21 January 2011
EMA/110390/2011

CHMP assessment report pursuant to Article 30 of Directive 2001/83/EC, as amended

Vascace Plus and associated names

INN of the active substance: cilazapril and hydrochlorothiazide

Marketing authorisation holder: Roche group of companies and associated companies

Procedure no: EMEA/H/A-30/1153

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 20 November 2009 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, as amended (Annex 3.1), in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products: Vascace Plus and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the December 2009 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Dr Alar Irs (EE) as rapporteur and Prof János Borvendég (HU) as co-rapporteur.

Vascace Plus medicinal products are authorised in the following EU Members States: Austria, Belgium, Czech Republic, Germany, Greece, Hungary, Italy, Luxembourg, Poland, Portugal, Spain.

Vascace Plus medicinal products are currently not authorised in the following EU Member States: Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Ireland, Latvia, Lithuania, Malta, the Netherlands, Romania, Slovak Republic, Slovenia, Sweden and United Kingdom and also in Iceland and Norway.

2. Scientific discussion during the referral procedure

2.1. Introduction

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 (cilazapril/hydrochlorothiazide) was first approved in Sweden on 26 June 1993, which marks its International Birth Date (IBD). Thereafter national approval was obtained in other European countries. As of 8 March 2010, Vascace Plus (cilazapril/hydrochlorothiazide) was approved in 11 EU Member States with different nationally approved Summaries of Product Characteristics (SPCs). Vascace Plus is currently authorised in: AT, BE, CZ, DE, EL, HU, IT, LU, PL, PT, and ES.

Vascace Plus is available in the form of film-coated tablets in the fixed combination 5 mg cilazapril / 12.5 mg hydrochlorothiazide.

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

Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned products (and its associated names), the European Commission notified the CHMP/EMEA Secretariat of an official referral under Article 30 of Directive 2001/83/EC as amended in order to resolve divergences amongst the nationally authorised SPCs and thus to harmonise its divergent SPCs across the EU.

To allow re-evaluation of data substantiating a harmonised Product Information (PI), the Marketing Authorisation Holder was asked to provide answers to this list of questions with the inclusion of a proposed harmonised PI taking into account the latest guidance document, all available information (efficacy and safety data) substantiating such proposed harmonised PI, updated expert reports justifying such proposal, addressing any changes to existing nationally approved SPCs and, as appropriate.

2.2. Critical Evaluation

A number of areas of disharmony in the Product Information have been considered as follows:

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 text describing the therapeutic indications for Vascace Plus was almost identical.
Some Member States had an amendment with regard to the combination of an angiotensin converting enzyme (ACE) inhibitor and a diuretic agent, which should be intended as maintenance therapy of the free combination of 5.0 mg Cilazapril and 12.5 mg hydrochlorothiazide (HCTZ).

Clinical data of the cilazapril-hydrochlorothiazide combination

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 2084 hypertensive patients. Of these patients with mild to moderate hypertension (sitting diastolic blood pressure 95 – 115 mm hg), 1027 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 1297 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. Response rates (defined as SDBP <90 mm Hg or a decrease in SDBP >10 mm Hg from baseline) calculated after the 16 weeks of treatment in this trial increased from 66% on monotherapy alone to 90% with the addition of hydrochlorothiazide. Normalization of SDBP (defined as SDBP <90 mm Hg) was calculated for this trial as 59% using monotherapy and 86% using the cilazapril/hydrochlorothiazide combination.

