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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Semintra (EMEA/V/C/002436)

International non-proprietary name: telmisartan

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 1 February 2012 an application for marketing authorisation to the European Medicines Agency (the Agency) for Semintra, through the centralised procedure falling within Article 3(2)a of Regulation (EC) No 726/2004 (new active substance).

The eligibility for the centralised procedure was agreed upon by the CVMP on 15 September 2011 as Semintra contains a new active substance which is not yet authorised as a veterinary medicinal product in the Community.

The product is intended for the reduction of proteinuria associated with chronic kidney disease (CKD). The target species is cats. Semintra contains telmisartan as active substance in a concentration of 4 mg/ml, and is presented in containers of 30 ml. The route of administration is oral use.

The dossier has been submitted in line with the requirements for submissions under Article 12 (3) of Directive 2001/82/EC, as amended.

The CVMP adopted an opinion and CVMP assessment report on 13 December 2012.

On 13 February 2013, the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC, as amended. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Declarations of compliance of the manufacture of the product with EU GMP requirements have been provided. Any additional inspection of these sites was not considered necessary.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites are considered in line with requirements.

Part 2 - Quality

Composition

The proposed veterinary medicinal product is a clear, colourless to yellowish viscous aqueous solution, containing 4 mg/ml telmisartan with benzalkonium chloride as a preservative. The product also contains sodium hydroxide and hydrochloric acid as pH adjusters. Hydroxyethylcellulose and maltitol are included to enhance viscosity.

Container

The product is presented in 45 ml translucent high density polyethylene (HDPE) bottles with translucent low density polyethylene (LDPE) plug-in adapters and white polypropylene child-resistant closures and white polyethylene sealing disks.

A 2 ml oral syringe with a kg-body weight scale is also provided. The syringe consists of a translucent polypropylene body and a blue HDPE plunger.

Development pharmaceutics

For cats, an aqueous solution 4 mg/ml concentration was chosen as it allows for easy administration, and convenient dosing volume of 0.25 ml to 2 ml, equivalent to 1 mg/kg of body weight for cats from 1 kg to 8 kg. The pH of the solution is controlled with sodium hydroxide and hydrochloric acid. Hydroxyethylcellulose and maltitol are viscosity enhancing excipients that are used to ensure that the formulation can be delivered accurately and conveniently by means of an oral syringeand to provide a suitable texture to promote its acceptance on administration to cats. As the product is a multidose aqueous solution, antimicrobial preservation is required. Benzalkonium chloride was chosen as preservative.

A specific bottle presentation was designed for the product consisting of a translucent 45 ml HDPE bottle, with a specific LDPE plug-in adapter and 2 ml oral syringe with a kg body-weight scale for easy dosing, and child-resistant, tamper-evident polypropylene closure with a polyethylene sealing disc. Dosing accuracy studies were performed on the proposed container-closure systems and dosing syringes which demonstrated that the doses delivered, at the maximum, minimum and intermediate doses, comply with Ph.Eur. requirements.

Method of manufacture

Detailed descriptions of the manufacturing process have been provided. A declaration has been provided that process validation will be performed on the first three consecutive production batches of each batch size, and a process validation protocol was provided in line with the requirements of "Note for Guidance on Process Validation" (EMEA/CVMP/598/99).

Control of starting materials

Active substance

For the active substance, telmisartan, a Ph. Eur. Certificate of Suitability (CEP) to the monograph of the Ph. Eur. has been provided.

Excipients

All of the excipients are controlled in accordance with their Ph. Eur. monographs. No additional tests or limits are required for any of the excipients, which is considered satisfactory given the dosage form.

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

None of the starting materials used for the active pharmaceutical ingredient telmisartan 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).

Control tests on the finished product

Acceptable specifications have been set and in sufficient detail and include parameters relevant to the dosage form. Finished product batch analysis data has been provided for three batches, with all results within specification. Characterisation data on the reference standards has been provided.

Stability

Supporting stability data to 36 months were provided for three batches of the product filled into HDPE bottles used during development, rather than the finished packaging as proposed for authorisation. All results are within the proposed limits, with all results for assay well within the release limits and no degradation products were found above the reporting limit of the method.

Primary stability data was provided for 3 pilot-scale batches of the product filled into the proposed 45 ml translucent HDPE bottles with the LDPE plug-in adapter and the white tamper-proof HDPE caps as proposed for authorisation. All results were within the release limits, and no degradation products were found above the reporting limit of the method for any of the batches on any of the storage conditions. No decreasing trends were noted for assay of the preservative benzalkonium chloride.

Primary stability data were also provided for 3 bulk batches of that were filled into 3 sub-batches each of the proposed container. Efficacy of antimicrobial preservation and microbial quality testing complied with requirements at all time-points tested. All results for assay were within the release limits with no trending observed. No degradation products were found above the reporting limit of the method for any of the batches on any of the storage conditions. The data provided support the proposed 3 year shelf-life of the finished product, with no special storage conditions. Two in-use stability studies have been provided on pilot-scale batches, testing batches up to 6 months. The samples were tested as per the end-of-shelf-life specification and included efficacy of antimicrobial preservation testing, and all results were compliant with requirements. Therefore, the proposed in-use shelf-life of 6 months is considered to be acceptable.

