15 March 2018
EMA/186850/2018
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Semintra to add new strength 10 mg/ml oral solution for cats to treat systemic hypertension (EMEA/V/C/002436/X/0008)

International non-proprietary name: telmisartan

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

The applicant Boehringer Ingelheim Vetmedica GmbH submitted on 15 May 2017 an application for an extension to the marketing authorisation for Semintra to the European Medicines Agency (The Agency) in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof.

Semintra contains telmisartan as an active substance, an angiotensin II antagonist, antihypertensive, and was first authorised in the EU on 13 February 2013 as an oral solution (4 mg/ml) for use in cats for the reduction of proteinuria associated with chronic kidney disease (CKD).

This extension application is to add a new strength (10 mg/ml) and a new indication (treatment of systemic hypertension in cats). This strength is to be presented in packs of 1 bottle containing 35 ml oral solution.

The rapporteur appointed is Rory Breathnach and the co-rapporteur is Cristina Muñoz Madero.

The dossier has been submitted in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I point 2c, change or addition of a new strength, thereof (extensions).

On 15 March 2018, the CVMP adopted an opinion and CVMP assessment report.

On 8 May 2018, the European Commission adopted a Commission Decision granting the extension to the marketing authorisation for Semintra.

Scientific advice

The applicant received scientific advice from the CVMP on 11 April 2013 (EMA/CVMP/SAWP/46625/2013), with a clarification on 18 July 2013 (EMA/CVMP/SAWP/420823/2013). The scientific advice pertained to efficacy issues, specifically the conduct of the pivotal EU field study. In terms of basic study design, it is accepted that the applicant followed the scientific advice of the CVMP; however, the approach to determining a clinically relevant effect of treatment that was applied in the study differed to the advice given. This is commented on further in Part 4.

MUMS/limited market status

The applicant requested classification of this application as MUMS/limited market by the CVMP, and the Committee confirmed that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) data requirements would be applied when assessing the application. MUMS/limited market status was granted in view of the low prevalence of feline hypertension and the treatment of systemic hypertension in cats is therefore considered a minor use/limited market.

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

Manufacture of the dosage form takes place outside the EEA. The site has a GMP Certificate issued by the German competent authority, issued following an inspection in October 2015.

Secondary packaging takes place within the EU at a site which holds a GMP Certificate issued by the German competent authority, issued following an inspection in February 2015.

Import into and batch release within the EU takes place at Boehringer Ingelheim Vetmedica GmbH, Ingelheim am Rhein, Germany, which holds a GMP Certificate issued by the German competent authority, issued following an inspection in October 2014.

A declaration has been provided from the QP of the batch release site stating that the active substance, telmisartan, is manufactured in accordance with GMP requirements for starting materials. The QP declaration is made following an audit of the site in October 2016. GMP certification for the site, issued by a competent authority within the EU on foot on an inspection in June 2015, is also provided for the site. The active substance telmisartan is listed on this GMP certificate.

The active substance is supported by a Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM).

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered 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.

Part 2 - Quality

Composition

The proposed veterinary medicinal product contains 10 mg/ml telmisartan in an aqueous solution with benzalkonium chloride as a preservative. The product may also contain sodium hydroxide and hydrochloric acid as pH adjusters. Hydroxyethylcellulose and maltitol are also included to enhance viscosity.

Containers

The product is presented in 45 ml (35 ml nominal content) translucent high density polyethylene (HDPE) bottles with translucent low density polyethylene (LDPE) plug-in adapters and white polypropylene child-resistant closures with white polyethylene sealing disks.

A 2 ml oral syringe marked with 0.1 ml graduations is also provided. The syringe consists of a translucent polypropylene body and a red HDPE plunger. This syringe, with a red plunger, can only be connected to the plug in adaptor of the 10 mg/ml strength and will not fit the 4 mg/ml bottle which is supplied with a syringe with a blue plunger to further differentiate between the two strengths.

Development pharmaceutics

Other than the concentration of active substance, the formulation of this 10 mg/ml solution is identical to that of the authorised 4 mg/ml solution.

All the excipients are commonly used in veterinary medicinal products. Sodium hydroxide and hydrochloric acid are used in the formulation for pH adjustment. Hydroxyethylcellulose and maltitol are viscosity enhancing excipients that are used to ensure that the formulation can be accurately and conveniently delivered by means of an oral syringe. Benzalkonium chloride is included as an antimicrobial preservative.

Compliance of this formulation with the European Pharmacopoeia (Ph. Eur.) requirements for preservative efficacy was confirmed.

The pivotal EU trial used the authorised 4 mg/ml strength formulation rather than the 10 mg/ml strength proposed in this application. As the formulations are identical apart from the strengths, the use of the lower strength in the pivotal EU trial has been accepted based on bioequivalence studies carried out which demonstrated that the two strengths are bioequivalent.

Method of manufacture

The product is a standard pharmaceutical form and the production process utilises standard pharmaceutical manufacturing techniques and equipment. Detailed descriptions of the manufacturing process have been provided. A process validation scheme has been provided, the content of which is in accordance with the requirements in the Process validation guideline for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev. 1).

Control of starting materials

Active substance

The active substance, telmisartan, is monographed in the Ph. Eur. and a Certificate of Suitability (CEP) to the monograph of the Ph. Eur. has been provided for the active substance. Certificates of Analysis have been provided for three batches of active substance manufactured at the active substance manufacturing site. All results for the batches were compliant with the requirements of the Ph. Eur. monograph and the CEP.

A re-test period of 5 years is applied to the active substance when stored in double LDPE bags in fibre drums, as detailed on the CEP.

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 for this particular 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

Specifications have been set for appearance, colour and clarity of solution, relative density, pH, identification of the active and of the preservative, assay of the active and of the preservative, related substances, fill volume and microbiological quality. The proposed specification is acceptable and includes parameters relevant to the dosage form. The methods provided have been described in sufficient detail and appropriate method validation provided. Finished product batch analysis data has been provided for three commercial scale batches, with all results within specification. Details of the reference standards are provided.

Stability

Stability data is presented for three pilot scale batches and three commercial scale batches packaged in the market containers (45 ml HDPE bottle (nominal content 35 ml) with LDPE plug-in adapter and polypropylene closure).

All results for appearance, colour and clarity of solution were within the proposed limits. For all batches the results for assay of the active substance remained within specification 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.

