Senvelgo®
(velagliflozin
oral solution)

ProZinc®
(protamine zinc recombinant
human insulin)

Care with confidence

FELINE DIABETES
PATIENT SUPPORT
PROGRAM™

Boehringer Ingelheim

Life forward

The Feline Diabetes Patient Support Program is here to cultivate confidence in prescribing once-daily **SENVELGO®** (velagliflozin oral solution) to feline patients by providing the resources to foster treatment success.

If **SENVELGO** oral solution proves not to be the right option for your feline diabetic patient and **PROZINC®** (protamine zinc recombinant human insulin) becomes clinically necessary, Boehringer Ingelheim will support the patient's transition to **PROZINC** insulin by:

1. **Reimbursing your clinic for the clinic's purchase price of the SENVELGO oral solution bottle**
2. **Providing a complimentary first bottle of PROZINC insulin**
3. **Offering a free PROZINC Care Kit, if requested***

Backed by the strength of both **SENVELGO** oral solution and **PROZINC** insulin, the Feline Diabetes Portfolio offers:

- **Flexible insulin and non-insulin options**
- **Convenient dosing**
- **Proven, trusted treatment of feline diabetes mellitus**

With the Feline Diabetes Patient Support Program, you can rest assured that every diabetic cat will receive the treatment that is best for them.

Call Boehringer Ingelheim Veterinary Technical Solutions Team at 1-888-637-4251 with the patient information for assistance.

*See the Feline Diabetes Patient Support Program eligibility requirements for more information.

IMPORTANT SAFETY INFORMATION: PROZINC® (protamine zinc recombinant human insulin) is for use in dogs and cats only. Keep out of the reach of children. Owners should be advised to observe for signs of hypoglycemia (low blood sugar). Signs may include weakness, depression, behavioral changes, muscle twitching, and anxiety. In severe cases of hypoglycemia, seizures and coma can occur. Hypoglycemia can be fatal if an affected animal does not receive prompt treatment. PROZINC should not be used during episodes of hypoglycemia (low blood sugar). Appropriate veterinary monitoring of blood glucose, adjustment of insulin dose and regimen as needed, and stabilization of diet and activity help minimize the risk of hypoglycemic episodes. The attending veterinarian should evaluate other adverse reactions on a case-by-case basis to determine if an adjustment in therapy is appropriate, or if alternative therapy should be considered. The safety and effectiveness of PROZINC in puppies, kittens, or breeding, pregnant, and lactating animals has not been evaluated. For more information, please see enclosed full prescribing information.

Boehringer Ingelheim

Senvelgo®
(velagliflozin oral solution)

ProZinc®
(protamine zinc recombinant human insulin)

By choosing to prescribe **SENVELGO®** (velagliflozin oral solution) or **PROZINC®** (protamine zinc recombinant human insulin) for your diabetic patients, your clinic and patients also benefit from:

- **Technical support**
- **Educational resources**
- **Streamlined, convenient treatment**

For a lower-stress treatment experience that supports you and your patients, no matter the treatment path.

IMPORTANT SAFETY INFORMATION: SENVELGO® is indicated to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin. **Before using this product, it is important to read the entire product insert, including the boxed warning. Cats treated with SENVELGO may be at an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis, both of which may result in death. Development of these conditions should be treated promptly, including insulin administration and discontinuation of SENVELGO. Do not use SENVELGO in cats with diabetes mellitus who have previously been treated with insulin, who are receiving insulin, or in cats with insulin-dependent diabetes mellitus.** The use of SENVELGO in cats with insulin-dependent diabetes mellitus, or the withdrawal of insulin and initiation of SENVELGO, is associated with an increased risk of diabetic ketoacidosis or euglycemic diabetic ketoacidosis and death. Sudden onset of hyporexia/anorexia, lethargy, dehydration, or weight loss in cats receiving SENVELGO should prompt immediate discontinuation of SENVELGO and assessment for diabetic ketoacidosis, regardless of blood glucose level. SENVELGO should not be initiated in cats with ketonuria, ketonemia, pancreatitis, anorexia, dehydration, or lethargy at the time of diagnosis of diabetes mellitus, as it may indicate the presence of other concurrent disease and increase the risk of diabetic ketoacidosis. Keep SENVELGO in a secure location out of reach of **children,** dogs, cats, and other animals to avoid accidental ingestion or overdose. **For more safety information, please refer to the package insert.**

Life forward

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Eligibility requirements

To qualify, a licensed veterinarian, veterinary clinic, or veterinary clinic staff must request a new bottle of PROZINC® (protamine zinc recombinant human insulin) and/or a PROZINC Diabetes Care Kit within 30 days after the pet owner starts treatment of their cat with SENVELGO® (velagliflozin oral solution) by:

- Calling the Veterinary Technical Solutions Team at 1-888-637-4251 and requesting assistance with the **Feline Diabetes Patient Support Program** ("Support Program"); and
- submitting an itemized, original receipt for the purchase of SENVELGO oral solution from a veterinarian to Boehringer Ingelheim. The receipt must show the place of purchase, the date of purchase, the product name, the amount of product purchased, and the purchase price. A fax number or address will be provided for submission of receipt.

Boehringer Ingelheim reserves the right to review the original receipt before a Support Program claim will be processed. A fax number or address will be provided for submission of receipt.

If the pet owner's name appears on the receipt, the Support Program claim can only be processed for that individual.

The Support Program is only valid on product labeled for sale in the United States.

The Support Program is not valid in situations where the product has not been used according to label directions, including, but not limited to, age- and weight-appropriate product, or was not purchased from a veterinarian.

One offer per household.

Please allow 2-6 weeks for any reimbursement processing. Standard shipping applies to the shipment of any PROZINC Care Kit or bottle of PROZINC insulin.

- In the event PROZINC insulin is needed sooner, Boehringer Ingelheim will reimburse veterinarian for one bottle of PROZINC insulin and/or PROZINC Care Kit provided to the pet owner from veterinarian's stock. An itemized, original receipt for the PROZINC insulin must be submitted to Boehringer Ingelheim, showing the product name, price, and the date.
- Upon returning the opened SENVELGO oral solution bottle to the veterinarian, Boehringer Ingelheim also will provide a refund of the clinic's purchase price. Taxes are not reimbursable.
- Any product that has been obtained free of charge is not eligible for the Support Program.
- Boehringer Ingelheim reserves the right to cancel or amend the Support Program at any time.

Package Insert for Cats

ProZinc®
(protamine zinc recombinant human insulin)

40 IU/mL

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

Description: PROZINC® is a sterile aqueous protamine zinc suspension of recombinant human insulin.

Each mL contains:

recombinant human insulin	40 International Units (IU)
protamine sulfate	0.466 mg
zinc oxide	0.088 mg
glycerin	16.00 mg
dibasic sodium phosphate, heptahydrate	3.78 mg
phenol (added as preservative)	2.50 mg
hydrochloric acid	1.63 mg
water for injection (maximum)	1005 mg

pH is adjusted with hydrochloric acid and/or sodium hydroxide.

Indication: PROZINC (protamine zinc recombinant human insulin) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus.

Dosage and Administration: USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCORRECT DOSING.

FOR SUBCUTANEOUS INJECTION ONLY.

DO NOT SHAKE OR AGITATE THE VIAL.

PROZINC should be mixed by gently rolling the vial prior to withdrawing each dose from the vial. Once mixed, PROZINC suspension has a white, cloudy appearance. Clumps or visible white particles can form in insulin suspensions: do not use the product if clumps or visible white particles persist after gently rolling the vial.

Using a U-40 insulin syringe, the injection should be administered subcutaneously on the back of the neck or on the side of the cat.

Always provide the Client Information Sheet with each prescription.

The initial recommended PROZINC dose is 0.1 – 0.3 IU insulin/pound of body weight (0.2 – 0.7 IU/kg) every 12 hours. The dose should be given concurrently with or right after a meal. The veterinarian should re-evaluate the cat at appropriate intervals and adjust the dose based on both clinical signs and glucose nadirs until adequate glycemic control has been attained. In the effectiveness field study, glycemic control was considered adequate if the glucose nadir from a 9-hour blood glucose curve was between 80 and 150 mg/dL and clinical signs of hyperglycemia such as polyuria, polydipsia, and weight loss were improved.

