05 October 2023
EMA/460512/2023
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Senvelgo (EMEA/V/C/005972/0000)

INN: velagliflozin

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant Boehringer Ingelheim Vetmedica GmbH submitted, on 19 April 2022, an application for a marketing authorisation to the European Medicines Agency (The Agency) for Senvelgo, through the centralised procedure under Article 42(2)(c) of Regulation (EU) 2019/6 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 15 July 2021, as Senvelgo contains an active substance which has not been authorised as a veterinary medicinal product within the Union at the date of the submission of the application (Article 42(2)(c)).

At the time of submission, the applicant applied for the following indication:

"For the treatment of diabetes mellitus in cats".

The active substance of Senvelgo is velagliflozin, a "sodium-dependent glucose co-transporter 2" (SGLT-2) inhibitor. SGLT-2 is mainly expressed in the renal proximal tubules and its inhibition decreases renal glucose reabsorption, which reduces blood glucose levels and thus allows for the control of hyperglycaemia. The target species are cats.

Senvelgo oral solution for cats contains 15 mg/ml velagliflozin and is presented in packs containing 1 bottle + 1 syringe.

The rapporteur appointed is Keith Baptiste and the co-rapporteur is Mary O'Grady.

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

On 5 October 2023, the CVMP adopted an opinion and CVMP assessment report.

On 20 November 2023, the European Commission adopted a Commission Decision granting the marketing authorisation for Senvelgo.

Scientific advice

Not applicable.

Limited market status

Not applicable.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file dated 18 January 2022 which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided, the applicant has in place a pharmacovigilance system master file (PSMF) with reference number PSMF-BIV-0001, has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

Manufacture of the active substance velagliflozin takes place outside the EEA. A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site.

GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the activities as indicated above, has been provided. As there is a mutual recognition agreement in place for Good Manufacturing Practice (GMP) between the EU and the country outside EEA, the site was considered appropriately certified as complying with GMP requirements.

Finished product

Processing of the non-sterile medicinal product, quality control testing (chemical/physical), primary packaging and secondary packaging, take place outside the EEA. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the activities as indicated above, has been provided. As there is a mutual recognition agreement in place for Good Manufacturing Practice (GMP) between the EU and the country outside EEA, the site was considered appropriately certified as complying with GMP requirements.

Quality control testing (chemical/physical/microbiological: non-sterility) takes place outside of the EEA. GMP certification available in EudraGMP confirms the date of the last inspection and shows that the sites are authorised for the activities as indicated above. As there is a mutual recognition agreement in place for Good Manufacturing Practice (GMP) between the EU and the country outside EEA, the sites are considered appropriately certified as complying with GMP requirements.

Importation of finished product is carried out by a suitably qualified site in the EEA. Quality control of imported product takes place in the EEA. GMP certification available in EudraGMP confirms the date of the last inspection and shows that the sites are authorised for the activities as indicated above.

Batch release takes place in the EEA takes place at Klifovet GmbH, München, Germany. The site has a manufacturing authorisation issued on 25 January 2022 by the competent authority in Germany. GMP certification, which confirms the date of the last inspection and shows that the site is authorised activities indicated above, has been provided.

Quick Response (QR) code

Application has been made to include a QR code on the outer carton and in the package leaflet. The QR code will provide access to a digital package leaflet.

The proposal for inclusion of a QR code is acceptable.

Overall conclusions on administrative particulars

The summary of the PSMF was considered to be in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

The proposal for inclusion of a QR code is acceptable.

Part 2 - Quality

Composition

The finished product is an oral solution, presented as a multidose preparation and filled in 45 ml capacity high density polyethylene (HDPE) bottles connected with a low-density polyethylene (LDPE) plug-in adapter and closed with a child resistant cap with sealing disc. Each bottle contains 30 ml of oral solution and each ml of solution contains 15 mg of velagliflozin in the form of velagliflozin L-proline H_2O.

Other ingredients are citric acid monohydrate, sodium hydroxide solution 1M, propylene glycol, ethanol (solvent), water, purified and honey flavour, as described in section 2 of SPC.

Containers and closure system

The finished product, Senvelgo 15 mg/ml oral solution for cats, is filled in 45 ml translucent HDPE bottles, which are fitted with translucent plug-in adapters made of LDPE. The bottles are closed with white, child-resistant screw caps and white sealing discs; the caps have translucent tamper-evident rings. The nominal fill volume of the bottle is 30 ml. A 0.6 ml oral dosing syringe made of a translucent barrel and a white plunger is included.

Product development

Senvelgo 15 mg/ml oral solution for cats was developed as an aqueous mixture containing 15 mg of the active moiety velagliflozin per ml of oral solution.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for the honey flavour, which is controlled by in-house specification. Sodium hydroxide 1M is confirmed to be compounded by the sodium hydroxide (Ph. Eur. 677) and purified water (Ph. Eur. 8). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

The quality target product profile (QTPP) for the proposed commercial product was established summarizing all attributes to ensure quality, safety and efficacy of the product.

The product is supplied with a dosing oral syringe which includes a bodyweight scale with 0.5 kg increments and compliance with the requirements of Ph. Eur. 2.9.27. "Uniformity and accuracy of delivered doses from multidose containers" was demonstrated at the minimum and maximum dosing increments of the syringe.

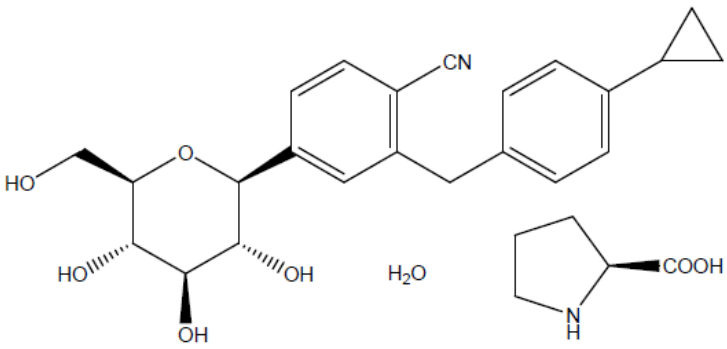
Description of the manufacturing method

The manufacturing process of Senvelgo 15 mg/ml oral solution for cats consists of three main manufacturing steps: dissolution, filtration, and filling. A holding time of the bulk solution prior to filling is proposed and justified by the bulk stability data and routine microbiological quality testing at release.

The manufacturing process is considered to be a standard process. A detailed process validation scheme has been provided which is considered acceptable.

Control of starting materials

Active substance

INN name	Velagliflozin
Chemical name	2-(4-cyclopropylbenzyl)-4-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-hydroxymethyl-tetrahydropyran-2-yl)-benzonitrile (S)-pyrrolidine-2-carboxylic acid monohydrate
Synonym	Velagliflozin L-proline H_2O
Molecular structure	
Molecular formula	$C_{28}H_{36}N_2O_8$ ($C_{23}H_{25}NO_5$ x $C_5H_9NO_2$ x H_2O)
Molecular mass	528.59 g/mol for the 1:1:1 co-crystal (395.46 g/mol for the free active part)
General information and chemical features	Velagliflozin is a white to off-white to slightly yellow crystalline solid. It is optically active and exhibits polymorphism.

Velagliflozin exhibits stereoisomerism due to the presence of 5 chiral centres. Several polymorphic forms are identified. Critical process parameters are specified to control formation of the crystalline polymorphic form.

Evidence of structure: The chemical structures of velagliflozin and velagliflozin L-proline monohydrate have been characterised by IR, UV, ^{1}H-NMR and ^{13}C-NMR data as well as elemental analysis.

Velagliflozin is synthesised using well-defined starting materials.

The characterisation of the active substance and its impurities is in accordance with the CVMP "Guideline on the chemistry of active substances for veterinary medicinal products" (EMA/CVMP/QWP/707366/2017).

Detailed information on the manufacture of the active substance has been provided and is considered satisfactory.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented along with batch analyses data to support the proposed specifications.

Potential impurities of velagliflozin are discussed with regards to their origin and characterisation, and sufficient information is provided to demonstrate that any impurities that may be present in the active substance, arising from the starting materials, intermediates or other sources, are detected by the validated HPLC-related substances method and are suitably controlled.

Acceptable specifications have been set in sufficient detail and analytical methods used have been described and validated in accordance with VICH GL1 and GL2. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (5 commercial scale batches of the active substance) have been provided. The results are within the specifications and consistent from batch to batch.

Stability data of the active substance from the proposed manufacturer in the packaging proposed for commercial batches, were provided for 3 scale-up batches and 3 commercial-scale batches up to 48 months under long-term conditions at 25 °C/60% RH and up to 6 months under accelerated conditions at 40 °C/75% RH according to relevant VICH guidelines.

Photostability testing in accordance with VICH GL5 was performed to demonstrate that velagliflozin is not sensitive to light. A forced degradation study has also been performed and results presented demonstrated that the method for assay and related substances is stability-indicating.

The stability parameters tested were in line with the active substance specification. The analytical methods used were the same as for the active substance specification.

All tested parameters were within the specifications. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months, with no special storage conditions in the proposed container.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for sodium hydroxide 1M solution and honey flavour, which are controlled by internal specifications. A declaration of the compliance of the honey flavour with Regulation (EC) No 1334/2008 has been provided. There are no novel excipients used in the finished product formulation. Limits for microbiological quality in accordance with Ph. Eur. 5.1.4. "Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use" are included, where necessary. The list of excipients is included in section 2 of the SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The product does not contain any materials derived from human or animal origin.

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01 rev.3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the above-mentioned "Note for guidance".

Control tests on the finished product

The release specifications comply with VICH guidelines and Ph. Eur. general monographs.

The finished product specification includes tests for appearance, colour of solution, clarity of solution, pH, fill volume, relative density, identification, assay and degradation products and microbial contamination.

An appropriate justification for each specified parameter has been provided.

Method descriptions have been provided for all methods (Ph. Eur. and in-house methods) and have been appropriately validated in accordance with VICH Guidelines, where relevant. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch data on three batches manufactured at production scale are presented. The results comply with the specifications.

An elemental impurity risk assessment has been provided for the finished product in accordance with the requirements of ICH Q3D.

Stability

A shelf life of 36 months with no storage precautions and an in-use shelf-life of 6 months is proposed. Stability data has been presented for three commercial batches from the proposed site of batch manufacture, and supportive stability data has been provided for three pilot-scale batches from a manufacturing site not proposed for registration. Results are presented for the primary stability for up to 18 months under long-term (25 °C/60% RH) and intermediate conditions (30 °C/75% RH) and up to 6 months under accelerated conditions (40 °C/75% RH). Results for supportive stability batches are provided for 36 months under long-term and intermediate conditions and for 6 months under accelerated conditions.

The specifications proposed at shelf-life are the same as those proposed at release except for identification, fill volume and relative density which are not tested at shelf-life. These differences have been appropriately justified.

No relevant changes in the appearance, physico-chemical, chemical and microbial characteristics have been observed under any of the storage conditions studied and all results met the established shelf-life specifications. The results observed at shelf-life are similar to data observed at release.

The finished product demonstrates good stability over the course of the studies (with reference to both primary and supportive stability data), and, as such, a shelf-life of 36 months is considered acceptable.

Photostability of the finished product in the proposed primary packaging has been demonstrated and, consequently, no special storage instructions are required to protect the product from light. An in-use stability study has been presented to support an in-use stability of 6 months and a protocol for an additional in-use study provided. The proposed in-use shelf-life of 6 months is considered acceptable.

New active substance (NAS) status

The applicant requested the active substance contained in Senvelgo, velagliflozin, to be considered a new active substance as it is novel and not hitherto authorised in a veterinary medicinal product in the European Union.

Based on the review of the data provided, the CVMP considered that the active substance velagliflozin contained in the veterinary medicinal product Senvelgo is a new active substance based on its quality and chemical structure.

Overall conclusions on quality

The chemical-pharmaceutical documentation and quality overall summary in relation to Senvelgo are of sufficient quality in view of European regulatory requirements.

The documentation on the active substance, velagliflozin, is presented as a full file. The manufacturing process has been described in detail and the control strategy for impurities is considered justified. Stability studies have been performed with the active substance. No significant changes in any

parameters were observed. The proposed retest period of 48 months with no special storage condition is justified.

The drug product Senvelgo 15 mg/ml is an oral solution presented as a multidose preparation. The development approach is based on the target quality product profile and clinical development works.

The final commercial product is a multi-dose oral solution preserved by the contribution of the excipient mixture of propylene glycol/ethanol. The effective antimicrobial properties have been demonstrated.

The suitability of the syringe and its dose accuracy have been adequately demonstrated.

The manufacturing process is considered a standard process consisting of dissolution, filling and packaging. Batch data has been presented and results comply with the specifications.

The release and shelf-life specifications comply with VICH guidelines and Ph. Eur. general monographs. The specification set for control of the drug product is considered sufficient.

Based on the 36 months stability data (primary and supportive stability studies) which are in compliance with the specifications, a shelf-life of 36 months is considered acceptable.

Photostability of the finished product in the proposed primary packaging has been demonstrated and supportive in-use stability data is provided to support an in-use shelf-life of 6 months for the drug product. The applicant is obliged to report any out of specification results to competent authorities once the product is approved.

