ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vascace Plus and associated names (see Annex I) 5 mg/12.5 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For a full list of excipients, see section 6.1.
[To be completed nationally]

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vascace Plus is indicated for the treatment of hypertension in adult patients whose blood pressure is not adequately controlled with cilazapril alone.

4.2 Posology and method of administration

Posology
The dose of Vascace Plus is one tablet (5.0 mg cilazapril and 12.5 mg hydrochlorothiazide) administered once daily.
As food intake has no clinically significant influence on absorption, Vascace Plus can be administered before or after a meal. The dose should always be taken at about the same time of day. The tablets must not be chewed or crushed and should always be swallowed with a drink of water.

Patients with renal impairment
When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic rather than a thiazide diuretic is preferred for use with cilazapril. Therefore, Vascace Plus is not recommended for patients with severe renal impairment (see section 4.3).

Patients with liver cirrhosis
Because significant hypotension may occur in patients with liver cirrhosis treated with standard doses of ACE inhibitors, cautious dose titration of each individual component is needed if patients with liver cirrhosis should require treatment with cilazapril and hydrochlorothiazide (see section 4.4).

Elderly
In clinical studies, the efficacy and tolerability of cilazapril and hydrochlorothiazide administered concomitantly was similar in both elderly and younger hypertensive patients, although pharmacokinetic data show that clearance of both components in elderly patients was reduced (see section 5.2).

Paediatric population
Safety and efficacy in children and adolescents below 18 years of age have not been established. Therefore, Vascace Plus is not recommended for administration to this population.

4.3 Contraindications

- Hypersensitivity to cilazapril, other ACE inhibitors, hydrochlorothiazide, other thiazide diuretics, sulphonamides or any excipients of Vascace Plus

- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Renal impairment (creatinine clearance <30 ml/min/1.73 m^2) or anuria
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)

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). There is limited experience with hydrochlorothiazide during pregnancy. Thiazides cross the placenta and may be associated with neonatal jaundice, thrombocytopenia and electrolyte abnormalities. Reductions in maternal blood volume could also adversely affect placental perfusion. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for the treatment of essential hypertension in pregnant women except in rare situations where no other therapy can be used.

Hypotension
Patients should start treatment with Vascace Plus only after they have been stabilized on each component given at the same dose as in the combined product.

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.

Renal impairment
Vascace Plus is contraindicated in patients with creatinine clearance <30 ml/min/1.73 m^2. In patients with mild renal impairment, the dosage of cilazapril should be adjusted according to creatinine clearance. Routine monitoring of potassium and creatinine is part of normal medical practice for patients with renal impairment.

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.

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 in patients treated with cilazapril. Patients who develop jaundice or marked elevations of hepatic enzymes should discontinue Vascace Plus 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 low dose and with great caution because significant hypotension may occur (see section 4.2). In patients with ascites, cilazapril is not recommended.
The use of thiazides in patients with cirrhosis may precipitate hepatic encephalopathy resulting from minor changes in fluid and electrolyte balance.

Neutropenia
Rarely, neutropenia and agranulocytosis have been associated with both thiazides and ACE inhibitors, especially 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 electrolytes
Electrolytes and renal function should be monitored in all patients receiving Vascace Plus.

ACE inhibitors can cause hyperkalemia due to suppression 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), hyperkalemia can occur.

Thiazides increase potassium excretion and can cause hypokalaemia. Hypokalaemia may also occur in patients receiving Vascace Plus, although to a lesser extent than that seen in patients receiving thiazide monotherapy. Thiazides may also cause hyponatraemia and dehydration. The risk of hyponatraemia is greater in women, patients with hypokalaemia or low sodium/solute intake, and in the elderly. Thiazides may decrease urinary calcium excretion and cause elevation of serum calcium levels, and should be discontinued before carrying out tests for parathyroid function.

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. Thiazides can oppose the blood glucose-lowering effect of oral hypoglycaemic agents or insulin, and may precipitate diabetes in at-risk patients. Glucose levels should be carefully monitored during initiation of treatment with each component of Vascace Plus.

