ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE VETERINARY MEDICINAL PRODUCTS, ANIMAL SPECIES, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State / EEA	Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration	Recommended dose
Austria	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet for dogs	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
Belgium	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet for dogs	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
Denmark	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
Germany	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet for dogs	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
Greece	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet for dogs	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
Spain	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet for dogs	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
Finland	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet for dogs	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
Ireland	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of

	The Netherlands						treatment
Luxemburg	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet for dogs	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
The Netherlands	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet for dogs	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
Norway	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment
Portugal	Intervet International B.V. P.O. Box 31 5830 AA Boxmeer The Netherlands	Vasotop P 0,625 mg; Vasotop P 1,25 mg; Vasotop P 2,5 mg, tablet for dogs	Tablet	0.625; 1.25 or 2.5 mg of ramipril	Dogs	Daily, oral	0.125 mg/kg; 0.25 mg/kg if the animal does not respond after 2 weeks of treatment

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR REFUSAL OF THE VARIATION

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF VASOTOP P 0.625 MG, TABLET FOR DOGS AND CATS, VASOTOP P 1.25 MG, TABLET FOR DOGS AND CATS AND VASOTOP P 2.5 MG, TABLET FOR DOGS AND CATS

1. Introduction

Vasotop P 0.625 mg, Vasotop P 1.25 mg and Vasotop P 2.5 mg tablets are veterinary medicinal products those contain the active ingredient ramipril at concentrations of 0.625 mg, 1.25 mg and 2.5 mg respectively. Ramipril is an angiotensin-converting enzyme (ACE) inhibitor. The products are currently authorised for use in dogs for the treatment of congestive heart failure (NYHA classification grade II, III and IV) due to chronic degenerative valvular heart disease or cardiomyopathy, with or without adjunct diuretic (furosemide) or cardiac glycocide (digoxin/methyldigoxin) therapy.

The Marketing Authorisation Holder (MAH) Intervet International B.V. submitted applications for Type II variation subject to Mutual Recognition Procedures (MRP) for Vasotop P 0.625 mg, Vasotop P 1.25 mg and Vasotop P 2.5 mg tablets for dogs in order to include a new indication for cats as follows:

> *"For the reduction of elevated systolic blood pressure (between 160 and 230 mm Hg) and the control of associated clinical signs."*

The proposed recommended therapeutic dose for this new indication is 0.125 mg ramipril/kg body weight once daily. Depending on the response to therapy, it is possible to double the dose to 0.25 mg ramipril/kg body weight per day. Three strengths of tablet are covered by the current application as follows; Vasotop P 0.625 mg tablet, Vasotop P 1.25 mg tablet and Vasotop P 2.5 mg tablet.

Following the absence of agreement between the Reference Member State and one Concerned Member State (Belgium) at Day 90 of the CMD(v) procedure, the matter was referred to CVMP. The National Competent Authority of Belgium was concerned that it was not possible to conclude on the clinical efficacy of the product in reducing systemic hypertension in cats in the absence of a placebo control group in the pivotal field trials.

2. Assessment of efficacy issues

2.1. Efficacy of Vasotop P in the treatment of arterial hypertension in cats

The MAH submitted data where ramipril (active substance of Vasotop P) produced a marked decrease of systolic blood pressure in mildly to severely hypertensive cats. Sustained decreased systolic blood pressure was observed for up to 6 months and blood pressure was controlled over the 24-hour time interval between two successive administrations of Vasotop P in all cats. In addition, ramipril was well tolerated in all treated cats.

The CVMP considered that due to the low case numbers and lack of comparative statistics, the main findings from this study were more "proof of concept" than proof of definitive clinical efficacy. However, the prolonged duration of effect over the course of 6 months, in addition to its efficacy during the entire inter-dosage interval, was noted.

2.2. A multicentre field trial with Vasotop P for the treatment of hypertension in cats

The MAH submitted data where 53 % (40 out of 76) of included cats had urea concentrations above the upper limit of the reference range. 22 % (17 out of 76) of included cats had creatinine concentrations above the threshold.

Around 33 % of the cases were between 160 and 180 mm Hg systolic blood pressure (risk category III) and 67 % ≥ 180 mm Hg systolic blood pressure (risk category IV) at inclusion.

Almost 82 % of the included cats presented at least one clinical sign related to hypertension. The most frequently observed clinical signs were polyuria-polydipsia (34 %), heart murmur (28 %) and retinal detachment/haemorrhages (25 %). No statistical difference was observed in the distribution of clinical signs among cases when stratified by risk category (p=0.5296). The average systolic blood pressure in

cats with or without clinical signs at inclusion were in the same range (188.2 and 195.8 mm Hg, respectively), and were not statistically different (p=0.2132).

