

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vascace 2.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

2.61 mg cilazapril equivalent to 2.5 mg cilazapril anhydrous

Excipients with known effect:

Each tablet contains 124.39 mg lactose monohydrate (2.5 mg)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet:

Dull red, biconvex film-coated tablets with a score on one side and imprinted "CIL 2.5" on the other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Vascace is indicated for the treatment of hypertension.

Vascace is indicated for the treatment of chronic heart failure.

4.2 Posology and method of administration

Posology

Hypertension

The initial dose is 1 mg/day. Blood pressure should be assessed, and dosage adjusted individually in accordance with the blood pressure response. The usual dose range of Vascace is 2.5 to 5.0 mg once daily.

Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A lower starting dose of 0.5 mg once daily is recommended in such patients and the initiation of treatment should take place under medical supervision.

Hypertensive patients receiving diuretics

If possible, the diuretic should be discontinued 2 - 3 days before beginning therapy with Vascace to reduce the likelihood of symptomatic hypotension. It may be resumed later if required. The recommended starting dose in these patients is 0.5 mg once daily.

Chronic heart failure

Therapy with Vascace should be initiated at a recommended starting dose of 0.5 mg once daily under close medical supervision. This dose should be maintained for about 1 week. If this dose has been well tolerated it may be increased

in weekly intervals and according to the clinical status of the patient to 1.0 mg or 2.5 mg. The maximum daily dose for these patients is 5.0 mg. The posology recommendation for cilazapril in chronic heart failure is based on effects on symptomatic improvement, rather than on data showing that cilazapril reduces morbidity and mortality in this patient group (see section 5.1).

Patients with renal impairment

Reduced dosages are required for patients with renal impairment, depending on their creatinine clearance (see section 4.4).

The following dosage schedules are recommended:

Table 1: Recommended dosage schedule for patients with renal impairment

Creatinine clearance	Initial dose of Vascace	Maximal dose of Vascace
> 40 ml/min	1 mg once daily	5 mg once daily
10 - 40 ml/min	0.5 mg once daily	2.5 mg once daily
< 10 ml/min	Not recommended	

If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor, they should be discontinued and renal function should be monitored during the first weeks of Vascace therapy.

Results from clinical trials showed that clearance of cilazapril was correlated with creatinine clearance in patients with chronic heart failure. The special dosage recommendation should thus be followed in chronic heart failure patients with impaired renal function.

Liver cirrhosis

In patients with liver cirrhosis (but without ascites) who require therapy for hypertension, cilazapril should be dosed with great caution not exceeding 0.5 mg/day accompanied by careful monitoring of the blood pressure, because significant hypotension may occur.

Older people with hypertension

Treatment with Vascace should be initiated with a dose between 0.5 and 1.0 mg once daily. Thereafter, the maintenance dose must be adapted to individual tolerability, response and clinical status.

Older people with chronic heart failure

The recommended starting dose of Vascace 0.5 mg must be strictly followed.

Paediatric population

The safety and efficacy of cilazapril in children and adolescents below 18 years of age have not been established. No data are available. Therefore, no recommendation on posology can be made.

Method of administration

Vascace should be administered once daily. As food intake has no clinically significant influence on absorption, Vascace can be administered before or after a meal. The dose should always be taken at about the same time of day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to other ACE inhibitors.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.

- Second and third trimesters of pregnancy (see sections 4.4. and 4.6).
- Concomitant use of Vascase with aliskiren containing products is contraindicated in patients with diabetes mellitus or renal impairment ($\text{GFR} < 60 \text{ ml/min/1.73 m}^2$) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Hypotension

ACE inhibitors may cause severe hypotension, especially when starting treatment. First-dose hypotension is most likely to occur in patients whose renin-angiotensin-aldosterone system is activated, such as in renovascular hypertension or other causes of renal hypoperfusion, sodium or volume depletion, or previous treatment with other vasodilators. These conditions can co-exist, particularly in severe heart failure.

