EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/CHMP/356249/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Copalia	AMLODIPINE / VALSARTAN
Dafiro	AMLODIPINE / VALSARTAN
Imprida	AMLODIPINE / VALSARTAN
Exforge	AMLODIPINE / VALSARTAN

Procedure No. EMEA/H/C/xxxx/WS/0360

Note

Variation 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. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 21 December 2012 an application for a variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal products:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Imprida	amlodipine / valsartan	See Annex A
Exforge	amlodipine / valsartan	See Annex A
Copalia	amlodipine / valsartan	See Annex A
Dafiro	amlodipine / valsartan	See Annex A

The following variation was requested:

Variation requested:		**Type**
C.I.4	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH proposed an update of SmPC sections 4.2, 4.3, 4.4 and 4.5 to reflect that the concomitant use of Angiotensin II Receptor Blockers (ARBs) or Angiotensin-Converting-Enzyme inhibitors (ACEi) with aliskiren is contraindicated in patients with renal impairment and in patients with diabetes mellitus. Further, the MAH proposed an update of section 4.4 of the SmPC to inform prescribers that caution is required, and monitoring of blood pressure, renal function and electrolytes is recommended, when co-administering agents acting on the renin angiotensin aldosterone system (RAAS) i.e. ACEi, ARBs or aliskiren as a direct renin inhibitor. The Package Leaflet was proposed to be updated accordingly. In addition, the MAH took the opportunity to update the SmPC, Annex II and the Package Leaflet in line with the latest QRD template, to implement minor editorial changes in the Package Leaflet and to add the contact details of the Croatian local representative in the Package Leaflet.

The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Appointed Rapporteur for the WS procedure: Jens Heisterberg

1.2. Steps taken for the assessment

Submission date:	21 December 2012
Start of procedure:	20 January 2013
Rapporteur's preliminary assessment report circulated on:	4 March 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 March 2013
MAH's responses submitted to the CHMP on:	29 April 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	7 June 2013
CHMP opinion:	27 June 2013

2. Scientific discussion

2.1. Introduction

Exforge and its clones Copalia, Dafiro and Imprida are fixed-dose combinations (FDC) of valsartan and amlodipin. Valsartan is an Angiotensive II Receptor Antagonist and amlodipine (with the active substance of amlodipine besylate) is a calcium channel blocker. In Exforge HCT and its clones Copalia HCT and Dafiro HCT, hydrochlorothiazide (HCT) is added to the Exforge FDC; thus Exforge HCT and its related clones are combinations of three drugs: valsartan, amlodipine besylate and HCT.

The indication for Exforge and its related clones as well as Exforge HCT and its related clones is treatment of arterial hypertension in adult patients not sufficiently treated with mono- or dual-therapy, respectively.

Exforge is registered in the EU since 17 Jan 2007 and subsequently a Commission Decision was adopted on 22 Nov 2011 for the renewal of the marketing authorisation. Exforge HCT was registered in the EU on 16 Oct 2009.

This MAH type II variation worksharing application concerns an update of the SmPC related to the safety of the medicinal products. The update concerns mainly section 4.4 of the SmPC and aims to inform prescribers that caution is required, and monitoring of blood pressure, renal function and electrolytes is recommended, when co-administering agents acting on the renin angiotensin aldosterone system (RAAS) i.e. angiotensin-converting-enzyme inhibitors (ACE-inhibitors), angiotensin II receptor blockers (ARBs) or direct renin inhibitors of which aliskiren is the only compound in this class. Furthermore, sections 4.2, 4.3 and 4.5 of the SmPCs have been updated to reflect that the concomitant use of ARBs or ACE-inhibitor with aliskiren is contraindicated in patients with renal impairment and in patients with diabetes mellitus.

The background for the application is a request from Swiss Medic and the U.S. Food and Drug Administration (FDA) regarding the combined use of agents acting on the RAAS (including ACE-Inhibitors, ARBs or aliskiren).

The Health Authorities' proposed text applying to all prescribing information of all ACE-inhibitors and ARBs available in Switzerland and in the U.S. was requested to be mentioned in the Drug Interaction section with a cross reference to the Warnings and Precautions section. A list of publications supporting the requests was provided by both health authorities. Swiss Medic also clarified in a letter dated 15 May 2012 that the product information of ARBs and ACEIs was to be brought in line with the product information of products containing the active substance aliskiren with regards to the combination with aliskiren.

Furthermore, a new contraindication for concomitant use of aliskiren with ACE-inhibitors or ARBs was included in the EU SmPC of the aliskiren-containing products as part of an Article 20 referral procedure in 2012.

The proposed wording concerning the contraindication for concomitant use of Exforge or Exforge HCT (including their clones) is in line with the currently approved SmPC for aliskiren.

The MAH proposed the following changes in the SmPC:

- Addition of concomitant use of valsartan with aliskiren as a contraindication in patients with renal impairment (GFR less than 60ml/min/1.73m2) to section 4.2 posology, under renal impairment and to section 4.3 Contraindications;
- Addition of a sub-section on diabetes mellitus to section 4.2 posology regarding the combined use of aliskiren with ARBs in patients with diabetes mellitus;
- Addition of a contraindication regarding the combined use of aliskiren with ARBs or ACE-inhibitors in patients with diabetes mellitus to the section 4.3 Contraindications;
- Addition of a cautionary statement on the concomitant use of valsartan with aliskiren contraindicated in patients with renal impairment (GFR less than 60ml/min/1.73m2); addition of a cautionary statement regarding RAAS dual blockade in general; addition of a cautionary statement on the co-administration of ARBs with ACEIs or aliskiren and addition of concomitant use of valsartan with aliskiren contraindicated in patients with renal impairment (GFR less than 60ml/min/1.73m2) to section 4.4 special warnings and precautions;
- Addition of a specific description of the risks associated with RAAS dual blockade to section 4.5 Interactions with other medicinal products and other forms of interaction.