Other metabolic disorders
Thiazides may increase serum uric acid levels and may precipitate acute gout. Hence, Vascace Plus should be used with caution in patients with a history of gout.

Vascace Plus should be used with caution in patients with porphyria.

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.

Lactose intolerance
Owing to the presence of lactose monohydrate, 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

Interactions mainly related to cilazapril
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 Vascace Plus 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.

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.

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 H_2-receptor blockers were concomitantly administered.

<u>Interactions mainly related to hydrochlorothiazide</u>
Digoxin
Since thiazide-induced hypokalaemia may occur during therapy with Vascace Plus, which may increase the risk of arrhythmia associated with digoxin therapy, monitoring of potassium plasma levels is advised.

Medicinal products that could induce torsades de pointes
Due to the risk of hypokalemia hydrochlorothiazide should be administered with caution when a patient is simultaneously being treated with medicinal products that could induce torsades de pointes such as:

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, defetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, trifluoperazine, sulpiride, tiapride, haloperidol, droperidol)

- Other medicinal products (e.g. bepridil, cisapride, diphemanil, halofantrine, ketanserin, pentamidine, terfenadine)

Non-depolarizing muscle relaxants
Non-depolarizing muscle relaxants should not be administered simultaneously, due to possible intensification and prolongation of the muscular relaxing effect.

Calcium salts and vitamin D
Simultaneous administration of hydrochlorothiazide together with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Cholestyramine/colestipol
Cholestyramine and colestipol reduce the absorption of hydrochlorothiazide.

Anticholinergics
Concomitant use of anticholinergics (e.g. atropine, biperiden) may increase the bioavailability of hydrochlorothiazide due to reduced gastrointestinal mobility and decreased gastric emptying.

Amantidine
Simultaneous administration of amantidine and hydrochlorothiazide may increase possible adverse effects of amantidine.

Cytotoxic drugs (e.g. methotrexate, cyclophosphamide)
Simultaneous administration of hydrochlorothiazide and cytotoxic drugs may decrease the elimination of the cytotoxic drug and consequently increase the risk of developing myelodepression.

Iodine containing contrast media
In case of dehydration induced by hydrochlorothiazide, there is an increased risk of acute renal impairment, in particular when larger doses of iodine containing contrast media are administered.

Cyclosporine
Simultaneous administration of cyclosporine and hydrochlorothiazide may increase the risk of developing hyperuricemia and gout-like complications.

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 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 inhibitor 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).

There is limited experience with hydrochlorothiazide during pregnancy. Thiazides cross the placenta and may be associated with neonatal jaundice, thrombocytopenia and electrolyte abnormalities.

Reductions in maternal blood volume could also adversely affect placental perfusion. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for the treatment of essential hypertension in pregnant women except in rare situations where no other therapy can be used.

Breastfeeding
Because no information is available regarding the use of Vascace Plus during breastfeeding, this product is not recommended, and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Fertility
Preclinical studies on the effect on fertility were not conducted with the fixed combination of cilazapril and hydrochlorothiazide.

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 during treatment with Vascace Plus (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequent drug-attributable adverse events observed in patients receiving ACE inhibitor monotherapy 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 resulting in treatment withdrawal occur in less than 5% of patients receiving ACE inhibitor monotherapy.

The most frequent drug-attributable adverse event observed in patients receiving thiazide monotherapy is dizziness. Some biochemical and metabolic abnormalities associated with thiazide diuretics appear to be attenuated by the co-administration of cilazapril. Treatment-related adverse events resulting in treatment withdrawal occur in around 0.1% of patients receiving thiazide monotherapy.

The overall risk of adverse effects due to treatment with Vascace Plus is similar to that observed in patients receiving cilazapril monotherapy.

