ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES
<table>
<thead>
<tr>
<th>Member State</th>
<th>Marketing Authorisation Holder</th>
<th>(Invented) Name</th>
<th>Strength</th>
<th>Pharmaceutical Form</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Roche Austria GmbH, Engelhorngasse 3, A - 1211 Vienna Austria</td>
<td>Inhibace plus «Roche » - Filmtabletten</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Belgium</td>
<td>N.V. Roche S.A. Rue Dante 75 1070 Bruxelles Belgium</td>
<td>Co-Inhibace</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Roche s.r.o. Dukelskych hrdinu 567/52 170 00 / Praha 7 Czech Republic</td>
<td>Inhibace Plus</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Germany</td>
<td>Roche Pharma AG Emil-Barell-Strasse 1 79639/Grenzach Germany</td>
<td>Dynorm Plus</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Greece</td>
<td>Roche (Hellas) SA 4, Alamanas &amp; Delfon Str. Maroussi 15125 Attiki Greece</td>
<td>Vascace Plus</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Hungary</td>
<td>Roche Hungary Ltd Edison ut 1 2040 / Budaörs Hungary</td>
<td>Inhibace Plus</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Member State EU/EEA</td>
<td>Marketing Authorisation Holder</td>
<td>(Invented) Name</td>
<td>Strength</td>
<td>Pharmaceutical Form</td>
<td>Route of administration</td>
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<tr>
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</tr>
<tr>
<td>Italy</td>
<td>Roche S.p.A Via G.B Stucchi 110 20052/Monza Italy</td>
<td>Inibace Plus</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>N.V. Roche S.A. Rue Dante 75 1070 Bruxelles Belgium</td>
<td>Co-Inhibace</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Poland</td>
<td>Roche Polska Sp.z.o.o. Ul. Domaniewska 39B 02-672 / Warsaw Poland</td>
<td>Inhibace Plus</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Portugal</td>
<td>Roche Farmacêutica Química, Lda Estrada Nacional 249-1 2720-413 / Amadora Portugal</td>
<td>Inibace Plus</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
<tr>
<td>Spain</td>
<td>Roche Farma S.A. Eucalipto nº 33 28016 / Madrid Spain</td>
<td>Inhibace Plus</td>
<td>5 mg/12.5 mg</td>
<td>Film-coated tablets</td>
<td>Oral use</td>
</tr>
</tbody>
</table>
ANNEX II

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

Overall summary of the scientific evaluation of Vascace Plus and associated names (see Annex I)

Vascace Plus is a combination of cilazapril (an angiotensin-converting enzyme inhibitor) and hydrochlorothiazide (a thiazide-diuretic agent). Vascace Plus is used in the treatment of hypertension in patients not responding satisfactorily to each component administered alone.

Vascace Plus was included in the list of products for Summary of Product Characteristics (SPC) harmonisation, due to the divergent national decisions taken by Member States concerning the authorisation of the product. The CHMP considered a number of areas of disharmony in the Product Information.

Section 4.1 Therapeutic indications

The MAH proposed as harmonised text the following wording: “Vascace Plus is indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled with cilazapril alone or hydrochlorothiazide alone and who have been stabilized on the individual components given in the same proportions.”

This wording of the therapeutic indications for Vascace Plus was identical in many EU countries.

A diuretic such as hydrochlorothiazide enhances efficacy of the ACE inhibitor by stimulating the renin-angiotensin system and shifting the hypertensive state to a more renin-dependent condition. To support the proposed indication the MAH presented 4 placebo controlled clinical trials sponsored by Roche and run in 2,084 hypertensive patients. Of these patients with mild to moderate hypertension (sitting diastolic blood pressure 95 – 115 mm Hg), 1,027 patients were treated with the cilazapril/hydrochlorothiazide combination, 453 patients with cilazapril and 366 with hydrochlorothiazide alone and 238 patients received placebo. Over 600 of these patients received the cilazapril/hydrochlorothiazide combination for 6 months and more, and approximately 200 of these patients were treated with the combination for one year or longer.

In addition to the patients of these clinical trials the efficacy of the combination was also assessed in 1,297 patients of the original cilazapril monotherapy new drug application (NDA) who were treated with cilazapril and adjunctive hydrochlorothiazide.

