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 (HCTZ).
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.

Also the MAH presented the studies published which evaluated the combination of cilazapril and hydrochlorothiazide: Pordy *et al* **(***1995; 1994*), Martina *et al (1994***),** Yodfat *et al.* (*1994*), and Sanchez (*1989*).

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 cilazaparil 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 hydroclorthiazide) 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 monotherapy.
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 Members 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'.

Moreover, according to the PhVWP recommendation, angiotensin converting enzyme inhibitors are contraindicated in second and third trimesters of pregnancy but not during 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 avaible:

- Aronson JK (editor). *Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions 2006.*
- Sweetman SC (editor), *Martindale: The Complete Drug Reference 36*. London: Pharmaceutical Press <http://www.medicinescomplete.com/> (Accessed Sep-Nov 2009)

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 may be 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 most of the MAH's proposal except for 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 "arrhythmia", 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).