22 May 2014
EMA/PRAC/294920/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC assessment report

For renin-angiotensin system (RAS)-acting agents

Procedure number: EMEA/H/A-31/1370

CAPs: Edarbi EMEA/H/A-31/1370/C/2293/0006, Ipreziv EMEA/H/A-31/1370/C/2517/0006, Aprovel EMEA/H/A-31/1370/C/141/0154, Karvea EMEA/H/A-31/1370/C/142/0159, Irbesartan Zentiva EMEA/H/A-31/1370/C/785/0063, Irbesartan Teva EMEA/H/A-31/1370/C/1093/0017, Ifirmasta EMEA/H/A-31/1370/C/962/0010, Sabervel EMEA/H/A-31/1370/C/2510/0005, CoAprovel EMEA/H/A-31/1370/C/222/0162, Karvezide EMEA/H/A-31/1370/C/221/0165, Irbesartan Hydrochlorothiazide Zentiva EMEA/H/A-31/1370/C/783/0075, Irbesartan/Hydrochlorothiazide Teva EMEA/H/A-31/1370/C/1112/0019, Ifirmacombi EMEA/H/A-31/1370/C/2302/0009, Micardis EMEA/H/A-31/1370/C/209/0099, Pritor EMEA/H/A-31/1370/C/210/0106, Kinzalmono EMEA/H/A-31/1370/C/211/0094, Telmisartan Teva EMEA/H/A-31/1370/C/1146/0010, Telmisartan Teva Pharma EMEA/H/A-31/1370/C/2511/0006, Tolura EMEA/H/A-31/1370/C/1196/0013, Telmisartan Actavis EMEA/H/A-31/1370/C/1168/0007, Twynsta EMEA/H/A-31/1370/C/1224/0017, MicardisPlus EMEA/H/A-31/1370/C/413/0085, PritorPlus EMEA/H/A-31/1370/C/414/0093, Kinzalkomb EMEA/H/A-31/1370/C/415/0084, Tolucombi EMEA/H/A-31/1370/C/2549/0007, Actelsar HCT EMEA/H/A-31/1370/C/2676/0003, Exforge EMEA/H/A-31/1370/C/716/0067, Dafiro EMEA/H/A-31/1370/C/776/0069, Copalia EMEA/H/A-31/1370/C/774/0069, Imprida EMEA/H/A-31/1370/C/775/0069, Exforge HCT EMEA/H/A-31/1370/C/1068/0029, Dafiro HCT EMEA/H/A-31/1370/C/1160/0030, Copalia HCT EMEA/H/A-31/1370/C/1159/0030, Rasilez EMEA/H/A-31/1370/C/780/0085, Rasilamlo EMEA/H/A-31/1370/C/2073/0084, Rasilez HCT EMEA/H/A-31/1370/C/964/0053

Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure 3

2. Scientific discussion 3

2.1. Introduction 3
2.2. Clinical aspects 6
2.2.1. Usage patterns 6
2.2.2. Clinical data 7
2.2.2.1. VAL-HeFT 7
2.2.2.2. CHARM-Added 9
2.2.2.3. VALIANT 10
2.2.2.4. ONTARGET 12
2.2.2.5. ALTITUDE 14
2.2.2.6. Makani et al meta-analysis 16
2.2.2.7. VA NEPHRON-D 19
2.2.3. Spontaneous reports 21
2.2.4. Guidelines 21
2.2.5. Consultation of the Scientific Advisory Group in Cardiovascular Issues (SAG CVS) 22
2.2.6. Overall discussion on efficacy 23
2.2.7. Overall discussion on safety 23
2.3. Risk minimisation activities 24
2.4. Changes to the product information 24
2.5. Communication plan 25
2.6. Overall benefit-risk assessment 26

3. Overall conclusion and grounds for the recommendation 28

Divergent position to PRAC recommendation 29

1. Background information on the procedure

On 17 April, further to the emergence of new evidence from the scientific literature on dual RAS blockade therapy and given the seriousness of the identified safety concerns, the Italian Medicines Agency (AIFA) decided to initiate a review under Article 31 of Council Directive 2001/83/EC, requesting the Pharmacovigilance Risk Assessment Committee (PRAC) to issue a recommendation on the benefit-risk of dual RAS blockade therapy through the combined use of angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin II receptor blockers (ARBs) or aliskiren and to determine whether any regulatory measures should be taken on the marketing authorisations of the products involved in this procedure.