Assessing the blood pressure lowering effect of the combination the results of these trials showed that the addition of hydrochlorothiazide to a cilazapril regimen increases the reduction in sitting diastolic blood pressure (SDBP).

In one trial (protocol no. N2960C) it was shown that patients had an overall decrease in SDBP of 4.3 mm Hg before the addition of hydrochlorothiazide and 11.1 mm Hg after the addition of hydrochlorothiazide.

In addition, a long-term, randomized, blinded, parallel group, multicenter study was conducted specifically in elderly patients with mild to moderate hypertension. A total of 214 patients (age range 64 – 81 years) were included in this trial. From these patients 108 patients had initially been treated with cilazapril and 106 patients with hydrochlorothiazide. Of these, 68 patients responded to monotherapy with cilazapril and 70 patients to hydrochlorothiazide. The 76 non-responders were treated with combination therapy. The antihypertensive effect for the combination group was maintained for the duration of this long-term study and was of a similar magnitude to that observed after the first weeks of cilazapril/hydrochlorothiazide therapy combination with no development of tolerance for the therapy. The magnitude of the antihypertensive effect of the combination at peak (i. e. 15 mm Hg) did not render an increased incidence of hypotensive events, which could be of concern in elderly patients.

The CHMP noted that the substitution of the free combination of the active substances given at the same dose is an acceptable indication based on the long experience of concomitant use. Also add-on to cilazapril can be accepted as the hydrochlorothiazide dose is low and suitable as an initial dose in combination therapy of ACEI non-responders and there are some data available on the efficacy and safety in cilazapril monotherapy non-responders. The CHMP also considered that add-on to hydrochlorothiazide and to the non-responders to hydrochlorothiazide cannot be accepted as only the highest cilazapril dose is available in the fixed combination and the dose has to be titrated up with single components.

The CHMP, on the basis of these considerations, endorsed the following harmonised wording for the indication: “Vascace Plus is indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled with cilazapril alone”

Section 4.2 Posology and Method of Administration

Several clinical trials showed that doses of 5 mg cilazapril and 12.5 mg hydrochlorothiazide generated a greater reduction in blood pressure than either of the individual components in patients with mild to moderate hypertension whose blood pressure could not be normalized with cilazapril alone.

To justify the proposed dosage (5 mg cilazapril and 12.5 mg hydrochlorothiazide) the MAH presented data from several placebo controlled randomized trials. These were conducted with patients randomized to one of several possible treatment groups with cilazapril doses of 0.5 mg, 1.0 mg or 2.5 mg and hydrochlorothiazide doses of 6.25 mg, 12.5 mg or 25 mg alone or in combination. The lowest dose which generated a significant effect was a dose of 2.5/6.25 mg. The recommendation for once-daily dosage is based on the finding that an apparently subtherapeutic dose of hydrochlorothiazide in combination with cilazapril results in potentiation of the antihypertensive effect. Doubling the initial dose (5.0 mg cilazapril 12.5 mg hydrochlorothiazide) resulted in a further increase in efficacy.

The analysis of individual studies suggested that virtually all cilazapril doses administered with 25 mg hydrochlorothiazide have similar effects on trough blood pressure.

Based on these data the combination of cilazapril 5 mg with hydrochlorothiazide 12.5 mg, given once daily, is a rational clinical choice for patients whose blood pressure is not normalized on cilazapril alone.

The CHMP endorsed the following harmonised wording for the posology: “The dosage of Vascace Plus is one tablet (5.0 mg cilazapril and 12.5 mg hydrochlorothiazide) administered once daily”.

Patients with renal impairment

The Core Data Sheet (CDS) wording for patients with impaired renal function has been used in this section of the SPCs in most of the countries. The CHMP agreed the following: “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

The dosing recommendations given for patients with cirrhosis/impaired liver function varied considerably among MSs. In several countries there was no information in section 4.2 on this group of patients. In other countries a modified statement including also impaired liver function was given, or patients with liver impairment were contraindicated.

The pathophysiological association between liver impairment, cardiovascular function and arterial hypertension is complex. Treatment is difficult and rather infrequent, since patients with cirrhosis have a tendency towards low blood pressure. Combination therapy with antihypertensive agents is rarely necessary. A very cautious treatment is required due to the therapeutic properties of cilazapril and a cross reference to section 4.4 has been added.