Hypotension should be treated by placing the patient supine and volume expansion. Cilazapril may be continued once the patient is volume replete, but should be given at a lower dose or discontinued if hypotension persists.

At-risk patients should start treatment with cilazapril under medical supervision, with a low initial dose and careful titration. If possible, diuretic therapy should be discontinued temporarily.

Similar caution should be taken for patients with angina pectoris or cerebrovascular disease, in whom hypotension can cause myocardial or cerebral ischaemia.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see section 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Renal impairment

In patients with renal impairment, the dosage of cilazapril should be adjusted according to creatinine clearance (see section 4.2). Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

ACE inhibitors have established renoprotective effects, but can cause reversible impairment of renal function in the setting of reduced renal perfusion, whether due to bilateral renal artery stenosis, severe congestive heart failure, volume depletion, hyponatraemia or high dosages of diuretics, and in those receiving treatment with NSAIDs. Preventive measures include withdrawing or temporarily withholding diuretics, beginning therapy with very small doses of ACE inhibitors, and cautious dose titration.

In patients with renal artery stenosis, activation of the renin-angiotensin-aldosterone system helps to maintain renal perfusion by causing constriction of the efferent arteriole. Hence, blockade of angiotensin II formation, and possibly also an increase in the formation of bradykinin, causes efferent arteriolar vasodilation resulting in a reduction in glomerular filtration pressure. Hypotension contributes further to a reduction in renal perfusion (see section 4.4

‘Hypotension’). As with other agents acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with cilazapril. Therefore, caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Hypersensitivity/angioedema

Angioedema has been associated with ACE inhibitors, with a reported incidence of 0.1-0.5%. Angioedema due to ACE inhibitors can present as recurrent episodes of facial swelling, which resolves on withdrawal, or as acute oropharyngeal edema and airways obstruction, which requires emergency treatment, and may be life-threatening. A variant form is angioedema of the intestine, which tends to occur within the first 24-48 hours of treatment. The risk of angioedema appears to be greater in black-skinned than non black-skinned patients. Patients with a history of angioedema unrelated to ACE inhibitors may be at greater risk.

Concomitant use of ACE inhibitors with mTOR inhibitor (e.g. temsirolimus, everolimus) or DPP-IV inhibitor (e.g. vildagliptin) therapy may lead to an increased risk for angioedema. Caution should be used when starting an mTOR inhibitor or a DPP-IV inhibitor in a patient already taking an ACE inhibitor.

Anaphylaxis

Haemodialysis

Anaphylaxis has occurred in patients dialysed with high flux membranes (e.g. AN 69) receiving ACE inhibitors. Consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent in such patients.

Low-density lipoproteins (LDL) apheresis

Patients receiving ACE inhibitors during LDL apheresis with dextran sulphate have experienced life-threatening anaphylaxis. This can be avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitization

Anaphylactic reactions can occur in patients undergoing desensitization therapy with wasp or bee venom while receiving an ACE inhibitor. Cilazapril must be stopped before the start of desensitization therapy, and should not be replaced by a β - blocker.

Hepatic disorders

Single cases of liver function disorders, such as increased values of liver function tests (transaminases, bilirubin, alkaline phosphatase, gamma GT) and cholestatic hepatitis with or without necrosis have been reported. Patients receiving cilazapril who develop jaundice or marked elevations of hepatic enzymes should discontinue cilazapril and receive appropriate medical follow-up. In patients with liver cirrhosis (but without ascites) who require therapy for hypertension, cilazapril should be initiated at a lower dose and with great caution because significant hypotension may occur (see section 4.2). In patients with ascites, cilazapril administration is not recommended.

Blood disorders

Thrombocytopenia neutropenia and agranulocytosis have been associated with ACE inhibitors. Agranulocytosis has been especially reported in patients with renal failure or collagen vascular disease and those receiving immunosuppressive therapy. Periodic monitoring of leukocyte count is recommended in such patients.