Part 3 – Safety documentation (safety tests)

Senvelgo 15 mg/ml is applied for as an oral solution for cats containing the active substance velagliflozin, which has not been authorised as a veterinary medicinal product within the Union at the date of the submission of the application in accordance with Article 42(2)(c) of Regulation (EU) 2019/6. Velagliflozin works by inhibiting SGLT-2 (glucoside sodium-dependent glucose co-transporter 2), thus reducing the amount of glucose being reabsorbed in the kidney. The gliflozin class of compounds is well-known in the area of human medicinal products, but SGLT-2 inhibitors are novel in cats.

A full safety file in accordance with Article 8 of Regulation (EU) 2019/6 has been provided.

Safety tests

Pharmacology

Pharmacodynamics

Regarding primary pharmacodynamics (PD), velagliflozin was shown to be a potent in vitro SGLT-2 inhibitor, with IC50 values for 14C-alpha-methyl-glucopyranoside (AMG) uptake of 0.3 and 0.8 nmol/l in human and rat cell lines, respectively. Furthermore, velagliflozin increased urinary volume and glucose excretion in diabetic ZDF rats and non-diabetic Beagle dogs following a single oral dose of 1.0 mg/kg bodyweight (bw) and 0.1 mg/kg bw, respectively. In diabetic ZDF rats, a single oral dose of velagliflozin also improved oral glucose tolerance shortly after dosing.

Regarding secondary PD characteristics, a number of studies were conducted in species other than cats. The studies include an in vitro study of hERG-mediated potassium current in HEK293 cells and on action potential configuration in isolated guinea pig papillary muscle. The cardiovascular system was evaluated in two in vivo studies in remote-monitored dogs. The potential for effects on the CNS and behaviour was addressed in two studies, one in rats and one in mice, while effects on respiratory function and on the GI tract were addressed in two rat studies and effects on renal and liver function were investigated in one rat study. Overall, despite the limitations noted, no findings were consistent with an increased risk of clinically relevant acute adverse effects, and data can be considered supportive of the applicant's premises.

PD in the target species is described in detail in part 4. Section 4.2 of the SPC adequately describes the compound's PD.

Pharmacokinetics

Regarding pharmacokinetics (PK), plasma protein binding and the distribution between plasma and blood cells were determined in vitro (see the paragraph on distribution below for details). In vivo, pharmacokinetics were investigated in Wistar rats (i.v. and p.o.), Beagle dogs (i.v. and p.o.) and cats (i.v. and p.o.). Some animal-to-animal variation regarding both Cmax, clearance and AUC was seen, but, in general, these studies support a log-linear depletion rate and dose-proportionality between doses of 1 mg/kg bw and the 10 mg/kg bw dose. In general, the plasma concentrations increased proportionally to dose in both rats and dogs, and there were no relevant differences in exposure between male and female animals. Dose proportionality was also observed for doses up to 5 mg/kg bw

in cats with little or no influence of gender (see part 4 "Pharmacology" for details). Section 4.3 of the SPC adequately describes the PK.

Absorption

In rats and dogs, velagliflozin was rapidly absorbed following administration via oral gavage of 1 and 10 mg/kg bw (Tmax 0.25–1.0 h), and the oral bioavailability was high at both doses (77% and 81% in rats, and 101% and 92% in dogs, respectively). In cats, bioavailability after oral administration was estimated using the individual animal's dose-normalized AUC_{inf} after oral and intravenous dosing and was high for all animals (95.5 ± 7.72%).

Distribution

In rats, a mean volume of distribution at steady state (V_{ss}) of 1.98 l/kg (i.e. higher than total body water) and a high clearance (CL) of 28.4 ml/min/kg was found, resulting in a short elimination half-life (t½) of 1.13 h. In dogs, mean V_{ss} was 0.571 l/kg (i.e. similar to total body water) and the clearance was 0.634 ml/min/kg, resulting in a t½ of 12.9 h. The dogs were fed four hours after dosing, and 6-8 h post-administration, a secondary plasma peak concentration was observed. This seems to be a species-specific phenomenon, as a secondary peak was not observed in the rat and cat studies. In vitro, the protein binding ranged from 89.0 to 90.2% in rat plasma, from 94.8 to 95.5% in dog plasma, from 91.6 to 92.1% in human plasma, and from 91.3 to 93.7% in feline plasma. However, it is important to note that the free (unbound) drug concentration can vary markedly despite seemingly small differences in protein binding. Thus, the free concentration at 90% protein binding will be twice that of the free concentration at 95% protein binding (as 10% versus 5% will be unbound). A moderate partitioning into blood cells was found in all species, with ratios of mean concentration in blood cells to plasma (Cbc/Cp) of approximately 0.65–0.66, 0.11–0.21 and 0.23–0.32 in rat, dog, and human blood, respectively. Interestingly, these findings correlate inversely with the findings regarding protein binding, likely reflecting that only the unbound fraction in plasma is free to diffuse into the blood cells.

Metabolism and excretion

In a study in feline liver microsomes and hepatocytes, a low turnover was observed (5–10% and 15–19%, respectively). The primary metabolic pathways observed were oxidation and direct O-glucuronidation. Other metabolic pathways included di-oxidation, tri-oxidation, combination of oxidation and dehydrogenation, oxidation and glucuronidation.

After oral administration of 1 mg/kg bw velagliflozin (15 mg/ml) oral solution to healthy cats, the majority of velagliflozin and its related metabolites was excreted via faeces primarily as unchanged velagliflozin. Only a minor fraction (approx. 4%) of velagliflozin or its related metabolites was excreted via the renal route.

Toxicology

Single-dose toxicity

A number of single-dose toxicity studies were provided in species other than cats.

Acute oral toxicity was determined in two single dose LD_{50} studies conducted in mice and rats in line with OECD TG 423. In both studies, velagliflozin L-proline-monohydrate was administered in 50% PEG and deionized water by oral gavage at doses of 1000 or 2000 mg/kg bw, and mortality was reported for both rats and mice at the 2000 mg/kg bw dose. However, mice appeared to be more sensitive than rats, with 4 deaths (out of 6 mice) versus 1 (out of 6 rats) in the rat study. Moreover, male mice appeared more sensitive to test item administration than female mice.

Velagliflozin L-proline-monohydrate was considered to be a category 4 test substance in mice (with an LD_{50} > 1000 and < 2000 mg/kg bw) and a category 5 test substance in rats (with an LD_{50} > 2000–5000 mg/kg bw). The two studies reported the use of doses close to the LD_{50}. However, the value of the results for human risk assessment is limited, as the studies did not determine an acute NOAEL. Instead, a 1-week oral (via gastric intubation) maximum tolerated dose study in the rat was used to set the short-term no observed adverse effect level (NOAEL). The groups were dosed 300, 500 or 700 mg/kg/day and the NOAEL was set at 300 mg/kg/day because higher doses caused greater than 30% decrements in mean bodyweight gains.

Repeat-dose toxicity

The pivotal repeat oral dose toxicity studies were carried out in rats and dogs.

In the GLP-compliant repeat dose toxicity study in rats, groups of 16 animals per sex and group were dosed by oral gavage for four-weeks followed by a four-week recovery period. The test substance (velagliflozin L-proline monohydrate suspension in 50% PEG 400/50% water, administered at 5 ml/kg bw) was dosed at dose levels of 0, 30, 100 and 300 mg/kg bw/day for at least 4 weeks. An additional 10 rats/sex/group received 0 or 300 mg/kg bw/day for at least 4 weeks, then underwent a 4-week recovery period.

Velagliflozin L-proline monohydrate resulted in increased food consumption at dose levels of 30, 100 and 300 mg/kg bw/day. Bodyweights compared to controls increased in 3–9% female rats given 100 and 300 mg/kg bw/day but decreased 6–10% in male rats at the 300 mg/kg bw/day dose level.

The majority of the velagliflozin-related effects were considered secondary to the pharmacological activity of the compound. However, elevations in blood urea nitrogen (BUN) were observed in all test article groups and elevations in creatinine in the 300 mg/kg bw group. At necropsy, mild tubular vacuolation and hydronephrosis was also observed in all test article groups. Microscopic changes were limited to an increase in severity for kidney tubular mineralization.

A dose-dependent and statistically significant increase in BUN was observed at all dose levels. Although this effect was reversible, a NOAEL could not be established from this study.

A four-week non-GLP-compliant oral toxicity study was conducted in four groups of three male and three female Beagle dogs to evaluate the potential toxicity of velagliflozin. Daily administration by oral gavage occurred for 28 days. Two additional dogs per sex were included in the control and the high dose group and were followed during a 56-day recovery period. Initial dose levels were 0, 10, 30 and 100 mg/kg bw/day in groups 1 to 4, respectively (see below for details on dosing changes). On study day 13, dosing in all dogs in group 4 was interrupted due to dehydration and decreased food consumption, with test item administration resuming at 60 mg/kg bw/day 2 days thereafter. Therefore, the final dose levels were as follows: 0, 10, 30 and 60 mg/kg bw/day. The toxicokinetics of velagliflozin were evaluated in all dogs (main and recovery group dogs) at six timepoints over a 24-hour period on days 1 and 28.

Velagliflozin plasma levels increased proportionally from 10 to 60 mg/kg bw/day on study day 28, demonstrating a constant clearance of velagliflozin over those doses and time intervals. No accumulation or effect of gender was noted.

The applicant's expert report concludes that the NOAEL value for velagliflozin L-proline monohydrate was 10 mg/kg bw/day, based on clinical (vomitus and diarrhoea), histopathologic (unequivocal pyelitis) observations and a clinically significant decrease in absolute bodyweight. The expert report calculated the combined sex C_{max} and AUC_{0-24} at the NOAEL to be 79,300 nM and 839,500 nM*h, respectively, on day 28. The final NOAEL of 10 mg/kg bw/day was used in the user risk assessment of repeated exposure.

In a non-GLP-compliant repeat dose toxicity and toxicokinetic study, mice were dosed by oral gavage for at least two weeks. The study involved four dose levels in both male and female mice. For each sex and dose, 10 mice were assigned to toxicology test groups, whereas 9 animals were assigned to groups investigating toxicokinetics. The test substance (velagliflozin L-proline monohydrate suspension in 50% PEG 400/50% water) was administered at dose levels of 0, 100, 300 and 500 mg/kg bw/day. Six mice in the 500 mg/kg bw toxicology group did not survive until scheduled termination of the study, while 3 animals in the toxicokinetic group died or were euthanised for humane reasons. Clinical signs considered related to test article administration included dehydration and decreased motor activity. Additionally, elevations in alanine aminotransferase and sorbitol dehydrogenase levels were observed in the 500 mg/kg bw group. Statistically significant liver weight increases were observed in the 300 and 500 mg/kg bw groups, and mild to marked hydropic change of hepatocytes was seen in the livers in mice of all dose groups. Microvesicular vacuolation of the liver and tubular vacuolation of the kidneys was additionally observed at necropsy of one animal from the 500 mg/kg bw group that died on study. The hepatic findings are ascribed to an exaggerated pharmacological response to reduced blood glucose.

Tolerance in the target species

Please refer to section 4.

Reproductive toxicity, including developmental toxicity

Two studies have been submitted studying the effects on fertility and embryo-foetal development in the rat following administration by oral gavage. The first study was a preliminary study, where the highest dose exceeded the maximum tolerated dose since one female and all male rats were euthanized due to poor clinical condition at 600 mg/kg bw/day.

Furthermore, a review was submitted integrating empirical data from non-clinical velagliflozin studies as well as information from peer-reviewed scientific literature to provide a more comprehensive and robust understanding of outcomes in the pivotal embryo-foetal developmental study.

The main study was designed to comply with GLP and ICH guideline S5 (R3) principles, combining the study of fertility and early embryonic development (FEED) with effects on implantation and effects on embryo-foetal development (EFD). The doses were selected based on the preliminary study, i.e. 0 (control), 40, 100 and 400 mg/kg bw/day.

Based on the lower parental bodyweights and bodyweight gains observed in the 400 mg/kg bw/day velagliflozin test group (54% reduction in mean bodyweight gain during gestation and 77% reduction in mean bodyweight gain adjusted for gravid uterus weight in female rats), the NOAEL retained for F0 male and female rats is 100 mg/kg bw/day.

In females, oestrous cycle regularity, mating performance, and fertility were all adversely affected at the 400 mg/kg bw/day dose level, but not at 40 or 100 mg/kg bw/day.

Based on the effects on oestrous cyclicity, pre-coital intervals, mating, fertility, numbers of *corpora lutea* and implantation sites as well as male reproductive organ weights in the 400 mg/kg bw/day dose group, the NOAEL retained for fertility and early embryonic development is 100 mg/kg bw/day.

Mean foetal weight was lower in the high dose group and higher in the mid dose group (statistically significant differences) and similar to controls in the lowest dose group. However, there was no indication that the slightly elevated foetal weight noted in the 100 mg/kg bw/day dose group was adverse. The higher post-implantation loss and lower litter size observed in the 400 mg/kg bw/day dose group were considered to be adverse effects related to velagliflozin administration. Post-implantation loss and live litter size were unaffected by velagliflozin administration in the 40 and 100 mg/kg bw/day dose groups. Major foetal morphology abnormalities in the 400 mg/kg bw/day dose group were reported and consisted of short, bent and/or thickened *scapulae*, *femora* and/or *humeri*. The same major abnormality was reported in one foetus of the 100 mg/kg bw/day dose group. No such findings were reported in the 40 mg/kg bw/day dose group. A minor skeletal variant of medially thickened/kinked ribs was encountered in all groups, including the control.