Tabulated list of adverse reactions

The following list of adverse reactions is derived from clinical trials and post-marketing data, and includes adverse drug reactions seen in patients receiving treatment with cilazapril and/or other ACE inhibitors alone, hydrochlorothiazide and/or other thiazide-type diuretics alone, and in those receiving combined therapy. Estimates of frequency are based on the proportion of patients reporting each adverse reaction during Vascace Plus clinical trials that included a total combined population of 1'097 patients. Adverse reactions that were not observed during Vascace Plus clinical trials but have been reported in association with monotherapy with either component or with other ACE inhibitors or thiazide diuretics, or derived from post-marketing case reports, are classified as `uncommon' (<1/100). The category `uncommon' incorporates `rare' (≥1/10'000 and <1/1'000) and `very rare' (<1/10'000), which may be used in some SPCs for other products.

Frequency categories are as follows:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	< 1/100

Adverse reactions to cilazapril

Blood and lymphatic system disorders

Uncommon
Neutropenia, agranulocytosis, thrombocytopenia, anaemia

Immune system disorders

Uncommon
Angioedema (may involve the face, lips, tongue, larynx or gastrointestinal tract) (see section 4.4), 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, cerebral ischaemia, transient ischaemic attack, ischaemic stroke, peripheral neuropathy

Cardiac disorders

Uncommon
Myocardial ischaemia, angina pectoris, tachycardia, palpitations, 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, interstitial lung disease, bronchitis, sinusitis

Gastrointestinal disorders

Common
Nausea

Uncommon
Dry mouth, aphthous stomatitis, decreased appetite, diarrhoea, vomiting, glossitis, pancreatitis

Hepatobiliary disorders

Uncommon

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, 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

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

Reproductive system and breast disorders

Uncommon
Sexual dysfunction, gynaecomastia

General disorders and administration site conditions

Common
Fatigue

Uncommon
Excess sweating, flushing, asthenia, sleep disorder

Adverse reactions to hydrochlorothiazide

Blood and lymphatic system disorders

Uncommon
Thrombocytopaenia, haemolytic anaemia, bone marrow failure, neutropenia

Immune system disorders

Uncommon
Hypersensitivity (angioedema, anaphylaxis), lupus-like syndrome

Metabolism and nutrition disorders

Uncommon
Hypokalaemia, hyponatraemia, hypochloraemia, hypomagnesaemia, hypercalcaemia, hypocalciuria, hypovolaemia/dehydration, metabolic alkalosis, hyperglycaemia, hyperuricaemia, gout, hypercholesterolaemia (increased total, LDL and VLDL cholesterol) hypertriglyceridaemia.

Psychiatric disorders

Uncommon

Sleep disorder, depression

Nervous system disorders

Common
Dizziness

Uncommon
Confusional state

Eye disorders

Uncommon
Lacrimation decreased, visual impairment, xanthopsia

Cardiac disorders

Uncommon
Arrhythmia

Vascular disorders

Uncommon
Hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon
Interstitial pneumonitis, acute pulmonary oedema

Gastrointestinal disorders

Common
Nausea

Uncommon
Dry mouth, sialoadenitis, loss of appetite, pancreatitis

Hepatobiliary disorders

Uncommon
Cholestatic jaundice

Skin and subcutaneous tissue disorders

Uncommon
Rash, photosensitivity, pseudoporphyria, cutaneous vasculitis

Musculoskeletal and connective tissue disorders

Uncommon
Muscle cramp

Renal and urinary disorders

Uncommon
Interstitial nephritis, renal impairment

Reproductive system and breast disorders

Uncommon
Sexual dysfunction

General disorders and administration site conditions

Common
Fatigue

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).

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.

Hypokalaemia may occur in patients receiving Vascace Plus, although less commonly than in patients receiving thiazide monotherapy.

The risk of hyponatraemia is greater in women, patients with hypokalaemia or low sodium/solute intake, and the elderly.

Electrolyte and renal function should be monitored in all patients receiving Vascace Plus.

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

The frequency of adverse reactions attributable to cilazapril, occurring in patients receiving combination therapy (cilazapril + hydrochlorothiazide), may differ from that seen in patients receiving cilazapril monotherapy. Reasons may include (i) differences between the target populations treated with Vascace Plus and Vascace, (ii) differences in cilazapril dose, and (iii) specific effects of combination therapy.