A photostability study was performed in line with the requirements of VICH GL5 "Photostability Testing of New Veterinary Drug Substances and Medicinal Products (CVMP/VICH/901/99)". As the provided data are considered to be sufficient to demonstrate the photostability of the product, no additional storage conditions are required regarding light-sensitivity.

Overall conclusions on quality

The dossier provides a suitable description of the active substance and the chosen formulations, with appropriate justification that the composition of the product is "fit-for-purpose". Overall, the dossier demonstrates that the production of the finished product leads to consistent quality. In view of the standard production manufacturing process of the drug product and the provided validation data on pilot-scale, full scale validation will be performed post-approval. The data relating to the active substance are provided in the form of a Ph. Eur. CEP. The excipients used in the manufacture of the finished product are listed in Ph. Eur., and so are acceptable. The container closure system chosen is suitable for the dosage form and the product. The finished product specification provides an assurance of the quality of the product and the tests comply with the requirements of the Ph. Eur. for the dosage form. In general, the analytical methods are adequate, and data of their validation confirm their suitability. Stability studies have been performed according to VICH guidelines. For the finished

product, the stability data provided supports the proposed shelf-life of 3 years with no special storage conditions. In-use stability studies support the proposed in-use shelf-life of 6 months. No additional storage conditions are required regarding light-sensitivity.

Part 3 – Safety

The proposed product, Semintra, contains the active substance telmisartan, an angiotensin II receptor antagonist.

Pharmacodynamics

Renin-Angiotensin-Aldosterone-System

The Renin-Angiotensin-Aldosterone-System (RAAS) plays an important role in the regulation of blood pressure, body fluid volume and electrolyte balance. Whenever blood flow to the kidney diminishes, renin is secreted by the juxtaglomerular cells of the kidney. Renin catalyzes the conversion of the plasma glycoprotein angiotensinogen to angiotensin I which is rapidly hydrolyzed to angiotensin II (AngII) by angiotensin converting enzyme (ACE). AngII causes vasoconstriction and elevation of blood pressure consequent to increased total peripheral resistance. A second effect of AngII is the increased secretion of aldosterone. Aldosterone causes sodium retention, water retention, increase in blood pressure, and restoration of renal perfusion, which shuts off the signal for renin release. Additionally, angiotensin acts directly on the kidneys to cause salt and water retention, which causes an increase in arterial blood pressure.

The actions of AngII are mediated by specific surface receptors on various target organs eliciting events such as vasoconstriction, renal sodium reabsorption, aldosterone formation, and norepinephrine release. AngII receptors have been classified into two main subtypes, the AT-1 and AT-2 receptors. AngII, via the AT-1 receptor, is responsible for most, if not all, the peripheral effects of the system.

Angiotensin converting enzyme (ACE) inhibitors block the enzymatic conversion of angiotensin I to AngII. However, alternative pathways exist for the generation of AngII, which may be active even when ACE is inhibited. Blockade of AngII receptors represents an alternative approach to the selective inhibition of the pressor response of the renin-angiotensin system and, therefore, to the reduction of blood pressure.

Data was provided to show that telmisartan is an orally active and specific AngII receptor antagonist acting directly at the AT-1 receptor, which causes a dose dependent decrease in mean arterial blood pressure. Telmisartan displaces AngII with very high affinity from its binding site at the AT-1 receptor, and selectively binds to the AT-1 receptor. By selectively binding to only the AT-1 receptor, the expected effects associated with stimulation of the AT-2 receptor such as vasodilatation, natriuresis and inhibition of inappropriate cell growth are not suppressed. The receptor binding is long lasting due to the slow dissociation of telmisartan from the AT-1 receptor binding site. Telmisartan does not exhibit any partial agonist activity at the type AT-1 receptor.

Pharmacodynamic data specific to the cat (including the approach to dose selection) are presented in Part 4.

Pharmacokinetics

Pharmacokinetic studies were performed in mice, rats, rabbits and dogs. Following oral administration, telmisartan was rapidly absorbed in mice and rats (T_{max} values of 2 hours), more slowly in rabbits and dogs (T_{max} values of 7 hours). Bioavailability was 56-75% in mice, 66% in rats and 14-22% in dogs. No clear gender differences in telmisartan plasma concentrations were observed in rats and dogs, whereas telmisartan plasma concentrations were higher in female mice compared to males. In rats, over a dose range of 1 to 30 mg/kg i.v. and 10 to 300 mg/kg orally, a supraproportional increase in exposure was observed (estimated by AUC and C_{max}). Similarly, in the dog, C_{max} and AUC were not proportional to the doses used beyond the i.v. dose of 3 mg/kg and the oral dose of 30 mg/kg.