The foetal findings (multiple indicators of effects on embryo-foetal development, i.e. increased post-implantation loss, lower foetal weight and an increase in skeletal morphologic findings) in the 400 mg/kg bw/day dose group were consistent with adverse events (AEs). Based on scientific literature, historical data and background findings, the slightly higher incidence of medially thickened/kinked ribs in the 40, 100 mg/kg bw/day and the control groups and the findings in a single foetus in the 100 mg/kg/day dose group (i.e. short, bent, and thickened humerus) were not considered to be related to velagliflozin toxicity or to be toxicologically significant. Therefore, the NOAEL for embryo-foetal development is retained at 100 mg/kg bw/day.

Genotoxicity

The genetic toxicological potential of velagliflozin L-proline monohydrate was evaluated in a standard test battery in accordance with VICH GL23, i.e. in an Ames assay for mutagenicity, in vitro mouse lymphoma TK gene mutation assay (MLA) for mutagenicity and chromosomal damage, and in an in vivo rat bone marrow micronucleus assay for chromosomal damage. As a supplement, the assessment of mutagenicity was assayed using a quantitative structure-activity relationship (QSAR) approach. The micronucleus assay included three dosing groups of 500, 1000 and 2000 mg/kg bw, in which the clinical sign of wet fur in the genital area was observed in all groups. All studies were conducted according to GLP and OECD test guidelines principles.

All three studies produced negative results, as did the QSAR evaluation. It is therefore concluded that velagliflozin does not possess a genotoxic potential.

Carcinogenicity

No carcinogenicity studies were submitted, based on the following points as outlined in VICH GL28: (i) negative outcomes in all assays included in the standard battery of genotoxicity tests; (ii) no findings in systemic toxicity tests relevant to neoplasia; and (iii) no established causative association to cancer using a QSAR approach of the SGLT-2 inhibitors class of substances in non-diabetic human populations. Furthermore, the latest publicly available meta-analysis, which was submitted in the dossier, evaluated 27 randomized clinical trials in humans of at least 52 weeks in duration identifiable in the open literature up to December 2018 for all SLGT-2 inhibitors, and concluded that the available

data did not suggest detrimental effects of SGLT-2 inhibitors on the incidence of malignancies in general or regarding bladder cancer in particular. The argumentation for not conducting any carcinogenicity studies is thus considered acceptable.

Other requirements

Special studies

An acute dermal toxicity study has not been performed. Its absence is supported by the results of the oral toxicity studies as well as OECD guidance document 237 ("Considerations for Waiving or Bridging of Mammalian Acute Toxicity Tests"). The acute oral LD_{50} of velagliflozin is greater than 2000 mg/kg bw in rats and referring to the acute oral toxicity studies as surrogate for classification is acceptable.

Skin sensitization testing has not been performed, which the applicant justifies by referencing OECD TG 168 ("The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins") stating that, for human contact allergic dermatitis to occur, the key molecular event is the formation of a hapten-protein complex or complete antigen via covalent binding of the molecule and skin proteins. In order for this to happen, velagliflozin would need to be an innate direct-acting electrophile or metabolised to become one. However, velagliflozin does not have any known structural functional groups that can lead to bioactivation in the skin to form reactive metabolites which may bind proteins or DNA. Furthermore, the possible oxidation of velagliflozin to hydroxylation metabolites are not known to bind covalently to proteins. An in-silico assessment predicting skin sensitization has been generated by using the DEREK Nexus software package (DEREK version 6.1.0; Nexus version 2.3.0), in which velagliflozin was classified as a non-sensitising substance. This approach and the conclusion are considered to be acceptable.

A dermal irritation/corrosion study in rabbits was conducted according to OECD TG 404 and method B4 ("Acute Toxicity (Skin irritation)") outlined in Council Regulation (EC) No 440/2008. Three rabbits received a single 4-hour, semi-occlusive, dermal administration of approximately 0.5 ml Senvelgo 15 mg/ml oral solution. Since no effects were reported in terms of erythema or oedema in any of the rabbits, it can be accepted that the product was shown not to be a dermal irritant.

The eye irritation potential of Senvelgo 15 mg/ml oral solution was tested in vitro and ex vivo according to OECD TG 492 and 437, respectively. In the former test, i.e. the EpiOcular™ Eye Irritation Test (EIT), the tissue viability was less than 60%, concluding the test article to be irritating to the eye. In the latter test, i.e. the Bovine Corneal Opacity and Permeability (BCOP) test, an IVIS score of -0.75 was determined, classifying velagliflozin as not causing serious eye damage. Combining these results, velagliflozin has been classified as an GHS class 2 eye irritant by the applicant, which is accepted.

Observations in humans

Velagliflozin is not authorised for use in humans, while other SGLT-2 inhibitors such as dapagliflozin, empagliflozin and canagliflozin are marketed for human use with the following indications: regulation of blood glucose, reduction of the risk of cardiovascular death and hospitalisation for heart failure and reduction of the progression of diabetic kidney disease. Adverse reactions listed are, among others, urinary tract infections, vaginitis, ketoacidosis, pollakiuria, dehydration, peripheral amputations and necrotic fasciitis in the perineum.

Excipients

The final product's excipients (and their use levels) are substances typically found in veterinary or human pharmaceutical products or in cosmetic products and are generally recognised as being safe.

User safety

The user safety assessment was performed according to the current guidelines, i.e. the "Guideline on user safety for pharmaceutical veterinary medicinal products" (EMA/CVMP/543/03-Rev.1) and the "Guideline on user safety of topically administered veterinary medicinal products" (EMA/CVMP/SWP/721059/2014).

Local effects were studied in rabbits for acute dermal irritation potential, in EIT and BCOP tests, where it was concluded that velagliflozin is not a dermal irritant, but a GHS class 2 eye irritant. Appropriate protection measures are described in the SPC. Based on the scientific assessment of the adverse outcome pathway (AOP) presented in OECD TGs and applying a weight of evidence approach, it is concluded that velagliflozin is not a skin sensitizer. Systemic toxicological and pharmacological effects are identified in the pre-clinical studies and encompass increased urine volume, decreased bodyweight, increased food consumption and lowered serum glucose, increases in blood urea nitrogen, triglycerides, and electrolytes as well as urine glucose and ketones, decreases in serum protein, albumin and cholesterol, tubular mineralization in the kidney and minimal creatinine elevations. A NOAEL of 100 mg/kg bw/day was established for embryo-foetal developmental toxicity.

Two LD_{50} studies cover acute toxicity, but, to conclude on the acute toxicological NOAEL, the lowest dose of 300 mg/kg bw from a subacute daily dosing 1-week rat study is applied. The relevant repeat dose toxicological NOAEL originating from a 28-day oral study in the dog is established at 10 mg/kg bw/day.

The person identified as the main user is the adult cat owner, who will possibly be exposed during the application phase either via the dermal, ocular or oral routes. It is unlikely that a child would be able to ingest the product directly from its container due to the plug-in adaptor on the container. The worst-case exposure scenario is considered to be the ingestion of a fully loaded syringe containing 0.6 ml. The risk for pregnant users is considered negligible due to an acceptably large margin of exposure.

The applied margins of exposure (MOE) are as follows: (i) pre-application acute oral exposure of a child: 417; application phase dermal exposure: 20,800; application phase oral exposure: 250,000; long-term dermal exposure: 417 and long-term oral exposure: 5,000. Since all MOEs are above 100, the safety of the candidate product for the above-mentioned exposure scenarios is considered acceptable.

The risk and appropriate mitigation measures related to pharmacological effects in a user accidentally exposed have been addressed. Worst-case exposure is considered to be the ingestion of the content of a fully loaded dosing syringe by a child, which will result in a dose very similar to the adult dose for other gliflozins.

Environmental risk assessment

A phase I environmental risk assessment (ERA) was provided according to VICH GL6 ("Guideline on environmental impact assessment (EIA) for veterinary medicinal products — Phase I"; CVMP/VICH/592//98-FINAL) and the revised "Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38" (EMEA/CVMP/ERA/418282/2005-Rev.1).

The environmental risk assessment can stop in phase I, and no phase II assessment is required because the veterinary medicinal product will only be used in non-food producing animals.

Senvelgo 15 mg/ml oral solution for cats is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation: safety tests

A number of safety pharmacology studies were conducted in species other than cats. Overall, no findings were consistent with an increased risk of clinically relevant acute adverse effects. Section 4.2 of the SPC adequately describes the PD.

In vitro studies showed that the protein binding ranged from 89.0–90.2% in rat plasma; from 94.8–95.5% in dog plasma, from 91.6–92.1% in human plasma and from 91.3 to 93.7% in feline plasma. In vivo, pharmacokinetics were investigated in Wistar rats (i.v. and p.o.), Beagle dogs (i.v. and p.o.), and cats (p.o. only). In general, plasma concentrations increased proportionally to dose, and there were no relevant differences in exposure between male and female animals.

In rats and dogs, velagliflozin was rapidly absorbed following administration via oral gavage of 1 and 10 mg/kg bw (T_{max} 0.25–1.0 h), and the oral bioavailability was high at both doses (77% and 81% in rats, and 101% and 92% in dogs). In rats, a mean volume of distribution at steady state (V_{ss}) of 1.98 l/kg (i.e. higher than total body water) and a high clearance (CL) of 28.4 ml/min/kg was found, resulting in a short elimination half-life ($t_{½}$) of 1.13 h. In dogs, the mean V_{ss} was 0.571 l/kg (i.e. similar to total body water) and the clearance was 0.634 ml/min/kg, resulting in a $t_{½}$ of 12.9 h. After oral administration in cats (fed/fasted), mean half-life ($t_{1/2}$) ranged from 4.5 to 6.4 hours. A moderate partitioning into blood cells was found in all species, with ratios of mean concentration in blood cell to plasma (Cbc/Cp) of approximately 0.65–0.66, 0.11–0.21 and 0.23–0.32 in rat, dog, and human blood, respectively.

A minor part of a velagliflozin dose will be metabolized in the cat, mainly via oxidation and direct O-glucuronidation. The majority of velagliflozin is excreted via faeces as the parent compound. Only a minor fraction (approx. 4%) of velagliflozin or its related metabolites were excreted via the renal route.

Acute oral toxicity was determined in two single-dose studies conducted in mice and rats in line with OECD TG 423, reporting the use of doses close to the LD_{50}. However, the value of the results for the user risk assessment is limited, as the studies did not determine an acute NOAEL.

The pivotal repeated oral dose toxicity studies were carried out in rats and dogs, from which a NOAEL of 10 mg/kg bw/day is retained for the user risk assessment.

One pivotal reproductive toxicity study was submitted, investigating the effects of velagliflozin on fertility and embryo-foetal development in rats. Based on the lower parental bodyweights and bodyweight gains observed, a NOAEL of 100 mg/kg bw/day for F0 male and female rats was retained. During gestation, a significant reduction in mean bodyweight gain was reported in pregnant rats dosed with 400 mg/kg bw/day. Based on the effects on oestrous cyclicity, pre-coital intervals, mating, fertility, numbers of corpora lutea and implantation sites as well as male reproductive organ weights, the NOAEL for fertility and early embryonic development was retained at 100 mg/kg bw/day. While major foetal morphological abnormalities were reported in the high dose group (i.e. 400 mg/kg bw/day), the overall NOAEL for embryo-foetal development is considered to be 100 mg/kg bw/day, since findings were not considered to be related to velagliflozin treatment or to be toxicologically significant. This conclusion is based on literature, historical data and background findings.

The genotoxicity of velagliflozin was evaluated in accordance with VICH GL23, with all three tests producing negative results. It is therefore concluded that velagliflozin does not possess a genotoxic potential.

No carcinogenicity studies were submitted based on a lack of genotoxic effects, no preneoplastic lesions reported in the 4-week repeated dose oral toxicity studies and the target animal safety study as well as no established causative association of the SGLT-2 inhibitors class of substances to cancer in non-diabetic human populations. This argumentation is considered acceptable.

An acute dermal toxicity study has not been performed and its absence is supported by the results obtained in the oral toxicity studies.

Skin sensitization testing has not been performed, which the applicant justifies by referencing OECD TG 168. As the velagliflozin molecule does not have any functional groups known to lead to relevant effects in the skin, this is considered acceptable.

A dermal irritation/corrosion study in rabbits was conducted according to OECD TG 404 and method B4 ("Acute Toxicity (Skin irritation)") outlined in Council Regulation (EC) No 440/2008, which support the conclusion that the product is not a dermal irritant.

The eye irritation potential of Senvelgo 15 mg/ml oral solution was investigated in accordance with OECD TG 492 and 437, respectively, showing that velagliflozin is a GHS class 2 eye irritant.

A user safety assessment was performed according to relevant guidelines, for which purpose a NOEL of 10 mg/kg bw/day was used.

The text proposed in the SPC currently mitigates the possible eye irritation potential of the product. The product container is deemed to be child-resistant and the worst-case acute exposure scenario is considered to be the ingestion of the content of a fully loaded dosing syringe (0.6 ml) by a child with an assumed standard bodyweight of 12.5 kg. Margins of exposure are above the toxicological trigger value of 100, the risk related to pharmacological effects are adequately addressed in the SPC.