Serum potassium

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes) or potassium-sparing diuretics, and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored.

Diabetes

Administration of ACE inhibitors to patients with diabetes may potentiate the blood glucose-lowering effect of oral hypoglycaemic agents or insulin, especially in patients with renal impairment. In such patients, glucose levels should be carefully monitored during initiation of treatment with an ACE inhibitor.

Surgery/anaesthesia

Anaesthetic agents with blood pressure lowering effects can cause hypotension in patients receiving ACE inhibitors. Hypotension in this setting can be corrected with volume expansion.

Aortic stenosis/hypertrophic cardiomyopathy

ACE inhibitors should be used with caution in patients with obstructive cardiac disorders (e.g. mitral stenosis, aortic stenosis, hypertrophic cardiomyopathy), since cardiac output cannot increase to compensate for systemic vasodilation, and there is a risk of severe hypotension.

Vascace contains lactose

Patients with hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ethnicity

ACE inhibitors are less effective as antihypertensives in patients with black skin colour. These patients also have a higher risk of angioedema.

4.5 Interaction with other medicinal products and other forms of interaction

Dual blockade of the RAAS

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

If dual blockade therapy of ACE inhibitors with ARBs is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes, and blood pressure (see section 4.4).

The combination of ACE inhibitors with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment ($\text{GFR} < 60 \text{ ml/min/1.73 m}^2$) and is not recommended in other patients (see sections 4.3 and 4.4).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors.

Use of cilazapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

Other antihypertensive agents

An additive effect may be observed when cilazapril is administered in combination with other antihypertensive agents.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with cilazapril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or

potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, the combination of cilazapril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with cilazapril (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of cilazapril.

Tricyclic antidepressants/antipsychotics/anesthetics/narcotics

Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including aspirin ≥ 3 g/day

When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

mTOR inhibitors

Concomitant use of ACE inhibitors with mTOR inhibitor (e.g. temsirolimus, everolimus) therapy may lead to an increased risk for angioedema (see section 4.4).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Concomitant use of ACE inhibitors with DPP-IV inhibitor (e.g. vildagliptin) therapy may lead to an increased risk for angioedema (see section 4.4).

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.

Others

No clinically significant interactions were observed when cilazapril and digoxin, nitrates, coumarin anticoagulants, and H₂ receptor blockers were concomitantly administered.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ACE inhibitors such as cilazapril is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors such as cilazapril is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative

antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound examination of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast-feeding

Because no information is available regarding the safety of cilazapril during breast-feeding, cilazapril is not recommended, and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

When driving and operating machines, it should be taken into account that occasionally dizziness and fatigue may occur, especially when starting therapy (see sections 4.4 and 4.8).

4.8 Undesirable effects

(a) Summary of the safety profile

The most frequent drug-attributable adverse events observed in patients taking ACE inhibitors are cough, skin rash and renal dysfunction. Cough is more common in women and non-smokers. Where the patient can tolerate the cough, it may be reasonable to continue treatment. In some cases, reducing the dose may help.

Treatment-related adverse events severe enough to stop treatment occur in less than 5% of patients receiving ACE inhibitors.

(b) Tabulated list of adverse reactions

The following list of adverse reactions is derived from clinical trials and post-marketing data in association with cilazapril and/or other ACE inhibitors. Estimates of frequency are based on the proportion of patients reporting each adverse reaction during cilazapril clinical trials that included a total combined population of 7171 patients. Adverse reactions that were not observed during cilazapril clinical trials but have been reported in association with other ACE inhibitors or derived from post-marketing case reports are classified as 'rare'.

