

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

Vasotop 2.5 mg Tablets

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Active substance:

Each tablet contains Ramipril 2.5mg

Excipient:

Yellow ferric oxide (E 172) 0.5mg

For full list of excipients, see section 6.1

### **3. PHARMACEUTICAL FORM**

Tablet.

Brownish yellow oblong flavoured tablets with dark spots, half scored on both sides with embossing of "V" and "2.5" on both sides of score line.

### **4. CLINICAL PARTICULARS**

#### **4.1 Target species**

Dogs

#### **4.2 Indications for use, specifying the target species**

For the treatment of congestive heart failure (NYHA: decompensation grades II-IV). The product can be used in combination with diuretics, and the cardiac glycosides digoxin or methyl-digoxin.

#### **4.3 Contraindications**

Not to be used in haemodynamically relevant vascular stenosis (e.g. aortic stenosis) or obstructive hypertrophic cardiomyopathy.

#### **4.4 Special warnings for each target species**

The use of ACE inhibitors in dogs with hypovolaemia/dehydration (e.g. due to large doses of a diuretic, vomiting or diarrhoea) can lead to acute hypotension. In such cases the fluid and electrolyte status should first be balanced and treatment suspended until it is stabilised.

This also applies if clinical signs of apathy or ataxia occur during treatment with the product (potential signs of hypotension). After these symptoms have subsided, the treatment should be continued at 50% of the original dose.

Substances that deplete blood volume, such as diuretics, or which vasodilate,

such as angiotensin-converting enzyme (ACE) inhibitors, may contribute to lowering systemic blood pressure. This may result in pre-renal uraemia (azotaemia). Renal function should be monitored both before and seven days after commencement of treatment with ACE inhibitors. This also applies when the dosage of ACE inhibitor or of a concurrently administered diuretic is increased. It is advisable to periodically monitor renal function throughout treatment.

Ramipril is a pro-drug and is metabolized in the liver to its active form. This conversion may be reduced in dogs with impaired liver function.

#### **4.5 Special precautions for use**

i. Special precautions for use in animals

In patients at risk of hypovolaemia it is advisable to introduce the product gradually over one week (starting with half the therapeutic dose).

As well as monitoring the hydration status the patient's renal function should be checked before and seven days after commencement of treatment with ACE inhibitors.

This also applies when the dosage of the product or of a concurrently administered diuretic is increased.

It is advisable to periodically monitor renal function throughout treatment.

In patients treated with the product and furosemide the dose of the diuretic can be reduced to achieve the same diuretic effect as with furosemide alone.

ii. Special precautions to be taken by the person administering the medicinal product to animals

Pregnant women should take special care to avoid accidental exposure, because ACE inhibitors have been found to affect the unborn child during pregnancy in humans. Wash hands after use. In case of accidental ingestion by children seek medical advice immediately and show label to the doctor.

#### **4.6 Adverse reactions (frequency and seriousness)**

No undesirable effects have been noted to date which might be linked with the use of the product. If you observe side-effects in your animal during treatment consult your veterinary surgeon.

#### **4.7 Use during pregnancy, lactation or lay**

Fertility disorders in male and female rats were not observed. In animal experiments ramipril passes into maternal milk. No studies have been carried out to assess the use of the drug in pregnancy

or lactation in bitches. ACE inhibitors have been found to be teratogenic in the second and third trimesters in other species. An angiotensin converting enzyme is known to be critical to the development of the neonatal kidney, this product should not be used in pregnancy or lactation.

#### **4.8 Interaction with other medicinal products and other forms of interaction**

Diuretics and a low-sodium diet both potentiate the effect of ACE inhibitors by activating the renin-angiotensin-aldosterone (RAAS). High doses of diuretics and a low-sodium diet should therefore be avoided during treatment with ACE inhibitors in order to prevent hypotension (with clinical signs such as apathy, ataxia, rarely syncope or acute renal failure).

Do not administer potassium-sparing diuretics.

The concomitant administration of ACE inhibitors with non-steroidal anti-inflammatory drugs (NSAIDs) leads to poor autoregulation of the glomerular blood pressure and can therefore trigger acute renal failure.

#### **4.9 Amount(s) to be administered and administration route**

The therapeutic dose in the dog is 0.125 mg ramipril per kg bw per day. Depending on the severity of pulmonary congestion the dose may be increased after 2 weeks to 0.25 mg ramipril per kg bw per day.

Treatment is by mouth once daily.

Suggested dosage schedule for standard dose (0.125 mg/kg/day)

Body Weight (kg)	Vasotop Standard dose		
	1.25 mg	2.5 mg	5 mg
6 - 10	1		
11 - 20		1	
21 - 40			1
41- 50	1		1
51 - 60		1	1

To ensure accurate dosing, each individual should be carefully weighed before calculating the dose.

The product may also be used in combination with the diuretic furosemide and/or the cardiac glycosides digoxin or methyl-digoxin.

#### **4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary**

Overdoses of up to 2.5 mg ramipril / kg bw (10 times the recommended highest dose) have been well tolerated in healthy young dogs.

