study end. Velagliflozin plasma concentrations were measured once during acclimation, and prior to dosing and at 15, 30, and 60 minutes and 2, 4, 8, and 24 hours after dosing on Days 0, 91, and 181. Necropsies, including histopathology and organ weights, were conducted after the last treatment day (Day 182) between Days 183-187.

Statistical Methods: Descriptive statistical summaries were generated for clinical assessments, serum chemistry, hematology, coagulation, urinalysis, body weight, systolic blood pressure, heart rate, respiratory rate, rectal temperature, Heinz body (percentage), organ weights, feed consumption, and water consumption.

Results:

Clinical Observations and Examinations: All cats survived the study. There were no consistent Senvelgo®-related findings during veterinary physical examinations, ophthalmic examinations, and indirect systolic blood pressure measurements.

There was an effect on heart rate (HR) in the groups administered Senvelgo® compared to the control group on Days 14 and 28. On Day 14 there were two cats in the control group, three cats in the 1X group, two cats in the 3X group, and four cats in the 5X group with HR < 140 bpm. The minimum HR for the individual cats in the 1X, 3X, and 5X groups ranged from 104-138 bpm on Day 14 compared to the control group HR range of 128-176 bpm. On Day 28 there were three cats each in the 1X, 3X, and 5X groups that had HR < 140; no cats in the control group had HR < 140 on Day 28. The minimum HRs for individual cats in the 1X, 3X, and 5X groups ranged from 108-136 bpm on Day 28 compared to the control group range of 150-188 bpm.

Two cats in the 3X and 5X groups were observed to have a reddened prepuce with white-yellow discharge twice during the study that were not associated with abnormal urinalyses.

One cat in the 5X group had vomiting and reduced activity with reduced feed consumption for one day. The same cat also had a reddened rectal mucous membrane that was observed over the next 5 days.

Hypersalivation occurred shortly after dose administration in three 1X, four 3X, and five 5X group cats. Vomitus was infrequently found within 30 minutes of dosing in two 3X and three 5X group cats.

A dose-dependent decrease in fecal consistency (soft feces or diarrhea) was observed in the 3X and 5X groups compared to the control group and 1X group. Reddish mucoid feces were observed in three instances in the 1X group cats.

Food consumption and body weight: From Days 28-90, mean total food consumption was higher in the 1X and 3X groups, compared to the control and 5X groups. For the remainder of the study, mean food consumption was higher in the 1X, 3X, and 5X groups compared to the control group, indicating that there was a treatment effect for increased feed consumption.

The group mean difference in body weight between Days 182 and -1 (6-month study period) was 0.97 kg for the control group, 0.86 kg for the 1X group, 0.83 kg for the 3X group, and 0.48 kg for the 5X group, indicating that there was a dose-dependent treatment effect of decreased overall weight gain.

Water intake: There was an approximate 60% increase in water intake in the 1X, 3X, and 5X groups compared to the control group. Male cats had a slightly higher water intake compared to female cats in the 1X, 3X, and 5X groups.

Hematology: There were Senvelgo®-related increases in reticulocyte count, mean corpuscular hemoglobin, mean corpuscular volume, and Heinz body percentage in the 1X, 3X, and 5X group cats compared to control cats. There was a slight treatment effect for mean corpuscular hemoglobin concentration that resulted in slightly lower group mean values in the 1X, 3X, and 5X groups compared to the control groups. None of the cats showed any signs of anemia and the number of erythrocytes, hemoglobin, and hematocrit values were normal in all cats. There was no effect of Senvelgo® on white blood cells and platelets.

Coagulation: There was no effect of Senvelgo® on the prothrombin time and activated partial thromboplastin time.

Serum Chemistry: There were Senvelgo®-related effects on magnesium and serum albumin. The group means for magnesium and serum albumin increased in the 3X and 5X groups but stayed within the reference ranges, while some individual cat values were slightly above reference ranges. There were slight increases in cholesterol and triglycerides in some cats in the Senvelgo® groups that stayed within the reference ranges, but in a few cats the triglyceride values were above the reference range. There was a decrease in mean BUN in the Senvelgo® groups compared to the control group. These changes in serum chemistry parameters were not associated with any clinical abnormalities. There were no other treatment-related changes in serum chemistry parameters, including serum glucose and SDMA.

Urinalysis: Glucosuria was present in all cats in the 1X, 3X, and 5X groups and the mean urine creatinine was lower in all 1X, 3X, and 5X group cats compared to the control group; these findings are secondary to the mechanism of action of Senvelgo®.

Necropsy and Histopathology: A reticular pattern was observed on the surface of the liver of one control, three 1X, four 3X, and three 5X group cats. The cats with the gross hepatic reticular pattern also had histologic evidence of increased hepatic

vacuolation (lipid or glycogen). Increased hepatic vacuolation was also noted in most of the cats from all groups. Therefore, the clinical relevance of the gross and microscopic hepatic lesions is unknown.

Pharmacokinetics: After repeat daily oral dosing for six months, a slight to moderate increase in exposure to velagliflozin was observed. In addition, a tendency for a less than dose-proportional increase of maximum plasma concentration (C_{max}) and exposure (AUC) over the tested dose range was noted.

Conclusions:

Senvelgo® had an adequate margin of safety when administered at 1, 3, and 5 mg/kg once daily in fasted, healthy, adult cats for 6 months. The effects of Senvelgo® on stool consistency (soft to diarrhea), increased water consumption, glucosuria, decreased urine creatinine, increased food consumption, increased serum albumin, and increased serum magnesium are consistent with the mechanism of action. The drug-related changes in the clinical pathology and urinalysis results were not clinically relevant. The absence of clinically relevant changes in clinical pathology parameters in healthy cats does not preclude the emergence of clinically relevant changes in cats with diabetes mellitus, or in cats with diabetes mellitus with concurrent chronic kidney disease.

Cats administered Senvelgo® at the 1 mg/kg/day dose receive 40 mg/kg/day of propylene glycol. Propylene glycol doses of > 80 mg/kg/day may result in increased glycogen stores in the liver and other tissues.

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 Senvelgo®:

Not for use in humans. Keep out of reach of children.

Wash hands after use. This product may cause mild eye irritation. Avoid contact with eyes. If the product accidentally gets into the eyes, rinse eyes immediately with plenty of water; if wearing contact lenses, rinse the eyes first then remove contact lens(es) and continue to rinse for 5-10 minutes. If eye irritation continues or accidental ingestion occurs, seek medical advice, and provide this product information to the physician. Exposure to product may induce a local or systemic allergic reaction in sensitized individuals. Oral exposure to velagliflozin may cause transient effects such as increased renal glucose excretion, increased urine volume, and hypoglycemia.

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 Senvelgo®, 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 Senvelgo®, to provide adequate instructions for post treatment care, and to monitor the safe use of the product, including treatment of adverse reactions.

B. Exclusivity

Senvelgo®, 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.