2.2. Clinical Safety aspects

2.2.1. Methods – analysis of data submitted

The proposed safety update is based on a review of published literature with specific attention to the adverse events of interest, i.e. hyperkalemia, renal impairment, syncope, and hypotension. For studies conducted by Novartis, i.e., Val-HeFT, VALIANT, and ALTITUDE, clinical study reports were also reviewed. Focus was made on the data reviewed by FDA, thus the following studies: Val-HeFT (Cohn et al 2001), VALIANT (Pfeffer et al 2003), ONTARGET (The ON-TARGET Investigators 2008) and CHARM-Added (McMurray et al 2003)], and preliminary data from the ALTITUDE study (Study CSPP100E2337)]. Furthermore, the Swiss Medic also referenced a meta-analysis by Lakhdar et al 2008 in their review, why this is also included in the clinical overview of the MAH.

The MAH argues that information from post-marketing safety information from spontaneous reports were not reviewed and not presented due to inherent limitations of such reports, e.g. uncertainty about the size of the population(s) from which these reports are derived, and most importantly the under-reporting bias which does not allow one to reliably characterize reporting rates of adverse events in patients exposed to two classes of medications.

2.2.2. Results of relevant studies

2.2.2.1. Randomised, controlled trials

Five randomised, placebo- or active-controlled, double-blind, parallel-group, multi-center, multi-national trials investigating the efficacy and safety of combination treatment with two drugs both affecting the Renin Angiotensin Aldosterone System (RAAS) together with a meta-analysis have been submitted in support of the proposed changes.

Four studies investigate efficacy and safety of concomitant treatment with an Angiotensin II receptor blocker and an ACE-inhibitor compared to mono-therapy with an ACE-inhibitor. The Altitude study is the only study comparing treatment with aliskiren, which is a direct renin inhibitor, or placebo as add-on therapy to an Angiotensin II receptor blocker or an ACE-inhibitor.

The Val-Heft and Charm-Added studies include patients with chronic heart failure, the Valiant studies include patients with acute myocardial infarct, the On-Target study includes patients with vascular disease or high-risk diabetes and the Altitude study includes patients with type II diabetes and chronic kidney disease or cardiovascular disease.

The Val-Heft study (2001)

In this study, patients with clinically stable heart failure and in standard treatment of heart failure including ACE inhibitors, diuretics, digoxin, and/or beta-blockers were randomised to add-on therapy with vasartan or placebo. The study was designed with two primary endpoints: Overall mortality from any cause during the study period and the combined endpoint of mortality and morbidity. Morbidity was defined as cardiac arrest with resuscitation, hospitalisation for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalisation.

There was no statistically significant difference between the two treatment groups in all-cause mortality; 495(19.7%) patients in the valsartan group and 484 (19.4%) patients in the placebo group died during the study (relative risk: 1.02 (98%CI: 0.88-1.18) (P=0.80)). The causes of death were also similar in the two treatment groups; there were 262 sudden deaths from cardiac causes in the valsartan group and 258 in the placebo group, and there were 118 deaths due to heart failure in the valsartan group and 125 in the placebo group.

The other primary endpoint, the combined endpoint of mortality and morbidity was significantly reduced among patients receiving valsartan (723 patients with events [28.8%]) as compared with those receiving placebo (801 patients with events [32.1%]), relative risk (97.5%CI): 0.87 (0.77–0.97) (P=0.009). The predominant benefit in terms of the combined end point was a 24% reduction in the rate of adjudicated hospitalisations for worsening heart failure as a first event in those receiving valsartan (13.8%) as compared with those receiving placebo (18.2%) (P<0.001). Hospitalisation for problems other than heart failure was similar for the two treatment groups.

Regarding the secondary endpoints, statistically significant more patients in the valsartan group than in the placebo group had improvements in NYHA classification (23.1% in the compared to 20.7% in the placebo group; P<0.001) and overall, the beneficial effect of valsartan on the combined mortality–morbidity endpoint was generally consistent among the predefined subgroups of patients (age, gender, diabetes, coronary heart disease, NYHA-class, ejection fraction). However, when dividing the patients in four sub-groups based on treatment (+/- ACE-inhibitors, +/- beta-blockers and placebo versus valsartan) the global test for the interaction between treatment and subgroup among the four subgroups was statistically significant for mortality (P=0.009) and the combined endpoint of mortality and morbidity (P=0.001). Thus, mortality was significantly reduced in the 226 patients who were treated with neither an

ACE inhibitor nor a beta-blocker (P=0.012). Among those who were receiving both drugs at base line, valsartan had an adverse effect on mortality (P=0.009) and was associated with a trend toward an increase in the combined endpoint of mortality and morbidity (P=0.10).

Statistically significant more patients in the valsartan-group compared to the placebo-group discontinued study medication due to renal impairment (1.1% versus 0.2%, P<0.001), and mean change in the serum creatinine concentration was statistically higher in the valsartan-group compared to the placebo-group (0.18 mg/dl [15.9 µmol/l]) in the valsartan-group compared to 0.10 mg/dl (8.8 µmol/l) in the placebo-group, P<0.001). Likewise, also the mean change in the serum potassium concentration was statistically significantly higher in the valsartan-group (+0.12 mmol/l) compared to the placebo-group (-0.07 mmol/l) (P<0.001).

Conclusion: The study found no statistically significant difference in all-cause mortality, but a significant difference in the combined endpoint of overall mortality and morbidity. This difference was mainly due to a reduction in hospitalisation due to worsening of heart failure. Significantly more patients discontinued treatment due to renal failure and there was also a statistically significant greater increase in serum concentration of creatinine as well as potassium. A post hoc analysis found that patients receiving valsartan and ACE-inhibitor and a beta-blocker had a statistically significantly increased risk of mortality.