Frequency categories are as follows:

Very common	$\geq 1/10$
Common	$\geq 1/100$ and $< 1/10$
Uncommon	$\geq 1/1,000$ and $< 1/100$
Rare	$< 1/1,000$

Blood and lymphatic system disorders

Rare

Neutropenia, agranulocytosis, thrombocytopenia, anaemia

Immune system disorders

Uncommon

Angioedema (may involve the face, lips, tongue, larynx or gastrointestinal tract) (see section 4.4)

Rare

Anaphylaxis (see section 4.4)

Lupus-like syndrome (symptoms may include vasculitis, myalgia, arthralgia/arthritis, positive antinuclear antibodies, increased erythrocyte sedimentation rate, eosinophilia and leukocytosis)

Nervous system disorders

Common

Headache

Uncommon

Dysgeusia

Rare

Cerebral ischaemia, transient ischaemic attack, ischaemic stroke

Peripheral neuropathy

Cardiac disorders

Uncommon

Myocardial ischaemia, angina pectoris, tachycardia, palpitations

Rare

Myocardial infarction, arrhythmia

Vascular disorders

Common

Dizziness

Uncommon

Hypotension, postural hypotension (see section 4.4). Symptoms of hypotension may include syncope, weakness, dizziness and visual impairment.

Respiratory, thoracic and mediastinal disorders

Common

Cough

Uncommon

Dyspnoea, bronchospasm, rhinitis

Rare

Interstitial lung disease, bronchitis, sinusitis

Gastrointestinal disorders

Common

Nausea

Uncommon

Dry mouth, aphthous stomatitis, decreased appetite, diarrhoea, vomiting

Rare

Glossitis, pancreatitis

Hepatobiliary disorders

Rare

Abnormal liver function test (including transaminases, bilirubin, alkaline phosphatase, gamma GT)

Cholestatic hepatitis with or without necrosis

Skin and subcutaneous tissue disorders

Uncommon

Rash, maculopapular rash

Rare

Psoriaform dermatitis, psoriasis (exacerbation), lichen planus, exfoliative dermatitis, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous pemphigoid, pemphigus, Karposi's sarcoma, vasculitis/purpura, photosensitivity reactions, alopecia, onycholysis

Musculoskeletal and connective tissue disorders

Uncommon

Muscle cramps, myalgia, arthralgia

Renal and urinary disorders

Rare

Renal impairment, acute renal failure (see section 4.4), blood creatinine increased, blood urea increased, hyperkalaemia, hyponatraemia, proteinuria, nephrotic syndrome, nephritis

Reproductive and breast disorders

Uncommon

Impotence

Rare

Gynaecomastia

General disorders and administration site conditions

Common

Fatigue

Uncommon

Excess sweating, flushing, asthenia, sleep disorder

(c) Description of selected adverse events

Hypotension and postural hypotension may occur when starting treatment or increasing dose, especially in at-risk patients (see section 4.4).

Renal impairment and acute renal failure are more likely in patients with severe heart failure, renal artery stenosis, pre-existing renal disorders or volume depletion (see section 4.4).

Hyperkalaemia is most likely to occur in patients with renal impairment and those taking potassium sparing diuretics or potassium supplements.

The events of cerebral ischaemia, transient ischaemic attack and ischaemic stroke reported rarely in association with ACE inhibitors may be related to hypotension in patients with underlying cerebrovascular disease. Similarly, myocardial ischaemia may be related to hypotension in patients with underlying ischaemic heart disease.

Headache is a commonly reported adverse event, although the incidence of headache is greater in patients receiving placebo than in those receiving ACE inhibitors.

(d) Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Limited data are available for overdosage in humans.

Symptoms

Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

Management

The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered.

Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

If indicated, cilazaprilat, the active form of cilazapril, may be removed from the general circulation by haemodialysis (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor, ATC code: C09AA08.

Mechanism of action

Vascace is a specific, long-acting angiotensin-converting enzyme (ACE) inhibitor which suppresses the renin-angiotensin-aldosterone system and thereby the conversion of the inactive angiotensin I to angiotensin II, which is a potent vasoconstrictor. At recommended doses, the effect of Vascace in hypertensive patients and in patients with chronic heart failure is maintained for up to 24 hours.

