ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State EU	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Roche Austria GmbH, Engelhorngasse 3, A - 1211 Vienna Austria	Inhibace "Roche" 0,5 mg - Filmtabletten	0.5 mg	Film-coated tablets	Oral use
Austria	Roche Austria GmbH, Engelhorngasse 3, A - 1211 Vienna Austria	Inhibace "Roche" 2,5 mg - Filmtabletten	2.5 mg	Film-coated tablets	Oral use
Austria	Roche Austria GmbH, Engelhorngasse 3, A - 1211 Vienna Austria	Inhibace "Roche" 5 mg - Filmtabletten	5 mg	Film-coated tablets	Oral use
Belgium	N.V. Roche S.A. Rue Dante 75 1070 Bruxelles Belgium	Inhibace	0.5 mg	Film-coated tablets	Oral use
Belgium	N.V. Roche S.A. Rue Dante 75 1070 Bruxelles Belgium	Inhibace	5 mg	Film-coated tablets	Oral use
Bulgaria	Roche Bulgaria EOOD 16, Bvalo pole Str. 1618 / Sofia Bulgaria	Inhibace	1 mg	Film-coated tablets	Oral use
Bulgaria	Roche Bulgaria EOOD 16, Bvalo pole Str. 1618 / Sofia Bulgaria	Inhibace	2.5 mg	Film-coated tablets	Oral use

Member State EU	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Bulgaria	Roche Bulgaria EOOD 16, Bvalo pole Str. 1618 / Sofia Bulgaria	Inhibace	5 mg	Film-coated tablets	Oral use
Czech Republic	Roche s.r.o. Dukelskych hrdinu 567/52 170 00 / Praha 7 Czech Republic	Inhibace 2.5 mg	2.5 mg	Film-coated tablets	Oral use
Czech Republic	Roche s.r.o. Dukelskych hrdinu 567/52 170 00 / Praha 7 Czech Republic	Inhibace 5 mg	5 mg	Film-coated tablets	Oral use
France	Chiesi SA Immeuble le Doublon, bâtiment B 11 avenue Dubonnet 92 400 Courbevoie France	Justor 0.5 mg	0.5 mg	Film-coated tablets	Oral use
France	Chiesi SA Immeuble le Doublon, bâtiment B 11 avenue Dubonnet 92 400 Courbevoie France	Justor 1 mg	1 mg	Film-coated tablets	Oral use
France	Chiesi SA Immeuble le Doublon, bâtiment B 11 avenue Dubonnet 92 400 Courbevoie France	Justor 2.5 mg	2.5 mg	Film-coated tablets	Oral use

Member State EU	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Germany	Roche Pharma AG Emil-Barell-Strasse 1 79639/Grenzach Germany	Dynorm 0,5	0.5 mg	Film-coated tablets	Oral use
Germany	Roche Pharma AG Emil-Barell-Strasse 1 79639/Grenzach Germany	Dynorm 1,0	1 mg	Film-coated tablets	Oral use
Germany	Roche Pharma AG Emil-Barell-Strasse 1 79639/Grenzach Germany	Dynorm 2,5	2.5 mg	Film-coated tablets	Oral use
Germany	Roche Pharma AG Emil-Barell-Strasse 1 79639/Grenzach Germany	Dynorm 5,0	5 mg	Film-coated tablets	Oral use
Greece	Roche (Hellas) SA 4, Alamanas & Delfon Str. Maroussi 15125 Attiki Greece	Vascace	0.5 mg	Film-coated tablets	Oral use
Greece	Roche (Hellas) SA 4, Alamanas & Delfon Str. Maroussi 15125 Attiki Greece	Vascace	1 mg	Film-coated tablets	Oral use
Greece	Roche (Hellas) SA 4, Alamanas & Delfon Str. Maroussi 15125 Attiki Greece	Vascace	2.5 mg	Film-coated tablets	Oral use