In vitro binding to plasma proteins was high in all species studied (about 99.6% in mice, rats and 98.7% in dogs).

Volume of distribution of telmisartan was 3-5-fold higher than that of total body water indicating a wide distribution. Half-life of elimination of telmisartan from plasma after oral administration was between 4 and 20 hours in all species. Tissue distribution studies showed that telmisartan-related radioactivity was mainly located in the liver, and only small amounts were detected in the central nervous system. In pregnant rats, telmisartan crossed the placenta, and it was also excreted in the milk of lactating rats.

The metabolism of telmisartan was similar in all species (mice, rats, dogs and humans) and consisted mainly in glucuronidation to a 1-*O*-acylglucuronide. This metabolite did not demonstrate antagonistic activity at AT-1 receptors. The parent compound represented the majority of the radioactivity in plasma. Metabolism predominantly occurs during the passage through the intestinal wall, but also occurs in liver and other tissues.

A supraproportional increase in exposure was observed in a number of toxicokinetic studies. Additional data from tissue distribution studies of ^{14}C-telmisartan after single and multiple dosing in rats demonstrated that there was no accumulation and/or retention of radioactivity in any tissue after multiple doses compared to the acute schedule.

In the laboratory species studies, biliary elimination into the faeces is the predominant route of excretion (86-100%). The majority of the excreted fraction corresponds to telmisartan 1-*O*-acylglucuronide. Biliary excretion is rapid, with 60-80% of the dose eliminated within 6 hours after dosing in rats.

Pharmacokinetic data specific to the cat are presented in Part 4.

Toxicological studies

The toxic potential of telmisartan has been fully investigated in a comprehensive range of laboratory animal studies. All toxicity studies were carried out in full compliance with GLP regulations.

Single dose toxicity

The acute toxicity of telmisartan in rats and dogs was low after oral administration, with no adverse effects being noted at doses of up to 2000 mg/kg bw.

Repeat dose toxicity

A large number of repeated-dose toxicity studies were generally carried out in the rat and the dog. The duration of the oral studies in the rat and the dog ranged from two weeks to six months in rats, and

twelve months in dogs. The duration of the intravenous studies was four weeks. All regular 4 and 13-weeks toxicity studies included a recovery period.

The principal toxicological target organs are the kidney and the gastrointestinal tract.

In rats and dogs, telmisartan induced renal juxtaglomerular hyperplasia with hypertrophy of the afferent glomerular arterioles of the kidneys. These effects are considered to be caused by the primary pharmacodynamic action of telmisartan (blockade of the AngII-induced inhibition of the renin release and thereby stimulation of renin producing cells) and have also been observed with ACE inhibitors and other AT-1 antagonists.

The mechanism responsible for gastrointestinal ulcer formation and erosion is not known.

Other effects observed were: reversible increases in serum potassium (attributed to AngII receptor antagonism which suppresses aldosterone secretion); reversible increases in urea nitrogen and creatinine (attributed to functional changes in the kidney); reversible decreases in red blood cell parameters (attributed to blockade of AngII-stimulated erythropoietin production); and slightly elevated values for AST, ALT and bilirubin. Given that pharmacodynamically-induced side-effects (particularly for the changes in red blood cell parameters and juxtaglomerular apparatus (JGA) hypertrophy) were observed at all doses of telmisartan tested, it was not possible to define a NOEL based on this series of studies.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

A series of studies investigating effects of telmisartan on fertility and embryo/foetal development in rats and rabbits was provided.

No effects of telmisartan on male or female fertility were observed.

The pivotal developmental toxicity study was conducted in rats, and these were given oral doses of 5, 15 and 50 mg/kg bw/day telmisartan on days 6 to 21 of gestation. Maternal toxicity occurred at 15 and 50 mg/kg and was characterised by reduced body weights and slight decreases in food intake. No effects in the conceptuses were noted at 5 and 15 mg/kg. Foetal weights were decreased (with a related delay in maturation, eye opening) at 50 mg/kg bw but there was no evidence of a teratogenic effect. Viability and weaning rates were comparable to controls. There were no effects on the fertility of the F1 animals. The maternal NOEL was 5 mg/kg and the NOEL for peri- and postnatal development was 15 mg/kg. It is considered possible that the effects on the foetus observed in this study are due to high exposure to telmisartan, particularly during late gestation, and of offspring during lactation. Concentration of telmisartan in the foetal compartment increases during late gestation from approximately 27% of peak maternal concentration on gestation day 12 to approximately 60% on gestation day 18. In addition, telmisartan was excreted in rat milk at concentrations of 1.5- to 2-fold higher than those in maternal plasma 4 - 8 hours post dose and were detectable over 48 hours post dose. Although the reprotoxicity studies in animals indicate that telmisartan poses no risk to embryos or foetuses at therapeutic doses, clinical experience with the use of ACE inhibitors in man has shown increased risk of foetal and neonatal toxicity and death ("ACE inhibitor foetopathy") when women are exposed to substances acting on RAAS during the last two trimesters of pregnancy.