In-use stability testing was carried out on 2 pilot scale batches of the product filled into the market packs. Samples were tested from one batch at the beginning of shelf life (6 months data available) and from the second batch approaching end of shelf life (3 months data available, but the study will continue to 6 months). Samples were stored at 25 ^{o}C/60% RH and sampling was designed to simulate use of the product. Although the in-use stability study on the aged batch is not yet complete, the data provided is considered adequate to support the proposed in-use shelf life of 6 months as no adverse trends are observed and the results for the aged batch 6 months following opening can reasonably be expected to remain within specification.

A photostability study was performed in line with the requirements of VICH GL5 (Photostability

Testing of New Veterinary Drug Substances and Medicinal Products). All results were within the proposed end of shelf life specifications and no differences were observed between the light samples and dark controls. Based on the available stability data, the proposed shelf life of 2 years and in-use shelf life of 6 months with no special storage conditions, as stated in the SPC, are acceptable.

Overall conclusions on quality

The dossier provides a suitable description of the chosen formulation, 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 full scale validation will be performed post-approval.

The data relating to the active substance is provided in the form of a CEP which also specifies a retest period of 5 years. The excipients used in the manufacture of the finished product are all of pharmacopoeial grade and so are acceptable. The container-closure system chosen is suitable for the dosage form and the product and is specifically designed to avoid dosing errors between this product and the authorised 4 mg/ml oral solution.

The finished product specification provides assurance of the quality of the product and the tests comply with the requirements of the Ph. Eur. for the dosage form. The analytical methods are adequate, and their validation data confirm their suitability.

Stability studies on the finished product have been performed according to VICH guidelines and support the proposed shelf life of 2 years with no specific storage precautions. In-use stability studies in line with the requirements of the CVMP guideline on In-use stability testing of veterinary medicinal products (EMEA/CVMP/424/01) have been provided to support an in-use shelf life of 6 months, with one study still remaining to be completed through to 6 months. A photostability study demonstrated that no storage conditions are required regarding protection from light.

Part 3 – Safety

Safety documentation

This application concerns an extension to an already authorised veterinary medicinal product, Semintra 4 mg/ml oral solution, which is indicated for cats for the reduction of proteinuria associated with chronic kidney disease (CKD). The applicant is proposing a new indication for cats, i.e. systemic hypertension. As the single doses in this indication are higher compared to the CKD related indication, the applicant also developed a higher strength (10 mg/ml) of the oral solution. Other than the concentration of active substance, the formulation of this 10 mg/ml oral solution is identical to that of the authorised 4 mg/ml oral solution.

As the source of the telmisartan active, the pharmaceutical form (oral solution) and the administration route (oral) are the same as in the 4 mg/ml strength presentation, cross reference is made to the safety data package submitted in support of the marketing authorisation application (MAA) for Semintra 4 mg/ml oral solution, and no new basic pharmacology or toxicology data are presented. However, given the higher strength presentation (10 mg/ml), the applicant has provided an updated user safety assessment and an environmental risk assessment.

Tolerance in the target species of animal

See Part 4.

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 have been described in some detail (see final CVMP assessment report for Semintra (EMEA/V/C/002436)). Information on the efficacy and safety assessment of telmisartan in human patients is also available in the EPAR for Micardis (marketing authorisation holder is also Boehringer Ingelheim), a medicinal product for human use. In the Micardis EPAR it is concluded that telmisartan "has been found to be safe and well tolerated" in humans. In respect of post-authorisation experience, the following is stated:

"Since the introduction of telmisartan in the market, cases of 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 is likely to be low. The worst-case dermal exposure was estimated to be 1.4 mg telmisartan per person (based on treatment of a 7 kg cat at a dose of 2 mg/kg (total dose of 14 mg), with the user exposed to 10% of the product) or 0.0233 mg/kg for a 60 kg individual.

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. Although the quantitative risk characterisation results in a slightly higher risk for the 10 mg/ml strength compared to the 4 mg/ml strength, it is accepted that this has no impact on the overall risk management for users because the margins of exposure are acceptably high. The normal oral therapeutic dose of telmisartan for essential hypertension in human patients is 40 (-80) mg per day. This approximates

to 0.67 to 1.3 mg/kg bw/day or to 34 to 67 fold the possible oral dose arising from skin contamination.

In terms of risk management, it is noted that the product will be subject to prescription and is supplied in child-resistant containers. 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.

In conclusion, the product is not considered to 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 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.

Residues documentation

Not applicable.

Overall conclusions on the safety documentation

Cross-reference has been made to pharmacology and toxicology studies, which have been submitted and assessed in support of the initial application for Semintra 4 mg/ml oral solution; this is considered acceptable. 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. 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 environmental risk assessment (ERA) can stop at Phase I. Semintra is not expected to pose a risk for the environment when used according to the label recommendations.

Part 4 – Efficacy

Semintra is already authorised as an oral solution (4 mg/ml) for cats for reduction of proteinuria associated with chronic kidney disease (CKD). The purpose of the current application is to add a new indication and a higher strength (10 mg/ml): "systemic hypertension".

Hypertension is reported to affect an increasing proportion of the cat population as it ages. The underlying aetiology of hypertension may be primary or secondary. Primary hypertension is also known as idiopathic hypertension. The pathogenesis of idiopathic hypertension in cats is not well

understood and it is a diagnosis of exclusion, thought to be linked to an abnormality of kidney function. Hypertension may develop secondary to a number of disease processes including CKD, hyperthyroidism and diabetes mellitus. Untreated hypertension can lead to target organ damage (TOD). TOD includes sudden onset blindness, proteinuria, progressive chronic kidney disease, left ventricular hypertrophy, and brain pathology (stroke).

At the time of submission the guidelines developed by the veterinary International Renal Interest Society ("IRIS guidelines") recommend that systolic blood pressure measurements above 160 mmHg are considered hypertensive and indicate a moderate to severe risk of TOD. A consensus statement made by the American College of Veterinary Internal Medicines (ACVIM) on hypertension recommends treatment of hypertension in cats where the perceived risk of TOD is significant or TOD is evident. Citing eight studies conducted measuring systolic blood pressure via the intra-arterial route, oscillometry and Doppler ultrasonography in normal cats, systolic blood pressure was determined to range from 115 mmHg to 162 mmHg, with the combined average from all studies being 132 mmHg.