Member State EU	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Greece	Roche (Hellas) SA 4, Alamanas & Delfon Str. Maroussi 15125 Attiki Greece	Vascace	5 mg	Film-coated tablets	Oral use
Hungary	Roche Hungary Ltd Edison ut 1 2040 / Budaörs Hungary	Inhibace	1 mg	Film-coated tablets	Oral use
Hungary	Roche Hungary Ltd Edison ut 1 2040 / Budaörs Hungary	Inhibace	2.5 mg	Film-coated tablets	Oral use
Hungary	Roche Hungary Ltd Edison ut 1 2040 / Budaörs Hungary	Inhibace	5 mg	Film-coated tablets	Oral use
Ireland	Roche Products Ltd 6 Falcon Way, Shire Park Welwyn Garden City / / AL7 1TW United Kingdom	Vascace	0.5 mg	Film-coated tablets	Oral use
Ireland	Roche Products Ltd 6 Falcon Way, Shire Park Welwyn Garden City / AL7 1TW United Kingdom	Vascace	1 mg	Film-coated tablets	Oral use

Member State EU	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Ireland	Roche Products Ltd 6 Falcon Way, Shire Park Welwyn Garden City / AL7 1TW United Kingdom	Vascace	2.5 mg	Film-coated tablets	Oral use
Ireland	Roche Products Ltd 6 Falcon Way, Shire Park Welwyn Garden City / AL7 1TW / United Kingdom	Vascace	5 mg	Film-coated tablets	Oral use
Italy	Roche S.p.A Via G.B Stucchi 110 20052/Monza Italy	Inibace	1 mg	Film-coated tablets	Oral use
Italy	Roche S.p.A Via G.B Stucchi 110 20052/Monza Italy	Inibace	5 mg	Film-coated tablets	Oral use
Luxembourg	N.V. Roche S.A. Rue Dante 75 1070 Bruxelles Belgium	Inhibace	0.5 mg	Film-coated tablets	Oral use
Luxembourg	N.V. Roche S.A. Rue Dante 75 1070 Bruxelles Belgium	Inhibace	5 mg	Film-coated tablets	Oral use
Netherlands	Roche Nederland BV Beneluxlaan 2A 3446 GG Woerden Netherlands	Vascase 0,5	0.5 mg	Film-coated tablets	Oral use

Member State EU	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Netherlands	Roche Nederland BV Beneluxlaan 2A 3446 GG Woerden Netherlands	Vascase 2,5	2.5 mg	Film-coated tablets	Oral use
Netherlands	Roche Nederland BV Beneluxlaan 2A 3446 GG Woerden Netherlands	Vascase 5	5 mg	Film-coated tablets	Oral use
Poland	Roche Polska Sp.z.o.o. Ul. Domaniewska 39B 02-672 / Warsaw Poland	Inhibace	0.5 mg	Film-coated tablets	Oral use
Poland	Roche Polska Sp.z.o.o. Ul. Domaniewska 39B 02-672 / Warsaw Poland	Inhibace	1 mg	Film-coated tablets	Oral use
Poland	Roche Polska Sp.z.o.o. Ul. Domaniewska 39B 02-672 / Warsaw Poland	Inhibace	2.5 mg	Film-coated tablets	Oral use
Poland	Roche Polska Sp.z.o.o. Ul. Domaniewska 39B 02-672 / Warsaw Poland	Inhibace	5 mg	Film-coated tablets	Oral use
Portugal	Roche Farmacêutica Química, Lda. Estrada Nacional 249-1 2720-413 / Amadora Portugal	Inibace	1 mg	Film-coated tablets	Oral use

Member State EU	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Portugal	Roche Farmacêutica Química, Lda. Estrada Nacional 249-1 2720-413 / Amadora Portugal	Inibace	2.5 mg	Film-coated tablets	Oral use
Portugal	Roche Farmacêutica Química, Lda. Estrada Nacional 249-1 2720-413 / Amadora Portugal	Inibace	5 mg	Film-coated tablets	Oral use
Spain	Roche Farma S.A. Eucalipto n° 33 28016 / Madrid Spain	Inhibace	1 mg	Film-coated tablets	Oral use
Spain	Roche Farma S.A. Eucalipto n° 33 28016 / Madrid Spain	Inhibace	2.5 mg	Film-coated tablets	Oral use
Spain	Roche Farma S.A. Eucalipto n° 33 28016 / Madrid Spain	Inhibace	5 mg	Film-coated tablets	Oral use
United Kingdom	Roche Products Ltd 6 Falcon Way, Shire Park Welwyn Garden City / AL7 1TW United Kingdom	Vascace	0.5 mg	Film-coated tablets	Oral use
United Kingdom	Roche Products Ltd 6 Falcon Way, Shire Park Welwyn Garden City / AL7 1TW United Kingdom	Vascace	1 mg	Film-coated tablets	Oral use

