College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Vasotop P 1,25 mg tablet for dogs

Juni 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0245/002
Name, strength and pharmaceutical form	Vasotop P 1,25 mg tablet for dogs
Applicant	Intervet Nederland bv Wim de Körverstraat 35 Postbus 50 5830 AB Boxmeer
Active substance(s)	Ramipril
ATC Vetcode	QC09AA05
Target species	Dog
Indication for use	For treatment of congestive heart failure (according to New York Heart Association (NYHA) classification grade II, III & IV) caused by valvular insufficiency due to chronic degenerative valvular heart disease (endocardiosis) or cardiomyopathy, with or without adjunct therapy with the diuretic furosemide and/or the cardiac glycosides digoxin or methyldigoxin.

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	Publicly available assessment report

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full dossier application in accordance with Article 17 of Directive 81/851/EEC as amended.
Date of completion of the original mutual recognition procedure	7th September 1999 NL was CMS of DE/V/0103/001
Date product first authorised in the Reference Member State (MRP only)	30th October 1998
Concerned Member States for original procedure	AT, BE, DE (former RMS), EL, IE, DK, FI, IT, LU, ES, NO, PT, NL (former CMS)

Product is withdrawn in these countries

I. SCIENTIFIC OVERVIEW

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

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains ramipril (1,25 mg) and the excipients:

Hydroxypropylmethylcellulose
Pregelatinised starch
Microcrystalline cellulose
Sodium stearyl fumarate
Artificial powdered beef flavour
Silica colloidal anhydrous

The container/closure system is a 15 mL HD polyethylene container containing 28 oblong tablets closed by LD polypropylene tamper evident child resistant screw cap. A desiccant capsule is inserted in the cap.

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

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

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B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is ramipril, an established substance described in the European/British Veterinary Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

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

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

D. Control on intermediate products

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

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

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

G. Other Information

Shelf life of the finished product as packaged for sale: 24 months

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III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has conducted studies / has provided bibliographical data which show that Ramipril is hydrolysed by esterases in the liver to its active metabolite ramiprilat, which acts by inhibiting the enzyme dipeptidycarboxypeptidase I (also called angiotensin-converting enzyme (ACE)), which catalyses the conversion of angtioensin I to angiotensin II and the breakdown of bradykinin. As angiotensin II has a potent vasoconstrictive action, while bradykinin is a vasodilator, the reduced formation of angiotensin II and the inhibition of bradykinin breakdown lead to vasodilation.

The applicant has also has provided bibliographical data which show Ramipril is rapidly absorbed in the gastrointestinal tract after oral administration and hydrolysed in the liver to the active metabolite ramiprilat. The relative bioavailability of the different tablets ranged from 87.9 to 97.7%. Rampiril is rapidly and extensively distributed into the various tissues and maximum ramiprilat concentrations occur on average after 1.2 hours (tablet), with a mean peak concentration of 18.1 ng/ml (tablet).

Toxicological Studies

The applicant has provided bibliographical data which show the following:

- Single Dose Toxicity

Oral LD_{50} in rats and mice is higher than 10 000 mg/kg bodyweight

Oral LD_{50} in dogs is higher than 1000 mg/kg bodyweight

Intra-venous LD_{50} in female rats is 600 mg/kg bodyweight and 700 mg/kg bodyweight in male rats

Intra-venous LD_{50} in mice is 1200 mg/kg bodyweight

In mice dose-dependent decreased spontaneous activity, crouching and slightly increased breathing rate occurred at all dose levels. In rats only slightly reduced spontaneous activity occurred.

Slightly reduced spontaneous activity occurred in dogs at 1000 mg/kg bodyweight and no differences in acute toxicity between males and females occurred.

- Repeated Dose Toxicity

NOAEL in dogs in a study with oral submission of ramipril for 12 months was 2.5 mg/kg bodyweight/day.

Dose-dependent effects reported included increased circulation concentrations of urea and creatinine, hyperplasia of renal juxta-glomerular cells, mild anaemia, slight neutrophilia, slight lymphopenia and a slight leucopoenia.

- Reproductive Toxicity, including Teratogenicity:

No effects were noticed in embryotoxicity/foetotoxicity studies performed in rat, rabbit, dog and monkey.

Other Studies

The applicant has conducted additional studies in cats which show that there were no significant differences between placebo and treated cats with respect to body weight and food consumption. No drop in blood pressure in cats treated with 5 times the RTD (0.625 mg/kg) was recorded and no changes in haematological and biochemical parameters, with exception of triglycerides, were observed. Lower plasma triglycerides concentrations were recorded for cats treated with 3 times the RTD (0.375 mg/kg) compared with cats that received the recommended starting dose (0.125 mg/kg). This shows that the product is well tolerated in cats and is devoid of toxic effects.