The Charm-Added-study (2003)

In this study, patients with clinically stable heart failure and already in treatment with an ACE-inhibitor were randomised to add-on therapy with candesartan or placebo.

The primary endpoint was a composite endpoint of cardiovascular death or hospital admission for management of worsening chronic heart failure. In the candesartan+ACE-inhibitor group statistically significant fewer patients experienced the primary outcome compared to patients in the ACE-inhibitor-only (=placebo) group: 483 (37.9%) patients in the candesartan+ACE-inhibitor group compared to 538 (42.3%) patients in the ACE-inhibitor-only group resulting in an adjusted hazard ratio of 0.85 (95%CI: 0.75–0.96), P=0.011.

For both components of the composite primary endpoint, candesartan+ACE-inhibitor was statistically significant better that ACE-inhibitor-only: The overall cardiovascular mortality was 302 (23.7%) patients in the candesartan+ACE-inhibitor group compared to 347 (27.3%) patients in the ACE-inhibitor-only group (unadjusted hazard ratio 0.84 [95%CI: 0.72–0.98], P=0.029). Likewise, 309 (24.2%) patients in the candesartan+ACE-inhibitor group compared to 56 (28.0%) patients in the ACE-inhibitor-only group were hospitalised due to chronic heart failure (unadjusted hazard ratio: 0.83 [95%CI: 0.71–0.96], P=0.014).

Candesartan+ACE-inhibitor also statistically significant decreased the risk of the secondary outcome measure of myocardial infarction (p=0.012), whereas the decrease in coronary revascularisation procedures and stroke were not statistically significant (P=0.46 and P=0.62 respectively).

In the study there was no difference in the proportion of patients who doubled the creatinine during the study period (7% in the candesartan+ACE-inhibitor group versus 6% in the ACE-inhibitor-only group; P=0.5) however, 7.8% in the candesartan+ACE-inhibitor group discontinued treatment due to increase in creatinine compared to 4.1% in the ACE-inhibitor-only group, which was statistically significant (P=0.001).

In the candesartan+ACE-inhibitor group statistically significant more patients (3.4%) discontinued treatment due to hyperkalemia compared to the ACE-inhibitor-only group (0.7%) (P<0.001).

Overall, statistically significant more patients in the candesartan+ACE-inhibitor group (309 [24%] patients) compared to the ACE-inhibitor-only group (233 [18%] patients) permanently discontinued study medication because of an adverse event or an abnormal laboratory value (p=0.0003).

Conclusion: The study found that additional treatment with candesartan to patients with cardiac failure and already treated with an ACE-inhibitor significantly decreases the risk of cardiovascular mortality and morbidity as compared to placebo. Statistically more patients in the candesartan+ACE-inhibitor group discontinued treatment because of increase in serum creatinine and hyperkalemia. Overall, statistically significant more patients in the candesartan+ACE-inhibitor group compared to the ACE-inhibitor-only group discontinued study medication because of an adverse event or an abnormal laboratory value.

The Valliant study (2003)

In this study, patients with acute myocardial infarction were randomised to treatment with either valsartan, valsartan+captopril or captopril.

The primary endpoint was mortality from any cause and no statistically significant difference was seen between the three treatment groups: 979 (19.9%) patients in the valsartan-only group died, as did 941 (19.3%) in the valsartan+captopril group and 958 (19.5%) in the captopril-only group. The hazard ratio for death in the valsartan-only group as compared to the captopril-only group was 1.00 (97.5%CI: 0.90-1.11; P=0.98), and the hazard ratio for death in the valsartan+captopril group as compared to the captopril-only group was 0.98 (97.5%CI: 0.89 to 1.09; P=0.73).

There was no statistically significant difference in death from cardiovascular causes: 827 (16.8%) patients in the valsartan-only group, 827 (16.9%) patients in the valsartan+captopril group and 830 (16.9%) patients in the captopril-only group died from a cardiovascular cause; resulting in a hazard ration of 0.98 (97.5%CI: 0.87–1.09, P=0.62) for the comparison between valsartan and captopril and a hazard ratio of 1.00 (97.5%CI: 0.89–1.11, P= 0.95) for the comparison between valsartan+captopril and captopril-only.

Dose reductions and permanent discontinuations of study medication due to hypotension and also due to renal causes were both statistically significant (P<0.05 for all comparisons) more frequent in the valsartan-only and the valsartan+captopril group compared to the captopril-only group, thus, 53 (1.1%) patients, 61 (1.3%) patients and 40 (0.8%) patients in the valsartan-only, valsartan+captopril and the captopril-only groups respectively permanently discontinued treatment with study drug due to renal causes. There was no significant difference in the frequency of hyperkalemia in the three treatment groups: 7 (0.1%) patients, 12 (0.2% patients) and 4 (0.1%) patients respectively in the studygroups (valsartan-only, valsartan+captopril and captopril-only group respectively).

Conclusion: In the present study treatment with valsartan-only, valsartan+captopril or captopril-only were found to be equal in preventing all-cause mortality with no statistically significant difference between the study groups. Neither did the study find any statistically significant difference between the treatment groups related to deaths of cardiovascular causes. Statistically significant more patients in the groups of valsartan-only and valsartan+captopril compared to the captopril-only treated group permanently discontinued treatment with study drug due to hypotension and renal causes.

The On-Target-study (2008)

In this study, high-risk patients with cardio-vascular disease or diabetes mellitus were randomised to treatment with either telmisartan, telmisartan+ramipril or ramipril.