Member State EU	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
United Kingdom	Roche Products Ltd 6 Falcon Way, Shire Park Welwyn Garden City / AL7 1TW United Kingdom	Vascace	2.5 mg	Film-coated tablets	Oral use
United Kingdom	Roche Products Ltd 6 Falcon Way, Shire Park Welwyn Garden City / AL7 1TW United Kingdom	Vascace	5 mg	Film-coated tablets	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF VASCASE AND ASSOCIATED NAMES (SEE ANNEX I)

The active substance of Vascace tablets is cilazapril. Cilazapril belongs to the family of angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors block the action of angiotensin converting enzyme and by doing so, the production of Angiotensin II which is a potent vasoconstrictor peptide will also be decreased.

Vascace was included in the list of products for Summary of Product Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended.

The following sections were harmonised:

Section 4.1 – Therapeutic Indications

- **Treatment of hypertension**

The efficacy of cilazapril in the treatment of hypertension has been documented in several clinical trials sponsored by Roche. The demographic data justifies the efficacy in patients of various age, gender, and weight with mild to moderate primary hypertension. The long term efficacy of cilazapril (alone or in combination) has also been accepted in the majority of the EU countries. The CHMP was of the view that specification (essential or according to updated definition - primary) and the grade (mild or moderate) of the hypertension should be omitted. Although ACE inhibitors decrease blood pressure in all forms of hypertension, the efficacy is different as they are less effective in patients with low-renin hypertension.

The CHMP was of the view that renovascular hypertension should not be included as an independent indication, as the MAH was unable to substantiate it with their own clinical data. However this does not mean that the use of cilazapril would have to be automatically contraindicated in all types of renovascular hypertension. Relatively limited evidence-based information is available on treatment of renovascular hypertension with ACE inhibitors (especially with cilazapril), but it cannot be ignored that ACE inhibitors are considered by many experts as effective medication for treatment of this condition. Specific dosing recommendation for renovascular hypertension has been covered by the dosing instructions for patients with impaired renal function in this section 4.2.

However it is also very well known that ACE inhibitors may have serious impact on the renal function, especially in the case of reduced renal perfusion.

Taking into account the recommendation of the CHMP, the following wording proposed by the MAH was agreed:

"Vascace is indicated for the treatment of hypertension."

- **Treatment of chronic heart failure (CHF)**

No data on overall survival, cardiovascular morbidity, frequency of CV hospitalisation of patients treated with cilazapril for CHF have been presented.

The MAH's response refers to the results achieved by other ACE inhibitors stating the beneficial therapeutic effect for patients with chronic heart failure. Most ACE inhibitors (e.g. captopril, cilazapril, enalapril, ramipril, perindopril, trandolapril, benazepril) were shown to have beneficial action on hard and intermediete outcomes in patients with chronic heart failure. Accordingly these results can be extrapolated also for cilazapril, where the beneficial effects of ACE inhibitors in CHF can be considered as a class effect.

Considering the data from cilazapril trials conducted as part of the clinical development program for Vascace, the published data on the therapeutic effect of ACE inhibitors on CHF, and the Guidelines of

the European Society of Cardiology, the CHMP agreed with the following wording proposed by the MAH for this indication:

"Vascace is indicated for the treatment of chronic heart failure."

Section 4.2 - Posology and method of administration

- **Treatment of hypertension**

The CHMP was of the view that it should be mentioned that the angiotensin escape phenomenon (renin-angiotensin system activation and increased activity in sympathetic system) can occur (and was observed) in patients treated with ACE inhibitors as monotherapy (Roig e, et al Eur. Heart J 2000: 21, 53-57). In such patients a lower starting dose (0.5mg) is recommended and the initiation of treatment should take place under medical supervision.

Taking into account the recommendation of the CHMP, the following wording proposed by the MAH was agreed:

"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."