Pharmacodynamics

Telmisartan is an angiotensin II (Ang II) receptor (subtype AT_1) antagonist. Telmisartan displaces Ang II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of Ang II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by Ang II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin mediated adverse effects.

In humans, an 80 mg oral dose of telmisartan almost completely inhibits the Ang II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

The pharmacodynamics of telmisartan have been investigated in the cat (*in vitro* and *in vivo*). The relevant studies have been previously assessed in the context of the initial application for marketing authorisation for Semintra 4 mg/ml oral solution for cats, and are summarised below:

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

In vivo data from two other non-GLP pilot studies investigating the effects of different doses of telmisartan (intravenous or oral) on anaesthetised cats provide further evidence of an Ang II antagonist effect in the cat. The studies were designed to evaluate the ability of telmisartan to inhibit the pressor response to exogenously administered Ang II. While the importance of angiotensin receptor activation in the pathophysiology of hypertension in the cat is not well studied, it can be considered that the model of intravenous infusion of Ang II to raise systemic blood pressure is a logical one to determine the potency and efficacy of telmisartan as an antihypertensive agent.

- One study was conducted to investigate the effects of an escalating intravenous dose of telmisartan on the blood pressure response of anaesthetized cats after administration of Ang II. This was a non-GLP pilot study and was limited in terms of numbers of animals included. Notwithstanding the limitations of the study, the overall conclusions are accepted: escalating intravenous doses of the test article led to an inhibition of the diastolic blood pressure increase in anaesthetised cats after administration of Ang II.
- Another other was conducted to investigate the PD and PK profile of telmisartan in anaesthetized cats following oral administration of the test compound (1 mg/kg or 3 mg/kg) or placebo for 7 consecutive days. Again, this was a non-GLP study, pilot in nature, conducted in a limited number of test animals using a prototype of the final formulation. In this study, the primary pharmacodynamic endpoint was diastolic blood pressure response. The findings of the study demonstrate that telmisartan at doses of 1 and 3 mg/kg significantly and persistently (up to 24 hours at both doses) inhibited the systemic pressor effect of Ang II in the anaesthetized cat.

These data provide evidence of an Ang II antagonist effect and support further development of this product as an anti-hypertensive agent.

Telmisartan as an angiotensin receptor blocker (ARB) has been demonstrated to have an antiproteinuric effect via antagonism of angiotensin at the AT-1 receptor. Proteinuria is a common presentation in cats with CKD and also a negative prognostic indicator of survival. The mechanism of reducing protein excretion in the urine is unknown. However, it is hypothesised that the proteinuria is due to a lack of functioning nephrons causing the renin–angiotensin–aldosterone system (RAAS) to drive hyperfiltration resulting in urine protein excretion and the ARB interferes with this mechanism. No data are presented in the dossier on the potential for telmisartan to interact with other drug substances. However, it is recognised that the administration of telmisartan with substances that interfere with RAAS could give rise to reduced glomerular filtration rate (GFR) (and worsening azotaemia) and hypotension (which would contribute to the azotaemia). In human medicine, although the combination of angiotensin converting enzyme (ACE) inhibitors and ARBs is used, caution has been suggested and close monitoring of plasma creatinine and potassium is necessary. Further, the administration of telmisartan in combination with other anti-hypertensive agents (e.g., amlodipine) has the potential to result in hypotension. An appropriate warning has been added to section 4.8 of the SPC for Semintra 10 mg/ml oral solution: "Very limited data are available regarding interactions in cats with hypertension between telmisartan and other medicinal products that lower blood pressure (such as amlodipine) or interfere with the RAAS (such as ARBs or ACEis). The combination of telmisartan with such agents may lead to additive hypotensive effects or may alter renal function."

Development of resistance

Not applicable.

Pharmacokinetics

The target species pharmacokinetic data presented in this dossier are the same studies that were presented in the dossier for telmisartan as an antiproteinuric agent where the target dose in cats was 1 mg/kg bw. In the original marketing authorisation application, the applicant presented

a comprehensive pharmacokinetic data package for the cat, and the following was accepted by the CVMP:

- 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 Ang II 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.

The applicant made cross-reference to these data, and justified not undertaking a comprehensive new PK analysis of the telmisartan 10 mg/ml formulation as they also conducted two bioequivalence studies (a pilot studyand one pivotal study, BIV 2014367), confirming that the 4 mg/ml and the 10 mg/ml formulations are bioequivalent.

The pivotal bioequivalence study was a GLP-compliant study conducted in accordance with relevant CVMP guidance (EMA/CVMP/016/00 – Rev.2), comparing plasma concentrations and pharmacokinetic parameters of telmisartan following a single oral administration of telmisartan 10mg/ml oral solution (test item) and 4 mg/ml oral solution (reference item) at the recommended target dose of 2 mg/kg body weight. The study was conducted in 2016 in France in 24 healthy cats (12 neutered males and 12 females, aged 45–133 months), involving a single-dose, two-sequence, cross-over design with randomization of experimental units to two treatment sequence groups (14 days apart). The test or reference items were administered directly into the mouth, using the oral dosing syringe provided. Blood samples were collected from before dosing, and up to 48 h post-dose.

Telmisartan plasma concentrations increased to reach the maximal concentration (C_{max}) between 0.25 and 1 h. This phase was followed by a rapid decline of concentration. The elimination phase was similar for both groups with an apparent terminal half-life of approximately 7 to 8 h. Mean ± standard deviation of the pivotal PK parameters (n=24) for telmisartan were:
10 mg/ml: C_{max} 282 ng/ml (± 138), AUC_{0-t} 310 ng.h/ml (± 131) and t_{max} 0.38 h [0.25-1.00],
4 mg/ml: C_{max} 283 ng/ml (± 128), AUC_{0-t} 296 ng.h/ml (± 114) and t_{max} 0.27 h [0.25-1.03].

Statistical analysis of the data generated in this study demonstrated bioequivalence of the two strengths: for both AUC_{0-t} and C_{max}, bioequivalence was achieved based on the accepted limits of

80% to 125%. Accordingly, the CVMP agreed that the pharmacokinetic, target animal safety and field safety and efficacy data generated with the Semintra 4 mg/ml formulation can be extrapolated to the new Semintra 10 mg/ml formulation.