2. Scientific discussion

2.1. Introduction

The renin-angiotensin system (RAS) or renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure and fluid balance. It plays an integral role in maintaining vascular tone, optimal salt and water homeostasis, and cardiac function in humans. The main active hormone of the RAS is angiotensin II, which is formed from angiotensin I through angiotensin-converting enzyme (ACE). Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and stimulation of aldosterone secretion. Angiotensin converting enzyme governs the equilibrium between the RAS and the renin system. These two systems influence among others mechanism involved in controlling renal sodium and fluid retention.

RAS-acting agents act by blocking different stages of RAS, lowering blood pressure. The benefits of RAS inhibition include favourable impact on ventricular remodelling, improvement in haemodynamics, reduction in congestive heart failure and nephroprotection. The use of RAS-acting agents in the treatment of hypertension and its complications (including acute myocardial infarction, congestive heart failure and chronic kidney disease) is recommended in many current clinical guidelines. These agents include angiotensin-converting enzyme inhibitors (ACE-inhibitors or ACEi), which specifically block the actions of angiotensin-converting enzyme involved in the conversion of angiotensin I to angiotensin II. This reduces the effects mediated by angiotensin II, i.e. vasoconstriction and production of aldosterone, which promotes the reabsorption of sodium and water in the renal tubules and elevates cardiac output and ultimately a reduction in blood pressure. Other RAS-acting agents are angiotensin receptor blockers (ARBs), also known as angiotensin II receptor antagonists (AIIRAs) or sartans, which act by preventing angiotensin II from acting on angiotensin receptors and direct renin inhibitors such as aliskiren which can also be used for hypertension.

RAS-acting agents are authorised in the EU as 'centrally authorised products' (CAPs) or 'nationally authorised products' (NAPs) (with all aliskiren-containing products being CAPs, all ACE-inhibitors being NAPS and ARBs being either NAPs or CAPS) and are widely available in the EU under a variety of tradenames. ACE-inhibitors include benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril,

spirapril, trandolapril and zofenopril. ARBs include candesartan, telmisartan, valsartan, irbesartan, eprosartan, olmesartan, losartan and azilsartan. Aliskiren is the only authorised substance in its class.

The concept of dual RAS blockade therapy through the combined use of several RAS-acting agents, emerged in the late 1990's based on an experimental model hypothesising that the combined use of an ARB, an ACE-inhibitor or aliskiren could provide a more complete blockade of the RAS which could translate into better control of blood pressure and nephroprotective and cardioprotective effects. The concept was based on improvements in surrogate endpoints such as blood pressure, proteinuria, and endothelial dysfunction which were considered as evidence of cardioprotective and nephroprotective effects. Despite a lack of solid evidence on the safety and efficacy of dual RAS blockade therapy was commonly used in patients with hypertension and with diabetes or proteinuria, or both and also to a lesser extent in those with heart failure resistant to treatment. Most dual RAS blockade therapy is achieved using the combination of an ARB and an ACE-inhibitor (70%), although other combinations are also used, such as two ACE-inhibitors (15%), two ARBs (5%), and ACE-inhibitors or ARBs in combination with a direct renin inhibitor (8%).

However, new data has emerged in the past years, raising doubts over the efficacy and identifying safety concerns associated with dual RAS blockade therapy through the combined use of ACE-inhibitors, ARBs or aliskiren. In particular, the publication of a meta-analysis by Makani et al[1] of 33 clinical studies involving over 68,000 patients, raised concerns that combining several RAS-acting agents may be associated with an increased risk of hyperkalaemia, hypotension and kidney failure, compared with the single use of one RAS-acting agent. In addition, the meta-analysis suggested that using multiple RAS-acting agents may not be more beneficial than using a single RAS-acting agent in terms of reducing overall mortality.

Concerns about the safety of combination treatment with an ACE-inhibitor and an ARB, particularly in patients with left ventricular dysfunction had already been identified in a previous meta-analysis by Lakhdar et al, 2007[2] and the conclusion of the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[3] also highlighted concerns of dual RAS blockade therapy, reporting an increased risk of acute dialysis and hyperkalaemia in patients prescribed ACE-inhibitors and ARBs together.