- **Treatment of chronic heart failure**

The dosing recommendation follows the "dosing by symptomatic relief" principle, which is not the current clinical practice. Nevertheless, as there are no outcome studies to provide a definite beneficial dose for the majority of patients, and since the MAH has not been able to provide a better dosing guide based e.g. on pharmacokinetic/pharmacodynamic data, the following wording proposed by the MAH, was considered to be acceptable by the CHMP.

The concept of adjunctive therapy with digitalis and diuretics is not supported by the current evidence on ACE inhibitors and clinical guidance documents on the management of CHF. Therefore the CHMP was of the view that digitalis should not necessarily be mentioned because concomitant therapy with digitalis in general use (as a basic therapy) is not recommended today.

The CHMP agreed with the following wording proposed by the MAH:

"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 posolgy 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)."

Time of medication intake and meals

Although the study by Carlsen *et al* (*Carlsen JE, Buchmann M, Hoeglund C, Pellinen T, Honkanen T, Soerensen OH, et al. 24-hour antihypertensive effect of oral cilazapril? A placebo-controlled study evaluating 1, 2.5 and 5mg once daily. Clin Drug Invest. 1995;10 (4):221-227*) raised the question of whether the once daily dosing schedule in hypertension is sufficient, no further discussion of the

results of this study in comparison with the other studies conducted with cilazapril was provided by the MAH. As this is a single study giving divergent results in this regard, the issue was not further questioned by the CHMP.

The dosing schedule of once daily, administered before or after a meal as proposed by the MAH was considered to be approvable by the CHMP.

Special populations
The results of an open label non-comparative dose-adjustment study in the elderly with uncomplicated essential hypertension were discussed by the MAH, to substantiate the dosing regimen for the elderly patients with hypertension.

The CHMP agreed with the following wording proposed by the MAH for the elderly and paediatric populations:

"Elderly 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.

Elderly with chronic heart failure: The recommended starting dose of Vascace 0.5 mg must be strictly followed.

Children: Safety and efficacy in children have not been established. Therefore, there is no recommendation for administration of cilazapril to children."

Since the submission of the original documentation no additional studies were conducted by Roche in patients with impaired liver function. In a careful literature search, covering the time period up to November 2009, only a single publication was identified, describing a case report of a patient with diabetic nephropathy and cirrhotic ascites. Due to the large variety of possible clinical situations for cirrhotic patients, conditions exist where patients require a carefully supervised treatment with cilazapril. For cirrhotic patients with ascites however, cilazapril is not recommended.

For patients with impaired liver function the CHMP agreed with the following wording proposed by the MAH:

"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 a careful monitoring of the blood pressure, because significant hypotension may occur."

For patients with impaired renal function, the dosing recommendations were based on data from a number of Roche studies and published clinical trials. Reduced doses are required for patients with renal impairment depending on their creatinine clearance.

The dosage schedule for patients with impaired renal function as recommended by the MAH was considered to be acceptable by the CHMP:

"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 cilazaprilat 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."

Section 4.3 - Contra-indications
Taking into account the recommendation of the CHMP, the following wording proposed by the MAH was agreed:

"Hypersensitivity to cilazapril or any components of the product, 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 section 4.4. and 4.6)"

Section 4.4 - Special warnings and precautions for use
With a few exceptions, the scientific basis for the proposed text in Section 4.4 is provided by reviews of adverse effects of ACE inhibitors found in the following texts: Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions 2006 and the Martindale: The Complete Drug Reference 36.

As recommended by the CHMP, the MAH has added an additional warning concerning the use of cilazapril in patients with high grade renal artery stenosis with renal impairment to the subsection entitled `Renal impairment' in section 4.4. The warning concerning anaphylaxis in dialysis patients receiving ACE inhibitors is discussed under a separate subheading in Section 4.4, "Anaphylaxis".

It was also recommended by the CHMP that in patients with liver cirrhosis (but without ascites), cilazapril should be initiated at a lower dose since significant hypotension could occur, and in patients with ascites, cilazapril should not be recommended.

Regarding pregnancy, the MAH agreed to comply with the wording agreed by the CHMP Pharmacovigilance Working Party (PhVWP) recommendation for this section.