Dose justification

A combination of laboratory studies and a pilot field study examining the antihypertensive effect of telmisartan at doses between 1–3 mg/kg bw, together with observations from the target animal safety study and a previously undertaken field safety and efficacy study designed to examine the effect of the telmisartan on proteinuria have been used by the applicant to determine the optimal dose to be further examined in a new field study designed to evaluate the antihypertensive effects of the telmisartan. The aim of the dose selection was to establish a dose that could produce an obvious blood pressure lowering effect within 14 days of starting treatment. This is recommended by the ACVIM consensus statement on hypertension.

Laboratory study: Pharmacodynamic and pharmacokinetic investigations in the anaesthetized cat following repeated oral administration (referenced in the pharmacodynamics section above, and submitted and assessed previously in the context of the initial application for Semintra 4 mg/ml).

This non-GLP study demonstrated a persistent (>24 hours) and substantial (approximately 50%) inhibition of the pressor effect of Ang II following administration of telmisartan at 1 and 3 mg/kg orally for 7 consecutive days once daily. 24 hours after the last oral dosing, telmisartan was administered intra-duodenally, in anaesthetised cats, and plasma concentration and diastolic blood pressure was determined at set time points. The results suggested that doses of telmisartan within this range should be able to inhibit the detrimental systemic effects of Ang II in naturally occurring hypertension in the cat. However, there were a number of limitations to this study; the limited number of test animals and use of a prototype of the final formulation (differing in amount of active substance and excipient content).

Pilot field study: Pilot clinical field study evaluating the oral dose of telmisartan for the control of hypertension and proteinuria associated with chronic kidney disease in cats (submitted and assessed previously in the context of the initial application for Semintra 4 mg/ml).

This was a blinded, randomised, placebo-controlled clinical field study conducted in the US at five independent sites. Telmisartan oral solution was administered to 9 cats at a dose of 1 mg/kg once daily for up to 56 days. UPC ratio, blood pressure and secondary parameters were measured at day -14, 0, 14, 28, 42 and 56. No significant changes were seen in UPC. Although significant reductions in SBP were seen in the treatment group, much of the reduction was seen in the acclimation period for the telmisartan cats. The reduction in blood pressure from the start of treatment to the end did not demonstrate a statistically significant difference between groups.

Telmisartan was well tolerated. Vomiting and anorexia were slightly more common in the telmisartan group, but CKD influences and the small population size preclude a conclusion on association with treatment.

Dose determination study: Pilot dose determination study of telmisartan for reduction of systolic blood pressure (SBP) in healthy laboratory cats in a 14 day period.

The purpose of this study was to evaluate the potential effectiveness of multiple oral doses and dose strategies of telmisartan in clinically normal healthy laboratory cats on the reduction of SBP within a 14 day time period. A secondary objective was to observe the effect of reducing the dose to 1 mg/kg

after treatment. The study was conducted using 28 adult, healthy cats. The doses of telmisartan investigated were placebo once daily (SID), 1 mg telmisartan/kg bw SID, 1 mg/kg bw twice daily (BID), 1.5 mg/kg bw SID, 1.5 mg/kg bw BID, 2 mg/kg bw SID, 3 mg/kg bw SID.

Although the study was designed as a cross-over design, so each cat would act as its own control, the washout period proved insufficiently long to allow blood pressure to re-establish its baseline and a period effect was detected with the statistical analysis. This finding resulted in the study being assessed as a parallel group design and the number of cats in each group being reduced to 4 (from the originally intended 12). Another limitation of the study is that the resting blood pressure of cats is probably minimally influenced by the RAAS system and so the decrease in blood pressure seen when Ang II is competitively antagonised by telmisartan is likely to be small. Notwithstanding the limitations of the study, the findings suggest that doses of ≥2 mg/kg produce an antihypertensive effect within a 14 day period and that single daily dosing is just as effective as dividing the dose and giving it in two equal portions.

The data derived from the studies discussed above do justify an oral dose rate of 2 mg/kg once daily as the starting dose in a pivotal clinical trial. While an oral dose of 1 mg/kg once daily may be adequate to effect a reduction in SBP, the available data suggest that this dose is not likely to provide adequate antihypertensive effects over the time period that one would expect to achieve blood pressure control in a clinical patient (14 days based on the ACVIM Consensus Statement on Hypertension).

Target animal tolerance

The applicant made cross-reference to the target animal safety data already submitted and assessed by the CVMP for the initial application for Semintra (4 mg/ml) in doses up to 5 mg/kg bw, i.e. 2.5 x the recommended treatment dose (RTD) for the new strength (see below).

Although the proposed new strength (10 mg/ml) for the new indication (management of feline hypertension) is used at a higher dose rate (2 mg/kg SID as opposed to the currently authorised 1 mg/kg SID dose rate for management of proteinuria in cats with CKD), the applicant justified the extrapolation to already existing data as follows:

a. The two strengths (4 mg/ml and 10 mg/ml) have been shown to be bioequivalent (see above),

b. Treatment of hypertension in cats is classified as "minor use",

c. The toxicity of telmisartan is well characterised in rodents and dogs as part of the human drug development programme and no major concerns were raised by these extensive studies,

d. The 3Rs issue of looking at higher doses in healthy cats should be taken into account given points (a) to (c).

In addition to these considerations, the product has been examined in two large field safety and efficacy trials in the target group of cats in which the product was administered at the recommended dose of 2 mg/kg bw for the treatment of hypertension.

Given the arguments presented, the absence of further experimental target animal species safety studies to evaluate 3x RTD or 5x RTD of the hypertensive dose (2 mg/kg) is considered justified. In addition, evaluation of safety in the context of large scale, placebo-controlled field studies in diseased cats is likely to provide more useful/relevant safety information than repeating overdose studies in healthy, normotensive cats.

Target animal safety studies

Two target animal safety studies were conducted and assessed by the CVMP as part of the previous application. The CVMP's conclusions on those studies are as follows:

Safety study: This 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.

Safety Study: This was a good quality study conducted in 2008–2009 in the USA in accordance with GLP. The safety of Semintra oral solution (4 mg/ml) was investigated at doses of 0, 1, 3 and 5 mg telmisartan/kg for a treatment period of six months (that is, 0, 0.5, 1.5 and 2.5 times the RTD for the new hypertensive indication). An adequate number of cats were 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.

Safety findings in the field studies

As noted above, the TAS studies are supplemented with data from two field studies where safety and efficacy was evaluated in the target group of cats with the disease (feline hypertension). For details on the study design, see "Clinical studies".