4.9 Overdose

Limited data are available for overdosage in humans.

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

In predisposed patients (e.g. prostatic hyperplasia) hydrochlorothiazide overdose may induce acute urinary retention.

The recommended treatment of Vascace Plus 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: Antihypertensive; ACE inhibitor and diuretic, ATC code: C09BA08

Mechanism of Action
Vascace Plus is a combination of cilazapril and hydrochlorothiazide. The antihypertensive effects of cilazapril and hydrochlorothiazide in the combination are additive resulting in a higher percentage of hypertensive patients responding satisfactorily as well as in a greater blood pressure reduction than to either component administered alone.

Cilazapril is converted to its active metabolite, cilazaprilat, 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 cilazapril in hypertensive patients is maintained for up to 24 hours.

Hydrochlorothiazide is a thiazide diuretic which acts as fluid-expelling and blood pressure-lowering agent by inhibition of substances which increase the tubular re-absorption of sodium in the cortical diluting segment. It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an anti-hypertensive effect. The use of this agent increases plasma renin activity and aldosterone secretion resulting in a decrease in serum potassium.

Clinical/Efficacy Studies
Studies performed with Vascace Plus have demonstrated that the combination of cilazapril and hydrochlorothiazide administered once daily at various doses reduces systolic and diastolic blood pressure compared to placebo 24 hours after dosing, to an extent that is both statistically significant and clinically meaningful. The combination at various doses produces greater blood pressure reduction than either of the two individual components. In patients not responding to 5 mg cilazapril given as monotherapy, the addition of hydrochlorothiazide at a low dose of 12.5 mg once daily substantially improves the response to treatment. The combination is effective irrespective of age, gender and race.

5.2 Pharmacokinetic properties

Absorption
Cilazapril is efficiently absorbed after oral administration of Vascace Plus and rapidly converted by ester cleavage to the active form, cilazaprilat. The bioavailability of cilazaprilat from oral cilazapril approximates 60% based on urinary recovery data. Maximum plasma concentrations of cilazaprilat are consistently achieved within 2 hours.

Hydrochlorothiazide is rapidly absorbed following oral administration of Vascace Plus. Maximum plasma concentrations are achieved within 2 hours post dosing. The bioavailability of hydrochlorothiazide after oral dose is about 65% based on urinary recovery.

AUC values increase proportionally for cilazaprilat and hydrochlorothiazide with increasing doses of cilazapril and hydrochlorothiazide in the combination dosage form. The pharmacokinetic parameters of cilazaprilat are not altered in the presence of increasing doses of the hydrochlorothiazide component. Concomitant administration of cilazapril with hydrochlorothiazide has no effect on the

bioavailability of either cilazapril or hydrochlorothiazide. Administration of cilazapril and hydrochlorothiazide in the presence of food delays cilazaprilat T_{max} by 1.5 hours and reduces C_{max} by 24%. It delays hydrochlorothiazide T_{max} by 1.4 hours and reduces C_{max} by 14% with no effect on overall bioavailability of both molecules as assessed by AUC_{0-24}-value. This indicates that there is an influence on rate but not on the extent of absorption of both medicines.

Distribution
For cilazaprilat, the volume of distribution has been determined to be approximately 0.5 to 0.7 l/kg. Plasma protein binding is approximately 25 to 30%.

Hydrochlorothiazide binds to 65% to plasma proteins; the relative volume of distribution has been determined to be 0.5 to 1.1 l/kg.

Elimination
Cilazaprilat is eliminated unchanged by the kidneys, with an effective half-life of about 9 hours.

Hydrochlorothiazide is eliminated largely unchanged by the kidney, with a half-life of 7 to 11 hours.

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.
Renal excretion of hydrochlorothiazide is reduced in patients with impaired renal function. Renal hydrochlorothiazide clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of hydrochlorothiazide, which decrease more slowly than in subjects with normal renal function.

Elderly patients
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.
Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly patients compared to young healthy volunteers.