Section 4.5 - Interaction with other medicinal products and other forms of interaction
The most important possible interactions (PK, PD or toxic) have been included in the harmonized label, since these drugs are frequently co-prescribed with cilazapril or other ACE inhibitors and scientific rationale is available. At the request of the CHMP, interactions with other medicinal products (diuretics, tricyclic antidepressants, renal effects in non-steroidal anti-inflammatory drugs, sympathomimetics, anti-diabetics and gold) were also included in the harmonized SPC, in line with the other representatives of the drug class.

Section 4.6 - Pregnancy and lactation
Taking into account the recommendation of the CHMP PhVWP, the following wording was agreed:

"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 section 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).

Because no information is available regarding the safety of cilazapril during breastfeeding, 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."

Section 4.7 - Effects on ability to drive and use machines
Taking into account the recommendation of the CHMP and those provided in the SPC guideline concerning Section 4.7, the wording proposed by the MAH was agreed.

Section 4.8 - Undesirable effects
All adverse drug reactions (ADRs) listed in the company reference safety information, the Core Data Sheet (CDS) have been included. Additional ADRs listed in local SPCs but not in the CDS have been included if appropriate references could be identified. In most of the cases the references originate from:

- Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions 2006.
- Martindale: The Complete Drug Reference 36.

The harmonised list of undesirable effects was derived from clinical trials and post-marketing data in association with cilazapril and/or other ACE inhibitors.

MedDRA System Organ Class (SOC) and Preferred Terms (PTs) are used where appropriate.

Section 4.9 – Overdose
Taking into account the recommendation of the CHMP, the following proposed wording was agreed:

"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.

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)."

Section 5.1 - Pharmacodynamic properties
The CHMP was of the view that the prescriber needs to be made aware that only symptomatic benefit has been demonstrated in clinical trials with cilazapril in heart failure and that no morbidity/mortality results are available, since outcome studies with cilazapril in chronic heart failure have not been performed.

Based on the information available, and taking into account the recommendation of the CHMP, the following statement was agreed by the MAH for the section under the subheading *'Chronic heart failure'*:

"No clinical trials have been carried out which prove the effect of cilazapril on morbidity and mortality in heart failure."

Section 5.3 - Preclinical safety data
Taking into account the recommendation of the CHMP, the following wording was agreed by the MAH:

"Preclinical 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."

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summary of Products Characteristics, labelling and package leaflet.

- the Summary of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Vascase and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and package leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the Member State Competent Authorities, in liaison with the Reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vascace and associated names (see Annex I) 0.5 mg film-coated tablets
Vascace and associated names (see Annex I) 1 mg film-coated tablets
Vascace and associated names (see Annex I) 2.5 mg film-coated tablets
Vascace and associated names (see Annex I) 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 is indicated for the treatment of hypertension.

Vascace is indicated for the treatment of chronic heart failure.

4.2 Posology and 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.

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 a careful monitoring of the blood pressure, because significant hypotension may occur.

Elderly 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.

Elderly with chronic heart failure: The recommended starting dose of Vascace 0.5 mg must be strictly followed.

Children: Safety and efficacy in children have not been established. Therefore, there is no recommendation for administration of cilazapril to children.

4.3 Contraindications

Hypersensitivity to cilazapril or any components of the product, 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)

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.

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.

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.

Neutropenia

Rarely, neutropenia and agranulocytosis have been associated with 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 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, hyperkalemia can occur. Potassium-sparing diuretics 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.

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

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.

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.

4.6 Pregnancy and lactation

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).

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	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 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.

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.

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 studies
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.

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 properties

Absorption
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.

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.

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

Preclinical 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

[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

[To be completed nationally]

[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]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vascace and associated names (see Annex I) 0.5 mg film-coated tablets
Vascace and associated names (see Annex I) 1 mg film-coated tablets
Vascace and associated names (see Annex I) 2.5 mg film-coated tablets
Vascace and associated names (see Annex I) 5 mg film-coated tablets
[See Annex I - To be completed nationally]

cilazapril

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 {MM YYYY}

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 and associated names (see Annex I) 0.5 mg film-coated tablets
Vascace and associated names (see Annex I) 1 mg film-coated tablets
Vascace and associated names (see Annex I) 2.5 mg film-coated tablets
Vascace and associated names (see Annex I) 5 mg film-coated tablets
[See Annex I - To be completed nationally]

cilazapril

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]
{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Vascace and associated names (see Annex I) 0.5 mg film-coated tablets
Vascace and associated names (see Annex I) 1 mg film-coated tablets
Vascace and associated names (see Annex I) 2.5 mg film-coated tablets
Vascace and associated names (see Annex I) 5 mg film-coated tablets
[See Annex I - To be completed nationally]