A phase I environmental risk assessment (ERA) was provided according to relevant guidelines. Senvelgo 15 mg/ml oral solution is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pre-clinical studies

Senvelgo is an oral solution containing the active substance velagliflozin, which has not been authorised as a veterinary medicinal product within the Union at the date of the submission of the application in accordance with Article 42(2)(c) of Regulation (EU) 2019/6. Velagliflozin is an SGLT-2 inhibitor belonging to the gliflozin class of antidiabetic compounds, which reduce blood glucose levels by inhibiting renal glucose reabsorption. The product is intended for use in cats with diabetes mellitus. The proposed oral dose is 1 mg/kg bw/day.

A full efficacy file in accordance with Article 8 of Regulation (EU) 2019/6 has been provided.

Pharmacology

Pharmacodynamics

Velagliflozin works by inhibiting SGLT-2 transporters, thus reducing the amount of glucose being reabsorbed in the kidney. Velagliflozin also has a minor inhibitory effect on the SGLT-1 which is predominantly expressed in the small intestine, but also expressed at a lower level in the proximal tubules of the kidneys. This class of compounds is well-known in the human field, but, in cats, SGLT-2 inhibitors are novel. Regarding the pharmacodynamics (PD) of velagliflozin in the cat, the in vitro potency is unknown as in vitro studies conducted did not include cells expressing feline SGLT-2. The potency, together with the degree of plasma protein binding (91.3–93.7% in cats), determine the plasma exposure needed for effect and is therefore important information.

Furthermore, in in vivo studies performed in ZDF rats and Beagle dogs, velagliflozin increased urinary volume and glucose excretion as well as improved oral glucose tolerance after a single oral dose of 1.0 mg/kg bw and 0.1 mg/kg bw, respectively. Effects compatible with SGLT-2 inhibition were confirmed after an oral dosing of 1.0 mg/kg bw in several studies. One study, evaluating the effect of prandial state on PK and PD of velagliflozin dosed once daily for 7 days, documented a marked effect of velagliflozin on urinary glucose excretion, an effect that was not influenced by prandial state or gender.

Another study, evaluating the effect of a 34-day treatment on glucose metabolism in obese, insulin-resistant cats, showed the expected pharmacodynamic effect (glucosuria), without changes in basal blood levels of glucose or insulin. In that study, signs of improved insulin sensitivity were found in an intravenous glucose tolerance test. Also, a significant decrease in bodyweight and a decrease in the respiratory exchange ratio (RER), reflecting an increased usage of fat as fuel source, was found. It is unclear if similar improvements in insulin sensitivity could have been obtained by a diet-induced weight loss similar to the one found in the study and also if the same effect can be expected in cats with insulin-dependent diabetes mellitus. The study also showed increased blood levels of ketone bodies, warranting a focus on the risk of ketosis in cats with diabetes. Given that increased lipid utilization may be observed, the potential for the development of hepatic lipidosis was considered of concern. However, noting that changes in other clinical and biochemical parameters that would be consistent with hepatic lipidosis were not observed in either this study or the target animal safety study conducted, this concern was considered resolved.

A low level of glucose will continue to be resorbed via incomplete inhibition of the SGLT-1 transporter via the proximal renal tubules, which should limit clinical hypoglycaemia. This minor inhibitory action

on SGLT-1 can also contribute to a dose-dependent softening of stool and loose stool/diarrhoea (mostly transient) due to the presence of SGLT-1 in the small intestine.

Pharmacokinetics

The pharmacokinetics of velagliflozin in male and female cats was investigated over a dose range of 0.01–5.0 mg/kg bw, in exploratory and GLP-compliant studies. In addition, the effect of prandial state on the pharmacokinetics was investigated. Overall, the pharmacokinetics of velagliflozin in cats are characterised by rapid absorption reaching maximum plasma concentration within 1 and 4 hours after administration in fasted and fed cats, respectively. In cats, bioavailability after oral administration of 1 mg/kg bw was estimated using the individual animal's dose-normalized AUC_{inf} after oral and intravenous dosing and was found to be high for all animals (95.5 ± 7.72%).

The elimination appears to follow simple 1st order kinetics, with a half-life of approximately 3.5–6.7 hours. It is important to note that half-life is a parameter derived from the two primary parameters, i.e. clearance and volume of distribution. The volume of distribution was 0.630 l/kg.

Overall, it appears that there is dose proportionality with little or no influence of gender. However, in the study on the effect of prandial state (where neutered animals were used), a longer $t_{1/2}$ was found, with values ranging from 4.5–6.4 hours. In the same study, it was found that oral dosing in fed cats resulted in a later mean T_{max} (1.0–3.7 h), a lower mean C_{max} (316–846 ng/ml) and a lower mean $AUC_{0-24\ h}$ (2786–7142 h*ng/ml) than oral dosing in fasted state (T_{max} = 0.5 h; C_{max} = 1700 ng/ml; AUC_{0-24} = 7780 h*ng/ml). Except from this study, it was generally found across the data submitted that a dose of 1 mg/kg bw resulted in a C_{max} of approximately 1000 ng/ml and a concentration after 24 h of only approximately 5–10 ng/ml. In a GLP-compliant margin of safety study, the PK of velagliflozin after repeated daily dosing of 1, 3 and 5 mg/kg bw (final formulation) was investigated over a period of six months, with PK profiles assessed on days 0, 91 and 181. The results suggested slightly less than a dose-proportional increase in exposure (especially C_{max}) of the highest dose on day 0 and of both the higher doses (both C_{max} and AUC) on days 91 and 181, respectively. Mean accumulation ratios (based on AUC values) were in a range of 1.3–1.9, indicating a slight increase of exposure after repeated dosing of the test article. Accumulation ratios were comparable on days 91 and 181, indicating that steady-state of exposure was reached prior to day 91.

Studies on metabolism in feline hepatocytes and microsomes confirmed the primary metabolic pathways observed in cats after oral administration of velagliflozin, i.e. oxidation, a combination of oxidation and dehydrogenation and sulfate conjugation.

After oral administration of 1 mg/kg bw of velagliflozin (15 mg/ml) oral solution to healthy cats, the majority of velagliflozin and its related metabolites was excreted via faeces primarily as unchanged velagliflozin. Only minor excretion (~ 4%) of velagliflozin or its related metabolites occurred via the renal route.

Dose determination and confirmation

Dose justification

The proposed dose for Senvelgo of 1 mg/kg bw p.o. once daily was established based on pre-clinical PK studies (two non-GLP-compliant studies performed in healthy cats). A limited number of doses were investigated. The basis of dose efficacy was its influence on blood glucose and glucosuria. Limited investigations were conducted regarding velagliflozin dose and insulin sensitivity.

There was no systematic monitoring of blood glucose concentrations (BGCs) between 9–24 h following administration of velagliflozin in the clinical studies.

Of the overall data available (19 cats), approximate 24-hour BGCs (in fasted cats) were lower than pre-treatment values in samples taken at the same time of the day, but considerable individual variation was observed with regard to 24-hour blood glucose control. Given the regular occurrence of adverse effects found later in clinical trials, then the velagliflozin dose should represent a balance between safety and efficacy.

Dose determination studies

Two pilot non-GLP-compliant laboratory studies were performed in healthy cats using a preliminary formulation and with only 3 cats in each dose group. The studies were focused on PK, but efficacy was also assessed based on glucose concentrations in urine. In one study, weak signs of a minor effect were seen at a dose of 0.1 mg/kg bw, whereas a marked effect was seen at 1.0 mg/kg bw. Another study indicated that a dose of 3 mg/kg bw only resulted in a slightly higher effect than 1.0 mg/kg bw. Thus, it appears from these two pilot studies in healthy cats that a dose of 1 mg/kg bw results in a marked effect. Whether lower doses (e.g. 0.5 mg/kg bw or 0.3 mg/kg bw) could be sufficient for a clinical effect was not assessed in clinical trials.

Dose confirmation studies

No dose confirmation studies are presented. A pilot multi-site field study in diabetic cats (see below for further details) was not submitted as dose determination/confirmation study, but functions as such, i.e. affecting the design of other studies and the pivotal clinical trials. The applicant concluded that the 1.0 mg/kg bw dose was more efficient in improving the clinical signs at day 30 and 60, and with a comparable safety profile.

Tolerance in the target animal species

The applicant has presented one pivotal target animal safety (TAS) study and one supportive pilot study.

In the supportive pilot study, the test item was administered orally in capsules at 0x, 1x, 3x and 5x the recommended dose. The study had a duration of 90 days and the animals returned to the animal pool after the end of the observation period. No mortality was observed and general appearance and behaviour were normal. There were no differences noted regarding bodyweight, body condition score or food consumption when compared to the control group. Significant increases of urine glucose were observed and a dose-dependent alteration of faecal consistency was evident. Female cats tended to have a slightly softer stool than male cats.

The pivotal TAS study was performed in a total of 32 healthy male and female cats, which were 8–9 months old at the beginning of the study. The animals were dosed once daily for 6 months with the final formulation of Senvelgo 15 mg/ml oral solution for cats at 0, 1, 3, or 5 times the recommended dose.

The study was performed according to GLP principles and in accordance with VICH GL43.

During the study, feed consumption was higher compared to the placebo group for the males in the 1x and 3x groups, with a corresponding increase in bodyweight gain. For males receiving the highest dose (5x), feed consumption was normal, but bodyweight gain was lower than in the placebo group. Feed consumption in treated females was comparable to the placebo group at all dose levels, whereas their

bodyweight gain was lower than in the placebo group. Water consumption was increased in all treated groups.

Changes in faecal consistency as looser faeces was observed regularly in the group receiving the highest dose (5x).

At the 1x, 3x and 5x dose levels, glucosuria was noted without a clear dose relationship, in conjunction with reduced creatinine concentrations in the urine of these animals. Blood glucose levels were not different regarding treatment-related effects between groups.

The changes observed were consistent with the pharmacological action of velagliflozin. Thus, higher renal loss of glucose would result in glucosuria, osmotic diuresis and lower urine creatinine concentration. This is also reflected in the increased water intake among the treated animals. Feed consumption was increased (in male cats of the 1x and 3x group), which could be associated with loss of glucose. Blood glucose levels were within the normal range indicating compensating mechanisms to control for the added renal loss of glucose in healthy animals.

The effect of velagliflozin on faecal consistency in terms of regular loose stools in the 5x group could be speculated to be a non-specific effect on the SGLT-1 receptors in the intestine, resulting in lower glucose absorption at high doses of velagliflozin and thereby inducing osmotic diarrhoea.

With regards to haematological parameters, elevations in mean reticulocyte numbers were observed in the 5x dose group. In the 3x and 5x dose groups, greater reductions in haematocrit (HCT) were observed over the control and 1x dose group. Also, much greater reductions in red blood cells (RBCs) were observed for the treated groups over the control. However, the mean values for all these parameters were within their respective reference ranges and no dose-related trend was observed.

Necropsy and microscopy findings revealed a higher incidence of a reticular pattern in the liver of treated animals, but a clear dose relationship was not established and it was considered to be a background finding without clinical relevance. Glycogen and perilobular lipid disposition was found in all groups, including the control group.

Additionally, it is noted that for the symmetric dimethylarginine (SDMA), values were observed to be higher at pre-treatment and at the last observation timepoint, describing a U-shaped dose-response curve. This applied to all groups, with the values mainly being below the proposed clinical cut-off value.

Although the pivotal TAS study was well-conducted, it should be noted that the study was carried out in healthy cats and the results cannot be directly extrapolated to the target population of diabetic cats, which are compromised with regard to their glucose metabolism.

Clinical trials

The applicant has provided a number of clinical trials, both pilot and pivotal, in pursuit of the intended indication for "the treatment of diabetes mellitus" in cats. Clinical trials were conducted in Europe and other countries outside Europe, with some differences in study design and objectives, including:

- Three pilot studies evaluating the effect of velagliflozin on hyperglycaemia and associated clinical signs in diabetic cats, including a proof-of-concept study (performed in the USA) focused on naïve diabetic cats, a pilot multi-site field study (performed in Europe) focused on insulin pre-treated diabetic cats as well as a pilot multi-site field study (performed in the USA) focused on naïve diabetic cats.

- A pivotal clinical multi-centre field study (performed in Europe) evaluating the efficacy and safety of velagliflozin in cats with diabetes mellitus.
- A supportive clinical multi-centre field study (performed in Japan) evaluating the effectiveness and safety of velagliflozin in cats with diabetes mellitus.
- A pivotal clinical multi-centre field study (performed in the USA) to evaluate the efficacy and safety of velagliflozin for the reduction of hyperglycaemia and hyperglycaemia-associated clinical signs in diabetic cats, including an extended-use phase to evaluate the safety.