The primary endpoint was a composite endpoint of death from cardiovascular causes, myocardial infarction, stroke or hospitalisation for heart failure, which occurred in 1412 patients (16.5%) in the ramipril-only group, in 1423 patients (16.7%) in the telmisartan-only group, and in 1386 patients (16.3%) in the ramipril+telmisartan group, thus both telmisartan-only and the combination therapy with telmisartan+ramipril were non-inferior to treatment with ramipril-only, the relative risk for telmisarta-only n vs. ramipril-only was 1.01 (95%CI: (0.94–1.09) and the relative risk for telmisartan+ramipril vs. ramipril-only was 0.99 (95% CI: 0.92–1.07). Likewise, also the secondary endpoint (death from cardiovascular causes, myocardial infarction, or stroke) occurred in a similar proportion of patients in the three treatment groups: 1190 (13.9%) patients in the telmisartan-only group, 1200 (14.1%) in the combined treatment group and 1210 (14.1%) patients in the ramipril-only group, thus also for this parameter, telmisartan-only and also the combination-therapy with telmisartan and ramipril was found to be non-inferior compared to ramipril-only treatment.

There was no significant difference in the total number of deaths from any cause between the three treatment groups. The relative risk for telmisartan-only vs. ramipril-only was 0.98 (95%CI: 0.90–1.07), and the relative risk for the combination therapy with telmisartan+ramipril vs. ramipril-only was 1.07 (95%CI: 0.98–1.16).

Other secondary endpoints included new-onset heart failure, new-onset diabetes mellitus, atrial fibrillation, dementia or cognitive decline, nephropathy and revascularisation procedures. The study did not find any significant differences in the rates of secondary endpoints. An exception to this was renal dysfunction which was seen more often: 13.5% in the group receiving combined therapy compared to 10.6% in the telmisartan-only group and 10.2% in the ramipril-only group. The relative risk of the combination therapy vs. ramipril-only was 1.33 (P<0.001).

The number of patients who had an increase in the potassium level of >5.5 mmol/l were similar in the ramipril-only group (283 patients) and the telmisartan-only group (287 patients), but the number was significantly higher in the combination-therapy group (480 patients, P<0.001 for the comparison between the combination therapy group and the ramipril-only group).

Conclusion: The study found the three treatments to be non-inferior with regard to the primary endpoint of death from cardiovascular causes, myocardial infarction, stroke or hospitalisation for heart failure. More patients treated with telmisartan+ramipril compared to patients treated with ramipril-only developed renal dysfunction and hyperkalemia defined as potassium level of >5.5 mmol/l.

Altitude study (2012)

The purpose of the Altitude study was to determine whether use of the direct renin inhibitor aliskiren co-administrated with an ACE-inhibitor or an angiotensin II receptor blocker would reduce cardiovascular and renal events in patients with type 2 diabetes and chronic kidney disease, cardiovascular disease, or both. By the second interim efficacy analysis the study was prematurely terminated due to an excess in adverse events; mainly increased potassium levels in the treatment group receiving add-on therapy with aliskiren compared to the group receiving add-on with placebo.

The primary endpoint was a composite of death from cardiovascular causes or the first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction; nonfatal stroke; unplanned hospitalisation for heart failure; end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy with no dialysis or transplantation available or initiated; or a serum creatinine value that was at least double the baseline value and that exceeded the upper limit of the normal range sustained for at least a month. By termination of the study approximately 69% of the projected events had occurred. By that time the primary endpoint had occurred in 783 (18.3%) patients in the aliskiren group and in 732 (17.1%) patients in the placebo group. The hazard ratio (HR) for this

endpoint in the aliskiren group as compared with the placebo group was 1.08 (95%CI 0.98-1.20; P = 0.12). There was no difference between study groups in death from any cause.

The secondary cardiovascular composite endpoint occurred in 590 (13.8%) patients in the aliskiren group and 539 (12.6%) in the placebo group; HR: 1.11 (95%CI: 0.99-1.25; P = 0.09). All components of the cardiovascular endpoint, with the exception of unplanned hospitalisation for heart failure, occurred more frequently in the aliskiren group however, only cardiac arrest with resuscitation was statistically significant (P=0.04 for this comparison and P>0.10 for the other comparisons).

The secondary renal composite endpoint occurred in 257 (6.0%) patients in the aliskiren group and 251 (5.9%) in the placebo group; HR: 1.03 (95%CI: 0.87-1.23; P = 0.74). There were no significant differences between study groups for any component of the renal endpoint.

Overall statistically significant more patients in the aliskiren group compared to the placebo group discontinued study medication permanently (P<0.001), most often due to adverse events. Hyperkalemia was the most common adverse event reported by investigators and the most common adverse event leading to discontinuation of the study drug. In the aliskiren treatment group 907 (21.2%) patients experienced a post-baseline potassium level of ≥5.5 to <6.0 mmol/l compared to 723 (16.9%) patients in the placebo group (P<0.001). Likewise also statistically significant more patients in the aliskiren group compared to the placebo group experienced a potassium level of ≥6.0 mmol/l: 479 (11.2%) patients in the aliskiren group versus 308 (7.2%) patients in the placebo group (P<0.001).

Conclusion: The study was terminated prematurely due to an increased incidence of adverse events; mainly increased potassium levels in the active treatment group compared to the placebo group. More patients in the aliskiren group compared to the placebo group terminated the study treatment due to adverse effects. Hyperkalemia was the most common adverse effect and marked elevation of serum potassium was seen significantly more often among patients treated with aliskiren as compared to patients treated with placebo. This difference was seen without a reduction in the primary endpoint or any of the two secondary endpoints as no statistically significant difference was seen in neither the composite primary endpoint nor any of the two secondary endpoints.

2.2.2.2. Meta-analyses

Two meta-analyses are included in the present application. Both are meta-analyses on adverse effects associated with combination with angiotensin II receptor blockers plus ACE-inhibitors in patients with left ventricular dysfunction.