In a recent meta-analysis of trials in chronic kidney disease by Susantitaphong et al[4], dual RAS blockade therapy was associated with an increased risk of hyperkalaemia and hypotension, but there was no effect on doubling of the serum creatinine, hospitalisation or mortality relative to monotherapy. Finally, the U.S. Veterans Affairs Cooperative Study "Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic

[1] Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomized trials. BMJ. 2013 Jan 28;346:f360. doi: 10.1136/bmj.f360.
[2] Lakhdar R, Al-Mallah MH, Lanfear DE. Safety and tolerability of angiotensin-converting enzyme inhibitor versus the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker in patients with left ventricular dysfunction: a systematic review and meta-analysis of randomized controlled trials. J Card Fail. 2008 Apr;14(3):181-8. doi: 10.1016/j.cardfail.2007.11.008.
[3] Mann JF, Anderson C, Gao P, Gerstein HC, Boehm M, Rydén L, Sleight P, Teo KK, Yusuf S; ONTARGET investigators. Dual inhibition of the renin-angiotensin system in high-risk diabetes and risk for stroke and other outcomes: results of the ONTARGET trial. J Hypertens. 2013 Feb;31(2):414-21. doi: 10.1097/HJH.0b013e32835bf7b0.
[4] Susantitaphong P, Sewaralthahab K, Balk EM, Eiam-Ong S, Madias NE, Jaber BL. Efficacy and Safety of Combined vs. Single Renin-Angiotensin-Aldosterone System Blockade in Chronic Kidney Disease: A Meta-Analysis. Am J Hypertens. 2013 Mar;26(3):424-41. doi: 10.1093/ajh/hps038

Nephropathy (VA NEPHRON-D)[5]" was recently terminated prematurely based on a greater number of observed acute kidney injury events and hyperkalaemia in the dual RAS blockade therapy group compared to patients receiving an ARB plus placebo.

The Committee for Medicinal Products for Human Use (CHMP) had already conducted a review under Article 20 of Regulation (EC) No 726/2004 for aliskiren-containing products, which was finalised in February 2012[6]. The review was initiated by the premature termination of the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints" (ALTITUDE) study, for which the interim results had shown that patients taking aliskiren added to a conventional treatment for hypertension (either an ARB or an ACE-inhibitor) were unlikely to benefit from treatment and were at an increased risk of adverse events including non-fatal stroke, renal impairment, hypotension and hyperkalaemia in compared to the placebo group receiving placebo plus an ARB or an ACE-inhibitor. As a result of this review, the CHMP concluded that aliskiren-containing products should be contraindicated in patients with diabetes mellitus or moderate to severe renal impairment who take ACE-inhibitors or ARBs and that the product information of these products should contain a warning that the combination of aliskiren with an ACE-inhibitor or ARB is not recommended in all other patients.

Having considered the new available evidence from the scientific literature and given the seriousness of the identified safety concerns, the Italian Medicines Agency (AIFA) decided to initiate a review under Article 31 of Council Directive 2001/83/EC on 17 April 2013, referring the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) and requesting the Committee to issue a recommendation on the benefit-risk of dual RAS blockade therapy through the combined use of ACE-inhibitors, ARBs or aliskiren and whether any regulatory measures should be taken on the marketing authorisations of the products involved in this procedure. The PRAC clarified that the benefit-risk of the individual RAS-acting agents used as monotherapy or as combination therapy with antihypertensive agents from other classes such as beta-blockers or mineralocorticoid antagonists (MRAs) was not part of the scope of this procedure as the safety concerns identified only applied to dual RAS blockade therapy through the combined use of ACE-inhibitors, ARBs or aliskiren. In its review, the PRAC considered the indication in hypertension as well as the heart failure indication, having noted that candesartan and valsartan are also authorised in heart failure.

Italy was appointed as the overall rapporteur while Germany, Ireland, Portugal, Slovakia, Spain, Sweden, the Netherlands and the United Kingdom were appointed co-rapporteurs, with the assessment of the 24 individual active substances divided amongst them.