Pilot studies

A prospective, positive-controlled, randomized, multi-site field study included 55 newly-diagnosed or previously treated with insulin (180 days or less) diabetic cats. Five cats were excluded from the efficacy analyses. Cats were initially randomly assigned to velagliflozin (IVP) 0.5 mg/kg bw, IVP 1.0 mg/kg bw or Vetsulin insulin (control product, CP), based on the order of enrolment at each site. The first ten cats treated with 0.5 mg/kg IVP demonstrated a mean BGC < 300 mg/dl (from the 9-hour blood glucose curve [BGCu]) and improvement in at least one clinical sign by day 30. Therefore, an IVP 0.1 mg/kg bw treatment group was added and 12 cats were enrolled into this arm of the study. According to the protocol, the 1.0 mg/kg bw IVP group was closed for enrolment when the 0.1 mg/kg bw IVP group was enrolled, but already included cases were continued. Primary efficacy assessment was a change in the 9-hour BGCu by visits, over time. The secondary efficacy parameter was treatment success defined as a composite variable of improvement in at least one clinical parameter (polyuria, polydipsia, bodyweight or appetite) and reduction of mean BGCs to < 300 mg/dl by day 60. The clinical parameters were rated by the owner at screening as "unknown, excessive, normal or decreased", and then assessed as "unknown, increased, same or decreased" compared to screening on day 30 and 60. There is a potential major bias in the clinical ratings by the owner, because these are exclusively subjective, and it is also difficult to assess some of the clinical parameters in multi-cat households and/or with outdoor cats (e.g. polyuria [PU]/polydipsia [PD]). Furthermore, there seems to have been no form of standardisation of the clinical ratings, no inter-rater study to assess consistency between cat owners, no definition described in the study report of the different ratings, and the statistical methods were not concluded prior to study commencement. Results revealed that the BGC means for the IVP groups reached the preferred clinical treatment goals (glucose < 250 mg/dl set from the desired American Animal Hospital Association (AAHA) clinical treatment goal and not the primary efficacy assessment of the study) by day 7 (0.5 mg/kg bw and 1.0 mg/kg bw groups) as well as by day 14 (0.1 mg/kg bw group) and maintained these glucose concentrations through day 60. The CP group required 60 days to approach the upper-end of the desired BGC mean. There were no significant differences between the IVP 0.5 mg/kg bw and 1.0 mg/kg bw dose groups in either the BGCs or timepoints. The most frequent AEs observed in all treatment groups were emesis, diarrhoea and lethargy. The frequency of occurrence of emesis and diarrhoea seemed dose-dependent with increasing dose of the IVP, and the CP showing less AEs than the lowest dose of the IVP. Nevertheless, the applicant concluded that the 1.0 mg/kg bw IVP group was more efficient in improving the clinical signs at day 30 and 60, and with a comparable safety profile.

In a prospective, open-label clinical field study, the effectiveness and safety of 1 mg/kg bw/day oral velagliflozin (pre-formulation, 10 mg/ml) as a stand-alone therapy over 28 days was evaluated. According to the study protocol, a dose adjustment was possible by lowering the dose to 0.5 mg/kg bw in case of repeated hypoglycaemia accompanied by typical clinical signs (e.g. lethargy, ataxia, seizure). Sixteen insulin pre-treated diabetic cats (pre-treated for at least one week prior to enrolment [median pre-treatment period: 22 weeks; median daily insulin dose: 4.3 I.U. (range: 1.0–10.0 IU)]) were directly switched to velagliflozin. Due to the exploratory nature of the study, no primary endpoint

was defined, and the majority of the data were evaluated descriptively. Many cats showed signs of being poorly controlled prior to the shift from insulin. After the shift to velagliflozin, increased glucosuria was observed in all cats, as well as a significant effect on both the mean BGC (assessed 9 h after dosing) and mean fructosamine concentrations over the 28-day treatment period (8.0 ± 1.6 mmol/l and 349 ± 58.0 µmol/l, respectively). All but one cat showed a weight loss over the 28-day period of > 5% of the bw. No hypoglycaemia was observed and a total of 16 AEs, including one or more clinical signs were reported in 12 cats. These encompassed emesis (3 cats), decreased faecal consistency (3 cats), anorexia (4 cats), lethargy (3 cats) and ketoacidosis (4 cats). One cat had its dose down regulated and eventually stopped due to the suspected development of ketoacidosis. The study is considered as providing supportive data only.

In a single-site pilot, prospective, open label, change-from-baseline field study, the effect of velagliflozin (IVP; administered orally at 1 mg/kg bw once daily for 28 days) on hyperglycaemia and associated clinical signs as stand-alone therapy when administered once-daily for 4 weeks to naïve diabetic cats was investigated. The dose could be increased to 3 mg/kg bw if no improvement was noted by day 14, but all cats remained at 1 mg/kg bw throughout the study. Six newly-diagnosed diabetic cats or diabetic cats treated with insulin for four days or less (out of 10 screened cats) were enrolled. Animals were > 1 year of age (ranging from 4 to 13 years with an average age of 8.3 years), of both sexes (m = 3, f = 3), all neutered and weighing 3.4–7.4 kg. Diabetes mellitus was defined as blood glucose (BGC) > 250 mg/dl (13.9 mmol/l), either glucosuria or serum fructosamine ≥ 400 µmol/l, and persistence of at least one clinical sign consistent with diabetes mellitus (lethargy, polyuria, polydipsia, polyphagia, weight loss, and/or plantigrade posture of hind legs). The primary efficacy parameter was baseline changes in mean blood glucose levels from 9-hour BGCu measurements. Secondary efficacy parameters included a baseline change in fructosamine and urine glucose, change in clinical signs (lethargy, polyuria, polydipsia, polyphagia, weight loss, plantigrade posture of hind limbs, and quality of life), change in investigator overall assessment of diabetes control and change in overall condition of the diabetic cat assessed by the owner by visit over time. Results showed a significant decrease in fasted plasma glucose and mean BGCs from the nine-hour BGCu from day 7 onwards in all cats ($p < 0.0001$). Maximum and minimum BGCs from day 7 onwards also decreased compared to baseline. Urine glucose concentrations were not significantly different throughout the 28-day period ($p = 0.1462$). Fructosamine concentrations by visit day were not statistically significant. The effect of treatment day on plasma insulin was significant ($p = 0.0106$). Fasted plasma insulin was significantly increased at day 7 (40.3 ± 1.9 pmol/l) compared to day -1 (30.3 ± 1.7 pmol/l; $p < 0.05$) and remained numerically increased at days 14 (38.7 ± 5.3 pmol/l) and 28 (37.3 ± 5.4 pmol/l). Average insulin-to-glucose ratios were significantly increased at days 7 (3.2 ± 0.4), 14 (3.4 ± 0.7), and 28 (4.3 ± 0.9) compared to day -1 (1.2 ± 0.1; all $p < 0.05$). No significant changes in haematology or blood chemistry parameters were noted. No animals had culture-positive urine during the study. The investigator assessed all animals as improved at day 28 compared to day -1 and owners assessed all cats as improved in at least one clinical sign by day 28. A total of 7 adverse events were reported for three cats (diarrhoea, small cutaneous crusted papule, transient inappetence, vomiting). The study was not blinded, did not include controls, had a low sample size, relatively short duration and did not use the final formulation. Thus, the results should be considered as being supportive only. Regarding the insulin-to-glucose ratios, an increase by approximately factor 3 from day 7 and onwards was registered.

Pivotal clinical trials

The applicant presented one EU pivotal clinical trial, which was designed as an open-label (no blinding), prospective, positive-controlled, multi-site field trial, focused on client-owned pre-treated diabetic cats (cats receiving treatment for diabetes mellitus > 4 days) and naïve diabetic cats (non-treated cats or cats receiving treatment for diabetes mellitus ≤ 4 days). The study included veterinary

investigators in 39 veterinary clinics in Germany, France and the Netherlands. The objective was to investigate the safety and efficacy of velagliflozin for the reduction of hyperglycaemia and hyperglycaemia-associated clinical signs of diabetes mellitus. Glycaemic control and clinical signs of diabetes mellitus were evaluated in cats that were dosed for 91 days with 1 mg/kg bw velagliflozin (IVP) in comparison to Caninsulin (CP). Naïve diabetic cats were thereby started at an insulin dose of 0.25 I.U./kg bw or 0.5 I.U./kg bw, but not more than 2 I.U./cat, via subcutaneous injections every 12 hours for 91 days. Pre-treated diabetic cats were maintained on their current insulin dose. The Caninsulin dose was freely titrated to obtain control of clinical signs and hyperglycaemia during the study according to the dose titration guidelines for the product. The study consisted of two phases: Phase 1 (efficacy phase) evaluated IVP safety and efficacy based on screening (day -7 to day -2) and a 45-day treatment period (day 1 to day 45 ± 2). Day 1 was the first day of IVP administration. Phase 2 was an extended-use phase continuing from the end of phase 1 to day 91 ± 3 days of dosing.

Enrolment eligibility of diabetic cats (age ≥ 1 year of any sex/breed) was based upon a complete history, physical examination, and clinical laboratory tests per the inclusion and exclusion criteria. Inclusion criteria included at least one clinical sign consistent with diabetes mellitus (PU, PD, excessive appetite, plantigrade or palmigrade stance related to diabetic polyneuropathy), fasting (minimum of 6 hours) BGCs > 13.9 mmol/l (> 250 mg/dl), glucosuria and serum fructosamine levels of > 400 µmol/l.

Phase 1 exclusion criteria included a history of decreased appetite, vomiting or diarrhoea within 14 days prior to the screening visit, ketonuria at the screening visit, any ongoing, frequently progressive or serious concurrent illness (e.g. pancreatitis, hyperthyroidism, pyelonephritis, renal failure, cardiac failure, liver failure, neoplasia and acromegaly) as well as diet change within 14 days prior to the screening visit or treatment with prohibited/disallowed medications (steroids, gestagen therapy, diuretics, antiemetics, antacids, appetite stimulants, or similar medications for treatment of gastrointestinal illness and pancreatitis). Also, if the cat was fractious (not amenable to administration of oral medications or with study procedures), or pregnant, lactating, or intended for breeding, it was excluded from the study.

The study was designed as a non-inferiority study. The primary endpoint was analysed on the full analysis set. To assess the treatment success, the responder rates for the IVP and CP were tested with the following hypotheses:

H0: Responder rate of CP vs responder rate of IVP ≥ 15%.

H1: Responder rate of CP vs responder rate of IVP < 15%, where 15% is the pre-specified non-inferiority margin.

The decision to accept or reject the null hypothesis was made based on the one-sided 97.5% confidence interval for the difference of the responder rates.

The primary efficacy parameter was individual treatment success (evaluated at day 45), based on improvement of at least one clinical sign (PU, PD, polyphagia, or diabetic neuropathy) in comparison to the screening visit, and improvement in at least one blood glucose variable (mean BGC ≤ 14 mmol/l at day 45 [mean blood glucose = average blood glucose concentration of the 9-hour BGCu], serum fructosamine ≤ 450 µmol/l at day 45, minimum blood glucose of the 9-hour BGC < 9 mmol/l). Treatment failures were cats removed for AEs related to study treatment as well as animals removed for perceived lack of efficacy after the visit at day 21. Secondary variables assessed included an owner assessment of the cat's quality-of-life (QoL) at each visit (attitude, energy, interaction with the owner and other pets, sleeping and grooming habits), physical examination parameters (bodyweight, rectal temperature, heart and respiratory rate, body condition score [BCS] according to the LaFlamme nine-point scale and mental attitude), laboratory results (complete blood count [CBC], serum chemistry, and urinalysis [UA]), change in activity level, incidence of hypoglycaemic events and overall change in

the cat's condition as assessed by the study investigator. Urine samples were obtained by cystocentesis at screening, day 21, day 45 and day 91 for a complete UA including urine culture/sensitivity (C/S).

In addition, proportions of cats with clinical and/or blood parameters (mean blood glucose, minimum blood glucose, fructosamine) classified as success over time in the IVP and CP groups were compared, as well as the proportion of cats with maximum BGCs ≥ 15 mmol/l over time. Comparisons were also made of the respective proportions of cats with documented symptomatic/suspected symptomatic and asymptomatic hypoglycaemic event until day 91 as well as the time until the occurrence of these events and the number of events until day 91 (adjusted rate per cat).

In total, 128 diabetic cats were enrolled, of which 116 comprised the final full analysis set (FAS) population (75 male and 41 female animals aged between 5–18 years [mean age: 11 years] and weighing between 2.5–10.2 kg (mean bw: 4.9 kg). All but three cats were neutered. The majority of cats were European shorthair (n = 99). Cats were kept at their homes throughout the study, the majority in both groups being indoor cats.

Baseline characteristics, concomitant treatment and efficacy analysis of the primary endpoint were assessed in the FAS population, which included 116 cats and the per protocol (PP) population consisted of 98 cats in total. The increase of overall treatment success rates (i.e. success in at least one clinical and at least one blood parameter) from study day 21 onwards was faster in the IVP group with success rates slightly above 50% (53.7% in the IVP group and 33.9% in the CP group at study day 21). At study day 45, the overall success rate was higher in the IVP group (53.7% vs 41.9%), whereas at study day 91 the overall success rate was higher in the CP group (55.6% vs 62.9%). The statistical analysis of the FAS population at day 45 showed non-inferiority of once daily oral IVP administration to twice daily CP injections in this study. PU/PD improved in a similar way in both groups until study day 45 (from 30–40% at study day 3 to 50–60% at study day 45). At study day 91, success rates were higher in the CP group than in the IVP group (urination frequency/volume: 54.8% vs 46.3%; water consumption: 64.5% vs 57.4%). Success rates for appetite and plantigrade or palmigrade stance related to diabetic polyneuropathy were below 20% on all visits but increased slightly from < 10% at study day 3 to 10–20% at study day 91 in both treatment groups.