Hepatic impairment
In patients with liver cirrhosis increased plasma concentrations and reduced plasma and renal clearance were observed.
Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

5.3 Preclinical safety data

Toxicity
The acute oral toxicity of cilazapril is low. The mean lethal doses in rats, mice, and cynomolgus monkeys were higher than 2000 mg/kg body weight. The acute oral toxicity of cilazapril in mice was not enhanced by the combination with hydrochlorothiazide.

As with other ACE inhibitors, the kidney was the primary target of systemic toxicity in subchronic and chronic toxicity studies with cilazapril alone. The findings included increased plasma urea and creatinine values, and thickening of the glomerular arterioles, occasionally in association with hyperplasia of the juxtaglomerular cells. These changes were demonstrated to be reversible and are a consequence of exaggerated pharmacodynamic activity of cilazapril occurring only at high multiples of the therapeutic human doses. Subchronic and chronic toxicity studies with hydro-chlorothiazide in rats and dogs showed no noticeable findings except for changes in the electrolyte balance (hypokalaemia). Combination studies with cilazapril and hydrochlorothiazide caused similar findings as observed with cilazapril alone. The main combination effects were the attenuation of thiazide induced potassium loss and decreased motoric activity at high doses in monkeys.

Carcinogenicity
There was no evidence of carcinogenicity of cilazapril and no relevant findings with hydrochlorothiazide in mice and rats. No tests of carcinogenicity were conducted with the combination.

Mutagenicity
Cilazapril did no show any mutagenic or genotoxic effect in various mutagenicity tests, performed in vitro and in vivo. The combination of cilazapril and hydrochlorothiazide caused no relevant signs of a mutagenic potential for the case of therapeutic treatment.

Impairment of Fertility
Studies on the effect on peri- and postnatal performance and on fertility were not conducted with the combination.

Teratogenicity
Cilazapril was not teratogenic in rats and cynomolgus monkeys. As with other ACE inhibitors, signs of foetotoxicity were observed in rats. The main findings were increased pre-implantation loss and fewer viable foetuses. They occurred only at 50 mg/kg corresponding to high multiples of therapeutic human doses. A slightly higher incidence of pelvic dilation was observed in rats at 5 mg/kg/day. Cilazapril had no effect on male or female fertility in rats. There was no evidence of teratogenicity with the combination of cilazapril and hydrochlorothiazide in rats and mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vascace Plus and associated names (see Annex I) 5 mg/12.5 mg film-coated tablets
[See Annex I - To be completed nationally]

cilazapril/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

[To be completed nationally]

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT

Vascace Plus and associated names (see Annex I) 5 mg/12.5 mg film-coated tablets
[See Annex I - To be completed nationally]

cilazapril/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Vascace Plus and associated names (see Annex I) 5 mg/12.5 mg film-coated tablets
[See Annex I - To be completed nationally]

cilazapril/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT VASCACE PLUS IS AND WHAT IT IS USED FOR

Vascace Plus is a combination of two medicines called cilazapril and hydrochlorothiazide.

Vascace Plus is used to treat high blood pressure. The two active substances work together to lower your blood pressure. They are used together when treatment with just one is insufficient.

Cilazapril belongs to a group of medicines called 'ACE inhibitors' (Angiotensin Converting Enzyme Inhibitors). It works by making your blood vessels relax and widen. This helps to lower your blood pressure. It also makes it easier for your heart to pump blood around your body.

Hydrochlorothiazide belongs to a group of medicines called 'thiazide diuretics' or 'water tablets'. It works by increasing the amount of water (urine) you produce. This lowers your blood pressure.

2. BEFORE YOU TAKE VASCACE PLUS

Do not take Vascace Plus
- if you are allergic (hypersensitive) to cilazapril, hydrochlorothiazide or any of the other ingredients of Vascace Plus (listed in section 6: Further information).
- if you are allergic (hypersensitive) to medicines similar to Vascace Plus such as other ACE inhibitors, other thiazide diuretics or sulphonamides.
- if you have had a serious side effect called angioedema after taking other ACE inhibitor medicines, hereditary angioedema or angioedema of unknown cause. The signs include swelling of the face, lips, mouth or tongue.
- If you have severe kidney problems (creatinine clearance less than 30 ml/min) or anuria (inability to pass urine).
- if you are more than 3 months pregnant. (It is also better to avoid Vascace Plus in early pregnancy - see the sections on "Pregnancy" and "Breastfeeding".)