Clinical efficacy and safety

Hypertension

Vascace induces a reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. It is effective in all degrees of essential hypertension as well as in renal hypertension. The antihypertensive effect of Vascace is usually apparent within the first hour after administration, with maximum effect observed between 3 and 7 hours after dosing. In general, the heart rate remains unchanged. Reflex tachycardia is not induced, although small, clinically insignificant alterations of heart rate may occur. In some patients blood pressure reduction may diminish towards the end of the dosage interval.

The antihypertensive effect of Vascace is maintained during long-term therapy. No rapid increase in blood pressure has been observed after abrupt withdrawal of Vascace.

In hypertensive patients with moderate to severe renal impairment, the glomerular filtration rate and renal blood flow generally remained unchanged with Vascace, despite a clinically significant blood pressure reduction.

As with other ACE inhibitors, the blood pressure-lowering effect of Vascace in black patients may be less pronounced than in non-blacks. However, racial differences in response are no longer evident when Vascace is administered in combination with hydrochlorothiazide.

Dual blockade of the RAAS

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE- inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Chronic heart failure

No clinical trials have been carried out which prove the effect of cilazapril on morbidity and mortality in heart failure. In patients with chronic heart failure, the renin-angiotensin-aldosterone and sympathetic nervous systems are generally activated, leading to enhanced systemic vasoconstriction and promotion of sodium and water retention. By suppressing the renin-angiotensin-aldosterone system, Vascace improves loading conditions in the failing heart by reducing systemic vascular resistance (afterload) and pulmonary capillary wedge pressure (preload) in patients on diuretics and/or digitalis. Furthermore, the exercise tolerance of these patients increases significantly. The haemodynamic and clinical effects occur promptly and persist.

5.2 Pharmacokinetic propertiesAbsorption

Cilazapril is efficiently absorbed and rapidly converted to the active form, cilazaprilat. Ingestion of food immediately prior to Vascace administration delays and reduces absorption to a minor extent which, however, is therapeutically irrelevant. The bioavailability of cilazaprilat from oral cilazapril approximates 60%, based on urinary recovery data. Maximum plasma concentrations are reached within 2 hours after administration and are directly related to dosage.

Elimination

Cilazaprilat is eliminated unchanged by the kidneys, with an effective half-life of 9 hours after once daily dosing with Vascace.

Pharmacokinetics in Special Populations

Renal impairment: In patients with renal impairment, higher plasma concentrations of cilazaprilat are observed than in patients with normal renal function, since drug clearance is reduced when creatinine clearance is lower. There is no elimination in patients with complete renal failure, but haemodialysis reduces concentrations of both cilazapril and cilazaprilat to a limited extent.

Older people

In elderly patients whose renal function is normal for age, plasma concentrations of cilazaprilat may be up to 40% higher and clearance 20% lower, than in younger patients.

Hepatic impairment

In patients with liver cirrhosis increased plasma concentrations and reduced plasma and renal clearance were observed, with a greater effect on cilazapril than on its active metabolite cilazaprilat.

Chronic heart failure

In patients with chronic heart failure, clearance of cilazaprilat is correlated with creatinine clearance. Thus, dosage adjustments beyond those recommended for patients with impaired renal function (see section 4.2) should not be necessary.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of general pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin-angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Maize starch
Hypromellose 3cP
Talc
Sodium stearyl fumarate

Film-coat:

Hypromellose 6cP
Talc
Titanium dioxide E171
in addition Iron oxide yellow (E 172) and Iron oxide Red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/Aluminium blisters containing 14, 20, 28, 30, 50, 56, 60, 98 film-coated tablets.
Amber glass bottles with tamper evident polyethylene screw closure containing 28, 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0050/083/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th August 1991.

Date of last renewal: 25th September 2012

10 DATE OF REVISION OF THE TEXT

February 2015