The proportion of cats with mean blood glucose, minimum blood glucose and fructosamine concentrations classified as success were higher in the IVP group compared to the CP group at all post-baseline visits. In the IVP group, the success rates increased after 7 study days (mean BGCs ≤ 14 mmol/l: 75.9%; minimum BGC ≤ 9 mmol/l: 63.0%; fructosamine ≤ 450 µmol/l: 35.2%) and remained at a high level for the subsequent visits, whereas in the CP group comparable success rates, in general, increased slower (study day 91: mean BGCs ≤ 14 mmol/l: IVP 77.8% vs CP 59.7%; minimum BGCs ≤ 9 mmol/l: IVP 75.9% vs CP 66.1%; fructosamine ≤ 450 µmol/l: IVP 75.9% vs CP 61.3%). Similarly, fructosamine levels decreased faster in the IVP group with a decrease of 109.8 µmol/l within the first week and a decrease of more than 244 µmol/l from screening to day 91. In the CP group, the decrease in fructosamine concentrations was slower, with a decrease of 48.3 µmol/l within the first week and with 181.7 µmol/l from screening to study end.

The study veterinarian assessed overall control of diabetes. The proportion of cats with improved diabetic control increased in both groups throughout the study. In the IVP group, it reached 81% at study day 91, whereas in the CP group diabetic control improved in 68% of the cats at study day 45, with a minor decrease to 64% at study day 91. Owners assessed their cat's QoL, which revealed that almost half of the population in both treatment groups had poor and fair QoL at screening. Increasing improvement rates in QoL were detected over time in both treatment groups with higher frequencies in the IVP group at study day 91 (80.9% vs 74.0%). Minor reductions in BCS were observed in both

groups of the FAS population, and in particular in cats which started with a BCS > 6. Differences between groups were not significant.

Overall, 86.6% of all cats experienced an AE (IVP group: 83.6%; CP: 89.4%) until study day 91. The most frequently reported AEs (VeDDRA PT) for both treatment groups in total were hypoglycaemic events (78 events in 43 cats) and diarrhoea (43 events in 33 cats). The most frequently reported AEs, which display a difference between the two treatment groups were diarrhoea, cystitis and hypoglycaemia. In the IVP group, diarrhoea occurred in 23 cats (37.7%) vs 10 cats (15.2%) in the CP group. The second most frequent AE in the IVP group was cystitis in 13 cats (21.3%) vs 10 cats (15.2%) in the CP group. Four euglycaemic diabetic ketoacidosis (DKA), events (6.6%) were observed during the study in four cats treated with velagliflozin (none in the CP group). Time to first DKA event ranged from 3–80 days. However, three of the four DKAs occurred within the first week after treatment start. The most common serious adverse event (SAE) was hypoglycaemia, which occurred only in the CP group, with 28 events in 16 cats (24.2%). Independent from the classification as serious or non-serious AE, all events with a glucose value < 2.8 mmol/l were defined as serious hypoglycaemic events. In the CP group, 7 cats had one serious hypoglycaemic event, while in the IVP group no serious hypoglycaemic events occurred and all events in the IVP group were asymptomatic.

Another clinical trial was designed as a prospective, non-controlled, open-label (no blinding/masking, blocking, or randomization), multicentric field study to investigate the effectiveness and safety of velagliflozin (IVP) regarding the reduction of hyperglycaemia and hyperglycaemia-associated clinical signs in client-owned cats (age ≥ 2 years of any sex/breed) with diabetes mellitus. The study involved seven veterinary hospitals in Japan.

Inclusion criteria at the screening visit (carried out day -7 to day -2) included at least one clinical sign consistent with diabetes mellitus (PU, PD, unintentional weight loss despite a good appetite), and fasting (minimum of 6 hours) BGCs > 270 mg/dl, glucosuria as well as serum fructosamine > 400 µmol/l. Exclusion criteria included a history of decreased appetite, vomiting or diarrhoea within 14 days prior to the screening visit, ongoing, frequently progressive or serious concurrent illness (e.g. chronic vomiting/diarrhoea, pancreatitis, hyperthyroidism, pyelonephritis, renal failure, cardiac failure, liver failure, neoplasia and acromegaly), serum creatinine levels > 2.0 mg/dl, serum bilirubin levels > 0.5 mg/dl, a history of ketonuria, diet change from standard commercial diet to a prescription diabetic diet within 14 days prior to the screening visit, treatment with prohibited/disallowed medications (steroids, gestagens, diuretics, antiemetics, antacids, appetite stimulants, or similar medications for treatment of gastrointestinal illness and pancreatitis) or if the cat was fractious (i.e. not amenable to administration of oral medications or with study procedures), pregnant, lactating or intended for breeding.

The primary efficacy parameter was individual treatment success (evaluated at day 30), based on improvements of at least one clinical sign (PU, PD, unintended weight loss, polyphagia, or diabetic neuropathy) in comparison to the screening visit, and at least one blood glucose variable (mean BGC ≤ 300 mg/dl at day 30 and below the fasted BGCs at the screening visit [mean blood glucose: average blood glucose value of the 9-hour BGCu]; serum fructosamine ≤ 450 µmol/l at day 30 and below the fructosamine value at the screening visit). Treatment failures were cats removed for AEs related to study treatment, cats removed for perceived lack of efficacy after day 7 and cats not defined as treatment success in the day-30 assessment. Secondary variables included were change in owner assessment of diabetes mellitus clinical signs over time, owner assessment of QoL, physical examination parameters (bodyweight, rectal temperature, heart and respiratory rate, BCS in accordance with the LaFlamme nine-point scale and mental attitude) at each visit, laboratory results (CBC, serum chemistry and UA), change in activity level, incidence of hypoglycaemic events and

change in overall condition as assessed by the investigator. Urine samples were obtained by cystocentesis at screening and day 30 for a complete UA, including urine C/S.

In total, 30 client-owned, diabetic cats were enrolled in the study, all with "poor overall control of DM". Twenty-nine cats were valid for efficacy evaluation and one cat withdrawn due to DKA. Enrolled cats included 13 of 30 (43.3%) that were pre-treated with insulin, while 17 were treatment-naïve. The 13 cats previously treated with insulin had been treated with long-acting insulin products BID for varying periods (22 days to approximately 10 years). Other concomitant conditions found during the screening visit physical exam were bacterial cystitis (n = 4), urolithiasis (n = 3), mycotic external otitis (n = 1) and pyoderma (n = 1). Cats included in the study represented multiple cat breeds, aged from 8-14.8 years (mean age: 10.9 ± 2.0 years) and weighing from 2.9–6.8 kg (mean bw: 4.5 ± 1.0 kg). The gender distribution was as follows: 14 females (10/14 spayed) and 16 males (11/16 neutered). Cats were housed with their owners and remained in their usual environments only interrupted by scheduled (or unscheduled) visits to the veterinary hospital. All cats received the IVP at a dose of 1.0 mg/kg bw (0.45 mg/lb), administered by the owner in the morning using the provided measuring syringe directly into the mouth or mixed with a small amount of wet cat food (approximately 1 teaspoon) on day 0–30. If a cat vomited/regurgitated within 30 minutes of dosing, owners were instructed to re-dose. If the cat vomited a second time, the cat was not re-dosed.

Twenty-seven out of 29 cases for efficacy assessment were deemed treatment success, with a success rate of 93.1%. The success rate for the treatment-naïve cats was 94.1% (16/17) and that for the previously treated cats was 91.7% (11/12). The mean BGC decreased after the IVP treatment start (353.3 ± 63.4 mg/dl at screening visit and 220.1 ± 64.4 mg/dl on day 7). The mean of the individual mean BGC and mean fructosamine concentration on day 30 (mean BGC: 201.8 ± 63.2 mg/dl; mean fructosamine concentration: 284.7 ± 60.4 µmol/l) were both significantly decreased compared to those on the screening visit (mean BGC: 353.3 ± 63.4 mg/dl; mean fructosamine concentration: 460.0 ± 51.1 µmol/l). When evaluating treatment success, the applicant considered a mean BGC on day 30 of ≤ 300 mg/dl (and below the fasted screening visit BGC) as a success. This mean BGC cut-off value is not within the normal range or below the renal threshold (252 mg/dl) and thus not indicative of controlled diabetes mellitus in cats. The investigators' assessment on overall control of diabetes at the screening visit and at the day 30 visit revealed that diabetes improved in 26 out of 29 cases. Two cats which had overall control indicated as "poor" on day 30 were evaluated as "treatment failure" in the efficacy evaluation, as they didn't show any improvement in their clinical signs.

A total of 19 AEs were recorded in 10 cats, including DKA in one cat and loose stool/diarrhoea as a non-serious adverse event in ten cats. The incident rate of loose stool was 33.3% and relatively high.

This field trial included a relatively small study population and the total study period was short (30 days). Therefore, uncertainties remain concerning efficacy and safety when used in the field on a more long-term basis. Furthermore, the study design (unblinded), inclusion and exclusion criteria as well as the definition of treatment success are considered problematic, as they may have influenced the results. Thus, the high treatment success rate of 93.1% demonstrated in this study is questioned, as is the overall study conclusion made by the applicant. The applicant presents this study as a pivotal field trial with an identical design to the study that was conducted in the USA in 200 client-owned cats (see below for details), albeit, for the reasons cited above, this study is only considered to be of supportive nature.

The second pivotal clinical trial was designed as an open-label (no blinding/masking, blocking, or randomization), prospective, multi-site field trial focused on client-owned pre-treated diabetic cats (treatment for diabetes mellitus > 4 days) and naïve diabetic cats (non-treated cats or cats receiving treatment for diabetes mellitus ≤ 4 days). The study included twenty veterinary investigators in private practice and one investigator at a university in the USA. The objective was to investigate the

safety and efficacy of velagliflozin regarding the reduction of hyperglycaemia and hyperglycaemia-associated clinical signs of diabetes mellitus. No positive or negative control groups were established. All enrolled patients received velagliflozin (IVP). The number of enrolled pre-treated diabetic cats was recommended not to exceed 30% per site. The study consisted of two phases: phase 1 evaluated IVP safety and efficacy administered at 1 mg/kg bw (0.45 mg/lb) p.o. once daily and consisted of a screening (day -7 to day -2) and a 30-day treatment period (day 0 to day 30 ± 2). Day 0 was thereby the first day of IVP administration. Phase 2 was an extended-use phase continuing from the end of phase 1 to 180 ± 7 days of dosing. For cats that completed phase 1, owners were given the option to continue into phase 2, if their cat met the phase 2 eligibility requirements.

Enrolment eligibility of diabetic cats (age ≥ 2 years of any sex/breed) was based upon a complete history, physical examination and clinical laboratory tests per the inclusion and exclusion criteria. Inclusion criteria included at least one clinical sign consistent with diabetes mellitus (PU, PD, unintentional weight loss despite a good appetite), fasting (minimum of 6 hours) BGCs of > 270 mg/dl, glucosuria and serum fructosamine concentrations of > 400 µmol/l. Phase 2 eligibility criteria included a diabetic cat that completed phase 1 with improvement of least one primary clinical sign (PU, PD, unintentional weight loss, polyphagia, or diabetic neuropathy) and a fructosamine value ≤ 550 µmol/l.

Phase 1 exclusion criteria included history of decreased appetite, vomiting or diarrhoea within 14 days prior to the screening visit and also any ongoing, frequently progressive or serious concurrent illness (e.g. pancreatitis, hyperthyroidism, pyelonephritis, renal failure, cardiac failure, liver failure, neoplasia and acromegaly), diet change within 14 days prior to the screening visit and treatment with prohibited/disallowed medications (steroids, gestagen therapy, diuretics, antiemetics, antacids, appetite stimulants, or similar medications for treatment of gastrointestinal illness and pancreatitis). The cat was also excluded if it was fractious (i.e. not amenable to administration of oral medications or with study procedures), pregnant, lactating or intended for breeding. Phase 2 removal criteria included any cat with a fructosamine value > 550 µmol/l or increased from the screening visit (baseline). All post-inclusion withdrawal criteria for phase 1 applied as post-inclusion withdrawal criteria for phase 2, except that the diet type may have been changed from a standard commercial diet to a prescription diabetic diet during phase 2.

The primary efficacy parameter was individual treatment success (evaluated at day 30), based on improvement of at least one clinical sign (PU, PD, unintended weight loss, polyphagia or diabetic neuropathy) in comparison to the screening visit, and improvement in at least one blood glucose variable (mean BGCs of ≤ 300 mg/dl at day 30 and below the BGCs at screening visit [mean blood glucose: average BGC of the 9-hour BGCu] and serum fructosamine ≤ 450 µmol/l at day 30 and below the fructosamine value at screening visit). Treatment failures were cats removed for AEs related to the treatment, cats removed from the study for perceived lack of efficacy after day 7 and/or before day 30 and cats not defined as treatment success in the assessment on day 30. Secondary variables assessed included an owner assessment of the cat's QoL at each visit (attitude, energy, interaction with the owner and other pets, sleeping habits, and grooming habits), physical examination parameters (bodyweight, rectal temperature, heart and respiratory rate, BCS in accordance with the LaFlamme nine-point scale, mental attitude), laboratory results (CBC, serum chemistry and UA), change in activity level, incidence of hypoglycaemic events and change in the cat’s overall condition as assessed by the study veterinarian. Urine samples were obtained by cystocentesis at screening, day 30 and day 180 for a complete UA, including urine C/S. At day 120, only a complete UA was done. One BGC measurement was performed in phase 2 (on day 60).