Do not take Vascace Plus if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Vascace Plus.

Take special care with Vascace Plus
Check with your doctor or pharmacist before taking Vascace Plus
- if you have a heart problem. Vascace Plus is not suitable for people with certain types of heart problem.
- if you have had a stroke or have problems with the blood supply to your brain.
- if you have severe liver problems or if you develop jaundice.
- if you have kidney problems or have a problem with the blood supply to your kidneys called renal artery stenosis.
- if you are on kidney dialysis.
- if you have recently been vomiting or have had diarrhoea.
- if you are on a diet to control how much salt (sodium) you take in.
- if you are planning to have treatment to reduce your allergy to bee or wasp stings (desensitization).
- if you are planning to have an operation (including dental surgery). This is because some anaesthetics can lower your blood pressure, and it may become too low.
- if you have a build up of fluid in your abdomen (ascites).
- if you have diabetes.
- if you have a collagen vascular disease.
- if you undergo LDL apheresis with dextrane sulphate.
- if you have gout.
- if you have porphyria.

If any of the above apply to you, or if you are not sure, talk to your doctor or pharmacist before you take Vascace Plus.

You must tell your doctor if you think you are (or might become) pregnant. Vascace Plus is not recommended in early pregnancy and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see the sections on ‘Pregnancy’ and ‘Breastfeeding’).

Use in children and adolescents
Vascace Plus is not recommended for use in children and adolescents below 18 years of age.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Vascace Plus can affect the way some medicines work. Also some medicines can affect the way Vascace Plus works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- Any medicines used to treat high blood pressure.
- Medicines called ‘non-steroidal anti-inflammatory drugs’ (NSAIDs). These include aspirin, indometacin and ibuprofen.
- Insulin or other medicines used to treat diabetes.
- Lithium (used to treat depression).
- Steroid medicines (such as hydrocortisone, prednisolone and dexamethasone) or other medication which suppress the immune system.
- Potassium supplements (including salt substitutes) or potassium-sparing diuretics.
- Aldosterone antagonists.
- Sympathomimetics.
- Anaesthetics, narcotics.
- Tricyclic antidepressants, antipsychotics.
- Gold compounds (used to treat rheumatoid arthritis).
- Medicines to treat heart failure or heart rhythm abnormalities.

- Calcium supplements and vitamin D.
- Cholestyramine/colestipol (used for reducing the amount of fat in your blood).
- Anticholinergics.
- Cytotoxic drugs (e.g. methotrexate, cyclophosphamide).
- Cyclosporine (used to stop the rejection of organs after transplantation).
- Iodine containing contrast media (given to patients before certain types of X-ray examination).

Taking Vascace Plus with food and drink
Vascace Plus my be taken with or without food.

Tell your doctor or pharmacist if you are taking food supplements that contain potassium.

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Vascace Plus before you become pregnant, or as soon as you know you are pregnant, and will advise you to take another medicine instead of Vascace Plus. Vascace Plus is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breastfeeding
Tell your doctor if you are breastfeeding or about to start breastfeeding. Vascace Plus is not recommended for mothers who are breastfeeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
You may feel dizzy while taking Vascace Plus. This is more likely to happen when you first start treatment. If you feel dizzy, do not drive or use any tools or machines.

Important information about some of the ingredients of Vascace Plus
Vascace Plus contains lactose, which is a type of sugar. If you have an intolerance to lactose, talk to your doctor before taking this medicine.

[To be completed nationally]

3. HOW TO TAKE VASCACE PLUS

Always take Vascace Plus exactly as prescribed. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one tablet each day.