Phillips (2007)

Included studies in the present meta-analysis were studies with minimum 500 patients to combination treatment with ACE-inhibitors+angiotensin II receptor blockers or standard therapy for left ventricle dysfunction including an ACE-inhibitor. The studies were to have a follow-up time of minimum three months and should report on adverse effects to the treatments. Four randomised, controlled trials were included in the statistical analysis including the Val-Heft, Charm-Added and the Valiant studies. Furthermore, the meta-analysis included the Resolvd study from 1999. The meta-analysis included a total of 17337 patients.

Compared with treatment with an ACE-inhibitors alone, combination treatment with an angiotensin II receptor blocker + an ACE-inhibitor was associated with an increased risk of developing adverse effects leading to discontinuation of therapy, symptomatic hypotension, hyperkalemia and worsening of renal function:

Discontinuation due to adverse effects: Combination therapy of an ACE-inhibitor + an angiotensin II receptor antagonist was associated with a significant increase in medication discontinuation because of adverse effects in chronic heart failure compared to treatment with an ACE-inhibitor-only: 15.0% vs. 11.0%; relative risk (RR): 1.38 (95%CI: 1.22-1.55), number needed to harm (NNH)=25 and also in patients with AMI and symptomatic left ventricle dysfunction: 9.0% vs. 7.6%; RR: 1.17 (95%CI: 1.03-1.34), NNH=71.

Symptomatic hypotension: Combination therapy of an ACE-inhibitor + an angiotensin II receptor antagonist was associated with a significant increased risk of symptomatic hypotension in chronic HF compared to treatment with an ACE-inhibitor-only: 2.4% vs. 1.5%; RR: 1.50 (95%CI: 1.09- 2.07), NNH=111. Likewise, in patients with AMI and symptomatic left ventricle dysfunction the meta-analysis found a significant increased risk in patients in combination treatment: 18.1% vs. 11.9%; RR: 1.48 (95%CI: 1.33-3.18), NNH=16.

Worsening of renal failure (defined as an increase in serum creatinine level >0.5 mg/dL, up to a doubling over baseline values): Combination therapy of an ACE-inhibitor + an angiotensin II receptor antagonist was associated with a significant increased risk of worsening renal function: 3.3% vs. 1.5%; RR: 2.17 (95%CI: 1.59-2.97); NNH: 56. Combination therapy vs. treatment with ACE-inhibitor-only was also associated with a significant increased risk of worsening renal function in patients with AMI and symptomatic left ventricle dysfunction: 4.8% vs. 3.0%; RR: 1.61 (95%CI: 1.31-1.98); NNH: 56.

Hyperkalemia (defined as a serum potassium level ≥5.5 mEq/L): Combination therapy of an ACE-inhibitor + an angiotensin II receptor antagonist was associated with a significant increased risk of hyperkalemia: 3.5% vs. 0.7%; RR: 4.87 (95%CI: 2.39-9.94); NNH: 36.

Conclusion: Compared with mono-therapy with an ACE-inhibitor alone, combination treatment with an angiotensin II receptor antagonist and an ACE-inhibitor was associated with an increased risk of adverse effects leading to discontinuation of treatment, symptomatic hypotension, hyperkalemia and worsening of renal failure.

Lakhdar (2008)

Included studies in the meta-analysis were studies in patients with New York Heart Association functional class II to IV heart failure and ejection fraction ≤45% or patients with left ventricular dysfunction acutely post-myocardial infarction. The meta-analysis included nine randomised clinical trials including the above mentioned Val-Heft, Charm Added and Valiant studies and a total of 18.160 patients. 9199 patients received combination therapy with an angiotensin II receptor blocker+ACE-inhibitor and 8961 patients received an ACE- inhibitor alone.

Results for the endpoints were as follows:

Compared with treatment with an ACE-inhibitors alone, combination treatment with an angiotensin II receptor blocker + an ACE-inhibitor was associated with an increased risk of developing adverse effects leading to discontinuation of therapy. These included:

Any side effect: Combination therapy vs. treatment with an ACE-inhibitor alone: 11.44% vs. 9.07%; relative risk (RR): 1.27 (95%CI: 1.15-1.40), P <0.00001, I^2: 15.9%; Numbers needed to harm (NNH): 42.

Hypotension: Combination therapy vs. treatment with an ACE-inhibitor alone: 2.28% vs. 1.16%; RR: 1.91 (95%CI: 1.37-2.66), P =0.0002, I^2: 26.6%; NNH: 89.

Increased risks of worsening renal function: Combination therapy vs. treatment with an ACE-inhibitor alone: 2.08% vs. 1.08%; RR: 2.12 (95%CI: 1.30-3.46), P =0.003, I^2: 67.3%; NNH: 100.

Hyperkalemia: Combination therapy vs. treatment with an ACE-inhibitor alone: 0.87% vs. 0.20%; RR: 4.17 (95%CI: 2.31-7.53), P <0.00001, I^2: 0%); NNH: 149,

There was no difference in the risk of angioedema (0.22% vs. 0.25%; RR: 0.88 (95%CI: 0.43-1.80), P =0.72, I^2: 0%) or cough (2.07% vs. 2.46%; RR: 0.84 (95%CI: 0.65-1.09), P =0.19, I^2: 0%).

As the Valiant study was the largest study and the only one to enroll patients with left ventricle dysfunction immediately post-myocardial infarction, a sensitivity analysis was performed. This showed no meaningful difference in the relative risk estimates across most adverse events (with the exception of cough). Likewise sub-group analyses including subgroups of subjects with diabetes mellitus (<25% vs. ≥25%), diuretic use (<75% vs. ≥75%), follow-up duration (>24 vs. ≤24 months), and gender (female with <25% vs. ≥25%) did not reveal any statistical significant differences from the primary analyses.