The CHMP agreed the following: “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 the SPC of several countries the same or slightly modified wording was used. As it is not foreseen to start treatment with the fixed combination, the CHMP endorsed the following: "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)."

Children
The CHMP agreed that the use of Vascace Plus is not recommended in children.

Section 4.3 Contraindications
The MAH acknowledged the number of contraindications in the SPCs of Member States and explained that:
• contraindications were sometimes relative rather than absolute. In some SPCs, relative contraindications were discussed in section 4.4 (Special Warnings and Precautions), rather than in section 4.3;
• lack of data concerning safety in specific patients groups was the only justification for listing certain contraindications;
• conditions for which Vascace Plus is not the recommended treatment (e.g. hyperaldosteronism), rather than causing specific harm, are listed as ‘contraindications’.

The CHMP did not agree on the inclusion of severe hepatic impairment and/or cholestasis as a contraindication, as well as inclusion of refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia as proposed by the MAH.

Moreover, according to the PhVWP recommendation, antihypertensive drugs are contraindicated in second and third trimesters of pregnancy and there is no contraindication in the first trimester of pregnancy or lactation. The CHMP agreed to change the text “Pregnancy and lactation (see section 4.6)” under this section to “Second and third trimesters of pregnancy (see sections 4.4 and 4.6).”

Section 4.4 Special Warnings and Precautions for Use
Differences in level of detail existed between Member States for special warnings and precautions for use.
Additional information was included in some Member States in warnings in respect of risk of hypotension, renovascular hypertension/renal artery stenosis, kidney transplantation, use in concomitant heart failure, anaemia, cough, ethnic groups, primary aldosteronism, and doping.

Where warnings and precautions concerned cilazapril, the MAH proposed a text similar to that used in the recently harmonized Vascace.
The MAH, to support the proposed section 4.4, presented reviews of adverse effects of ACE inhibitors and thiazide diuretics from the scientific literature available:

Some SPCs included under the heading “hypotension” warnings about the use of anaesthetics. The MAH proposed to include a separate warning concerning this issue in section 4.4.
**Renal impairment**
The MAH proposed to include a warning concerning hypotension and renal impairment resulting from combination therapy with cilazapril and hydrochlorothiazide in patients with renal artery stenosis. The CHMP asked the MAH to align the SPC for Vascace Plus with the approved SPC of Vascace and endorsed the harmonized wording for this subparagraph.

**Angioedema**
The MAH proposed to describe the symptoms/signs of angioedema more succinctly than in some current SPCs, and to use the term “acute oropharyngeal edema and airways obstruction” (as in Meyler’s review). The proposed text included a general statement concerning emergency treatment of angioedema. Specific treatment advice was not included as treatment protocols may vary between countries.

**Anaphylaxis**
Some SPCs included a detailed description of the symptoms of anaphylaxis. The text proposed by the MAH and endorsed by CHMP for anaphylaxis was consistent with the current Vascace Plus CDS and reviews of ACE inhibitors in Meyler and Martindale.

**Hepatic disorders**
The proposed text for hepatic disorders incorporated all the information which was provided in the CDS and in local SPCs for Vascace Plus, and was consistent with wording used in the reviews in Meyler and Martindale. The comment concerning the greater risk of hypotension in patients with cirrhosis, already included in some SPCs, was supported by Meyler’s review. The MAH proposed text also included an additional comment concerning the use of ACE inhibitors in patients with liver cirrhosis and ascites, as suggested by the CHMP for the EU harmonized Vascace SPC.

**Serum electrolytes**
Electrolyte disturbances including hypokalaemia, hyponatraemia and dehydration are mainly associated with thiazides, whilst ACE inhibitors can cause hyperkalaemia. The text proposed by the MAH was based on Meyler’s reviews of ACE inhibitors and thiazide diuretics, and it is consistent with the CDS and most current SPCs for Vascace Plus. Some SPCs recommend that fluid and electrolyte disturbances should be corrected before starting treatment. However, the MAH did not propose to include such a warning as considered that this is implied in the warning that patients should have regular monitoring of renal function and electrolytes which is included in the proposed SPC. The CHMP agreed with such approach.