No reproductive toxicity safety studies investigating the use of telmisartan in the target species have been conducted. It is unclear whether or not telmisartan may pose a risk of "ACE inhibitor foetopathy"

if administered during pregnancy in the cat. For these reasons, the product is contraindicated during pregnancy.

Mutagenicity/genotoxicity

No evidence of mutagenicity or relevant clastogenic activity was observed in a standard battery of *in vitro* and *in vivo* genotoxicity tests.

Carcinogenicity

The carcinogenic potential of telmisartan was assessed in 2-year feeding studies in mice at doses of 10, 100 and 1000 mg/kg, and in rats at 3, 15 and 100 mg/kg. No telmisartan-related carcinogenic effects were observed at oral doses of up to 1000 mg/kg/day in mice, and up to 100 mg/kg/day in rats.

Studies of other effects

The potential for telmisartan to induce cytochrome P-450 was investigated in the rat. The data obtained do not provide any evidence for the induction of P-450 dependent enzyme activity.

In two GLP-compliant studies, the applicant confirmed that telmisartan is not a dermal or an ocular irritant. These studies were conducted in accordance with OECD guidelines 404 and 405 (acute dermal irritation/corrosion and acute eye irritation/corrosion), respectively.

Absence of local effect studies using the final formulation proposed for marketing (as distinct from individual components of the product) has been adequately justified.

User safety

The applicant has presented a User Safety Risk Assessment which has been conducted in accordance with CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-FINAL-Rev.1).

Based on the information presented in respect of the excipients, it is accepted that the substance of most interest for safety assessment is the active ingredient, telmisartan. The toxicological properties of telmisartan are described in detail. Telmisartan is also authorised as a medicinal product in humans and is considered safe and well tolerated. Adverse reactions in humans are described as erythema, pruritus, faintness, insomnia, depression, stomach upset, vomiting, hypotension, bradycardia, tachycardia, dyspnoea, eosinophilia, thrombocytopenia, weakness and lack of efficacy have been reported rarely. As with other angiotensin II antagonists, isolated cases of angioedema, pruritus, rash and urticaria have been reported.

Clinical experience with the use of ACE inhibitors in man has shown increased risk of foetal and neonatal toxicity and death ("ACE inhibitor foetopathy") when women are exposed to substances acting on the renin-angiotensin-aldosterone-system during the last two trimesters of pregnancy. Consequently, in human medicines, use of telmisartan in pregnant women is contraindicated during the 2nd and 3rd trimesters. Given the known risk of telmisartan exposure in pregnant women, the product literature for this veterinary medicinal product includes a recommendation that pregnant women should avoid contact with the product.

Exposure assessment:

The product will be administered to cats by their owners or by veterinary professionals. The product will be administered by owners daily for prolonged periods; therefore, there is the potential for repeat exposure. In view of the presentation (bottles with syringe plug-in adapter), the risk of user exposure to the active ingredient in Semintra is low. Exposure will most likely arise from contact with the surface of the syringe (rather than spilling). In this situation, the volume to which the user may be exposed to is likely to be low.

Based on a quantitative risk assessment, it would appear that the quantity of product to which a user will be exposed under worst-case conditions will not be of toxicological concern. The normal therapeutic dose of telmisartan for essential hypertension in human patients is 40(-80) mg per day. This approximates to 0.6 to 1.2 mg/kg bw/day or to 65 to 130 fold the possible oral dose arising from skin contamination (estimated to be 0.01 mg/kg).

In terms of risk management, it is noted that the product will be subject to prescription and is supplied in containers with child-resistant packaging. The product is presented in bottles with syringe plug-in adapter; therefore, limiting potential for user exposure. In addition, although the risk of adverse effects in humans is considered minimal under normal conditions of use, a number of user safety statements are included in the product literature.

The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

In line with the Guideline on Environmental Impact Assessment for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-FINAL), given that the product is for individual treatment under veterinary prescription, and indicated for non-food producing animals that are not intensively reared, the environmental risk assessment can stop at Phase I.

Based on the data provided, Semintra is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The pharmacodynamics and pharmacokinetics of the test compound have been adequately described in laboratory animal species and man.

The acute oral toxicity of telmisartan in the rat and dog is low. A large number of references investigating the toxicity of telmisartan following repeated administration to laboratory animals were provided with the application. Based on the information presented, it appears that the principal toxicological target organs are the kidney and the gastrointestinal tract. Other effects were: reversible increases in serum potassium; reversible increases in urea nitrogen and creatinine; reversible decreases in red blood cell parameters; and slightly elevated values for AST, ALT and bilirubin. Given that pharmacodynamically-induced side-effects (particularly for the changes in red cell parameters and juxtaglomerular apparatus hypertrophy) were observed at all doses of telmisartan tested, it was not possible to define a NOEL based on this series of studies. No effects of telmisartan on male or female fertility were observed in studies carried out in rats and rabbits. There was no evidence of teratogenic effects. Although the reproductive toxicity studies in animals indicate that telmisartan poses no risk to embryos or foetuses at therapeutic doses, clinical experience with the use of ACE inhibitors in man has shown increased risk of foetal and neonatal toxicity and death ("ACE inhibitor foetopathy") when women are exposed to substances acting on the renin-angiotensin-aldosterone-system during the last

two trimesters of pregnancy. The product is therefore contraindicated for use during pregnancy in the cat.