#### **4.11 Withdrawal period(s)**

Not applicable

## **5. PHARMACOLOGICAL PROPERTIES**

**ATCVet code:** QC09AA05

**Pharmacotherapeutic group:** ACE Inhibitors

### **5.1 Pharmacodynamic properties**

Ramipril is hydrolysed in the liver by esterases to its active metabolite ramiprilat. Ramipril inhibits the enzyme dipeptidylcarboxypeptidase I, also referred to as angiotensin-converting enzyme (ACE). This enzyme catalyses the conversion of angiotensin I to angiotensin II in blood plasma and in vascular endothelial tissues and degrades bradykinin. As on the one hand angiotensin II acts as a strong vasoconstrictor, bradykinin on the other hand acts as a vasodilator, the reduced formation of angiotensin II and the inhibition of bradykinin degradation resulting in systemic vasodilation.

Angiotensin II also causes the release of aldosterone (within the renin-angiotensin-aldosterone-system – RAAS). Consequently, ramiprilat reduces aldosterone secretion. This in turn leads to an increase in the serum potassium concentration.

Inhibition of tissue ACE in the heart results in locally reduced levels of angiotensin II and in potentiation of bradykinin effects. Angiotensin II induces cell proliferation in smooth muscle, while bradykinin leads to increases in local prostacyclin (PGI<sub>2</sub>) and nitric oxide (NO), both inhibiting smooth muscle cell proliferation. The two effects of local ACE inhibition act synergistically in reducing myotropic factors and result in distinct reduction of cardiac and vascular smooth muscle cell proliferation. In this way ramipril prevents or reduces, with lasting effect, myogenous hypertrophy in patients with congestive heart failure (CHF) and results in reduction of peripheral vascular resistance.

The plasma ACE-activity was measured as the principal criterion of the pharmacodynamic effect. After oral administration of ramipril a significant inhibition of this activity occurs quickly and gradually increases again during the dosage interval, reaching 50% of the initial value by 24 hours post administration. Administration of ramipril in patients with congestive heart failure improves the haemodynamics, the related symptomatology and the prognosis. Ramipril has also been shown to reduce the mortality rate among patients with persistent or transient heart failure following an acute myocardial infarction (man, dog).

### **5.2 Pharmacokinetic particulars**

Ramipril is rapidly and completely adsorbed in the gastrointestinal tract after oral administration and is hydrolysed to the active metabolite ramiprilat in the liver.

Metabolism studies in rats, mice and dogs with <sup>14</sup>C-labelled ramipril show that the active ingredient is quickly and extensively distributed in the various

tissues. In the rat the highest concentrations are measured in the liver, the kidney and the lungs.

Following oral administration of 0.125 mg/kg BW ramipril (aqueous solution) to dogs, the maximum ramiprilat concentration of 12.1 ng/ml (day 1) and 17.7 ng/ml (day 8) respectively appear on average after one hour. The concentrations then decline in a biphasic pattern with biological half-lives of 0.5 and 8.9 hours (day 1) and 0.7 and 10.5 hours (day 8) on average, respectively.

Following oral administration of 0.25 mg/kg BW ramipril (aqueous solution) to dogs, maximum ramiprilat concentrations are reached on average after 1.2 hours (tablet) and 1 hour (aqueous solution) respectively. The mean of these peak concentrations is 18.1 ng/ml (tablet) and 23.0ng/ml (aqueous solution), respectively.

Following oral administration of 0.5 mg/kg BW ramipril (aqueous solution) to dogs, maximum ramiprilat concentration) of 95.5ng/m; appear after 0.8 hours (day 1) and 81.5 ng/ml after 0.9 hours (day 8) on average respectively. The half lives are 13.7 hours (day 1) and 15.7 hours (day 8) respectively.

It would appear from the AUC (area under the plasma concentration versus time curve) that the kinetics in the tested dosage range are linearly related to the dose rate. Cumulative effects were not observed.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Yellow ferric oxide (E172)  
Hydroxypropyl methylcellulose  
Pregelatinised starch  
Microcrystalline cellulose  
Sodium stearyl fumarate  
Artificial powdered beef flavour  
Silica colloidal anhydrous

### **6.2 Major incompatibilities**

None known

### **6.3 Shelf life**

Shelf life of the veterinary medicinal product as packaged for sale: 18 months.

### **6.4 Storage precautions for storage**

Do not store above 25°C  
Store in a dry place.  
After each opening, please replace the cap tightly.  
Do not remove the desiccant capsule.

**6.5 Nature and composition of immediate packaging**

Boxes of 1 x 28 oblong flavoured scored tablets in 15ml HD polyethylene containers

Boxes of 3 x 28 oblong flavoured scored tablets in 15ml HD polyethylene containers

Boxes of 6 x 28 oblong flavoured scored tablets in 15ml HD polyethylene containers

Not all pack sizes may be marketed

**6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products, if appropriate**

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

MSD Animal Health UK Limited  
Walton Manor, Walton  
Milton Keynes  
Buckinghamshire  
MK7 7AJ

**8. MARKETING AUTHORISATION NUMBER**

Vm 01708/4404

**9. DATE OF FIRST AUTHORISATION**

25 February 1999

**10. DATE OF REVISION OF THE TEXT**

February 2022

Approved 11 February 2022

A handwritten signature in black ink, appearing to read 'M. Hunter.', is written below the approval date.