There were no significant differences between risk categories III and IV for age, bodyweight, heart rate, and total thyroxine, urea and creatinine concentrations.

The CVMP considers that a notable decrease in blood pressure measurements was evident between pre-treatment and post-treatment values. However the issue in question was whether or not it could be ascertained that the beneficial response was truly treatment-related, rather than being due to a placebo (white coat hypertensive habituation) effect. In addition, while no authorised reference product exists (positive control), it was argued that it would not have been unethical to have included a negative control group as hypertension is not necessarily life-threatening. Clinical signs like retinal haemorrhage and even polyuria-polydipsia can be quite severe and are not expected to readily respond to a placebo effect. However, any clinical disease sees its signs evolve over the life of the animal and the duration of the clinical trial; it is the delta in the study that either decreases or increases spontaneously. Therefore, the clinical signs as mentioned may resolve (except for complete retinal detachment). Because of the delta, a control group is necessary. A placebo effect must always be assumed to be present. How big or small the effect of this placebo effect depends as much on the disease as it does on the clinical setting and can only be determined through comparison with another group. In the context of the current study, a white coat effect should impact both groups equally in order to allow a treatment effect to emerge.

2.3. Percentage of cats with different number of clinical signs and their response to the treatment

The MAH provided data to show that of the 82 % of cats showing at least one clinical sign, 46 % had two clinical signs or more. In addition at Day 63, only 53 % of cats still exhibited at least one clinical sign. When broken down further, 32 % of cats had one clinical sign only and the remaining 21 % of cats had two clinical signs or more.

The CVMP noted that better responses were obtained for the relatively non-specific clinical signs noted (e.g. polyuria, polydipsia, lethargy etc.), whilst the poorest responses were obtained for the ocular lesions (blindness, vascular tortuosity and retinal detachment). The CVMP is of the opinion that hypertension-related ocular lesions (once present) are harder to resolve/reverse even if the hypertension is subsequently controlled. In relation to the non-specific signs such as polyuria, polydipsia etc., the CVMP opinion is that it is plausible that a correlation exists between the improvement in blood pressure measurements and the resolution of such signs.

In addition the MAH was requested to submit a further clarification in relation to the percentage of severely hypertensive cats (i.e. systolic blood pressure > 180 mm Hg) that subsequently became normotensive or had a >20 mm Hg decrease in systolic blood pressure following treatment.

The MAH clarified that the mean decrease in the severely affected group (systolic blood pressure > 180 mm Hg) was of –25.5 mm Hg (while it was of –18.3 mm Hg in the moderately affected group (systolic blood pressure between 160 mm Hg and 180 mm Hg). From the 43 cats belonging to the severe group at Day 0, 26 cats in total (60.5 %) became normotensive or had a >20 mm Hg decrease in systolic blood pressure at Day 63. From these 26 cats, 14 cats were normotensive by Day 63. The other 12 cats had a >20 mm Hg decrease in systolic blood pressure at Day 63 (mean decrease of 36.6 mm Hg, range 20 mm Hg to 57.8 mm Hg) but were still above the normotensive limit of 160 mm Hg.

The CVMP considered that it is important to emphasise that it is known from the literature that no one agent currently available is 100 % effective in the treatment of feline hypertension, and success rates of about 50 % are considered the norm. Thus, the finding that 63 % of severely affected cats became normotensive or had a >20 mm Hg reduction in systolic blood pressure following treatment with Vasotop P is noted; whilst it is accepted that 12/26 cats did not become normotensive, a mean reduction of 37 mm Hg in systolic blood pressure in severely hypertensive cats has also been noted. However, without direct comparison to a negative control group, it is not possible to say if this effect is due to treatment.

2.4. The measurement error of the apparatus used for the measurement of the blood pressure of cats

The MAH provided information on the two Doppler machines employed to measure systolic blood pressure in the pivotal field study. Literature reports were provided to support the correlation between direct blood pressure measurements and the Doppler machines used. In addition, the MAH specified that only experienced investigators with appropriate machine training were used in the study, and that measurements were performed according to the ACVIM consensus statement[1]. The MAH provided data on the Coefficient of Variation (CV) between the 5 individual measurements performed at the different study time points. The mean CV was approximately 3 % at all time points studied; these values were similar to the CV values reported in the literature by Snyder[2] (1998). Based on the argumentation submitted, the CVMP is of the opinion that the blood pressure measuring devices used were appropriate and the data generated robust.