A total of 94% mixed breed cats and 6% purebreds were included, aged 4–18 years (mean age: 10.9 years) and weighing on average 5.5 kg (mean BCS: 5.2). The gender distribution was as follows: 30% females and 70% males (all spayed or neutered, respectively). The cats were housed with their owners

and remained in their usual environments, only interrupted by scheduled (or unscheduled) study clinic visits (phase 1: days 7, 30, and 60; phase 2: days 2/3, 90, 120, 150, and 180). All cats were administered the IVP by the owner in the morning, using the provided measuring syringe directly into the mouth or mixed with a small amount of wet cat food (approximately 1 teaspoon) on day 0 to day 30. If a cat vomited/regurgitated within 30 minutes of dosing, owners were instructed to re-dose. If the cat vomited a second time, the cat was not re-dosed.

In total, 412 cat study screening evaluations were performed (a cat may have been screened more than once), and 254 cats were enrolled, with two cats excluded from the safety population (n = 252). Of the 252 cats included in the safety population, 54 cats were not included in the efficacy analysis, and this resulted in an efficacy population comprised of 198 cats. Reasons for exclusion from the efficacy population included enrolment errors (5 cats), medical history (4 cats), screening laboratory results (4 cats), AEs indicating a pre-existing disease (5 cats), developing DKA (25 cats) as well as other reasons (cat non-compliance, withdrawal of owner consent, GCP violation). A total of 38 of the 252 cats were pre-treated with insulin and 214 were treatment-naïve. Of these 38 pre-treated cats, 21 were included in the efficacy analysis (all 38 cats were included in the safety population) corresponding to 11% being pre-treated in the efficacy population (21/198). Treatment success was demonstrated in 177 out of 198 cats treated with velagliflozin when evaluated at day 30 ± 2, but two cats were coded as treatment failures corresponding to a total treatment success of 88.4%. Many of the clinical parameters were reported as "non-evaluable" because the clinical signs had to be present at screening to be included in the evaluation of treatment success, representing 85% of cats in the assessment of neuropathy. Owners assessed their cat's QoL, which revealed that 67% of owners reported a "very good" or "excellent" QoL by the day 30 visit, compared to 42% at screening. This continued to improve, and 87% (134/154) of owners assessed that QoL was "very good" or "excellent" at day 180. The study veterinarian assessed overall control of diabetes. At screening, 82% (31/38) of pre-treated cats were regarded as only having poor or fair regulation of their diabetes. By day 30, 87% of study veterinarians reported good, very good or excellent overall diabetic control, which continued to improve to 95% (147/154) at the day 180 visit.

Many cats were excluded during the study. By day 180, only 63% of the enrolled cats (158/252) were still participating in the study. Most cats enrolled experienced AEs. In total, 12/252 cats did not experience an AE during study involvement. 4 out of these 12 cats completed the study through the day 180 visit, and of these 12 cats, 3 cats were removed as post-inclusion screen failures. In total, 1314 AEs were recorded in 240 cats, including 1215 (92%) non-serious and 99 (8%) serious AEs. 6 cats which were included in the efficacy analysis were removed from the study due to AEs that occurred prior to the day 30 visit and were not related to diabetic ketonuria or ketosis (DK) or DKA according to the investigator. In total, 33 cats had AEs described as DKA or DK. Two sub-clinical hypoglycaemic events were reported. Diarrhoea was the most frequently recorded non-serious AE, being reported in 102 cats (at least once). 27 cases of dehydration were recorded as AEs. 17 cats were euthanised or died. In total, 7 out of the 17 deceased patients were necropsied, where in 5 animals the causality was assessed as "possibly", in 2 as "unknown" and in 10 as "unlikely" to treatment-related.

In summary, the applicant conducted three pivotal field studies. The studies were not blinded, and only the EU study included a comparator product (insulin).

The one study comparing the efficacy of oral velagliflozin (1 mg/kg bw) with a positive comparator product (subcutaneous insulin) demonstrated non-inferiority of the IVP to insulin injections in terms of pre-defined treatment success criteria in diabetic cats. Insulin and velagliflozin have completely different modes of action, and some feline diabetics require exogenous insulin therapy. Velagliflozin reduces excess blood glucose via renal excretion (glucosuria), but does not improve the impaired cellular uptake of glucose and the disturbed cellular energy metabolism (i.e. role of insulin).

DKA occurred in the IVP group but not in the comparator product groups (most cases were observed after few days of velagliflozin treatment). The subpopulation of diabetic cats that could benefit from velagliflozin as safe and efficacious, would be those diabetic cases that still possess adequate endogenous insulin.

Considering the above and based on the results of the studies presented in support of this application, the following indication was accepted: "For the reduction of hyperglycaemia in cats with non-insulin-dependent diabetes mellitus".

Overall conclusions on efficacy

Pharmacology

Pharmacodynamics

Velagliflozin, as a member of the gliflozin class, works by inhibiting SGLT-2 transporters, thereby reducing the amount of glucose being reabsorbed in the kidney. Gliflozins also have some activity on the SGLT-1 transporter, but the affinity is far lower than for the SGLT-2. The in vitro potency of velagliflozin in the cat is unknown, as the in vitro studies did not include cells expressing feline SGLT-2. Effects compatible with SGLT-2 inhibition were confirmed after an oral dosing of 1.0 mg/kg bw. One study, evaluating the effect of prandial state on PK and PD of velagliflozin dosed once daily for 7 days, documented a marked effect on urinary glucose excretion, independent of prandial state or gender. Another study, evaluating the effect of a 34-day treatment on the glucose metabolism in obese, insulin-resistant cats, showed glucosuria without changes in basal blood levels of glucose or insulin. Signs of improved insulin sensitivity were found in an intravenous glucose tolerance test in that study. Also, a significant decrease in bodyweight and a decrease in the respiratory exchange ratio was found. The study also showed increased blood levels of ketone bodies, warranting a focus on the risk of diabetic ketosis in treated cats with diabetes. The potential for the development of hepatic lipidosis was also considered, but clinical and biochemical parameters consistent with hepatic lipidosis were not observed.

Pharmacokinetics

The pharmacokinetics (PK) of velagliflozin in male and female cats was investigated over a dose range of 0.01 to 5.0 mg/kg bw, in exploratory and GLP-compliant studies. The effect of prandial state on the PK was also investigated. Overall, the PK of oral velagliflozin in cats is characterised by rapid absorption reaching maximum plasma concentration within one and four hours after administration in fasted and fed cats, respectively. The elimination appears to follow simple 1st order kinetics, with a half-life of approximately 3.5–6.7 hours. There appears to be dose proportionality with little or no influence of gender. Dosing in fed cats resulted in a later mean Tmax (1.0–3.7 h), a lower mean C_{max} (316–846 ng/ml) and a lower mean $AUC_{0-24\,h}$ (2786–7142 h*ng/ml) than dosing in the fasted state. It was generally found that a dose of 1 mg/kg bw resulted in a Cmax of approximately 1,000 ng/ml and a concentration after 24 h of only approximately 5–10 ng/ml. In a GLP-compliant margin-of-safety study, the PK of velagliflozin after repeat daily dosing of 1, 3 and 5 mg/kg bw (final formulation) was investigated over a period of six months, with PK profiles assessed on days 0, 91 and 181. Results were slightly less than a dose-proportional increase in exposure (especially C_{max}) of the highest dose on day 0 and of both the high doses (both C_{max} and AUC) on days 91 and 181. Mean accumulation ratios (based on AUC values) were in a range of 1.3–1.9. Accumulation ratios were comparable on days 91 and 181, indicating steady-state of exposure prior to day 91. Studies on metabolism in feline

hepatocytes and microsomes confirmed the primary metabolic pathways of velagliflozin as oxidation, a combination of oxidation as well as dehydrogenation and sulfate conjugation.

After oral administration of 1 mg/kg bw of velagliflozin (15 mg/ml) oral solution to healthy cats, the majority of velagliflozin and related metabolites were excreted via faeces primarily as unchanged velagliflozin. Only minor excretion (~ 4%) of velagliflozin or its related metabolites occurred via the renal route.

Dose determination and confirmation

Dose determination was based on two non-GLP-compliant laboratory studies performed in normal cats using a preliminary formulation, with three cats in each dose group. In one study, minor effects were seen at a dose of 0.1 mg/kg bw, whereas a marked effect was noted at 1.0 mg/kg bw. The other study indicated that 3 mg/kg bw dose only resulted in slightly higher effects than the 1.0 mg/kg bw dose.

No dose confirmation studies were presented. Albeit a pilot multi-site field study in diabetic cats was not labelled as a dose determination/confirmation study, it functions as such by affecting the design of other studies and the pivotal clinical trials. The applicant concluded that the 1.0 mg/kg bw dose was more efficient in improving the clinical signs at day 30 and 60, and with a comparable safety profile.

Tolerance in the target animal species

The applicant has presented one pivotal target animal safety study and one supportive pilot study.

The supportive pilot study was carried out using dosing with capsules at 0x, 1x, 3x and 5x the recommended dose for 90 days. No mortality was observed, and general appearance and behaviour were normal. There were no differences noted for bodyweight, BCS or food consumption compared to the control group. Significant increases of urine glucose were observed. A dose-dependent alteration of faecal consistency was evident.

The pivotal target animal safety study was performed in a total of 32 healthy male and female cats which were 8–9 months old. Cats were dosed once daily for 6 months with the final formulation of Senvelgo 15 mg/ml oral solution for cats at 0, 1, 3, or 5 times the recommended dose rate.

During the study, feed consumption was higher compared to the placebo group for the males in the 1x and 3x groups, with a corresponding increase in bodyweight gain. For males receiving the highest dose (5x), feed consumption was normal, but bodyweight gain was lower than in the placebo group. Feed consumption in treated females was comparable to the placebo group at all dose levels, whereas their bodyweight gain was lower than in the placebo group. Water consumption was increased in all treated groups. Changes in faecal consistency including diarrhoea were observed in the group receiving the highest dose (5x).

At the 1x, 3x and 5x dose levels, glucosuria was noted without a clear dose relationship, in conjunction with reduced creatinine concentrations in the urine of these animals. Blood glucose levels did not reveal treatment-related differences between groups.

Clinical trials

Clinical trials were conducted in Europe, Japan and the USA, with some differences in study design and objectives, including:

- Three pilot studies evaluating the effect of velagliflozin on hyperglycaemia and associated clinical signs in diabetic cats, including a proof-of-concept study (performed in the USA) focused on naïve diabetic cats, a pilot multi-site field study (performed in Europe) focused on pre-treated diabetic cats as well as a pilot multi-site field study (performed in the USA) focused on naïve diabetic cats.

- A pivotal clinical multi-centre field study (performed in Europe) evaluating the efficacy and safety of velagliflozin in cats with diabetes mellitus.
- A supportive clinical multi-centre field study (performed in Japan) evaluating the effectiveness and safety of velagliflozin in cats with diabetes mellitus.
- A pivotal clinical multi-centre field study (performed in the USA) to evaluate the efficacy and safety of velagliflozin for the reduction of hyperglycaemia and hyperglycaemia-associated clinical signs in diabetic cats, including an extended-use phase to evaluate the safety.

None of the clinical trials involved study blinding. Some clinical parameters (e.g. PU, PD and QoL) were rated by the owner using a semi-quantitative scoring system (e.g. "unknown", "excessive", "normal" or "decreased"). Cats with other co-morbidities commonly seen in feline diabetes were also excluded. Given that some of these co-morbidities could have introduced confounding variables impacting on efficacy conclusions or could have posed a risk to the study animals, these exclusions are acceptable and are appropriately reflected in the product information.

The efficacy parameter known as "treatment success", defined as a composite variable of improvement in at least one clinical parameter (PU, PD, bodyweight or appetite) and reduction of mean BGCs to < 300 mg/dl by the end of the study, was the primary efficacy parameter for pivotal clinical trials and secondary efficacy parameter for pilot studies. This represented a risk of bias of clinical parameters, due to lack of study blinding, and mean blood glucose treatment success thresholds were above normal feline reference ranges. The primary efficacy assessment in two pilot studies was a change in the 9-hour BGCu by visits, over time, while for the other pilot study no endpoint was defined.

In general, all studies revealed a high proportion of AEs related to velagliflozin treatment. These included serious adverse events (e.g. DKA, ketonuria and ketosis) as well as other adverse events (diarrhoea, lethargy and vomiting).

Pilot studies

An unblinded, positive-controlled, randomized, multi-site field study based on 55 diabetic cats, newly-diagnosed or previously treated with insulin (180 days or less), randomly assigned to velagliflozin (IVP) 0.5 mg/kg, IVP 1.0 mg/kg, or Vetsulin insulin (CP). The means for the IVP groups reached the preferred clinical treatment goals (glucose < 250 mg/dl) by day 7 (0.5 mg/kg and 1.0 mg/kg) and by day 14 (0.1 mg/kg) and maintained these BGC through day 60. The CP group required 60 days to approach the upper-end of the desired mean.