Cilazapril

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 IS AND WHAT IT IS USED FOR

Vascace contains a medicine called cilazapril. This belongs to a group of medicines called 'ACE inhibitors' (Angiotensin Converting Enzyme Inhibitors).

Vascace is used to treat the following:
- High blood pressure (hypertension)
- Chronic (long-term) heart failure.

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 if you have chronic heart failure.

Your doctor may give you other medicines as well as Vascace to help treat your condition.

2. BEFORE YOU TAKE VASCACE

Do not take Vascace
- if you are allergic (hypersensitive) to cilazapril or any of the other ingredients of Vascace (listed in section 6: Further information).
- if you are allergic (hypersensitive) to other ACE inhibitor medicines. These include captopril, enalapril, lisinopril and ramipril.
- 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 are more than 3 months pregnant. (It is also better to avoid Vascace in early pregnancy - see the sections on 'Pregnancy' and 'Breast-feeding'.)

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

Take special care with Vascace
Check with your doctor or pharmacist before taking Vascace
- if you have a heart problem. Vascace 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 any of the above apply to you, or if you are not sure, talk to your doctor or pharmacist before you take Vascace.

You must tell your doctor if you think you are (or might become) pregnant. Vascace 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 'Breast-feeding').

Vascace is not recommended for use in children.

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 can affect the way some medicines work. Also some medicines can affect the way Vascace works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- Diuretics ('water tablets') – see 'High blood pressure (hypertension)' in section 3 on 'How to take Vascace'.
- 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).
- Steroide 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).

Taking Vascace with food and drink
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 before you become pregnant, or as soon as you know you are pregnant, and will advise you to take another medicine instead of Vascace. Vascace 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.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Vascace is not recommended for mothers who are breast-feeding, 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. 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
Vascace 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

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

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

High blood pressure (hypertension)
- The usual starting dose for adults is 1 mg per day.
- Your doctor will then increase your dose until your blood pressure is under control – the usual maintenance dose is between 2.5 mg and 5 mg per day.
- If you have problems with your kidneys, or if you are elderly, your doctor may give you a lower dose.
- If you are already taking a diuretic (‘water tablets’), your doctor may tell you to stop taking it about 3 days before you start taking Vascace. The usual starting dose of Vascace is then 0.5 mg per day. Your doctor will then increase your dose until your blood pressure is under control.

Chronic heart failure
- The usual starting dose is 0.5 mg per day.
- Your doctor will then increase the dose – the usual maintenance dose is between 1 mg and 2.5 mg per day.
- If you have problems with your kidneys, or if you are elderly, your doctor may give you a lower dose.
- If you have liver cirrhosis without ascites, your doctor will not give you a dose of more than 0.5 mg per day and will carefully monitor your blood pressure.

If you take more Vascace than you should
If you take more Vascace than you should, or if someone else takes your Vascace 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 heart beat.

If you forget to take Vascace
- 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 can cause side effects, although not everybody gets them.

Severe reactions:
If you have a severe reaction called angioedema, stop taking Vascace 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 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

Rare (affects less than 1 in 1'000 people)

- Blood tests showing a decrease in the number of red blood cells, white blood cells or platelets (anemia, neutropenia, agranulocytosis and thrombocytopenia)
- 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

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

[To be completed nationally]

Keep out of the reach and sight of children.

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

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 contains

- The active substance in Vascace is cilazapril.
- The other ingredient(s) is (are)...
  [To be completed nationally]

What Vascace 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 "Roche"
Belgium, Bulgaria, Czech Republic, Hungary, Luxembourg, Poland, Spain: Inhibace
France: Justor
Germany: Dynorm
Greece, Ireland, United Kingdom: Vascace
Italy, Portugal: Inibace
Netherlands: Vascase

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

[To be completed nationally]