European Field study

This was a GCP, prospective, double-blind, randomised, placebo-controlled clinical field study conducted in 2014–16 in 24 centres in Germany, 9 in France, 11 in UK, 4 in Netherlands, 3 in Switzerland. The objective of this study was to evaluate the efficacy of Semintra 4 mg/ml oral solution for the treatment of systemic hypertension in cats over a placebo controlled 28-day

treatment period (efficacy phase. Cats received either telmisartan at a dose of 2 mg/kg or placebo orally once a day for 28 days. At the end of the efficacy phase, cats on telmisartan with SBP ≤200 mmHg continued into the "extended use phase") for a further 92 days. The safety population (SAF) consisted of 294 cats (194 in the telmisartan and 100 in the placebo control group).

A total of eight cats required euthanasia (n=7 telmisartan-treated cats; n=1 placebo-treated cat) or died (n=1, telmisartan group) during the study. A similar proportion of cats in both treatment groups were euthanized during the efficacy phase (n=2 telmisartan-treated cats (1%); n=1 placebo-treated cat (1%)). All other cats (n=6) either died or were euthanized during the extended use phase. Four of these 6 cats died or were euthanized because of kidney disease.

During the efficacy phase, adverse events (AEs) were recorded in 29% of cats in the telmisartan group and 29% of cats in the placebo group. While there was no difference in terms of incidence of AEs overall, some differences were observed between groups in the following categories: renal and urinary disorders (n=15 cats (7.7%) in the telmisartan group vs n=1 cat (1%) in the placebo group), eye disorders (n=4 cats (2.1%) in the telmisartan group vs n=7 cat (7.0%) in the placebo group), systemic disorders (n=25 cats (12.9%) in the telmisartan group vs n=3 cat (3.0%) in the placebo group) and respiratory tract disorders (n=10 cats (5.2%) in the telmisartan group vs n=1 cat (1%) in the placebo group). The applicant suggests that the difference in the above mentioned disorders was related to various non-frequent medical conditions which are typical for the included feline population except for respiratory tract disorders. This point is acknowledged, but noting the differences between groups in relation to death (see above) and renal/urinary disorders, the available data appear to suggest a telmisartan-related effect on renal function.

It is noted that, during the efficacy phase, a lower percentage of cats in the telmisartan group (n=4, 2.1%) were diagnosed with severe hypertension compared to the placebo group (n=4, 4%) suggesting an effect of treatment. After 28 days of treatment with telmisartan, there appears to be a slight decrease in erythrocytes, PCV and haemoglobin (however, by Day 120 there is evidence of recovery). This change is associated with the known pharmacological effects of the product.

During the extended use phase, 32% of cats had at least one AE. The most commonly reported AEs related to digestive tract disorders (n=29, 14.9%) followed by systemic disorders (n=20, 10.3%). Renal and urinary tract disorders were recorded in 7 (3.6%) of telmisartan treated cats. In the absence of a comparator group, it is difficult to determine the association with treatment. However, an effect on renal function cannot be excluded. Further, it is noted that digestive tract disorders (vomiting, diarrhoea) are listed in the SPC as possible adverse effects of telmisartan.

In conclusion, it is accepted that the adverse effects reported in this study are likely to be typical for the target feline population (aging population, many of which have underlying medical conditions in particular CKD and hyperthyroidism); however, for certain categories, there is a clear difference between telmisartan treated cats and placebo during the first 28-days of the study suggesting a treatment related effect for some of the AEs observed. One concern is that initiation of therapy with telmisartan may reduce GFR adversely affecting renal function. Based on the safety findings of the efficacy phase of the study, there does appear to be a treatment related effect on renal function.

First American field study

The efficacy and safety of Semintra 4 mg/ml oral solution for the treatment of systemic hypertension in cats was evaluated over a 28 day period. This was a GCP, prospective, double-blind, randomised, placebo-controlled clinical field study conducted using client owned cats in the US and Canada at 20 independent sites. Cats in the telmisartan group were started on a dose of 1.5 mg/kg twice a day

(BID) for 14 days, tapering to 2 mg/kg SID or lower (if hypotensive) after 14 days as a maintenance dose.

The safety population consisted of 288 cats (192 in the telmisartan group and 96 in the control group) of which half had pre-existing chronic kidney disease. The overall incidence of serious adverse events in both groups was similar, 12% in the telmisartan group and 10.4% in the control group. It is accepted that the age of the population and the incidence of concurrent diseases are likely to be the basis for the majority of SAEs across treatment groups. However, it is noted that acute renal failure, elevated blood urea nitrogen (BUN) and death were seen twice as frequently, leucocytosis and anaemia three times as frequently, and hypotension four times as frequently in the telmisartan group than the control group.

Treatment with ARBs can lead to a worsening of azotaemia and the associated clinical signs by lowering GFR, particularly in those cases that are close to decompensating due to dehydration and reduced renal perfusion. In this study, there were six cases of deterioration in renal function associated with telmisartan treatment: three were considered not related to telmisartan use as primary active disease was found in the kidneys at post-mortem and, for the other three, additional complications were reported (one cat had diabetes, the other urinary tract stones and the other inadvertently was on an ACE inhibitor as well as telmisartan). While it is accepted that telmisartan may not have been the sole reason for deterioration in renal function in these cases, it cannot be excluded that it was a contributory factor. Information pertaining to the potential for such effects is included in section 4.5 and section 4.6 of the SPC. It is noted that for one cat deterioration in renal function was attributed to telmisartan when administered in conjunction with an ACE inhibitor. While the safety of telmisartan when administered in conjunction with other substances that are known anti-hypertensive agents or have the potential to lower blood pressure has not been investigated, appropriate information/warning statements have been included in section 4.8 of the SPC.

Anaemia was identified at a higher incidence in the telmisartan group than in the placebo group. Such an effect was not noted in the EU field study. While it is accepted that the anaemia may be due to worsening kidney disease (in those cats with CKD), it is a known adverse effect of telmisartan (reduction in red cell mass is a class effect of the substance known from the TAS studies). The findings from this study show that anaemia is a possible adverse effect of telmisartan. The SPC includes a statement to the effect that red blood cell count should be monitored during therapy.