Conclusion: Compared with mono-therapy with an ACE-inhibitor alone, combination treatment with an angiotensin II receptor antagonist and an ACE-inhibitor was associated with an increased risk of adverse effects (by 2.37%) including an increased risk of hypotension (by 1.12%), worsening of renal failure (by 1.0%) and hyperkalemia (by 0.67%). The authors raise the concern, that "the excess risk, coupled with a lack of consistent mortality benefit, suggests that angiotensin II receptor blockers should not routinely be added to ACE-inhibitors therapy for left ventricular dysfunction, and if chosen, the combination strategy may warrant closer patient monitoring to detect adverse effects".

2.2.3. Discussion

Results from five clinical studies and two meta-analyses have been presented. All five clinical studies are well-designed, well-conducted, large clinical, randomised double-blinded, multi-center, multinational studies including more than 50.000 patients in total (range: 2548-25620). Four studies (Val-Heft, Charm-Added, Valiant and On-Target) evaluated efficacy and safety of concomitant treatment with an Angiotensin II receptor blocker and an ACE-inhibitor compared to mono-therapy with an ACE-inhibitor.

The Altitude study differs from the other studies as it is the only study investigating treatment with aliskiren, which is a direct renin inhibitor. In this study patients with type 2 diabetes chronic kidney disease with evidence of microalbuminuria or macroalbuminuria or cardiovascular disease and were already taking an ACE inhibitor or an angiotensin II receptor blocker per standard practice were randomized to add-on therapy with either aliskiren or placebo. The study was terminated prematurely due to an excess in adverse effects (predominantly hyperkalaemia) without a reduction in major cardiovascular and renal events, and this study is the basis for the present application of adding the contraindications of concomitant treatment with aliskiren and an ACE-inhibitor or an angiotensin II receptor blocker.

The four other studies included patients with chronic heart failure (the Val-Heft and Charm-added studies), patients treated after acute myocardial infarct (the Valiant study) and patients with vascular disease or high-risk diabetes (the On-Target study).

As could be expected, more adverse effects were seen in the active treatment groups and groups with dual therapy as compared to placebo. Combination of an angiotensin II receptor blocker plus an ACE-inhibitor compared to mono-therapy was associated with significant increases in the risk of symptomatic hypotension. This is not unexpected considering the known safety profiles and pharmacologic mechanisms of action of these drugs.

More worrying is that the studies also found that treatment with an ACE-inhibitor and angiotensin II receptor blocker is associated with an increase in creatinine and an increased risk of renal failure; both in the Val-Heft study, the Charm-Added study and the Valiant study statistically significant more patients

treated with dual action therapy permanently discontinued therapy due to renal failure. Likewise, also statistically significant more patients developed hyperkalemia in these studies.

This excess in adverse events including (potential) serious adverse events should be compared with the fact that only the Charm-Added study found a significant reduction in the composite endpoint of cardiovascular death or hospital admission for management of worsening chronic heart failure. The other studies found no statistically significant difference in the primary endpoints including deaths when treatment with ACE-inhibitors+angiotensin II receptor blockers was compared to mono-therapy with ACE-inhibitors. Thus, according to these studies, combination therapy is associated with more (serious) adverse events without an increase in efficacy.

2.3. Changes to the Product Information

The proposed changes in the updated SmPC are as follows for Exforge and related clones (Copalia, Dafiro and Imprida):

PRESENT [10,11]	PROPOSED [10, 11]
Note: additions to the SmPC and PL are presented in **blue/bold** and deletions in ~~red/strikethrough~~	
SUMMARY OF PRODUCT CHARACTERISTICS	SUMMARY OF PRODUCT CHARACTERISTICS
4.2 Posology and method of administration	**4.2 Posology and method of administration**
(…)	(…)
No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.	No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment. **The concomitant use of Exforge with aliskiren is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).** ***Diabetes mellitus*** **The concomitant use of Exforge with aliskiren is contraindicated in patients with diabetes mellitus (see section 4.3).**

4.3 Contraindications • Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1. • Severe hepatic impairment, biliary cirrhosis or cholestasis. • Severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2) and patients undergoing dialysis.	**4.3 Contraindications** • Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1. • Severe hepatic impairment, biliary cirrhosis or cholestasis. • Severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2) and patients undergoing dialysis. • **Concomitant use of angiotensin receptor antagonists (ARB) - including valsartan - or of angiotensin converting enzyme (ACE) inhibitors with aliskiren in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73m^2) (see sections 4.4 and 4.5).**
4.4 Special warnings and precautions for use <u>Renal impairment</u> No dosage adjustment of Exforge is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.	**4.4 Special warnings and precautions for use** <u>Renal impairment</u> No dosage adjustment of Exforge is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment. **The concomitant use of ARBs - including valsartan - or of ACE inhibitors with aliskiren is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73m^2) (see sections 4.3 and 4.5).**
4.4 Special warnings and precautions for use -	**4.4 Special warnings and precautions for use** **Dual blockade of the renin-angiotensin-aldosterone system (RAAS)** **The concomitant use of ARBs, including valsartan, with other agents acting on the RAAS is associated with an increased incidence of hypotension, hyperkalaemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Exforge and other agents that affect the RAAS.** **Caution is required when co-administering ARBs - including valsartan - with other agents blocking the RAAS such as ACE inhibitors or aliskiren (see section 4.5).** **The concomitant use of ARBs - including valsartan - or of ACE inhibitors with aliskiren in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73m^2) is contraindicated (see sections 4.3 and 4.5).**

4.5 Interaction with other medicinal products and other forms of interaction -	**4.5 Interaction with other medicinal products and other forms of interaction** *Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren* **The concomitant use of ARBs - including valsartan - or of ACE inhibitors with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73m^2) (see sections 4.3 and 4.4).**

In addition to the suggested changes above, the corresponding sections of the Package Leaflet have also been updated to reflect the SmPC changes.