Telmisartan was not found to have any mutagenic or relevant clastogenic effects and, in two year carcinogenicity studies carried out in rats and mice, no evidence of any drug-induced tumorigenic effect was seen.

The applicant has presented a User Safety Risk Assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/543/03-FINAL-Rev.1. While the risk of toxic effects is considered minimal under normal conditions of use, a number of user safety statements are proposed. Inclusion of these statements is considered prudent and it is considered that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Based on the data provided the ERA can stop at Phase I. Semintra is not expected to pose a risk for the environment when used according to the label recommendations.

Residues documentation

Not applicable

Part 4 – Efficacy

The current state of knowledge in the management of naturally occurring feline chronic kidney disease (CKD) focuses on measures aimed at addressing: (i) those factors known to be associated with intrinsic progression of the disease and (ii) measures thought to improve the Quality of Life (QoL) of the cat as it nears the end stage of CKD. Proteinuria and hyperphosphataemia are two factors for which there is some evidence to suggest these are logical targets to slow intrinsic progression of feline CKD and, as such, are two major targets of treatments designed to slow progression particularly in International Renal Interest Society (IRIS) stages II and III CKD.

It is accepted that there is evidence to suggest that inhibition of the renin-angiotensin-aldosterone-system (RAAS) leads to a reduction in proteinuria in cats with CKD and that reduction in proteinuria may slow down progression of renal disease. However, there is at present no definitive proof of a benefit on the progression (in terms of either renal pathology or survival) of CKD in the cat.

To date, ACE inhibitors to inhibit the RAAS have been used for the pharmacological management of proteinuria in the cat. Benazepril is used therapeutically for the management of proteinuria associated with CKD in cats at a dose rate of 0.5 to 1 mg/kg once daily. With Semintra, the applicant is putting forward an alternative to ACE inhibitors. Telmisartan is a competitive antagonist of angiotensin II (AngII) at the AT-1 receptor. This will inhibit AngII or other mediators activating the AT-1 receptor.

Based on the information presented, the therapeutic rationale for use of anti-proteinuric treatment in cats with CKD can be accepted.

Pharmacodynamics

Telmisartan is a selective antagonist of AT-1 receptors. Blockade of AngII receptors represents an alternative approach to the selective inhibition of the pressor response of the renin-angiotensin system and, therefore, to the reduction of blood pressure.

It is accepted that available pharmacodynamic data make an AngII receptor antagonist a candidate to develop as a renoprotective medicine in cats with naturally occurring CKD, where local activation of RAAS is thought to drive hyperfiltration, glomerular capillary hypertension, lead to increased protein

entering the glomerular filtrate and trigger interstitial fibrosis. However, specific pharmacodynamic data supporting such an effect in the cat are limited.

The findings of an *in vitro* uterine artery study supports the fact that telmisartan inhibits the vasoconstriction induced by AngII in cat resistance arteries. It is suggested that this result can be extrapolated to other vascular beds.

In vivo data from two other studies investigating the effects of different doses of telmisartan (intravenous or oral) on anaesthetised cats provide further evidence of an AngII antagonist effect in the cat; however, the studies were pilot in nature (non-GLP and limited in terms of animal numbers) and the model used was designed to evaluate the ability of telmisartan to inhibit the pressor response to exogenously administered AngII. How this relates to the ability to prevent hyperfiltration and progressive renal injury in the kidney in cats with naturally occurring CKD is not entirely clear. That said it is accepted that the pressor response to AngII is a well established model that was used in laboratory animals in the development of telmisartan for human use. Furthermore, the direct relevance of models of renal impairment (e.g. renal mass reduction model) to the naturally occurring disease may also be questioned. For these reasons, the model used was accepted.

In the principal dose determination study, the effect (inhibition of the pressor response to exogenously administered AngII) of telmisartan in 12 adult and healthy cats, 7-8 months of age, was investigated following oral administration of the test compound (1 mg/kg or 3 mg/kg) or placebo for 7 consecutive days. Relative to placebo, a persistent (> 24 hours) and substantial (approximately 50%) inhibition of the pressor effect of AngII following administration of telmisartan at 1 mg/kg orally was demonstrated. Twenty-four hours after product administration, no difference in diastolic blood pressure response between the two telmisartan groups was noted. Given the effects on blood pressure response, it is suggested that a dose rate of 1 mg/kg should be able to inhibit the detrimental effects of AngII in the kidney in naturally occurring CKD in the cat.

Development of resistance

Not applicable.