The MAH considering the efficacy assessment of the clinical trials drew the following major conclusions:

- these studies showed that the addition of hydrochlorothiazide to cilazapril improved the efficacy of the antihypertensive therapy with no additional safety risk. Therefore, combining both drugs is considered a rational clinical choice for patients whose blood pressures do not normalize on cilazapril monotherapy.
- the cilazapril/hydrochlorothiazide combination is an effective antihypertensive medicine in patients with mild to moderate hypertension when compared to its individual components. This could be documented in the individual studies as well as in the overall analysis of all trials of the clinical development program.
- the cilazapril/hydrochlorothiazide combination maintains an antihypertensive effect over a 24 hour dosing interval; no large peak antihypertensive effects were observed.
- the combination is effective in all age groups and over broad geographical areas.
- based on efficacy as well as on safety data the combination of 2.5 mg cilazapril and 6.25 mg hydrochlorothiazide was shown in two placebo controlled trials to safely lower blood pressure at trough to a statistically and clinically significant degree.
- the low dose combination (2.5/6.25 mg cilazapril/hydrochlorothiazide) demonstrated a more than additive effect when compared to its individual subtherapeutic components, suggesting synergy.
- based on efficacy, as well as safety data, the 2.5/6.25mg cilazapril/hydrochlorothiazide combination administered once a day was documented in two placebo controlled trials to safely lower trough blood pressure to a statistically and clinically significant degree.

- given as initial therapy the cilazapril/hydrochlorothiazide combination is titratable. Doubling the initial dose to 5.0/12.5 mg cilazapril/hydrochlorothiazide results in a further increase in efficacy at trough, with no marked increase in clinical or laboratory adverse events. Patients whose blood pressure is not well controlled on 5.0 mg cilazapril alone can be treated with the 5.0/12.5 mg cilazapril/hydrochlorothiazide combination. In general, low doses of hydrochlorothiazide can be added to cilazapril monotherapy with no worsening of the safety profile, but with a further reduction of blood pressure.

In addition, a long-term, randomized, blinded, parallel group, multicenter study (*Sachinis Z et Al. FSR b-155'017, November 29, 1993: Multicenter Study Evaluating the efficacy and safety of the cilazapril/hydrochlorothiazide combination in elderly patients with mild to moderate hypertension (Protocol K-12'953*) was conducted specifically in elderly patients with mild to moderate hypertension. This trial consisted of a 4-week, single-blind placebo run-in phase and a 4-week, double-blind treatment with cilazapril or hydrochlorothiazide monotherapy. A 1-week single-blind placebo wash-out phase was followed by a 52-week treatment with monotherapy (cilazapril or hydrochlorothiazide, double blind) in responders or a combination therapy (cilazapril/hydrochlorothiazide 5/25 mg, single blind) in non respnders.
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 effects at 4 – 8 hours post dose after 4 weeks of monotherapy treatment were for patients on cilazapril or hydrochlorothiazide, 11.9 mm Hg and 13.0 mm Hg, respectively. After 4 weeks of treatment with combination therapy the antihypertensive effect was 15 mm Hg. 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 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. 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 ~~or hydrochlorothiazide alone and who have been stabilized on the individual components given in the same proportions doses.~~"*

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 sub therapeutic 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".*

Use in patients with *renal and hepatic impairment* was contraindicated in some Member States, but not in others. In some Member States there was a contraindication in *children* due to insufficient experience.

Patients with renal impairment
The Core Data Sheet (CDS) wording for patients with impaired renal function is being used in this section of the SPCs in all countries except one.
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 vary 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
In the SPC of several countries the same or slightly modified wording is used. Use in children is contraindicated in one MS.
The CHMP agreed with the MAH proposal to use the wording in the CDS and endorsed the following: *"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".*

Section 4.3 Contraindications

The MAH acknowledged the number of contraindications in the SPCs of Members States and explained that some discrepancies between SPCs appeared to be due to the following:
- 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 SmPC guideline recommends that where there is insufficient data to make treatment recommendations in patient sub-groups, these should be considered under section 4.3 of the SmPC only if a specific safety concern is predicted.

Moreover, according to the PhVWP recommendation, angiotensin converting enzyme inhibitors are contraindicated in second and third trimesters of pregnancy but not during 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)".*

The CHMP endorsed the following harmonised wording under this section:

- *"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/1.73m^2) or anuria*
- *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, but not in others, in warnings in respect of risk of hypotension, renovascular hypertension/renal artery stenosis, kidney transplantation, use in concomitant heart failure, anemia, 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 and presented reviews of adverse effects of ACE inhibitors and thiazide diuretics from the scientific literature available:

- 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)

The MAH proposed to use the term "*hypotension*" rather than "*symptomatic hypotension*", given that asymptomatic hypotension also may be harmful, especially in patients with pre-existing cardiac or cerebral ischaemia, and those with renal artery stenosis.
The MAH proposed to refer to "*sodium or volume depletion*" generally, rather than include a list of the many possible causes of sodium or volume depletion in this section.
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.
The CHMP endorsed the following wording for this subparagraph "Renal impairment":
Vascace Plus is contraindicated in patients with creatinine clearance <30mL/min/1.73m2.
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.

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 for anaphylaxis was consistent with the current Vascace Plus CDS and reviews of ACE inhibitors in Meyler and Martindale. Subheadings were also included to improve clarity.

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.

Diabetes
ACE inhibitors appear to potentiate the hypoglycaemic effect of oral agents or insulin by increasing insulin sensitivity, whilst thiazide diuretics oppose the blood-glucose lowering effect of these drugs. These effects were described in all standard reference texts.

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 MAH proposed to include this adverse effect of thiazides in section 4.8 but not under 4.4 because:

- The meta-analysis by *Law et al*. (*2003*) provided additional confirmation of the most important and previously recognized metabolic and electrolyte disturbances associated with thiazides; namely decreased potassium and elevation of glucose, uric acid and cholesterol levels, although the effect on cholesterol was small and did not affect the atherogenic LDL and HDL subfractions.
- The ALLHAT study (*2002*) found that despite effects on lipid profile, the thiazide diuretic chlorthalidone was equally protective against cardiovascular events compared to other

antihypertensive agents. Hence, any effect which chlorthalidone may have on lipid profile does not appear to confirm an increased cardiovascular risk.

The CHMP agreed with the MAH proposal to include this adverse effect of thiazides in section 4.8 but not under 4.4 of the SPC.

The CHMP endorsed most of the MAH's proposal except for pregnancy. Regarding pregnancy the CHMP requested the MAH to follow the wording recommended by the PhVWP and to align the text with the final harmonised SPC of Vascace as far as the ACEI component is concerned.
The MAH agreed with the CHMP 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.
Frequently products were listed in local SPCs, where similar interactions had been observed with other diuretics and/or where they may interfere with renal function and electrolyte balance. These were not listed in the new proposal.

The CHMP requested the MAH to align 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 such as non-depolarizing muscle relaxants, calcium slats and vitamin D, anticholinergics, amantidine, cytotoxic drugs, cyclosporine.

Following the request of the CHMP, interactions of cilazapril have been aligned with the Vascace SPC and interactions for HCTZ have been added to section 4.5 of the Vascace Plus SPC:

Interactions mainly related to cilazapril
Lithium
Other antihypertensive agents
Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
Diuretics (thiazide or loop diuretics)
Tricyclic antidepressants/antipsychotics/anesthetics/narcotics
Non-steroidal anti-inflammatory medicinal products (NSAIDs) including aspirin ≥ 3 g/day
Sympathomimetics
Antidiabetics
Gold

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

- *Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)*
- *Class III antiarrhythmics (e.g. amiodarone, sotalol, defetilide, ibutilide)*
- *Some antipsychotics (e.g. thioridazine, chlorpromazine, trifluoperazine, sulpiride, tiapride, haloperidol, droperidol)*
- *Other medicinal products (e.g. bepridil, cisapride, diphemanil, halofantrine, ketanserin, pentamidine, terfenadine)*

Non-depolarizing muscle relaxants
Calcium salts and vitamin D
Cholestyramine/colestipol
Anticholinergics
Amantidine
Cytotoxic drugs (e.g. methotrexate, cyclophosphamide)
Iodine containing contrast media
Cyclosporine

The CHMP found the MAH's proposal acceptable. 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 Cooper's study published in the NEJM in June 2006 identified a signal of increased risk of congenital malformations, particularly cardiac defects after exposure to ACE inhibitors during the first trimester of pregnancy. Since the role of confounding factors such as diabetes and hypertension cannot be accurately defined based on the available data, the teratogenic potential of ACE inhibitors is not demonstrated, even though data suggest that such exposure cannot be considered as safe and should be avoided. This conclusion is further supported by data from a couple of European based pregnancy registries as well as two other studies, published as abstracts:
- A French study compared the outcome of 159 pregnancies with exposure to ACE inhibitors during the first trimester of pregnancy and 159 control pregnancies and did not show an increased risk of congenital malformation (RR=1.5; 95% CI 0.3- 6.5).
- ENTIS data have included the analysis of the outcome of 452 prospectively collected pregnancies exposed to ACE inhibitors during the first trimester of pregnancy. A rate of birth defects of 3.1% was found which is not indicative of teratogenic effects for ACE inhibitors and no pattern of defects was over-represented
Clinical practice shows that some women with severe hypertension and other risk factors such as diabetes or renal disease benefit from continuing therapy with ACE inhibitors until the beginning of pregnancy, before switching to a suitable alternative treatment.

The CHMP concluded that the contraindication during the first trimester of pregnancy must be deleted from the product information of Vascace Plus. Furthermore, to harmonise the class wording, the SPC and PL 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 recommendation was supported by a number of studies, which have found that fatigue, dizziness and hypotension appear to be associated with ACE inhibitors and thiazides.

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 from 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.

The tabulated list of adverse drug reactions (ADRs) included adverse 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. However, estimates of frequency were based on the proportion of patients reporting each adverse reaction during Vascace Plus clinical trials.
ADRs were listed under separate subheadings depending on whether the ADR was attributable to the cilazapril or hydrochlorothiazide component.
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 categories `uncommon' `rare' and `very rare' have been collapsed into a single category `uncommon' (defined as <1/100), given that the sample used to estimate frequency consisted of just 1'097 patients.

The ADR `headache' has been included in subsection (b) *Tabulated list of adverse reactions*, in the list of ADRs attributable to cilazapril as requested by the CHMP. However, as for cilazapril monotherapy, headache is more common in patients receiving placebo than those receiving cilazapril + hydrochlorothiazide combination therapy. In Vascace Plus clinical trials, headache occurred in 6.7% of patients receiving placebo compared to 5.5% in patients receiving active treatment. Therefore, headache has been included in the list of ADRs attributable to cilazapril 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.
In general, clinical effects of ACE inhibitor overdoses are mild and therefore supportive management of the patient, ensuring adequate hydration and maintaining appropriate systemic blood pressure, is normally sufficient to allow recovery of the patient. Clinical observation and measurement of urea and electrolytes may be sufficient for less severe cases.

The CHMP acknowledged that the cilazapril part had been aligned with the approved Vascace SPC. The information on HCTZ overdose is consistent with other approved ACEI and hydrochlorothiazide combinations. 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 MAH aligned the information on cilazapril with the approved Vascace SPC and the information on hydrochlorothiazide has been complemented as suggested by the CHMP. In addition, the paragraph 'Clinical/Efficacy Studies' has been slightly rewording for more clarity.

The CHMP endorsed the harmonised wording under this section.
"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".

Section 5.2 Pharmacokinetic properties

Apart from some additional information which is provided on the distribution of cilazaprilat and hydrochlorothiazide the text suggested for this section of the harmonized label is 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:" *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".

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 non-clinical safety data with cilazapril and hydrochlorothiazide and was consistent with the Preclinical Expert Report dated November 1992.

The CHMP endorsed the harmonised wording.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

Based on the assessment of the MAH responses, the total body of available data and the input of the CHMP drafting group, the CHMP adopted a harmonised SPC, labelling and package leaflet for Vascace Plus and associated names.

2.5. Conclusions

The basis for this referral procedure was a harmonisation of the SPC, labelling and package leaflet. The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,
- scientific discussion within the Committee,

was of the opinion that the benefit/risk ratio of Vascace Plus and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SPC, labelling and package leaflet as set out in Annex III of the CHMP opinion for Vascace Plus and associated names (see Annex I).