Further, the MAH took the opportunity to update the SmPC, Annex II and the Package Leaflet in line with the latest QRD template, to implement minor editorial changes in the Package Leaflet and to add the contact details of the Croatian local representative in the Package Leaflet.

During the procedure, the CHMP raised the following issues:

New text:

*(Additions are in **bold/italics**)*

For Exforge / Copalia / Dafiro / Imprida EU SmPCs:

4.2 Posology and method of administration

[…]

The concomitant use of Exforge with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73 m^2) (see section 4.3).

Diabetes Mellitus

The concomitant use of Exforge with aliskiren is contraindicated in patients with diabetes mellitus (see section 4.3).

CHMP comments:

According to the current SmPC guideline Section 4.2 should be started by specifying the conditions where medical prescription is restricted. It therefore seems relevant to add the text as outlined above.
Cumulative evidence (see above) supports the contraindications mentioned above.
The cross-reference to Section 4.3 of the SmPC is endorsed. The proposed changes are acceptable.

Hypotension, hyperkalemia and increase in creatinine/compromised kidney function have been shown as adverse effects to combination treatment in various patient categories including patients with left ventricle dysfunction, patients with recent AMI, patients with vascular disease and patients with diabetes. Furthermore, the adverse effects can be explained by the nature of the drugs and might be caused by the additive effect of the adverse effects of ACE-inhibitors and angiotensin II receptor antagonists as these adverse effects are known adverse effects to both ACE-inhibitors and angiotensin II receptor antagonists.

Therefore, the applicant was asked during the procedure to discuss whether the mentioned adverse effects can be expected in all patient-groups (and not only in patients with decreased kidney function or

diabetes), and also to justify why no warning is considered necessary in patients with left ventricle dysfunction and in patients with recent AMI.

In their response, the MAH stated that dual blockade of the RAAS with ARBs, ACEIs, or aliskiren is associated with increased incidence of hypotension, hyperkalemia, and changes in renal function (including acute renal failure). The MAH acknowledged that these adverse effects were observed in various patient categories and agrees that it cannot be excluded that these adverse effects may also occur with dual RAAS therapy in other patient subgroups. As a result, no qualifier regarding patient subgroups is mentioned in Section 4.4 "Special warnings and precautions" where it is stated that "Caution is required when co-administering ARBs, including valsartan, with other agents blocking the RAAS such as ACE inhibitors or aliskiren".

Overall, it is considered, that the MAH has sufficiently discussed whether the mentioned adverse effects can be expected in all patient-groups (and not only in patients with decreased kidney function or diabetes).

Further, the MAH emphasised that "no special warning is required in patients with left ventricular dysfunction and patients with recent AMI", due to the fact that:

a) Positive long-term outcomes with dual RAAS therapy have been observed in chronic heart failure patients (Val-HeFT and Charm-Added). While a benefit was not observed in a subgroup of patients using both a beta-blocker and an ACE inhibitor in Val-HeFT, a significantly favorable effect on morbidity was observed in valsartan patients receiving either a beta-blocker alone or an ACE inhibitor alone.

b) Dual RAAS therapy had no adverse effect on long term outcomes compared to mono-therapy in acute MI patients (VALIANT).

The MAH referred to the results from the Val-HeFT-, Charm-Added- and VALLIANT studies. It is agreed that dual RAAS therapy resulted in positive long-term outcomes of all-cause mortality and morbidity (Val-HeFT-study) and in cardiovascular mortality (Charm-Added-study). In both studies as well as in the VALLIANT study, more patients discontinued treatment due to hypotension or renal cause including increase in creatinine and potassium. These results were confirmed in the meta-analyses of Philips and Lakhdar.

These results are considered adequately reflected in the updated PI as the MAH has included a warning in the relevant Section 4.4 of the SmPC "Special warnings and precautions" informing that "Caution is required when co-administering ARBs, including valsartan, with other agents blocking the RAAS such as ACE inhibitors or aliskiren". Notably no specific patient-subgroups are mentioned in this paragraph, which is endorsed as it also includes (but is not limited to) patients with left ventricle dysfunction and patients with recent AMI. Furthermore, the MAH has included the following information in the SmPC, section 4.4 "Special warnings and precautions": "It is recommended to monitor blood pressure, renal function and electrolytes in patients on Exforge and other agents that affect the RAAS". This is endorsed; especially the fact that the MAH includes relevant recommendations on how to monitor the patients.

Overall, the CHMP is of the view that the MAH has provided acceptable justifications and that sufficient information for all patients (including patients with cardiac diseases) is given in the updated SmPC.

4.3 Contraindications

[…]

Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2) (see sections 4.4 and 4.5).

CHMP comments:

Cumulative evidence (see section 2 of this report) supports the contraindications mentioned above.

The contraindication of "Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2)" is acceptable and the cross-reference to Section 4.4 and 4.5 is endorsed.

However, during the procedure, the applicant was asked to justify the relevance of mentioning also the contra-indication of concomitant treatment with ACE-inhibitors and aliskiren in the present SmPC, which only concerns an angiotensin II receptor blocker.

The MAH responded that reference is made to ACE inhibitors to reflect the class effect and to ensure that adequate information is provided to the physician about the combined use of dual agents acting on the RAAS. Thus, the MAH seeks to avoid that the physician could misleadingly assume that an ARB could be replaced by an ACE inhibitor.

It is endorsed that the SmPCs are brought in line with the product information of products containing the active substance aliskiren, and the aim of informing the physicians not to replace an ARB with an ACE-inhibitor is acknowledged.