Observations in Humans

The applicant has provided information which show that no or only very limited effects in humans will be triggered by accidental ingestion of the product. The most likely adverse reaction would be a transient and reversible hypotension.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that no special risk management is necessary for professional and non-professional users.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

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

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical datato show that ramipril is a potent ACE inhibitor when administred orally as tablets and provides a rapid and sustained suppression of ACE activity at a dose as low as 0.125 mg/kg bodyweight following both single and repeated administrations. Following oral administration, rampiril is rapidly converted into its biologically active metabolite ramiprilat with peak concentrations about 2h following oral administration. Steady state concentrations of ramiprilat are reached by the second to the fourth dose and ACE inhibition is maintained for 24h at the lowest dose rate (0.125 mg/kg bodyweight once daily). Administration of the product at or around feedeing does nog significantly alter the pharmacokinetics of ramipril or ramiprilat.

Excretion pattern is predominantly faecal in all target species.

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study using multiples of the recommended dose in the target species. All doses were administered once daily by oral submission for one week..

Parameters evaluated were physical performance, heart and respiratory rates and plasma ACE-activity at rest and after 5 and 10 min exercise on the treadmill, plasma renin concentration and –activity, plasma electrolytes (sodium, calcium, magnesium, potassium) and plasma catecholamines.

Minimal changes were seen during this study..

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

IV.B Clinical Studies

Field Trials

The applicant has provided bibliographical data which show that enalapril and ramipril were equivalent regarding improvement of NYHA classes, dyspnoea, activity and pulmonary oedema. Enalapril gave better results for coughing while ramipril gave better results for general demeanour, but tests for superiority failed for both parameters. Tolerance to both products was rated as good.

This trial was designed as a multicentre, randomised, positive controlled, double blinded field trial, which tested the therapeutic equivalence between the test drug ramipril and the reference drug enalapril in the treatment of dogs with chronic heart failure (NYHA classification II, III or IV). 151 dogs (99 males and 52 females) of different breeds, age and weight were included. 110 of these dogs showed heart failure due to chronic valvular disease (CVD) and 39 dogs suffered from dilated cardiomyopathy (DCM). 20 dogs from 151 were withdrawn from the trial pre- and post-admission. Duration of the study treatment period was 8 weeks.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Summary of change	**Section updated**	**Approval date**
Change in the name and/or address of the marketing authorisation holder (DE/V/0103/001/V001)	Module 1	17th May 2000
Repeat use procedure to add CMSs EL, IE and NO (DE/V/0103/001/E/002)	NA	21st September 2000
Repeat use procedure to add CMS SE (DE/V/0103/001/E/003)	NA	4th February 2002
Change in the name of a manufacturer of the medicinal product (DE/V/0103/001/V002)	NA	28th March 2003
Renewal – DE as RMS (DE/V/0103/001/N001)	NA	6th December 2003
Change in the test procedure of the finished product, including replacement or addition of a test procedure (DE/V/0103/001/IB/001)	NA	8th May 2006
Minor change to an approved test procedure for an excipient (DE/V/0103/001/IA/002)	NA	22nd June 2006
Change in flavouring system currently used in the finished product; Replacement of an excipient with a comparable excipient. (DE/V/0103/001/IB/003)	Module 3 II.A	6th November 2006
Change in the qualitative and/or quantitative composition of the immediate packaging of the finished product; change in pack size of the finished product outside the range of currently approved pack sizes. (DE/V/0103/001/IB/004)	Module 3 II.A	6th November 2006

Change in the name of the medicinal product. (DE/V/0103/001/IB/005)	Module 1	6th November 2006
Renewal – DE as RMS (DE/V/0103/001/R/002)	NA	18th November 2008
Deletion of a manufacturing site for bulk manufacturing. (DE/V/0301/001/IA/008)	NA	10th March 2009
Increase of specification limits for the main impurity (DE/V/0103/001/II/009)	NA	13th August 2009
Change of the name and/or address of the marketing authorisation holder in Portugal only (DE/V/0301/01/IA/010) Withdrawal of SE 6-2-2009	NA	1st December 2009
Change of specification limit for total impurities of the finished product as a consequence of variation DE/V/001-005/II/009 (DE/V/0103/001/IB/011)	NA	6th August 2010
Change of RMS – DE > NL DE/V/0103/001 > NL/V/0245/002	Module 1	6th October 2017
Addition of a new specification parameter, with its corresponding test method; Deletion of a non-significant specification parameter; Change of the shelf life of the finished product as packaged for sale (NL/V/0245/002/IB/001/G)	NA NA Module 3 II.G	7th March 2018