Taking this medicine
- Swallow each tablet with a drink of water.
- It does not matter what time of day you take Vascace Plus. However, always take it around the same time.
- Vascace Plus may be taken before or after a meal.
- Do not crush or chew the tablets

If you take more Vascace Plus than you should
If you take more Vascace Plus than you should, or if someone else takes your Vascace Plus tablets, talk to a doctor or go to a hospital straight away. Take the medicine pack with you. The following effects may happen: feeling dizzy or light-headed, shallow breathing, cold clammy skin, being unable to move or speak and a slow or irregular heart beat.

If you forget to take Vascace Plus
- If you forget to take a dose, skip the missed dose. Then take the next dose when it is due.

- Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Vascace Plus can cause side effects, although not everybody gets them.

Severe reactions:
If you have a severe reaction called angioedema, stop taking Vascace Plus and see a doctor straight away. The signs may include:
- Sudden swelling of the face, throat, lips or mouth. This can make it difficult to breathe or swallow.

Blood problems reported with ACE inhibitors and thiazide-type diuretics include:
- Low numbers of red blood cells (anaemia). The signs include feeling tired, pale skin, fast or uneven heart beat (palpitations), and feeling short of breath.
- Low numbers of all types of white blood cells. The signs include increased number of infections, for example in your mouth, gums, throat and lungs.
- Low numbers of platelets in your blood. The signs include bruising easily and nose bleeds.

Other possible side effects:

Common (affects less than 1 in 10 people)

- Feeling dizzy
- Coughing
- Nausea
- Feeling tired
- Headache

Uncommon (affects less than 1 in 100 people)

- Low blood pressure. This may make you feel weak, dizzy or light-headed, and may lead to blurred vision and fainting. Excessive lowering of blood pressure may increase the chance of heart attack or stroke in certain patients
- Increased heart rate
- Feeling weak
- Pains in the chest
- Breathing problems, including shortness of breath and tightness in the chest
- A runny or blocked nose and sneezing (rhinitis)
- Dry or swollen mouth
- Lack of appetite
- Change in the way things taste
- Diarrhoea and vomiting
- Skin rash (which may be severe)
- Muscle cramps or pain in your muscles or joints
- Impotence
- Sweating more than usual
- Flushing
- Sleeping problems
- Blood tests showing a decrease in the number of red blood cells, white blood cells or platelets (anemia, neutropenia, agranulocytosis and thrombocytopenia)
- Blood tests showing abnormal electrolyte levels (sodium, potassium, chloride, magnesium, calcium, bicarbonate), or elevated glucose, urate, cholesterol and triglyceride levels
- A type of severe allergic reaction (anaphylaxis)

- Cerebral ischaemia, transient ischaemic attack, ischaemic stroke (may occur if blood pressure becomes too low)
- Myocardial infarction (may occur if blood pressure becomes too low)
- Irregular heartbeat
- Interstitial lung disease
- A disorder resembling systemic lupus erythematosus
- Pins and needles or numbness in the hands or feet
- Wheezing
- A feeling of fullness or a throbbing pain behind the nose, cheeks and eyes (sinusitis).
- Soreness of your tongue
- Pancreatitis (inflammation of the pancreas). The signs include severe pain in the stomach which spreads to your back
- Changes in the way your liver or kidneys work (shown in blood and urine tests)
- Liver problems such as hepatitis (inflammation of the liver) or liver damage
- Severe skin reactions including blistering or peeling of skin
- Increased sensitivity to light
- Hair loss (which may be temporary)
- Loosening or separation of a nail from its bed
- Breast enlargement in men
- Depression
- Confusion
- Dry eyes
- Yellow colour vision distortion

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE VASCACE PLUS

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use Vascace Plus after the expiry date which is stated on the pack after EXP.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Vascace Plus contains

- The active substances are cilazapril and hydrochlorothiazide
- The other ingredient(s) is (are)...
  [To be completed nationally]

What Vascace Plus looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria: Inhibace Plus “Roche”
Belgium, Luxembourg: Co-Inhibace
Cyprus, Greece: Vascace Plus
Czech Republic, Hungary, Poland, Spain: Inhibace Plus
Germany: Dynorm Plus
Italy, Portugal: Inibace Plus

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]