Pharmacokinetics

The applicant presented a comprehensive pharmacokinetic data package for the cat. Based on the information provided, the following is accepted:

- Telmisartan is systemically rapidly available following oral dosing: plasma levels peak at approximately 20–30 minutes and rapidly decline over the following 4 hours. Oral bioavailability is approximately 30%.
- Food reduces the rate and extent of absorption of the active substance. However, the effect of food intake at, or around, the time of product administration on the plasma kinetics of telmisartan is unlikely to influence the ability to chronically inhibit the action of AngII on the kidney. For much of the interdosing interval (from 4 hours post-dosing onwards), the plasma concentrations recorded in cats treated at, or around, the time of feeding were similar to those found in cats treated in the fasted state. Further, slow dissociation of the active substance from the target site is an important determinant of the extent and duration of AT-1 receptor inhibition and this is not influenced by fed versus fasted state.
- The plasma concentration versus time profile is suggestive of enterohepatic circulation occurring.
- There is no influence of gender on the pharmacokinetic properties of telmisartan in the cat.
- There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose.

- In a number of species (mice, rats and dogs), telmisartan is largely bound to plasma protein (>99.5%)
- Although no radiolabelled studies have been undertaken and so the precise routes of elimination have not been characterised in the cat, the applicant has shown that the cat is capable of efficiently glucuronidating telmisartan, and it seems likely that, as in other species, this is the major route of metabolism of the drug.

It is accepted that the pharmacokinetics of telmisartan in the cat have been adequately described.

Dose determination/justification

See pharmacodynamic section above.

Target animal tolerance

Two target animal safety studies were conducted.

The first was a non-GLP, exploratory study where tolerance of a single dose of 0, 1 or 3 mg telmisartan/kg over a period of 28 days was investigated. Based on the findings of this study, telmisartan appears to have been well tolerated. However, given the exploratory nature of the study, in particular the fact that the number of animals per treatment group was low (n=4/group) and that it relates to a treatment duration of 28 days only, it is not adequate to base any definitive conclusions on target animal safety.

The second was a good quality study conducted in 2008-2009 in the USA in accordance with GLP. The safety of the final formulation (product proposed for marketing) was investigated at doses of 0, 1, 3 and 5 times the maximum daily dose for a treatment period of six months. An adequate number of cats was included in the study (4 male and 4 female per treatment group). The study was appropriately designed to control for any potential bias. The basic design and conduct of the study meets with the VICH target animal safety guideline requirements (CVMP/VICH/393388/2006). It is noted that the test animals were treated after overnight fasting. This is considered appropriate given that fasting is associated with greater systemic exposure (relative to administration with food) and can be considered worst-case (see pharmacokinetics section).

There were no treatment-related adverse effects evident clinically: All clinical observations in the telmisartan groups were noted with similar incidence in the control group; however, they were not noted in a dose-related manner and/or were isolated findings that were considered spurious. Emesis, which was recorded in a number of the pharmacokinetics studies, was noted on very few occasions during the 6 month treatment period and there was no evidence of a treatment related effect. During this study, treatment related effects on blood pressure, red blood cell parameters and appearance of the juxtaglomerular apparatus were recorded. These effects are attributable to the pharmacological activity of the product and, therefore, are not unexpected. Effects were noted at the recommended treatment dose; however, there were no related clinical signs in the test animals (that is, test animals did not show signs of hypotension or clinical anaemia). However, it is considered appropriate that such effects (potential for hypotension and anaemia) are mentioned in the SPC.

The pharmacokinetic data generated in the context of the target animal safety study indicate that systemic exposure to telmisartan (estimated by AUC and C_{max}) was generally higher for females than for males, especially at the 5 mg/kg/day dosage, which is consistent with a majority of the gender differences in toxicity noted in this study. It is noted that the gender differences (in pharmacokinetics) observed in this study were not observed in the pivotal pharmacokinetics study.

For additional information on safety in the target population, see comments on the pivotal field study.

Field trials

Two field studies were presented by the applicant in support of this application.

The first was a limited study and the test population was too small to derive any conclusions with respect to either safety or efficacy.

The second was a good quality, multicentre non-inferiority GCP study of two parallel-group design, conducted at centres in Belgium, Germany, France, Italy, the Netherlands and the United Kingdom.The study was designed to show that telmisartan is as efficacious as an authorised ACE inhibitor containing benazepril to reduce proteinuria in CKD in the cat. The CVMP considered benazepril as a valid reference product for this non-inferiority study because efficacy of benazepril had been established in a randomized placebo controlled study with a similar study design, and in the context of a recent referral procedure under Article 34 of Directive 2001/82/EC, CVMP concluded that "data from clinical trials in conjunction with bibliographic information and experience of clinical experts is regarded to sufficiently support that benazepril treatment is beneficial for cats with CKD and proteinuria... The appropriate harmonised indication should be "Reduction of proteinuria associated with chronic kidney disease".

The study included 224 cats (intention-to-treat (ITT) population) presenting with CKD, the International Renal Interest Society (IRIS) stage IIa to IV, and urine specific gravity (USG) of less than 1.035, but no evidence of other co-morbid condition. Animals were treated once daily with telmisartan (1 mg/kg) or the control (benazeprilat, 0.5 – 1.0 mg/kg bw).

Cats were evenly distributed between treatment groups with respect to age, gender, body weight and breed. In both groups most of the cats were more than 11 years old. Medical history showed that clinical symptomatology suggestive for CKD (e.g. polyuria/polydipsia (PU/PD), reduced appetite, weight loss, and palpably small kidneys) were present for more than 3 months in the majority of cats before inclusion. A proportion of around 30% of cats in both groups were fed a commercial kidney diet when being allocated to the study. The majority of cats (up to 80%) considered suitable for inclusion were classified IRIS stage II (IIa & IIb) (benazepril 91/112, telmisartan 84/112). There were slightly more cats with IRIS stage IIb in the telmisartan group (48 vs. 44 for benazepril) and less than 20% of cats in both groups were staged IRIS III at inclusion. Most of the cats presenting with CKD for inclusion were borderline proteinuric (urine protein:creatinine ratio (UP/C) 0.2-0.4), with hardly any difference between treatment groups (benazepril 89/112 or telmisartan 83/111). As the therapeutic rationale behind treatment of CKD in the cat aims at early management and therapeutic intervention, this ITT-population is considered representative for the target population.

Primary and secondary efficacy analysis was based on the per-protocol-population (PPS) data set, including 176 valid cases (n=85 telmisartan, n=91 benazepril). The primary variable is reduction in proteinuria, calculated by UP/C change from baseline. The statistical analysis for efficacy was based on the PPS-population and the decision on non-inferiority based solely on the confidence interval approach with a predefined lower margin considered clinically relevant. The statistical approach used is considered appropriate.

The effect of telmisartan on proteinuria was non-inferior to benazepril as assessed based on the 2-sided 95% confidence interval approach for the primary efficacy variable: overall mean UP/C values at D180 decreased in both groups when compared to baseline with -0.02 for benazepril and -0.05 for telmisartan. These data would suggest that for the population as a whole, a sustained reduction in proteinuria is not seen and that the effect of both test and reference products is to postpone or delay deterioration in proteinuria. It is noted that subgroup analysis for UP/C ≥ 0.4 demonstrated for telmisartan a significant difference to baseline for proteinuria at all time points (except D120 p=0.0637).

The overall number of treatment failures (death or euthanasia of any cause, owner non-compliance or deterioration of clinical signs requiring hospitalization) was less in the telmisartan groups with 15.3% (13/85) compared to 19.8% (18/91) for benazepril. Telmisartan was well tolerated during the course of the study and frequency and type of adverse events reported was common for CKD and in most of the cases unlikely to be treatment related. Most of the cats survived the scheduled study end, with the number of all cause mortality in telmisartan treated cats being significantly lower (13/112) when compared to benazepril (22/112) (ITT-population). The difference between treatment groups in favour of telmisartan was seen as well when comparing cats being euthanatized because of CKD only (9/112 vs. 14/112). There was no clinical evidence of hypotension, although some cats (benazepril 6/112; telmisartan 10/112) were stabilized on adjunct antihypertensive treatment with amlodipine first before allocation to test treatment. Adjunct treatment with amlodipine was well tolerated as no clinical evidence of hypotension was reported during a six month observation period except in one cat treated with benazepril (reported as showing signs of dizziness one hour after treatment).

Two cats randomly allocated to telmisartan showed extremely high ALT levels during the study. The possibility for increases in liver enzymes in treated animals is mentioned in section 4.6 of the SPC.

Anaemia in cats with CKD is known to be of multifactorial origin, while erythropoietin deficiency has a major role in the pathogenesis. Haematology variables were monitored during the study to assess changes in the red blood cell counts, which might be caused either due to progression of CKD or due to drug interaction with the RAS. At baseline 3.6% cats in the benazepril group and 2.7% cats in the telmisartan cat population had red blood cell counts (RBC) below the lower limit of the reference range. The mean values for red blood cell count (RBC), haemoglobin (HGB) and haematocrit (HCT) were comparable between both treatment groups and within the normal range at the end of the 6 month observation period. The proportion of cats with RBC values below the lower reference limit slightly increased in both groups, with 7.6% for benazepril and 9.5% for telmisartan at study end. In only 2 cats, clinical evidence of anaemia was reported during the study (one in the benazepril group and one in the telmisartan group). Based on the findings of this study, it would appear that the effects of telmisartan on red blood cell parameters observed in the pivotal target animal safety study are of limited clinical relevance.

In addition to the field study, a pilot study was provided to assess telmisartan palatability in the cat. Based on the results of the study, it was concluded that telmisartan as a 4 mg/ml oral solution was well accepted by most cats.

Overall conclusion on efficacy

Two field studies were presented by the applicant in support of this application.

The first was a limited study and the test population is too small to derive any conclusions with respect to either safety or efficacy.

The second was a good quality, multicenter GCP study. The study was designed to show that telmisartan is as efficacious as the comparator, the ACE inhibitor benazepril, to reduce proteinuria in CKD in the cat. The effect of telmisartan when administered at a dose of 1 mg/kg bw, once daily, on proteinuria was non-inferior to benazepril as assessed based on the 2-sided 95% confidence interval approach using the primary efficacy variable reduction in proteinuria, calculated by overall mean urine protein:creatinine ratio (UP/C) change from baseline.

Given that non-inferiority versus benazepril has been accepted for the primary efficacy variable, the CVMP concluded that the indication for the test product should read: 'Reduction of proteinuria

associated with chronic kidney disease (CKD) in cats'. This is identical to the indication considered most appropriate by CVMP for the reference product.

Telmisartan was well tolerated during the course of the study, and frequency and type of adverse events reported were common for the underlying disease (CKD) and in most of the cases unlikely to be treatment related. .

Part 5 – Benefit risk assessment

Introduction

Semintra 4 mg/ml oral solution for cats is an aqueous solution containing 4 mg/ml telmisartan and is intended for oral administration.

The product is presented in HDPE bottles with plug-in adapters and child-resistant closures. A 2 ml measuring syringe which fits directly onto the bottle and has a kg body weight scale is also provided.

The proposed indication is "Reduction of proteinuria associated with chronic kidney disease (CKD) in cats".

The recommended treatment dose is 1 mg telmisartan per kg bw.

Benefit assessment

Direct therapeutic benefit

Telmisartan is a competitive antagonist of Angiotensin II at the AT-I receptor. Blockade of AngII receptors represents an alternative approach to the selective inhibition of the pressor response of the renin-angiotensin system and, therefore, to the reduction of blood pressure. Given its effects on RAAS, it is suggested that telmisartan may have renoprotective effects in cats with naturally occurring CKD, where local (pathological) activation of angiotensin via the RAAS is thought to drive hyperfiltration and glomerular capillary hypertension, resulting in increased amount of protein entering the glomerular filtrate triggering interstitial fibrosis. Based on the pivotal efficacy data provided, it is accepted that the test product is non-inferior to an authorised reference product in terms of effect for the indication 'reduction of proteinuria associated with chronic kidney disease'.

Additional benefits

Telmisartan is a new active substance in the veterinary field.

Blockade of AngII receptors represents an alternative approach to the selective inhibition of the pressor response of the renin-angiotensin system and, therefore, to the reduction of blood pressure. Semintra increases the range of available treatment possibilities for reduction in proteinuria in cats with CKD.

Risk assessment

In the target animal safety study, treatment related effects (on healthy cats) on blood pressure, red blood cell parameters and appearance of the juxtaglomerular apparatus were recorded at the recommended treatment dose (1 mg/kg bw). While there were no related clinical signs noted in cats included in the clinical study (that is, test animals did not show signs of hypotension or clinical anaemia), it is considered appropriate that such potential effects are nevertheless mentioned in the SPC.

Although the reproductive toxicity studies in animals indicate that telmisartan poses no risk to embryos or foetuses at therapeutic doses, clinical experience with the use of ACE inhibitors in man has shown increased risk of foetal and neonatal toxicity and death ("ACE inhibitor foetopathy") when women are exposed to substances acting on the renin-angiotensin-aldosterone-system during the last two trimesters of pregnancy.

There would appear to be negligible risk of toxic effects to the user. Also, given the presentation of the product, it is unlikely under normal conditions of use that children will have access to the product or will be able to open the product if they gain access.

The product is not expected to pose a risk for the environment when used according to the SPC.

Risk management or mitigation measures

Given the possibility for effects on blood pressure, the SPC includes a recommendation that blood pressure should be monitored during anaesthesia of treated animals.

Given the possibility for effects on red blood cell parameters, the SPC includes a recommendation that red cell count should be monitored during therapy.

No reproductive toxicity studies investigating the use of telmisartan in the target species have been conducted. It is unclear whether or not telmisartan may pose a risk of "ACE inhibitor foetopathy" if administered during pregnancy in the cat. For these reasons, the product is contraindicated for use in cats during pregnancy, and the SPC and product information includes a recommendation that pregnant women should avoid contact with the product.

A number of other user safety statements are also included in the SPC and product literature.

Evaluation of the benefit risk balance

The formulation and manufacture of Semintra is well described and specifications set will ensure that product of consistent quality will be produced.

It is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings have been included in the SPC and product literature.

The product has been shown to be efficacious for the indication "reduction of proteinuria associated with chronic kidney disease (CKD) in cats".

The CVMP therefore concluded that the product has been shown to have a positive benefit/risk balance overall.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy Semintra are considered to be in accordance with the requirements of Directive 2001/82/EC, as amended. The overall benefit/risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.