**Gout**
Gout was listed as a contraindication in some SPCs for Vascace Plus, and was included under section 4.4 in most others and in the CDS. The MAH proposed to include a warning concerning gout in section 4.4. It is widely known that thiazides as a class can increase uric acid levels (Meyler; Martindale). However, a review of the literature suggests that low dose hydrochlorothiazide (e.g. 12.5 mg/day) is associated with only minimal increase in serum uric acid, and to an extent which may not be clinically relevant. Furthermore, the addition of an ACE inhibitor may further attenuate this effect. Considering this, the MAH suggested to include a warning concerning the use of thiazides in patients with a history of gout, but not to include gout as a contraindication.

**Porphyria**
The current CDS and some SPCs included a warning concerning the use of thiazides in patients with porphyria based on a warning in Martindale’s review. The warning is maybe based on concerns about crossreactivity with sulfonamide antibiotics, which are know to aggravate porphyria. However, hydrochlorothiazide is currently listed as ‘safe’ or ‘probably safe’ by several authorities (e.g. European Porphyria Initiative http://www.porphyria-europe.com/03-drugs/drugs-and-porphyrias.asp; The Drug Data-base for Acute Porphyria http://www.drugs-porphyria.com. Given this, the MAH proposed to modify the wording as follow: “Vascace Plus should be used with caution in patients with porphyria”.


**Lipid profile**

Several Vascace Plus SPCs included a warning concerning the effect of thiazide on lipid profile. The CHMP agreed with the MAH proposal to include this adverse effect of thiazides in section 4.8 but not under 4.4.

The CHMP endorsed the most of the MAH’s proposal except pregnancy. The MAH agreed with the CHMP comment and the wording recommended by the PhVWP was used as harmonised text.

**Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**

Many medicinal products were listed for Vascace Plus in one or several local SPCs. The number of products for Vascace Plus is considerably higher than for cilazapril alone, since numerous molecules had been added where a potential interaction with hydrochlorothiazide was suspected.

The CHMP requested the MAH to align this section with the harmonised Vascace SPC as far as ACEI component is concerned. For hydrochlorothiazide, the MAH was requested to include the possible interactions with digoxin and complete the list with the agents as such non-depolarizing muscle relaxants, calcium slats and vitamin D, anticholinergics, amantidine, cytotoxic drugs, cyclosporine.

Following the request of the CHMP, the SPC has been amended by the MAH. The list of drugs which may interact either with cilazapril or with hydrochlorothiazide was updated. The information which is given about the possible interactions and their outcome are endorsed by the CHMP.

**Section 4.6 Pregnancy and Lactation**

The MAH’s initially proposed SPC and CDS included some additional information concerning the use of ACE inhibitors in the 1st trimester of pregnancy as a contraindication to ACE inhibitors. This was based on results of an epidemiological study which found that exposure to ACE inhibitors restricted to the first trimester of pregnancy was associated with increased risk of major congenital malformations including central nervous system and kidney malformations.

The CHMP did not agree with the MAH’s position. Following review and discussion regarding the teratogenic potential of ACE inhibitors, the Pharmacovigilance Working Party (PhVWP) concluded that the contraindication of ACE inhibitors during the first trimester of pregnancy is not justified given the limited evidence related to a teratogenic risk.

The CHMP concluded that the contraindication during the first trimester of pregnancy must be deleted from the product information of Vascace Plus and the PI should be updated to include the wording recommended by the PhVWP for both pregnancy and lactation.

The original proposed text concerning the hydrochlorothiazide component of Vascace Plus was already in agreement with the PhVWP wording. Hence, this has not been changed. The revised proposed text concerning breast feeding has been aligned to the one approved for the Vascace SPC, with minor changes to reflect the combination of cilazapril + hydrochlorothiazide. The CHMP endorsed the harmonised text.

**Section 4.7 Effects on Ability to Drive and Use Machines**

The proposed text was consistent with the wording used in current local SPCs for Vascace Plus, and was the same as that proposed for the revised version of the EU harmonized SPC for Vascace.

The CHMP, considering that there is plausible effect based on the pharmacologic action of the drug to affect the ability to drive, endorsed the following: “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)”.
Section 4.8 Undesirable Effects

The proposed summary of the safety profile has been updated by the MAH taking into account the most recent guidelines and the definition of “frequency” used in the studies as supporting evidence. The MAH used the published meta-analyses of mono- and combination therapy as basis for this section.

Estimates of frequency were based on the proportion of patients reporting each adverse reaction during Vascace Plus clinical trials. For ADRs listed in the SPC that were not reported in the clinical trials, the relevant frequency category had been assigned using the ‘rule of 3’ approach recommended in the SmPC guideline.

The ADR ‘headache’ has been included in the list of ADRs attributable to cilazapril, as requested by the CHMP, in the category ‘common’. An explanatory note has been included in subsection (c) Description of selected adverse reactions as follows: “Headache is a commonly reported adverse event, although the incidence of headache is greater in patients receiving placebo than in those receiving cilazapril + hydrochlorothiazide”.

Moreover, the names and order of System Organ Classes (SOCs) have been aligned for cilazapril and hydrochlorothiazide according to MedDRA.

The ADR ‘lupus like syndrome’ is now listed under the SOC Immune System Disorders in both subsections of the table of ADRs (i.e., ADRs attributable to cilazapril and ADRs attributable to HCTZ).

The CHMP endorsed the MAH proposal after the frequency categories used in the SPC of Vascace Plus had been harmonised with the ones of the SPC for Vascace. As requested, the ADR “arythmia”, already shown in the table of ADRs attributable to cilazapril, has been added to the table of ADRs attributable to hydrochlorothiazide.

Section 4.9 Overdose

The MAH proposed sufficiently concise instructions for the treatment of an overdose with the cilazapril/hydrochlorothiazide combination as too detailed information may not reflect the situation of a specific overdose patient.

The CHMP acknowledged that the cilazapril part of this section had been aligned with the approved Vascace SPC. The information on HCTZ overdose is consistent with other approved ACEI and hydrochlorothiazide combinations (ramipril/HCTZ) SPC. The CHMP endorsed this section.

Section 5.1 Pharmacodynamic properties

The text suggested for this section of the harmonized label was identical to the wording in the CDS. It presented in a succinct manner some important facts on these two molecules. Reviewing recent publications on this topic new information on cilazapril, which was considered relevant for physicians to treat their patients with Vascace Plus and which should be included in this document was not identified. The paragraph ‘Clinical/Efficacy Studies’ has been slightly rewording for more clarity.

The CHMP endorsed the harmonised wording under this section.

Section 5.2 Pharmacokinetic properties

Apart from some additional information which is provided on the distribution of cilazapril and hydrochlorothiazide the text suggested for this section of the harmonized label was identical to the wording in the CDS of the MAH. It presented in a succinct manner some important facts on these two molecules. Reviewing recent publications on this topic information on the pharmacokinetic properties of cilazapril and hydrochlorothiazide, which was considered relevant for physicians to treat their patients with Vascace Plus and which should be included in this document was not identified.

Information on pharmacokinetics of hydrochlorothiazide in special populations has been added to section 5.2.
The CHMP endorsed the harmonised wording

**Section 5.3 Preclinical safety data**

The wording proposed by the MAH integrated all information provided in individual SPCs in different countries. It reflected the relevant information on nonclinical safety data with cilazapril and hydrochlorothiazide.

The CHMP endorsed the harmonised wording.
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 characteristics, 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 Vascace Plus and associated names (see Annex I).
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 m²) 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 hyperperfusion, 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 m². 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 H2-receptor blockers were concomitantly administered.

**Interactions mainly related to hydrochlorothiazide**

**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, diphenamid, 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, 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, onycholyis

**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 cilazapril T\text{max} by 1.5 hours and reduces C\text{max} by 24%. It delays hydrochlorothiazide T\text{max} by 1.4 hours and reduces C\text{max} by 14% with no effect on overall bioavailability of both molecules as assessed by AUC0-24-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 hydrochlorothiazide 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 not 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]  
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<td>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
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<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
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<td>16. INFORMATION IN BRAILLE</td>
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<td>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</td>
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<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORITYISATION HOLDER</th>
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<th>3. EXPIRY DATE</th>
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<th>4. BATCH NUMBER</th>
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<th>5. OTHER</th>
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</table>
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
2. Before you take Vascace Plus
3. How to take Vascace Plus
4. Possible side effects
5. How to store Vascace Plus
6. Further information

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 (anaemia, 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]