A prospective, open-label clinical field study evaluated the effectiveness and safety of 1 mg/kg/day oral velagliflozin (pre-formulation, 10 mg/ml) as a monotherapy in 16 cats over 28 days. Insulin pre-treated diabetic cats (pre-treated for at least one week before enrolment) were directly switched from insulin to velagliflozin. Velagliflozin administration resulted in increased glucosuria as well as a significant effect on both the mean BGC (assessed 9 h after dosing) and mean fructosamine concentrations. Several BGC were missing, since eight of sixteen cats were withdrawn before D28, with four developing DKA. A total of 16 AEs including one or more clinical signs were reported in 12 cats, including emesis (3 cats), decreased faecal consistency (3 cats), anorexia (4 cats), lethargy (3 cats), and ketoacidosis (4 cats, 1 died). All but one cat had weight loss over the 28-day period of > 5% bodyweight. One cat had its dose down regulated.

A single-site pilot, prospective, open label, change-from-baseline field study investigated the effect of velagliflozin (IVP, administered at 1 mg/kg bw p.o. once daily for 28 days) on hyperglycaemia and associated clinical signs as monotherapy when administered once-daily for four weeks to either six newly diagnosed or pre-treated (four days or less) insulin diabetic cats. Significant decreases were found in fasted plasma glucose and mean BGC from the nine-hour BGCu from day 7 onwards in all cats

($p < 0.0001$). Maximum and minimum BG values from day 7 onwards also decreased compared to baseline. Urine glucose concentrations and blood fructosamine were not significantly different. Average insulin to glucose ratios were significantly increased at days 7, 14, and 28 compared to day -1. No significant changes in haematology or blood chemistry parameters were noted.

Pivotal clinical trials

The two pivotal clinical trials were designed similarly as a prospective, open-label (no blinding/masking, blocking or randomization), multicentric field studies investigating safety and efficacy of velagliflozin (IVP) for the reduction of hyperglycaemia and hyperglycaemia-associated clinical signs in client-owned DM cats (Age ≥ 1–2 years of any sex/ breed). Inclusion/exclusion criteria, as well as primary and secondary efficacy parameters were similar between the trials.

The EU study included thirty-nine veterinary clinics in Germany, France and the Netherlands. Glycaemic parameters and DM clinical signs of DM were evaluated over 91 days with either 1 mg/kg PO SID velagliflozin (IVP) or Caninsulin (CP). Study consisted of two phases: phase 1 (efficacy phase) evaluated IVP safety and efficacy based on screening (day -7 to day -2; day 1 was the first IVP administration) and a 45-day treatment period (day 1 to day 45 ± 2). Phase 2 was an extended-use period continuing from phase 1 to day 91±3 days.

In total, 116 cats were used for efficacy evaluation and 18 cats excluded. Overall treatment success rates (i.e. improvement in at least one clinical and one blood parameter) from day 21 onwards to day 45, were higher in the IVP group (day 45: 53.7% vs. 41.9%), but higher in the CP group by day 91 (55.6% vs. 62.9%). Statistical analysis of the FAS population at day 45 showed non-inferiority of once daily oral IVP administration to twice daily CP injections. PU/PD improved in both groups until study day 45 (from 30–40% at day 3 to 50-60% at day 45). Success rates for appetite and plantigrade or palmigrade stance (diabetic polyneuropathy) were below 20% at all visits but increased slightly from <10% (day 3) to 10–20% (day 91), in both treatment groups.

In the field study conducted in Japan, twenty-nine cats were used for efficacy evaluation. Enrolled cats included 13 of 30 (43.3%) that were pre-treated with insulin and 17 were treatment-naïve.

Twenty-seven of 29 cases were deemed treatment success (93.1%). Haematology parameters, serum chemistry parameters and urinalysis didn’t show clinically significant changes related to IVP administration. A total of 19 adverse events were recorded in 10 cats (DKA in one cat, loose stool/diarrhoea in ten cats). The incident rate of loose stool was 33.3%.

This field trial included a relatively small study population and short study period (30 days). This study is considered to be only supportive.

The USA field study included twenty-one veterinary (mainly private) practices. No positive or negative control groups were established, and all enrolled patients received velagliflozin (IVP). Study consisted of two phases: phase 1 evaluated IVP safety and efficacy administered at 1 mg/kg p.o. once daily and consisted of screening (day -7 to day -2; day 0 was first day of IVP administration) and a 30-day treatment period. Phase 2 was an extended-use phase continuing from the end of phase 1 to day 180 ± 7 days of dosing. The last BGC measurement was at day 60.

In total, 412 cats were screened and 252 included in the safety population. A total of 38 (15%) of 252 cats were pre-treated with insulin and 214 (85%) were treatment-naïve. Treatment success was demonstrated in 177 of 198 IVP treated cats evaluated at day 30 ± 2, but two cats were later coded as treatment failures (total treatment success of 88.4%). Many clinical parameters were reported as "non-evaluable" because clinical signs were not present at screening. By day 180 (end of phase 2), 63% of enrolled cats (158/252) were still in the study.

In total, 12/252 cats did not experience an AE and 1314 AEs were recorded in 240 cats, including 1215 (92%) non-serious and 99 (8%) serious AEs. Of these 33 cats had AE's described as DKA, or DK. Seventeen cats were euthanised or died. Diarrhoea was the most frequently recorded NSAE, being reported in 102 cats (at least once).

Part 5 – Benefit-risk assessment

Introduction

Senvelgo is an oral solution containing velagliflozin, which is a new active substance not previously authorised as a veterinary medicinal product within the Union at the date of the submission of the application in accordance with Article 42(2)(c) of Regulation (EU) 2019/6. Velagliflozin is an SGLT-2 inhibitor belonging to the gliflozin class of compounds, which reduce blood glucose levels by inhibiting renal glucose reabsorption. The product is intended for the reduction of hyperglycaemia in cats with non-insulin-dependent diabetes mellitus at an oral dose of 1 mg/kg bw/day.

The application has been submitted in accordance with Article 8 of Regulation (EU) 2019/6 (full application).

Benefit assessment

Direct benefit

Velagliflozin is a new active substance in veterinary medicine, with the proposed benefit for the treatment of diabetes mellitus in cats. Velagliflozin is part of the class of SGLT-2 inhibitors, of which other compounds are used successfully in human medicine for the management of type 2 diabetes, mostly for milder cases and not as stand-alone therapies. The use of SGLT-2 inhibitors for human type 1 diabetes is contraindicated, due to the risk for development of DKA. Since many of the manifestations of diabetes are directly related to glucose toxicity, the gliflozin class of compounds offers a novel way of controlling hyperglycaemia.

One well-designed, non-controlled pivotal clinical multi-centre field study and one pivotal, positive-controlled clinical field trial were presented that confirm the blood glucose-lowering effect of velagliflozin in the majority of diabetic cats treated, both in the short-term and medium-term treatment courses. This further resulted in the improvement of clinical signs associated with diabetes mellitus in cats such as polyneuropathy, weight loss and PU/PD, although several potential sources of unmitigated bias were identified in these studies. The benefit of lowering toxic levels of blood glucose in feline diabetic patients is acknowledged, albeit these improvements come at the cost of several adverse events not associated with other diabetic management measures in cats (e.g. insulin treatment and/or prescription diet).

Clinical trials conducted in accordance with GCP principles demonstrated that the product is efficacious in reducing hyperglycaemia in cats with non-insulin-dependent diabetes mellitus at a dose of 1 mg/kg bw/day.

However, the safety and efficacy of velagliflozin in diabetic cats with co-morbidities (e.g. pancreatitis, hepatic disease, infectious disease, cardiac disease, urinary tract infection, neoplasia, hyperthyroidism and acromegaly) was not documented. Use of the veterinary medicinal product in cats with co-morbidities is only according to the benefit-risk assessment by the prescribing veterinarian. The safety and efficacy of a combined treatment with insulin or other blood glucose lowering treatments and velagliflozin in cats was not investigated. Due to the mode of action of insulin there is an increased risk for hypoglycaemia, therefore combined treatment is not recommended.

Additional benefits

The current standard of care for clinical cases of diabetes mellitus in cats involves daily injections with insulin, followed by regular monitoring of glycaemic control and clinical signs. The gliflozin class of compounds offers a novel way of controlling hyperglycaemia and thus increases the range of available treatment possibilities for the management of diabetes mellitus in cats. As an oral formulation for diabetic management, the product could lead to better treatment compliance for cat patients, where it is easier for the owner to administer compared to insulin injections. As identified in the clinical trials, Senvelgo appears to have a low risk of inducing hypoglycaemia that can lead to serious health implications and thus higher standards for glycaemic control can be aimed for. Also, in some patients, weight loss was associated with the treatment, representing a potential benefit for obese cats with early stages of diabetes. Velagliflozin increases the range of available management options for diabetes mellitus in cats.

Risk assessment

Since there is no comparable veterinary medicinal product currently on the EU/EEA market, the risk assessment is focused on the general management of diabetes mellitus in cats as well as the current standard of care.

The primary efficacy parameter used for one pilot and one pivotal field trial involves comparing blood glycaemic control (glucose, fructosamine) between insulin and velagliflozin. It is worth noting that treatment with insulin provides more than just glycaemic control in cats with diabetes. Also, glycaemic control from insulin is fundamentally different from that induced by velagliflozin, i.e. the former induces cell utilization of glucose while velagliflozin induces glucosuria. Depending on the severity and chronicity of diabetes, an external source of insulin may be critical for the cat to utilize glucose throughout the body. Senvelgo is not intended for cats with insulin-dependent diabetes mellitus, but for those diabetic cases with adequate endogenous insulin production. For example, if a cat has advanced diabetes with a high degree of insulin resistance and pancreatic beta-cell "burn-out", then treatment with velagliflozin would be insufficient to manage the disease.

Since all the clinical characteristics of diabetes were not evaluated in the clinical trials, the indication initially proposed by the applicant is not considered to wholly reflect the data derived from the studies presented with the application.

One field trial where oral treatment with velagliflozin was compared to insulin injections showed non-inferiority of the product to insulin treatment in terms of blood glycaemic control and certain clinical parameters. A higher risk of DKA in pre-treated cats which need exogenous insulin was identified. Reduction of hyperglycaemia in cats with diabetes mellitus is the main aspect of this complex disease, for which the effect of velagliflozin has been firmly justified by the data package.

No dose-finding/confirmation studies are presented. The applicant concluded that the 1.0 mg/kg IVP group was more efficient in improving the clinical signs at day 30 and 60, and with a comparable safety profile.

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety

Some of the basic PK/PD characteristics of velagliflozin are not known in cats (e.g. SGLT-2 sensitivity). That being said, it is known that velagliflozin disappears rapidly from plasma and the target site of action is kidney SGLT-2 receptors.

Risks for the target animal

The main risk of using velagliflozin for advanced diabetes mellitus in cats is that these animals would not receive the required insulin, plus an added risk of developing DKA, which is a serious, potentially life-threatening condition. Further risks of using velagliflozin include the number of AEs recorded in the clinical trials.

The main reported adverse reactions include diarrhoea or loose stool, polydipsia/polyuria, weight loss, dehydration and vomiting.

Diabetic ketoacidosis (DKA), diabetic ketonuria (DK), urinary tract infection (UTI) and dehydration have been observed in diabetes mellitus cats administered velagliflozin, especially diabetic cats pretreated with insulin. Specific measures are necessary to address this risk to animals exhibiting symptoms of DKA, DK, UTI or dehydration.

The safety of the veterinary medicinal product has not been established during breeding, pregnancy or lactation. Use only according to the benefit-risk assessment by the responsible veterinarian.

Risk for the user

The product is classified as a potential eye irritant.

At high doses (400 mg/kg bw/day) in rats, the test substance is toxic to embryo-foetal development.

Accidental ingestion of the product by a child would exceed the typically applied acceptable margin of exposure of 100. The risk related to pharmacological effects and mitigation measures thereof is stated in the SPC and mitigation measures are stated in the package leaflet and on the packaging.

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Appropriate safety advice is included in the SPC.

Risk for the environment

Senvelgo is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the management of diabetes mellitus in cats as well as the user. Appropriate advice on how to prevent or reduce these risks is provided in the product information.

User safety:

User safety risks have been identified, mainly the risks associated with exposure in children. These risks are mitigated by the presentation of the product in a child-resistant packaging and the warnings stated in the SPC, package leaflet and on the packaging.

The risk to pregnant users is negligible due to a sufficiently large margin of safety.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status):

The veterinary medicinal product is subject to a veterinary prescription.

Specific pharmacovigilance requirements:

Given the NAS status for this product as well as the fact that this is the first of a new class of molecules for management of diabetes in cats, it is considered prudent for pharmacovigilance reporting to take place at an interval of 6 months for the first two years after product launch. This is also justified based on the adverse events recorded, especially DKA.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication for Senvelgo: "For the treatment of diabetes mellitus in cats".

Based on the data presented to date, the overall benefit-risk balance is considered positive.

The product has been shown to be efficacious for diabetes mellitus in cats with adequate endogenous insulin production, and the CVMP agreed to the following indication: "For the reduction of hyperglycaemia in cats with non-insulin-dependent diabetes mellitus".

Information on development, manufacture and control of the active substance and finished product has been presented and leads to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

The product information has been reviewed and is considered to be satisfactory and in line with the assessment.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Senvelgo is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.

Evaluation of new active substance status

In addition, based on the review of data on the quality-related properties of the active substance, the CVMP considers that velagliflozin is to be qualified as a new active substance based on quality and chemical structure.