In this study, four cats suffered an episode of hypotension and all were in the telmisartan group. Hypotension is a known potential adverse reaction to telmisartan although the applicant's clinical expert suggests that all 4 cases appeared to have other problems that will have contributed to their susceptibility to hypotension occurring (e.g. concomitant ACE inhibitor therapy; traumatic intestinal perforation). It is noted that section 4.10 of the proposed SPC includes the following statement: "In the event that hypotension does occur, symptomatic treatment, e.g. fluid therapy, should be provided."

In relation to non-serious adverse events, vomiting (21.9 vs. 13.5%), diarrhoea (8.3 vs. 3.1%) and lethargy (3.6 vs. 1%) were different between groups occurring more often in the telmisartan treated cats. If vomiting was divided into cats exhibiting single episodes (transient vomiting) and those cats that had multiple episodes the difference between the telmisartan and placebo group was mostly in the group that had multiple episodes (5.7 vs. 2.1%) suggesting that there may be some cats that vomit on multiple occasions associated with telmisartan administration. It is noted that vomiting and diarrhoea are known adverse effects associated with telmisartan therapy and the potential for such effects to occur is included in section 4.6 of the SPC.

Second American field safety study

At the end of the first American field study, cats on telmisartan with SBP ≤180 mmHg continued into the "extended use phase" for a further 5 months. The objective of this pivotal study was to evaluate the 6 month safety of telmisartan oral solution administered orally at a maintenance dose of 2 mg/kg SID to client owned cats for the control of hypertension associated with chronic kidney disease.

107 hypertensive cats of average age 14 years, various breeds, male and female, neutered and unneutered, were included in the study.

34 serious adverse events occurred in 24 (22.4%) cats. Of the 24 cats experiencing SAEs, 7 reported multiple SAEs and 21 of these cats were also CKD cases. The SAEs most commonly reported include weight loss, anaemia and lethargy. Four cases were rescued due to hypertension and five were reported with hypotensive episodes.

Eleven SAEs were determined to be possibly attributable to telmisartan. Of these eleven, three of these related to worsening of renal function, five were related to anaemia, one related to worsening elevation of liver enzymes and weight loss. Overall of those SAEs assigned a causality of possibly/unknown (10.3% of the study population) the most frequently noted are anaemia (5.6%), weight loss (4.7%), and lethargy (4.7%). 88.9% of these cases were amongst the CKD subpopulation. Those AEs mentioned are as highlighted by the applicant common findings in geriatric cats, particularly those with CKD.

Of the 13 cats which died or were euthanised (some of which were after completion of the study) 4 were due to renal failure. The others comprised of the following pathologies; nephritis (2), carcinoma (3), lymphoma (2) and paralysis.

Overall the adverse events seen in this extended study are in line with those noted in the other field studies conducted as part of this application. It is accepted that in the absence of a placebo group and in view of the demographic of the study population (geriatric cats with comorbidities, 68.2% with concurrent CKD), there are challenges in determining a causal association with the test product.

Clinical field trials

Dose confirmation

None conducted. Efficacy of the proposed dose/dosing schedule was evaluated in the context of a field study. This is acceptable for a MUMS application.

Clinical studies

The applicant provided three GCP field studies in support of the safety and efficacy of telmisartan when administered to cats for the treatment of systemic hypertension, one conducted in the EU and one conducted in the USA and Canada.

In the first EU study, telmisartan was administered at an oral dose of 2 mg/kg once a day. This dose/treatment interval reflects the proposed recommended treatment dose for the EU authorisation and, therefore, this is considered the pivotal field safety and efficacy study. The American field study was conducted over 28 days using a different dosing schedule (1.5 mg telmisartan BID, reducing to 2

mg SID) and, therefore, is considered supportive only. A second American field study ("extended phase") investigated the field safety over 5 months.

Pivotal EU Field study

This was a GCP, prospective, double-blind, randomised, placebo-controlled clinical field study conducted in 24 centres in Germany, 9 in France, 11 in UK, 4 in Netherlands, 3 in Switzerland. The objective of this study was to evaluate the efficacy of Semintra 4 mg/ml oral solution for the treatment of systemic hypertension in cats over a placebo controlled 28-day treatment period (efficacy phase). Additionally, the effect and safety of telmisartan on systolic blood pressure (SBP) control over an extended treatment period of 92 days was evaluated (extended use phase). The applicant had previously asked for a scientific advice on the study design, and in terms of basic design, the applicant followed the scientific advice of the CVMP.

294 hypertensive cats of average age 13 years, various breeds, male and female, neutered and unneutered, were enrolled in the study. The primary inclusion criterion was cats presenting with a mean SBP of between 160 mmHg and 200 mmHg. During the efficacy phase, SPB was evaluated on days 0, 14 and 28. Blood pressure was measured according to the ACVIM guidelines.

Cats were allocated to treatment group on a 2:1 basis, telmisartan: placebo. Both groups were consistent regarding breed, gender, age, body weight, baseline mSBP, medical history and classification of hypertension. For those cats in the ITT population, the aetiology of the hypertension was classified as due to: CKD (n=87; 30.5%), CKD and controlled hyperthyroidism (n=14; 4.9%), controlled hyperthyroidism (n=21; 7.4%) and idiopathic (n=163; 57.2%). As noted by the applicant's clinical expert, the population of cats diagnosed with idiopathic hypertension was surprisingly high (much higher than that reported in the literature and twice that reported in the US field study (29.1%)). In response to a question on this point, the applicant clarified that the difference in the proportion of cats diagnosed as idiopathic hypertension (a diagnosis of exclusion) between the EU and US studies is linked to a difference in the definition of CKD applied in the two studies. When the test population in the EU study are re-categorised using the CKD definition applied in the US study, the proportion of animals categorised as idiopathic hypertension is more in line with the findings of the study conducted in the US and studies in the public domain. Based on the clarification provided, it can be accepted that the test population is representative for the target population.

Cats received either telmisartan at a dose of 2 mg/kg or placebo orally (directly into the mouth or with a very small amount of food) once a day for 28 days, using a dosing syringe. At the conclusion of the efficacy phase, cats on telmisartan with SBP ≤200 mmHg continued into the extended use phase. During the 92 days extended use phase, the dosage of telmisartan could be reduced in cats with SBP measurement <160 mmHg in 0.5 mg/kg increments to the lowest possible dose of 0.5 mg/kg once a day upon the discretion of the Investigator (based on their BP).

In this study, the co-primary efficacy variables were to confirm superiority of telmisartan over placebo after 14 days of treatment and to demonstrate a clinically relevant decrease in SBP (defined as greater than or equal to 20 mmHg) after 28 days of treatment. For the first co-primary endpoint, the SBP changes on Day 14 in comparison to baseline were statistically significantly different for the PPS population: the mean differences were -19.319 mmHg for the telmisartan group and -9.045 mmHg for the placebo group. For the second co-primary endpoint, the mean difference between baseline SBP and SBP on Day 28 was -24.629 mmHg for the telmisartan group. This value exceeded the target of 20 mmHg, considered by the applicant as being clinically relevant. For the placebo group, the reduction at Day 28 relative to baseline was -11.44 mmHg. Treatment with telmisartan

resulted in a sustained reduction in SBP of greater than 20 mmHg for the whole study duration (up to study day 120): mSBP appeared to continue to decrease between day 28 and day 56 (-24.46 to -26.94 mmHg, relative to baseline) and again between day 84 and day 120 (-26.5 to -27.62 mmHg, relative to baseline).

Safety: See Target animal tolerance section.

First American Field study.

The efficacy and safety of Semintra 4 mg/ml oral solution for the treatment of systemic hypertension in cats was evaluated over a 28 day period. This was a GCP, prospective, double-blind, randomised, placebo-controlled clinical field study conducted in client owned cats in the US and Canada at 20 independent sites.

288 hypertensive cats of average age 14 years, various breeds, male and female, neutered and unneutered, were included in the study.

The primary inclusion criterion was cats presenting with a mean SBP of between 160 mmHg and 200 mmHg. During the trial, SPB was evaluated on days 0 (visit 1), 14 (visit 2) and 28 (visit 3). Blood pressure was measured according to the ACVIM guidelines.

Cats were allocated to treatment group on a 2:1 basis, telmisartan:placebo. Both groups were consistent regarding breed, gender, age, body weight, baseline mSBP, medical history and classification of hypertension.

The telmisartan group were started on a dose of 1.5 mg/kg twice a day (BID) for 14 days, tapering to 2 mg/kg SID or lower (if hypotensive) after 14 days as a maintenance dose. The dose was further reduced to 1 mg/kg and then 0.5 mg/kg SID if the mSBP remained below 120 mmHg after visit 2. Any cats presenting with an mSBP of <80 mmHg or >180 mmHg at visit 2 were removed from the study for rescue treatment.

Treatment success was defined as the following two conditions being met.

1) The reduction of mSBP from baseline in the telmisartan-treated group was statistically different than the placebo group at Visit 2.

2) The reduction of mSBP from baseline in the telmisartan-treated group was at least 20 mmHg at Visit 3, as this was the threshold for clinical relevance.

The results of the efficacy analysis of this study show that telmisartan is effective at reducing systemic hypertension in cats. This conclusion is based on the statistically significant difference (p=0.0005) between the telmisartan and placebo groups at Visit 2, in which the telmisartan group had a mean decrease of 23.3 mmHg in mSBP, and the placebo group had a mean decrease in of 7.5 mmHg in mSBP. In addition, a reduction in mSBP was maintained at Visit 3 (arithmetic mean decrease of 23.9 mmHg, considered by the applicant to be 'clinically relevant' (predefined as ≥20 mmHg)).

However, this study differed from the EU study design (and the proposed conditions of use for Europe) in that it used a higher starting dose and different treatment interval. In this study, cats in the telmisartan group were administered 1.5 mg/kg twice daily for 14 days and the dose was then reduced to 2 mg/kg once daily. In effect, for the first 14 days of this study, telmisartan-treated cats received 3 mg/kg per day, 1 mg/kg/day more than the proposed RTD for the present application (2 mg telmisartan/kg SID). Given the difference in dose, the efficacy findings cannot be considered pivotal for the current marketing authorisation application.

Safety: See Target animal tolerance section.

In addition to the comments above, and specifically regarding severely hypertensive cats, the SPC reflects that the safety and efficacy of telmisartan for the management of systemic hypertension above 200 mmHg has not been investigated.

Second American field safety study.

At the end of the first American field study , cats on telmisartan with SBP ≤180 mmHg continued into the "extended use phase" for a further 5 months. The objective of this pivotal study was to evaluate the 6 month safety of telmisartan oral solution administered orally at a maintenance dose of 2 mg/kg SID to client owned cats for the control of hypertension associated with chronic kidney disease.

See Target animal tolerance section.

Overall conclusion on efficacy

Pharmacodynamics:

Telmisartan is an Ang II receptor (subtype AT_1) antagonist, which causes a dose-dependent decrease in mean arterial blood pressure in mammalian species, including the cat. Cross-reference is made to studies previously submitted and assessed by the CVMP, including an in vitro study where telmisartan inhibited the vasoconstriction induced by Ang II and two non-GLP i*n vivo* pilot studies investigating the effects of different doses of telmisartan on anaesthetised cats. The data provide evidence of an Ang II antagonist effect, and support further development of this product as an anti-hypertensive agent.

Pharmacokinetics/bioequivalence:

The applicant demonstrated bioequivalence of the two strengths, the authorised 4 mg/ml and the new 10 mg/ml, by providing two bioequivalence studies. The pharmacokinetic, target animal safety and field safety and efficacy data generated with the Semintra 4 mg/ml formulation can therefore be extrapolated to the new 10 mg/ml strength.

Dose determination/justification:

Data derived from a new pilot field study, and several preclinical studies previously submitted and assessed, justify a single oral dose of 2 mg/kg bw applied once daily as a starting dose. This dose was then used in the pivotal European field study.

Target animal tolerance:

During the target animal safety studies previously submitted and assessed by the CVMP, no treatment-related adverse effects were evident clinically. However, administration of the product at overdose (1.5 to 2.5 times the recommended dose of 2 mg/kg bw for 6 months) resulted in marked reductions in blood pressure, decreases in red blood cell count (effects attributable to the pharmacological activity of the product) and increases in BUN in healthy animals. The potential for these effects is noted in section 4.10 of the SPC.

The safety of the product has been examined in three large field trials in the target group of cats in which the product was administered for the treatment of hypertension. The adverse effects reported in these studies are likely to be typical for the target feline population (aging population, many of which have underlying medical conditions in particular CKD and hyperthyroidism). However, the

available data do suggest possible treatment related effects on renal function, red cell mass and gastrointestinal function (mild transient vomiting and diarrhoea). In addition, the findings highlight the possibility of interaction, and adverse effects on renal function as a consequence, when telmisartan is administered with other agents that lower blood pressure.

Clinical trials:

The applicant provided two field studies in support of the safety and efficacy of telmisartan when administered to cats for the treatment of systemic hypertension, one conducted in the EU and one conducted in the USA and Canada.

In the pivotal EU study, telmisartan was administered at the recommended oral dose of 2 mg/kg once a day. This dose/treatment interval reflects the proposed recommended treatment dose for the EU authorisation and, therefore, this is considered the pivotal field study. However, the American field study was conducted using a different dosing schedule (1.5 mg telmisartan BID, reducing to 2 mg SID) and, therefore, is considered supportive only. In both studies, the currently authorised strength (4 mg/ml) but not the new 10 mg/ml strength was used.

In the pivotal EU study, the co-primary efficacy variables were to confirm superiority of telmisartan over placebo after 14 days of treatment and to demonstrate a clinically relevant decrease in SBP (defined as greater than or equal to 20 mmHg) after 28 days of treatment. For the first co-primary endpoint, the SBP changes on Day 14 in comparison to baseline were statistically significantly different for the PPS, the ITT and the SAF populations. For the PPS population, the mean differences were -19.319 mmHg for the telmisartan group and -9.045 mmHg for the placebo group. For the second co-primary endpoint, the mean difference between baseline SBP and SBP on Day 28 was -24.629 mmHg for the telmisartan group. This value exceeded the target of 20 mmHg, considered by the applicant as being clinically relevant. For the placebo group, the reduction at Day 28 relative to baseline was -11.44 mmHg. Treatment with telmisartan resulted in a sustained reduction in SBP of greater than 20 mmHg for the whole study duration (up to study day 120).

Based on the data presented, the CVMP considered that the efficacy of Semintra 10 mg/ml at a daily oral dose of 2 mg/ml was adequately supported.

Part 5 – Benefit-risk assessment

Introduction

Semintra (active substance: telmisartan) is already authorised as a 4 mg/ml oral solution for use in cats for the reduction of proteinuria associated with chronic kidney disease (CKD). This extension application is to add a new strength (10 mg/ml) and a new indication (treatment of systemic hypertension in cats) at a proposed dose of 2 mg/kg bw (i.e. a higher dose than for the current use).

The dossier has been submitted in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I point 2c, change or addition of a new strength, thereof (extensions).

Benefit assessment

Direct therapeutic benefit

Hypertension is a chronic problem of the ageing cat, most often occurring secondary to CKD and/or hyperthyroidism but sometimes seen in the absence of an underlying disease. If left untreated, the evidence from experimental models and clinical observation is that it may cause significant damage to the eye, the brain, the heart and the kidney. The extent to which blood pressure needs to be lowered to afford optimal protection against harmful effects will depend on multiple factors which will differ for each individual animal undergoing treatment.

Based on the preclinical data presented in this dossier, the CVMP agreed that telmisartan exhibits an Ang II antagonist effect, resulting in antihypertensive properties. In the pivotal EU efficacy study, there was a significantly superior antihypertensive effect of Semintra when administered to cats at an oral dose of 2 mg/kg once a day compared to placebo at 14 days of treatment, and a persistent antihypertensive effect (relative to baseline) over 120 days of study.

Additional benefits

This product increases the range of available treatment possibilities for feline hypertension, an indication classified as MUMS/limited market.

Risk assessment

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:

Risks for the target animal:

During the target animal safety studies, no treatment-related adverse effects were evident clinically. However, administration of the product at overdose (1.5 to 2.5 times the recommended dose of 2 mg/kg bw for 6 months) resulted in marked reductions in blood pressure, decreases in red blood cell count (effects attributable to the pharmacological activity of the product) and increases in BUN in healthy animals. The potential for these effects is noted in section 4.10 of the SPC.

The safety of the product has been examined in two large field trials in the target group of cats, in which the product was administered for the treatment of hypertension. The adverse effects reported in these studies are likely to be typical for the target feline population (aging population, many of which have underlying medical conditions in particular CKD and hyperthyroidism). However, the available data do suggest possible treatment related effects on renal function, red cell mass and gastrointestinal function (mild transient vomiting and diarrhoea). In addition, the findings highlight the possibility of interaction, and adverse effects on renal function as a consequence, when telmisartan is administered with other agents that lower blood pressure. The potential for these

effects is noted in sections 4.5, 4.6 and 4.8 of the SPC. It can be accepted that the product was generally well tolerated.

In view of the extension to a new strength and the addition of a new indication (requiring a higher dose) and that there are concerns about effects of the increased dose on renal function in cats, re-start of the periodic safety update report (PSUR) submission cycle for Semintra is appropriate. The MAH's proposal concerning PSUR submissions was considered by the CVMP, also taking into account that the MAH voluntarily submits all adverse event reports (including non-expedited) electronically. The CVMP, however, recommended that PSURs covering both presentations are submitted at 6 months, 12 months and 24 months following authorisation of the 10 mg/ml presentation. Taking into account the current PSUR submission schedule and to avoid any gaps in data submission, for ease of reference the PSURs submission schedule is clarified as follows:

- 01/09/2017 – 31/08/2018;
- 01/09/2018 – 28/02/2019;
- 01/03/2019 - 31/08/2019;
- 01/09/2019 - 31/08/2020; and
- 01/09/2020 - 31/08/2023.

Unless otherwise required, PSURs should continue thereafter on a three-yearly submission schedule.

Risk for the user:

The user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment:

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

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 user and the environment and to provide advice on how to prevent or reduce these risks.

Risk management or mitigation measures relevant to target animal safety will be further considered pending additional information from the applicant.

Given that the new indication requires an increase in dose and that there are potential concerns about effects of the increased dose on renal function in cats, the PSUR cycle should be re-started to ensure more frequent monitoring of adverse events.

Evaluation of the benefit-risk balance

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

The applicant applied for the following indication: "Treatment of systemic hypertension in cats." The product has been shown to be efficacious for the treatment of systemic hypertension in cats and the CVMP agreed to the proposed indication.

Information on development, manufacture and control of the active substance and finished product has been presented and lead 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.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the Extension application for Semintra 10 mg/ml oral solution for cats is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

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.