2.5. Improvement in hypertension in the absence of a negative control group

The MAH presented data from their own study and the literature to refute the possibility that the improvement in systolic blood pressure measurements was related to habituation to the "white coat effect". The MAH's data did show that the mean reading for the first measurement (discarded) was 6–10 mm Hg higher than the subsequent 5 measurements used for calculating the reported value (this is in line with the ACVM Consensus Statement approach); this finding was independent of the point in time when the measurement was performed, and thus no evidence of habituation was found. The MAH stated that their finding was in agreement with that reported previously by Belew[3] (1999), who investigated the possibility of habituation in laboratory cats subjected to "sham" clinic visits to measure their blood pressure. The CVMP is of the opinion that the data from the MAH's study and that reported by Belew (1999) do not support the concept of habituation in cats in terms of blood pressure measurements.

The MAH also considered if the mean decrease in systolic blood pressure measurements could have been attributable to other non-treatment related factors in the study. Whilst none could be identified, the CVMP is concerned that the list of factors studied was hardly exhaustive, and in effect, only two such parameters were actually investigated (i.e. diet and concomitant treatment). It is agreed that the white coat effect, when big, is up to 20 % or so. It is agreed that the effect noted by the MAH in a follow-up response (see 2.3) is bigger than that. However, the sheer chance factor cannot be quantified in this study without placebo group.

2.6. Comments on whether it is possible to devise and conduct a trial with a placebo control where an escape therapy is identified at certain points in the study period

The MAH submitted argumentation which covered the following grounds:

- Untreated hypertension is associated with a significant risk of target organ damage.
- Some recent studies report low median survival times for hypertension in cats – 4–7 months if untreated (Chetboul[4] et al., 2003) and approximately 9 months even with treatment.
- The only prospective placebo-controlled study of feline hypertension reported that all 4 placebo cats were switched to the treatment group (amlodipine) after only 7 days (no reasons given – Snyder, 1998).

[1] ACVIM Consensus Statement 2007. J Vet Intern Med, 2007, 21. P. 542–558.

[2] Snyder P.S. Amlodipine: A randomized, blinded clinical trial in 9 cats with systemic hypertension. J Vet Intern Med, 1998, 12. P. 157–162.

[3] Belew A.M., Barlett T., Brown S.A. Evaluation of the white-coat effect in cats. J Vet Intern Med, 1999, 13. P. 134–142.

[4] Chetboul V., Lefebvre H.P., Pinhas C., Clerc B., Boussouf M., Pouchelon J.L. Spontaneous feline hypertension: Clinical and echocardiographic abnormalities, and survival rate. J Vet Intern Med, 2003, 17. P. 89–95.

- Even a short placebo treatment of 28 or 63 days could be associated with irreversible pathological changes to organs such as the eye (e.g. detached retina/blindness).
- The MAH already had experience of having to abandon a placebo control group in a separate Chronic Renal Failure study, due to the unwillingness of owners to provide consent for treatment to be potentially withheld.

Whilst fully accepting the scientific validity of requiring control groups in clinical studies, the CVMP is of the opinion that a significant proportion of placebo-control cats suffering from moderate-to-severe hypertension (i.e. systolic blood pressure >180 mm Hg) would be at risk of developing target organ damage if left untreated over a potential period of 63 days. The CVMP is of the opinion that there are ethical issues for veterinarians in allowing cats with significant hypertension to remain untreated, contrary to current-day best clinical practice (ACVIM Consensus Statement 2007). As many of the clinical signs are non-specific, and are cardiovascular in nature, an escape therapy could be possible and more than adequate in addressing those signs. The CVMP considers that it would be less unethical to risk non-treatment of a small number of animal patients for a shorter time period than to authorise an un-efficacious product.

2.7. Benefit/Risk assessment

Despite a notable reduction in systolic blood pressure and a plausible link between hypertension reduction and improvement of clinical signs, there is no certainty that this effect is due to treatment without comparison to a control group. Thus, the benefit/risk assessment is deemed unfavourable for the proposed indication in cats.

GROUNDS FOR THE REFUSAL OF THE VARIATION OF THE MARKETING AUTHORISATIONS

Whereas,

- the CVMP considered the referral made under Article 6(12) of Commission Regulation EC No 1084/2003, for Vasotop P 0.625 mg, Vasotop P 1.25 mg and Vasotop P 2.5 mg, tablets for dogs and associated names (see Annex I), all the overall submitted data in writing and in the oral explanations,
- the CVMP concluded that it is not clear, if the recorded reduction in systolic blood pressure and clinical signs in hypertensive cats following treatment with Vasotop P was a true treatment-related effect,
- the CVMP concluded that the absence of a negative control group (placebo group) in the pivotal clinical field trial was considered unacceptable,
- the CVMP agreed that the benefit/risk balance for Vasotop P in this variation currently is unfavourable,

Therefore, the CVMP recommends the refusal of the variation of the Marketing Authorisations for the veterinary medicinal products referred to in Annex I.