Overall, the justification for mentioning the contra-indication of concomitant treatment with ACE-inhibitors and aliskiren in the present SmPC is accepted.

4.4 Special warnings and precautions for use

Renal impairment

[…]

The concomitant use of ARBs - including valsartan - or of ACE inhibitors with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73m^2) (see sections 4.3 and 4.5).

[…]

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

The concomitant use of ARBs, including valsartan, with other agents acting on the RAAS is associated with an increased incidence of hypotension, hyperkalaemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Exforge and other agents that affect the RAAS.

Caution is required when co-administering ARBs, including valsartan, with other agents blocking the RAAS such as ACEIs or aliskiren (see section 4.5).

The concomitant use of ARBs - including valsartan - or of ACE inhibitors with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2) is contraindicated (see sections 4.3 and 4.5).

CHMP comments:

The proposed text is in line with the suggested wording for SmPC sections 4.2 and 4.3 and is acceptable (see discussion above).

4.5 Interaction with other medicinal products and other forms of interaction

Dual blockade of the RAAS with ARBs, ACE inhibitors , or aliskiren:

The concomitant use of ARBs - including valsartan - or of ACE inhibitors with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m^2) (see sections 4.3 and 4.4).

[…]

CHMP comments:

The proposed text is identical to the wording suggested for SmPC sections 4.2, 4.3 and 4.4 and is acceptable.

Package Leaflet

In addition to the suggested changes above, the corresponding sections of the Package Leaflet have also been updated to reflect the SmPC changes, which is acceptable.

Further, the MAH took the opportunity to update the SmPC, Annex II and the Package Leaflet in line with the latest QRD template, to implement minor editorial changes in the Package Leaflet and to add the contact details of the Croatian local representative in the Package Leaflet. Further, the MAH took the opportunity to propose minor editorial changes in the Package Leaflet. These changes to the product information are acceptable.

3. Overall conclusion and impact on the benefit/risk balance

Several large clinical studies investigating the efficacy and safety of concomitant treatment with drugs acting on (blocking) the renin angiotensin aldosterone system have been conducted. The studies have investigated different patient populations including patients with chronic heart failure, patients with acute myocardial infarction and patient with vascular disease and/or chronic kidney disease and/or high-risk diabetes. Accumulated evidence demonstrates that combination treatment with angiotensin II receptor blockers and ACE-inhibitors does not improve mortality and is associated with an increased risk of hypotension, renal dysfunction and hyperkalemia. These findings are in association with the results from two meta-analyses of the adverse effects associated with combination of angiotensin II receptor blockers plus ACE-inhibitors in patients with left ventricular dysfunction.

At present, the current cumulative evidence shows that the possible benefit from dual action therapy (e.g. a decrease in blood pressure) does not lead to an overall better survival and does not outweigh the increased associated risk of symptomatic hypotension, increased risk of hyperkalemia and decreased renal function. The risk-benefit of dual-action therapy is currently negative and cannot be routinely recommended. It therefore seems relevant and justified to add this information in the relevant SmPC sections. Relevant information has already been included in the EU SmPC of aliskiren as part of a recent article 20 referral procedure, and the current application for an update of the PI for Exforge and its clones aims at reflecting the evidence of increased risk of concomitant treatment with drugs acting on (blocking) the renin angiotensin aldosterone system. Furthermore, the MAH proposes to put the product information of Exforge and its clones in line with the product information of the aliskiren range of products, which is acceptable.

During the procedure, the CHMP raised questions related to the information in the PI regarding the adverse effects of hypotension, hyperkalemia and increase in creatinine/compromised kidney function.

The MAH acknowledged that the mentioned adverse effects may occur with dual RAAS therapy in different patient subgroups. However, by referring to the long-term results in terms of all-cause mortality/cardiovascular mortality and morbidity from the Val-HeFT-, Charm-Added- and VALLIANT studies, the MAH justified the view that no special warning be required in patients with left ventricular dysfunction and patients with recent AMI, which is considered acceptable as section 4.4 of the SmPC includes a general statement informing prescribers of the fact that "*Caution is required when co-administering ARBs, including valsartan, with other agents blocking the RAAS such as ACE inhibitors or aliskiren*". No specific patient-subgroups are mentioned in this paragraph, which thus also applies to (but is not limited to) patients with left ventricle dysfunction and patients with recent AMI. Overall, the CHMP considers that all questions raised during the procedure have been addressed satisfactorily.

The overall conclusion of CHMP is that the changes in the SmPC, Annex II and Package Leaflet for Exforge and its clones are approvable with no further comments.

The benefit-risk balance for the medicinal products included in this worksharing procedure remains positive.

Furthermore, the CHMP considers that this variation implements changes to the decision granting the marketing authorisation due to a significant public health concern on the following grounds:

This variation concerns a new contraindication related to concomitant use of angiotensin receptor antagonists - including valsartan - with aliskiren in patients with diabetes mellitus or renal impairment as discussed in section 2.3 above.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation requested		**Type**
C.I.4	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of SmPC sections 4.2, 4.3, 4.4 and 4.5 to reflect that the concomitant use of Angiotensin II Receptor Blockers (ARBs) or Angiotensin-Converting-Enzyme inhibitors (ACEi) with aliskiren is contraindicated in patients with renal impairment and in patients with diabetes mellitus. Further, section 4.4 of the SmPC has been updated to inform prescribers that caution is required, and monitoring of blood pressure, renal function and electrolytes is recommended, when co-administering agents acting on the renin angiotensin aldosterone system (RAAS) i.e. ACEi, ARBs or aliskiren as a direct renin inhibitor. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the SmPC, Annex II and the Package Leaflet in line with the latest QRD template, to implement minor editorial changes in the Package Leaflet and to add the contact details of the Croatian local representative in the Package Leaflet.

The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable.