Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Senvelgo 15 mg/ml Oral Solution for Cats

Date Created: October 2023

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Senvelgo 15 mg/ml Oral Solution for Cats, Oral solution
Applicant	Boehringer Ingelheim Animal Health UK Ltd, Ellesfield Avenue, Bracknell, Berkshire, RG12 8YS
Active substance	Velagliflozin L-proline H_2O
ATC Vetcode	QI01AD09
Target species	Cats
Indication for use	For the treatment of diabetes mellitus in cats

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	1st August 2023

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains velagliflozin and the excipients ethanol (anhydrous), propylene glycol, citric acid monohydrate, sodium hydroxide, honey flavour and purified water.

The container/closure system consists of a polyethylene bottle with an polyethylene plug-in adapter, closed with a child-resistant cap with liner. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of: dissolution and filtration.

Process validation data on the product have been presented in accordance with the relevant European guideline.

II.C. Control of Starting Materials

The active substance is velagliflozin L-proline H_2O, a novel active substance described in the in-house monographs. The active substance is manufactured in accordance with the principles of good manufacturing practice. The active part is velagliflozin

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

The excipients and packaging comply with Ph. Eur.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, colour, clarity, pH, identification assay and degradation of the active substance, microbial contamination.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 36 months.
Shelf life after first opening the immediate packaging: 6 months.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Studies have been conducted which show that velagliflozin inhibits the sodium-glucose co-transporter 2 (SGLT-2) which is predominantly expressed in the kidney. SGLT-2 is the primary transporter for the reabsorption of glucose from the urine. The inhibition of the SGLT-2 leads to glucose elimination in the urine and consequently results in a constant and reliable decrease in elevated blood glucose levels in diabetic patients.

Toxicological Studies

The applicant has conducted laboratory studies.

Single Dose Toxicity

The standard acute toxicity testing battery studies were conducted, with the exception of dermal toxicity, and skin sensitisation studies. All studies were conducted in a GLP laboratory in compliance with GLP standards compatible with international GLP regulations.
Two acute toxicity guideline studies were conducted, one on rats and one on mice, employing the Acute Toxic Class Method (OECD TG 423, 2001).
All animals were treated with the test substance and observed for 14 days.
Dosing materials were appropriately analysed for concentration and homogeneity of velagliflozin in 50% PEG 400 and deionised water.
In the mouse study, mice were administered 2000 mg/kg velagliflozin the test substance resulting in one female mouse mortality on day 13. One male mouse died on each of study days 4, 9 and 12 at the 2000 mg/kg dose level. At 1000 mg/kg dose level, no mortality was observed in either group of three male or female mice.
In the rat study, rats were administered 2000 mg/kg velagliflozin test substance, with one female rat mortality reported on study day 3. There was no mortality in the male study group.

Mortality was reported for both rats and mice at 2000 mg/kg velagliflozin test substance. However, mice appeared more sensitive than rats to the administration of 2000 mg/kg with 4 deaths versus 1 in the rat study; moreover, male mice appeared more sensitive to test item administration than female mice.
An acute dermal toxicity study (OECD TG 402, 2017) was not conducted by the applicant; oral toxicity study results were used as a surrogate to assess dermal toxicity.
Acute inhalation toxicity testing is deemed out of scope due to the low vapour pressure of the final formulation, which is not aerosolized under conditions of use, storage, handling, or transport and its oral administration to the cat, via a 'closed' delivery system, a syringe.

Repeated Dose Toxicity

The applicant tested repeated dose toxicity in three species; cat, dog and rat, fulfilling the requirements of EMA (2021). An oral margin of safety study in the target species was conducted and is reviewed in the Clinical Expert Report.
A four week oral toxicity study was conducted in four groups of male and female dogs to evaluate the potential toxicity of velagliflozin following once daily oral administration for 28 days, followed by a 56-day recovery period in 2 additional dogs per sex in the control and high dose groups. The study concluded NOAEL for velagliflozin test substance is 30mg/kg/day and no accumulation or effect of gender was noted.
In the rats there was a 4 week oral toxicity study followed by a 4 week recovery period. This resulted in no adverse effects reported and the majority of effects on rats were non -adverse secondary effects of the pharmacological activity of velagliflozin.
The tolerance/safety of 1x, 3x and 5x doses of the product in healthy adult male and female cats following daily oral administration for 6 months was established.

Reproductive Toxicity, including Teratogenicity:

The applicant submitted two studies and an integrative review which investigated reproductive and developmental toxicity.
The preliminary and definitive studies assessed the potential of velagliflozin to adversely affect the fertility and embryo-foetal development in rats.
The preliminary study concluded that the high dose level for the pivotal fertility and development study should be 300 mg/kg/day to 600 mg/kg/day.

The definitive study concluded that the NOAEL for parental F0 generation systemic toxicity is 100 mg/kg/day due to lower parental bodyweights and bodyweight gains observed in the 400 mg/kg/day study group. 100 mg/kg/day of velagliflozin test substance is deemed to be NOAEL for F0 male and female parental rats.
This study also concluded that the NOAEL for fertility and early embryonic development is also 100 mg/kg/day. Based on the effects on oestrous cyclicity, pre-coital intervals, mating, fertility, numbers of corpora lutea and implantation sites, and male reproductive organ weights in the 400 mg/kg/day dose group, the NOAEL for fertility and early embryonic development is 100 mg/kg/day.

Mutagenicity

An Ames assay was conducted with velagliflozin. Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay. In this GLP study, velagliflozin was tested to assess its ability to induce reverse mutations at the histidine locus in the genome of four strains of *Salmonella typhimurium* and at the tryptophan locus of *Escherichia coli* tester strain WP2uvrA. Dose-ranging, mutagenicity and confirmatory assays were designated as Trial A1, B1 and C1, respectively.
In the dose-range-finding study (Trial A1), velagliflozin was suspended or solubilised. Ten concentrations of velagliflozin per plate were tested for cytotoxicity in one plate per dose. This results in no decrease in the number of revertant colonies per plate or a thinning of the bacterial lawn was observed.
No positive increases were reported in either the mutagenicity (Trial B1) assay or a similarly conducted confirmatory (Trial C1) assay, either in the presence or absence of microsomal enzymes prepared from Aroclor-induced rat liver.
Velagliflozin is negative for mutagenicity.

A Mouse Lymphoma Mutation Assay (MLA) was conducted to evaluate velagliflozin's ability to induce forward mutations or chromosomal damage. Four Mouse Lymphoma Assays were conducted; 1) initial mutagenicity assay, 2) confirmatory assay, 3) first retest assay and 4) second retest assay.
The initial mutagenicity assay, assay 1, resulted in a positive mutagenic response in the 4-h -S9 trial.
In the confirmatory assay, assay 2, no mutagenicity response was produced. This lack of reproducibility between the initial mutagenicity and the confirmatory triggered the First Retest Assay, assay 3, which produced a negative result for mutagenicity and did not resolve this mutagenic response discrepancy.
A Second Retest Assay, assay 4, was then triggered to resolve the disparate results between the initial mutagenicity and the First Retest. Velagliflozin was deemed negative for induced mutagenicity in this Second Retest Assay.
Based on these three assays and their inability to reproduce the induced mutagenic response in the initial mutagenicity assay, the weight of evidence supports the conclusion that velagliflozin is not mutagenic in this Mouse Lymphoma Assay.

An *in vivo* test for chromosomal damage, rat bone marrow micronucleus (MN) assay, was conducted. This GLP study was conducted to determine the maximum tolerated dose (MTD) of velagliflozin when given orally to male and female rats. Mild clinical and general signs of toxicity were observed across all dose groups; no mortality was observed. Therefore, velagliflozin was neither genotoxic nor toxic to bone marrow in this MN assay in male rats. The number of cells evaluated for micronuclei are fewer than current guideline recommendations. It can be accepted that velagliflozin does not cause an increase in micronuclei in the doses tested.

Carcinogenicity

No carcinogenicity testing was conducted for velagliflozin; the applicant considered this justified for the following reasons:

- velagliflozin was not demonstrated to be mutagenic, clastogenic, or to induce aneuploidy in a battery of standard genotoxicity tests.
- Repeat dose toxicity studies in dogs and rats did not show any evidence of concern in this respect (e.g., preneoplastic lesions).
- Published literature on the class of SGLT-2 inhibitors in humans does not raise any concern with regards to potential carcinogenicity.

Observations in Humans

Velagliflozin is not authorised for use in human medicine; therefore, no pharmacovigilance or other human data are available. However, accidental and incidental user exposure data, gathered in clinical trials for the product, are summarised in the supporting critical review of eye and skin irritation and skin sensitisation data.
It was concluded from clinical trial eye and skin irritation and skin sensitisation data that exposed users had no dermal reactions and experienced only slight ocular irritation that resolved after flushing the eye with water.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which showed that the main routes of exposure are accidental ingestion of the product by a child and dermal contact as a result of spillage, including hand-to-eye contact by the adult user. Additional routes of exposure identified by the assessor, such as a child consuming uneaten medicated food (if the product is administered in this way), are secondary, and would not affect further the calculated risk. Risks to a child accessing a filled syringe and/or uneaten medicated food, and those to an adult from spillage of the product were identified, and appropriate user warnings have been included in the SPC.
There has not been any identified additional risk for reproductive or developmental toxicity, beyond that already identified as a result of the pharmacological action.
The studies supplied showed velagliflozin to be negative for genotoxicity and mutagenicity.
No sensitisation was identified, but the excipient propylene glycol may lead to hypersensitivity reactions.

Warnings and precautions as listed on the product literature (listed below) are adequate to ensure safety to users of the product.

- Keep out of the sight and reach of children.
- After administration of the veterinary medicinal product close bottle tightly with the cap.
- This product may cause slight irritation to the eyes.
- Avoid contact with the eyes.

- If contact with the eyes, rinse immediately with water.
- If symptoms occur, seek medical advice.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data describing the pharmacodynamic and pharmacokinetic properties of the active substance.

Pharmacodynamics

The applicant submitted a number of studies investigating the pharmacodynamics of the active part, velagliflozin, in non-target species including dogs, human and rats, as well as *in vitro* studies, where applicable. The applicant submitted four studies within the preclinical section which assessed pharmacodynamic parameters in the target species, cats. The pivotal study was conducted in accordance with GLP-guidelines and used the final formulation of the proposed product. Further supportive studies were conducted in accordance with required standards.

Selectivity and potency

An *in vitro* study demonstrated velagliflozin has high potency and selectivity for SGLT-2 receptors compared to other glucose transporters, including SGLT-1 and GLUT-1, in human and rat cell cultures. This is important since high receptor selectivity suggests the active substance will not cause widespread disruption of cellular glucose transport. It is noted that findings were similar between rat and human glucose receptors, which may infer a tendency for inter-species similarity in glucose receptor behaviour in the target species.

Induction of glucosuria

The applicant provided numerous studies demonstrating glucosuria following administration of velagliflozin in several species, including cats. Although these studies were generally not conducted in accordance with GLP guidelines, there

are considered to be sufficient data to support the primary pharmacodynamic effect of velagliflozin of inducing glucosuria.

Reduction in blood glucose (BG)

Although there is evidence that administration of velagliflozin reduces blood glucose (BG) levels in a diabetic model in rats and in healthy dogs, there is no preclinical evidence presented of an effect on BG levels in healthy or obese cats. Hypoglycaemia did not occur in any preclinical study investigating administration of the active substance in any species, including when doses higher than the proposed dose rate were administered.

Insulin and oral glucose tolerance

There was an improvement in oral glucose tolerance in ZDF rats at all doses of velagliflozin tested. When glucose and insulin tolerance tests were conducted in obese non-diabetic cats, there was a trend for reduced baseline-corrected insulin AUCs and increased insulin sensitivity in the treatment group. In a murine diabetic model, an alternative SGLT-2 inhibitor, empagliflozin, improved insulin sensitivity and was reported to contribute to improvements in glycaemic control in insulin resistant states in the mice studied. There are no statistically significant data to support increased glucose tolerance and insulin sensitivity in cats.

Increase in urine volume

There was evidence of a significant increase in urinary volume in rats and dogs following a single administration of velagliflozin; in dogs this effect persisted for up to approximately 48 hours. In obese cats, urine volume significantly increased following treatment, and in healthy cats no treatment-related change in urine production was identified. Given that results regarding urine volume and water intake appear inconsistent, and that there was no evidence of hypovolaemia or dehydration in clinical, haematological or biochemical parameters, this is not currently considered of importance.

Effect on the pancreas

A consequence of the primary pharmacodynamic effect of velagliflozin, i.e. induction of glucosuria, the secondary pharmacodynamic effect of BG concentration decrease may potentially lead to elimination of glucose toxicity exerted on pancreatic beta-cells, improved endogenous insulin secretion, ultimately, potentially normalising BG-insulin interactions in diabetic cats.

Effects on other organs/systems

The clinical expert states that velagliflozin had no adverse effects on cardiovascular function, no relevant effects on CNS function, and only slight effects on respiratory and gastrointestinal function at higher dose levels.

Drug interactions

Potential for drug-drug interactions with velagliflozin at the concentrations examined is predicted to be negligible.

Posology
The posology is once daily administration of 1 mg/kg velagliflozin.

Pharmacokinetics
The applicant provided some evidence relating to absorption, distribution, metabolism and excretion of the active substance using data from studies conducted in a range of species. Velagliflozin showed rapid systemic absorption following oral administration in cats. Faster absorption occurred when the active substance was administered in a fasting prandial state compared to fed. Repeat dosing led to slight accumulation, with steady state reached within three months. Half-life was approximately 3 – 4 hours for all dose rates, and plasma levels of velagliflozin 24 hours post-dosing were low but quantifiable in most cats.

Tolerance in the Target Species

Adverse effects observed in a tolerance study evaluating repeadted doses of 1 mg/kg, 3 mg/kg and 5 mg/kg of the product over 180 days:

- Increased water consumption
- Transient increased triglyceride and cholesterol levels
- Paler urine
- Reduced urinary creatinine levels
- Vomiting (3x and 5x overdose groups)
- Softer/loose stool (5x overdose group only)
- Reticulocyte counts were elevated, with no other associated haematological or clinical signs of anaemia (5x overdose group only)
- Mean calcium and magnesium values were higher in the 3x and 5x groups and appeared dose-related

Bibliographical data also been provided which shows that these findings were observed in other pre-clinical and clinical studies, and that no additional adverse events of significant concern were observed in these overdose studies.

Symptomatic hypoglycaemia did not occur in healthy animals even at 5x overdose.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Velagliflozin does not possess any antibiotic or antiparasitic properties.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has conducted two proof of concept studies investigating efficacy and safety of velagliflozin, one field study in both naïve and pre-treated cats which also served as a dose determining study, and three field studies investigating the efficacy and safety of velagliflozin in the target species (cats).

Field Trials

The first of the 3 trials investigated the effects of velagliflozin on glycaemic control and clinical signs of diabetes mellitus when administered orally and once-daily for 91 days in comparison to Caninsulin in naïve and insulin pre-treated diabetic cats. Client-owned cats of either gender, spayed/neutered or entire, any breed, age ≥1 year meeting all of the criteria were included in the study. Cats with a history of decreased appetite, chronic or acute vomiting, chronic or acute diarrhoea, ultrasonographical changes consistent with pancreatitis, blood serum fPL >12 µg/L, history of recurrent, symptomatic chronic pancreatitis, ketonuria, suspicion of or confirmed uncontrolled hyperthyroidism or any other known concomitant disease/condition were excluded from the study. Cats were housed with their owners in their usual environment. The study confirmed that once daily oral treatment with 1 mg/kg velagliflozin was noninferior to twice daily insulin injections in naïve or insulin pre-treated diabetic cats with regards to glycaemic control and improvement in clinical signs related to diabetes mellitus.

The second trial investigated the safety and efficacy of velagliflozin for the reduction of hyperglycaemia and hyperglycaemia-associated clinical signs of diabetes mellitus for 180 days. Client-owned cats of either gender (entire or spayed/neutered), any breed aged ≥2 years, otherwise healthy, naïve diabetic cats or diabetic cats previously treated for more than four days with insulin or an oral anti-diabetic drug, that met the criteria at the screening visit were included in the study. No dose of insulin or other anti-diabetic medication was administered after the morning of Day -1. Cats were excluded from the study if they had a history of decreased appetite, vomiting or diarrhoea within 14 days prior to the screening visit; had an ongoing, frequently progressive or serious concurrent illness(such as pancreatitis or hyperthyroidism); had ketonuria; had their diet changed within 14 days prior to the screening visit; were being treated with prohibited/disallowed medications; were enrolled in another clinical study within 30 days prior to the screening visit; demonstrated fractious behaviour, or were pregnant, lactating or intended for breeding. Cats were housed with their owners in their usual environment and 1 mg/kg of velagliflozin was administered in the morning directly into the mouth or with a small amount of food. To ensure consistent dosing the velagliflozin was administered at the same time each morning (+/- 4 hours). The data from this study provided substantial evidence that once-daily administration of velagliflozin oral solution is safe and effective.

The third study was conducted to investigate the effectiveness and safety of velagliflozin for the reduction of hyperglycaemia and hyperglycaemia-associated clinical signs in cats with diabetes mellitus. Client-owned cats of either gender (entire or spayed/neutered) and any breed were eligible for the study. The eligibility criteria were the same as above. The administration of 1 mg/kg velagliflozin per day for 30 days decreased the blood glucose levels and improved the clinical signs of cats with newly diagnosed or poorly controlled diabetes mellitus, successfully meeting the criteria for the primary efficacy variable. Thus, the administration of velagliflozin to cats with diabetes mellitus was considered to be efficacious and safe for clinical use.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics the benefit/risk profile of the product is favourable.

MODULE 4

POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)