Further adjustments in the dosage may be necessary with changes in the cat's diet, body weight, or concomitant medication, or if the cat develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other medical disorder.

Contraindications: PROZINC is contraindicated in cats sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. PROZINC is contraindicated during episodes of hypoglycemia.

Warnings: User Safety: For use in cats and dogs only. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with running water for at least 15 minutes. Accidental injection may cause hypoglycemia. In case of accidental injection, seek medical attention immediately. Exposure to product may induce a local or systemic allergic reaction in sensitized individuals.

Animal Safety: Owners should be advised to observe for signs of hypoglycemia (see Client Information Sheet). Use of this product, even at established doses, has been associated with hypoglycemia. A cat with signs of hypoglycemia should be treated immediately. Glucose should be given orally or intravenously as dictated by clinical signs. Insulin should be temporarily withheld and, if indicated, the dosage adjusted.

Any change in insulin should be made cautiously and only under a veterinarian's supervision. Changes in insulin strength, manufacturer, type, species (human, animal) or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Appropriate diagnostic tests should be performed to rule out other endocrinopathies in diabetic cats that are difficult to regulate.

Precautions: Cats presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death.

Glucocorticoids, progestogens, and certain endocrinopathies can have an antagonistic effect on insulin activity. Glucocorticoid and progestogen use should be avoided.

The safety and effectiveness of PROZINC in breeding, pregnant, and lactating cats has not been evaluated.

The safety and effectiveness of PROZINC in kittens has not been evaluated.

Adverse Reactions: Effectiveness Field Study

In a 45-day effectiveness field study, 176 cats received PROZINC. Hypoglycemia (defined as a blood glucose value of < 50 mg/dL) occurred in 71 of the cats at various times throughout the study. Clinical signs of hypoglycemia were generally mild in nature (described as lethargic, sluggish, weak, trembling, uncoordinated, groggy, glassy-eyed or dazed). In 17 cases, the veterinarian provided oral glucose supplementation or food as treatment. Most cases were not associated with clinical signs and received no treatment. One cat had a serious hypoglycemic event associated with stupor, lateral recumbency, hypothermia and seizures.

All cases of hypoglycemia resolved with appropriate therapy and if needed, a dose reduction.

Three cats had injection site reactions which were described as either small, punctate, red lesions; lesions on neck; or palpable subcutaneous thickening. All injection site reactions resolved without cessation of therapy.

Four cats developed diabetic neuropathy during the study as evidenced by plantigrade stance. Three cats entered the study with plantigrade stance, one of which resolved by Day 45. Four cats were diagnosed with diabetic ketoacidosis during the study. Two were euthanized due to poor response to treatment. Five other cats were euthanized during the study, one of which had hypoglycemia. Four cats had received PROZINC for less than a week and were euthanized due to worsening concurrent medical conditions.

The following additional clinical observations or diagnoses were reported in cats during the effectiveness field study: vomiting, lethargy, diarrhea, cystitis/hematuria, upper respiratory infection, dry coat, hair loss, ocular discharge, abnormal vocalization, black stool, and rapid breathing.

Extended Use Field Study

Cats that completed the effectiveness study were enrolled into an extended use field study. In this study, 145 cats received PROZINC for up to an additional 136 days. Adverse reactions were similar to those reported during the 45-day effectiveness study and are listed in order of decreasing frequency: vomiting, hypoglycemia, anorexia/poor appetite, diarrhea, lethargy, cystitis/hematuria, and weakness. Twenty cats had signs consistent with hypoglycemia described as: sluggish, lethargic, unsteady, wobbly, seizures, trembling, or dazed. Most of these were treated by the owner or veterinarian with oral glucose supplementation or food; others received intravenous glucose. One cat had a serious hypoglycemic event associated with seizures and blindness. The cat fully recovered after supportive therapy and finished the study. All cases of hypoglycemia resolved with appropriate therapy and if needed, a dose reduction.

Fourteen cats died or were euthanized during the extended use study. In two cases, continued use of insulin despite anorexia and signs of hypoglycemia contributed to the deaths. In one case, the owner decided not to continue therapy after a presumed episode of hypoglycemia. The rest were due to concurrent medical conditions or worsening of the diabetes mellitus.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim at 1-888-637-4251.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

Information for Cat Owners: Please refer to the Client Information Sheet for Cats for more information about PROZINC. PROZINC, like other insulin products, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the associated clinical signs. Potential adverse reactions include: hypoglycemia, insulin antagonism/resistance, rapid insulin metabolism, insulin-induced hyperglycemia (Somogyi Effect), and local or systemic reactions. The most common adverse reaction observed is hypoglycemia. Signs may include: weakness, depression, behavioral changes, muscle twitching, and anxiety. In severe cases of hypoglycemia, seizures and coma can occur. Hypoglycemia can be fatal if an affected cat does not receive prompt treatment. Appropriate veterinary monitoring of blood glucose, adjustment of insulin dose and regimen as needed, and stabilization of diet and activity help minimize the risk of hypoglycemic episodes. The attending veterinarian should evaluate other adverse reactions on a case-by-case basis to determine if an adjustment in therapy is appropriate, or if alternative therapy should be considered.

Effectiveness: A total of 187 client-owned cats were enrolled in a 45-day field study, with 176 receiving PROZINC. One hundred and fifty-one cats were included in the effectiveness analysis. The patients included various purebred and mixed breed cats ranging in age from 3 to 19 years and in weight from 4.6 to 20.8 pounds. Of the cats included in the effectiveness analysis, 101 were castrated males, 49 were spayed females, and 1 was an intact female.

Cats were started on PROZINC at a dose of 0.1-0.3 IU/lb (0.2-0.7 IU/kg) twice daily. Cats were evaluated at 7, 14, 30, and 45 days after initiation of therapy and the dose was adjusted based on clinical signs and results of 9-hour blood glucose curves on Days 7, 14, and 30.

Effectiveness was based on successful control of diabetes which was defined as improvement in at least one blood glucose variable (glucose curve mean, nadir, or fructosamine) and at least one clinical sign (polyuria, polydipsia, or body weight). Based on this definition, 115 of 151 cases (76.2%) were considered successful. Blood glucose curve means decreased from 415.3 mg/dL on Day 0 to 203.2 mg/dL by Day 45 and the mean blood glucose nadir decreased from 407.9 mg/dL on Day 0 to 142.4 mg/dL on Day 45. Mean fructosamine values decreased from 505.9 µmol/L on Day 0 to 380.7 µmol/L on Day 45.

Cats that completed the effectiveness study were enrolled in an extended use field study. The mean fructosamine value was 342.0 µmol/L after a total of 181 days of PROZINC therapy.

How Supplied: PROZINC is supplied as a sterile injectable suspension in 10 mL and 20 mL multi-dose vials. Each mL of PROZINC contains 40 IU recombinant human insulin.

Storage Conditions: Store in an upright position under refrigeration at 36-46°F (2-8°C). Do not freeze. Protect from light. **Use the 10 mL vial within 60 days of first puncture. Use the 20 mL vial within 80 days of first puncture.**

Approved by FDA under NADA # 141-297

Marketed by:
Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

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Boehringer Ingelheim

L6528
Package Insert

Senvelgo®
(velagliflozin oral solution)

15mg/ mL

For oral use in cats only

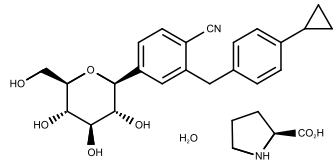
Sodium-glucose cotransporter 2 (SGLT2) inhibitor

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

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

Description: SENVELGO® (velagliflozin oral solution) equal to velagliflozin L-proline H_2O 20.051 mg/mL, is a clear, colorless to slightly yellow, to slightly brown, liquid multi-dose preparation consisting of 1.5% w/v velagliflozin in an aqueous mixture of propylene glycol and ethanol intended for oral use in cats. SENVELGO is an orally active, sodium-glucose cotransporter 2 (SGLT2) inhibitor.

The chemical name of velagliflozin is 2-(4-cyclopropyl-benzyl)-4-((2S,3R,4R,5S,6R)- 3,4,5-trihydroxy-6-hydroxymethyltetrahydropyran-2-yl)-benzonitrile. It forms a co-crystal with L-proline ((S)-pyrrolidine-2-carboxylic acid) as a monohydrate and velagliflozin, L-proline and H2O are in 1:1:1 ratios. Its empirical formula is $C_{23}H_{25}NO_5$ x $C_5H_9NO_2$ x H_2O, its molecular formula is $C_{28}H_{36}N_2O_8$, and its structural formula is:



Indication: SENVELGO is indicated to improve glycemic control in otherwise healthy cats with diabetes mellitus not previously treated with insulin.

Dosage and Administration: Always provide the Client Information Sheet with each prescription.

Dosing instructions:
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.

SENVELGO should be administered using the dosing syringe provided in the package. The dosing syringe fits onto the bottle and has a body weight scale with increments per pound of body weight. The dose should be rounded down to the nearest pound. After administration, close the bottle tightly with the cap. If needed, the syringe can be cleaned with a clean, dry cloth.

Prior to initiation of treatment:
Prior to initiation of SENVELGO, the veterinarian should ensure the cat is alert, active, eating, and drinking. The veterinarian should conduct a physical examination, obtain a medical history, CBC, serum chemistry, serum fructosamine, and urinalysis including evaluation for ketonuria (see **Animal Safety Warnings**).

If there is a delay of more than a week between diagnosis of diabetes mellitus and initiation of SENVELGO, the veterinarian should re-evaluate the cat with a full physical examination and updated history to ensure the cat still meets the criteria described above. A delay of more than a week between diagnosis and starting SENVELGO may increase the risk of developing diabetic ketoacidosis.

Monitoring of cats receiving SENVELGO:
- Sudden onset of hyporexia/anorexia, lethargy, dehydration, or weight loss in cats receiving SENVELGO should prompt immediate discontinuation of SENVELGO and assessment of diabetic ketoacidosis, regardless of blood glucose level.
- **Evaluate for ketonuria 2 to 3 days after initiation of treatment and approximately 7 days after initiation of treatment and anytime the cat shows signs of illness.** If ketonuria is present, discontinue SENVELGO and promptly treat with insulin, even if blood glucose is normal.
- During the first 4 weeks after initiation of SENVELGO, glycemic control and clinical improvement should be evaluated.
  - A physical examination, blood glucose curve, serum fructosamine, and body weight should be assessed at 1 and 4 weeks after initiating SENVELGO.
  - SENVELGO should be discontinued, and initiation of insulin considered, in cats demonstrating poor glycemic control (weight loss, average blood glucose from a glucose curve > 300 mg/dL or fructosamine values suggesting poor control (> 450 µmol/L) after 4 weeks of treatment.
- During ongoing treatment with SENVELGO, blood glucose, fructosamine, urinary ketones, serum chemistry, body weight, hydration status, and clinical signs of diabetes mellitus should be routinely monitored.
  - Presence of ketonuria should prompt discontinuation of SENVELGO and transition to insulin.
  - Cats with increasing or persistently elevated triglyceride or cholesterol levels may have declining glycemic control or pancreatitis, and may be at risk of developing diabetic ketoacidosis or euglycemic diabetic ketoacidosis (diabetic ketoacidosis with normal blood glucose levels). Consider further evaluation and discontinuation of SENVELGO in these cats.
  - Increasing or persistently elevated feline pancreas-specific lipase (fPL) should prompt further evaluation for pancreatitis and consideration of discontinuation of SENVELGO.
  - Initial mild weight loss may be seen with SENVELGO associated with its mode of action (glucosuria and caloric wasting). Unintentional weight loss which doesn't improve or stabilize within 7 days may indicate the need to evaluate for concurrent disease and consideration of discontinuation of SENVELGO (see **Adverse Reactions**).
  - If clinical signs of illness occur, evaluate the cat as soon as possible to ensure it is not at risk for diabetic ketoacidosis or euglycemic diabetic ketoacidosis (see **Animal Safety Warnings**).
  - SENVELGO should be discontinued if the cat's clinical condition declines and/or glycemic control worsens after initial improvement.
- Cats may present with diabetic ketoacidosis and a normal blood glucose concentration (euglycemic diabetic ketoacidosis). Delay in recognition and treatment of diabetic ketoacidosis and euglycemic diabetic ketoacidosis may result in increased morbidity and mortality.
- Development of diabetic ketoacidosis or euglycemic ketoacidosis requires the following actions:
  - Discontinuation of SENVELGO
  - Prompt initiation of insulin therapy
  - Administration of dextrose or other carbohydrate source, regardless of blood glucose concentration
  - Appropriate nutritional support should be promptly initiated to prevent or treat hepatic lipidosis.

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

Warnings:
User Safety Warnings: 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 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.

Animal Safety Warnings:
- SENVELGO should not be initiated in cats with:
  - Anorexia, dehydration, or lethargy at the time of diagnosis of diabetes mellitus as it may indicate the presence of other concurrent disease and increase the risk of diabetic ketoacidosis.
  - Ketonuria, ketonemia, or suspected diabetic ketoacidosis or a history of the same
  - Clinical suspicion of pancreatitis within the last month based on clinical signs, serum fPL > 12 mcg/L, and/or diagnostic imaging consistent with pancreatitis.
  - Chronic or unresponsive diarrhea
  - Cachexia
  - Bilirubin > 0.5 mg/dL
  - Creatinine > 2 mg/dL
- SENVELGO may cause a mild increase in serum creatinine, blood urea nitrogen (BUN), phosphorus, and sodium in cats with or without chronic kidney disease within weeks of starting therapy, followed by a stabilization of values.
- Cats with baseline creatinine between 1.6 and 2 mg/dL when SENVELGO treatment is started should be closely monitored for signs of volume depletion/dehydration and body weight loss. Renal function should be monitored within the first week of treatment initiation and then according to standard chronic kidney disease guidelines. SENVELGO has not been evaluated in cats with baseline creatinine > 2 mg/dL.
- Cats should be screened for urinary tract infections and treated, if indicated, when initiating SENVELGO. Cats treated with SENVELGO should be monitored for urinary tract infections and treated promptly.
- Cats should be evaluated for concurrent disease including pancreatitis, infectious disease, urinary tract infection, neoplasia, and hypersomatotropism (acromegaly) before initiating and while receiving SENVELGO as these conditions may increase the risk of developing diabetic ketoacidosis.
- Persistently low or worsening serum chloride values compared to the pre-treatment value may indicate the development of diabetic ketoacidosis or euglycemic diabetic ketoacidosis.
- SENVELGO may cause increased serum calcium and persistent elevations may require additional diagnostics. Persistent elevated calcium has been associated with increased risk of calcium-containing urolith formation in other SGLT2 inhibitors.
- Cats should be closely monitored for development of diabetic ketoacidosis or euglycemic diabetic ketoacidosis (for example, ketonuria or anorexia) after stopping SENVELGO. Euglycemia may persist for 2 to 3 days after stopping SENVELGO.
- Keep SENVELGO in a secure location out of reach of dogs, cats, and other animals to avoid accidental ingestion or overdose.

Precautions:
- Consider temporarily discontinuing SENVELGO during times of decreased caloric intake, such as surgery or decreased appetite, as continued administration of SENVLEGO may increase the risk of diabetic ketoacidosis.
- SENVELGO contains propylene glycol. When cats are administered SENVELGO at the 1 mg/kg/day dose, cats receive 40 mg/kg/day of propylene glycol. Exceeding 80 mg/kg/day of propylene glycol may result in excess hepatic glycogen stores. Use caution when administering SENVELGO to cats receiving other products that contain propylene glycol.
- Glucosuria may persist for 2-3 days after stopping SENVELGO. In cats receiving SENVELGO, glucosuria is not a reliable indicator for monitoring glycemic control.
- The safety and effectiveness of SENVELGO has not been evaluated in cats with chronic kidney disease (IRIS (International Renal Interest Society) Stages 3 and 4).
- The concurrent use of volume depleting drugs in cats treated with SENVELGO has not been evaluated.
- SENVELGO has not been evaluated with concurrent use of insulin or other blood glucose lowering treatments.
- The safety and effectiveness of SENVELGO in breeding, pregnant, and lactating cats has not been evaluated.

Adverse Reactions:
Two hundred fifty-two (252) cats with diabetes mellitus were enrolled in a 180-day multicenter field study. Safety data were evaluated in 252 cats treated with at least one dose of SENVELGO. Regardless of blood glucose level, cats received SENVELGO at a dose of 0.45 mg/lb once daily. The most common adverse reactions were diarrhea or loose stool, weight loss, vomiting, polyuria, polydipsia, and elevated blood urea nitrogen (BUN). The table below summarizes the adverse reactions reported in the study.

Adverse Reactions	Frequency (N=252) Number (%)
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 cats had elevations ≤ 1.5X upper limit of normal (ULN).

‡ All but 5 cases occurred within 2 weeks of starting SENVELGO. Twelve of these cats had euglycemic diabetic ketoacidosis.

§ These cats did not progress to diabetic ketoacidosis and all but one 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) > 2X ULN.

†† 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 without clinical signs (glucose ≤ 50 mg/dL), anemia, abnormal behavior, bradycardia, and dermatitis.

Ketonuria and diabetic ketoacidosis: Thirty-two (32) cats developed ketonuria, diabetic ketoacidosis or euglycemic diabetic ketoacidosis and were removed from the study. Twenty-six (26) of these cats developed ketonuria, diabetic ketoacidosis, or euglycemic diabetic ketoacidosis within the first 7 days of treatment with SENVELGO. Thirteen (13) of these cats developed ketonuria without further progression to diabetic ketoacidosis or euglycemic ketoacidosis and were transitioned to insulin. An additional thirteen (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 hospitalization 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 cats (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.

Death and euthanasia: Nineteen cats died (3) or were euthanized (16) during the study, or shortly following removal from the study, with thirteen possibly related to SENVELGO use or declining glycemic control. In addition to 6 of the cases associated with diabetic 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).

Contact Information: To report suspected adverse drug events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim Animal Health at 1-888-637-4251. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

Information for Cat Owners: Please provide and review the Client Information Sheet with cat owners to ensure they understand the entire contents before SENVELGO is administered. The Client Information Sheet contains important information regarding the use of SENVELGO. Owners should be advised to discontinue SENVELGO and contact a veterinarian immediately if their cat develops anorexia, lethargy, vomiting, diarrhea, or weakness.

Clinical Pharmacology:

Mechanism of Action:

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

Pharmacokinetics: In a laboratory study conducted to determine the prandial state of maximum exposure, systemic exposure for velagliflozin was greater in the fasted state than in the fed state by 170% for the mean maximum observed plasma concentration (C_{max}), and by 45% for the mean area under the plasma concentration versus time curve (AUC) from dosing (time 0) to the last quantifiable concentration ($AUC_{0\text{-}last}$), respectively.

In a well-controlled, laboratory margin of safety study in healthy, adult cats (see **Target Animal Safety**), 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.

Following oral administration of SENVELGO in cats at 1 mg/kg, velagliflozin was rapidly absorbed with a median time to maximum concentration of 0.25 hours. The velagliflozin mean (± standard deviation) C_{max} was 1030 (± 361) ng/mL and the mean $AUC_{0\text{-}last}$ to the last quantifiable plasma concentration was 3295 (± 1098) day*ng/mL. The elimination half-life of velagliflozin was 3.68 (± 0.34) hours.

Effectiveness: Two hundred and fifty-two (252) cats diagnosed with diabetes mellitus were enrolled in a 180-day multicenter field study. The cats included various purebred and mixed breed cats ranging in age from 4 to 18 years and in weight from 5.7 to 26.5 lbs (2.6 to 12 kg). Cats were administered SENVELGO at a dose of 0.45 mg/lb (1 mg/kg) orally, once daily, regardless of blood glucose level, beginning on Day 0. Cats were evaluated at Days 2 or 3, and Days 7 and 30 and then monthly.

Treatment success was evaluated on Day 30 and was defined as improvement in at least one clinical sign of diabetes mellitus (polyuria, polydipsia, unintended weight loss, polyphagia, or diabetic neuropathy) and improvement in at least one blood glucose variable (blood glucose curve mean or serum fructosamine).

Of 198 cats included in the effectiveness-evaluable population:

- 175 cats (88.4%) were considered a treatment success on Day 30 (lower bound of the two-sided 90% confidence interval was 84%).
- Mean blood glucose decreased from 446.4 mg/dL (single fasted sample) prior to Day 0 to 169.8 mg/dL (blood glucose curve mean) on Day 30
- Mean fructosamine levels decreased from 551.4 µmol/L prior to Day 0 to 332.0 µmol/L on Day 30.
- Improvements in the clinical signs of polyuria, polydipsia, body weight, polyphagia, and diabetic neuropathy on Day 30 were observed in 125/177 (71%), 128/176 (73%), 133/167 (80%), 33/80 (41%), and 7/30 cats (23%), respectively.
- 157 cats completed the 180-day study

Target Animal Safety: In a well-controlled laboratory margin of safety study, SENVELGO was administered orally to fasted, healthy, 8 to 9 month old cats at 0, 1, 3, or 5 mg/kg body weight (corresponding to 1X, 3X or 5X the intended labeled point dose of 1 mg/kg) once daily for 26 weeks (6 months). Control cats (0 mg/kg) received saline at a volume equal to the 5 mg/kg dose. There were eight cats per group (4 females, 4 males). All cats survived the study and there were no SENVELGO-related effects on ophthalmic examinations, indirect systolic blood pressure measurements, and blood coagulation parameters. Hypersalivation and vomiting after dose administration occurred infrequently and was only observed in the groups that received SENVELGO.

During physical examinations on Days 14 and 28, there was a drug-related decrease in heart rate (< 140 bpm) in the cats that received SENVELGO compared to the control cats. There were no other drug-related effects on physical examinations.

Polydipsia, glucosuria, decreased urine creatinine, and diarrhea were reported more frequently in cats that received SENVELGO than in control cats.

Reddish, mucoid feces were observed in three instances in the 1X group cats. One cat in the 5X group had decreased activity, vomiting, and reduced feed consumption for one day, and reddened rectal mucous membranes were observed over the next 5 days. Two cats (3X and 5X groups) were each observed to have a reddened prepuce with white-yellow discharge twice during the study that was not associated with abnormal urinalyses.

Food consumption was higher in the cats that received SENVELGO compared to the control cats. The rate of body weight gain was lower in the 5X group cats compared to cats in the control, 1X and 3X groups.

There were drug-related increases in reticulocyte count, mean corpuscular hemoglobin, mean corpuscular volume, and Heinz body percentage, and a decrease in mean corpuscular hemoglobin concentration in the cats that received SENVELGO compared to control cats. None of the cats showed any clinical signs of anemia and the number of erythrocytes, hemoglobin, and hematocrit values were normal. There was no effect of SENVELGO on white blood cells and platelets.

There were drug-related increases in serum magnesium, albumin, cholesterol, and triglycerides in the cats that received SENVELGO, with some magnesium, serum albumin and triglyceride values above the reference range. There was a drug-related decrease in mean BUN in the cats that received SENVELGO. There were no other treatment-related changes in serum chemistry parameters, including serum glucose and symmetric dimethylarginine (SDMA).

A reticular pattern was observed on the surface of the liver of one control, three 1X, four 3X, and three 5X group cats.

How Supplied: SENVELGO (velagliflozin oral solution) 15 mg/mL, 30 mL nominal fill volume is supplied in a 45 mL plastic bottle with dosing syringe.

NDC 0010-4614-01

Storage Information: SENVELGO can be stored at or below 77°F (25°C) with excursions permitted up to 104°F (40°C). Once the bottle is opened, use the contents within six months.

Approved by FDA under NADA # 141-568

Marketed by:
Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

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