At the start of the procedure, the PRAC reviewed the wording of the product information (PI) of all the individual products involved in the procedure, for which information was provided by the MAHs. It was noted that the PI of some products contained specific reference to dual RAS blockade therapy and that while information was present regarding hypotension and hyperkalaemia as potential adverse reactions of therapy with ACE-inhibitors or ARBs for some products, this was generally only in the context of monotherapy, with no reference to combination therapy. The above-mentioned adverse events were mentioned only in some cases in the context of dual RAS blockade therapy. Overall, there were inconsistencies with regard to

[5] Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy, the VA NEPHRON-D Investigators, N Engl J Med 2013; 369:1892-1903November 14, 2013DOI: 10.1056/NEJMoa1303154

[6] European Medicines Agency recommends new contraindications and warnings for aliskiren-containing medicines, 17/02/2012, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001446.jsp&mid=WC0b01ac058004d5c1

the wording, with some PIs already containing wording introduced to reflect the outcome of the 2012 CHMP review of aliskiren-containing products, which include the contraindication of the concomitant use of ACE inhibitors or ARBs with aliskiren containing products in patients with type II diabetes or with moderate to severe renal impairment. For other products, variations to implement this wording were ongoing, while for others, no variations have been submitted.

In its assessment, the PRAC reviewed all the available data, including data from clinical studies, publications and meta-analyses. The responses submitted by the MAHs in response to the questions raised by PRAC, including of the impact of the Makani et al publication on the benefit-risk balance of their products, were assessed, along with the report from Scientific Advisory Group in Cardiovascular Issues (SAG CVS) meeting held on 11 February 2014. This report presents a summary of the relevant data for the procedure.

2.2. Clinical aspects

2.2.1. Usage patterns

The PRAC noted a study carried out by the EMA[7] to describe the extent and the patterns of co-prescription of RAS-acting agents in clinical practice in the European Union and thereby the potential public health impact of any regulatory action, in order to support the PRAC in its decision-making. The study was conducted using data retrieved and analysed from the IMS Health database from France, Germany and the UK (approximating 40% of the total EU population) during the study period 1st January 2001 to 31st December 2012. Sub-group analyses in patients with diabetes mellitus and chronic kidney disease were also conducted.

From the IMS Health UK database a total of 960,232 patients were included in the analysis, of which 117,920 (12.3%) were treated with an RAS-acting drug and 1,129 (0.1%) were co-prescribed different drug classes acting on the RAS. From the IMS Health Germany database a total of 2,902,195 patients were included in the analysis, of which 529,679 (18.3%) were treated with an RAS-acting drug and 8,723 (0.3%) were co-prescribed different drug classes acting on the RAS. Finally, from the IMS Health France database, a total of 1,297,596 were included in the analysis, of which 133,999 (10.3%) were treated with an RAS-acting drug and 1,767 (0.1%) were co-prescribed different drug classes acting on the RAS.

The results of the analysis showed that while the proportion of patients with a prescription of RAS-acting agents was high (with ACE-inhibitors being the most prescribed in the UK and Germany and ARBs the most prescribed in France), only a small proportion of these patients were co-prescribed two different RAS drug classes. Moreover, the co-prescribing was more common in the diabetes and chronic kidney disease sub-populations than in the general population. In the total active population, there was an initial increase in co-prescribing in all countries followed by a decrease in 2012 (earlier in the UK); a similar trend was observed in the diabetes sub-population while the decreasing trend in co-prescribing started earlier in the chronic kidney disease sup-population. In the total active population, the decrease in co-prescribing was sharper in all the countries analysed and in the UK and Germany started earlier when focusing in patients treated with any RAS-acting agents. The study authors considered that

[7] Trends in co-prescribing of renin-angiotensin system (RAS)-acting agents in France, Germany and the UK during 2001 – 2012 - EMA/479605/2013, 27 August 2013

this trend seems to reflect the current therapeutic guidelines in use in Europe where the co-prescription of RAS-acting agents is not recommended. Most of the patients receiving a co-prescription were treated with a combination of an ACE-inhibitor and an ARB. The use of aliskiren was low in Germany and France and minimal in the UK; however, a large percentage of these users were co-prescribed another class of RAS-acting agents. The decrease in 2012 seems to suggest that the recommendations from EMA in early 2012 to avoid co-prescription with aliskiren and contraindicating it in diabetes and chronic kidney disease patients may have been effective. However, other external factors and reasons influencing the observed trend cannot be excluded. In conclusion, the results show that while the prevalence of RAS-acting agents was high, only a small proportion of these patients were co-prescribed two different RAS drug classes (0.1% - 0.3% of the active population). The study also shows a decreasing trend in the proportion of patients co-prescribed at least two different RAS drug classes. Of note, co-prescribing was more common in the diabetes and chronic kidney disease sub-populations, which are sub-populations of patients more prone to the adverse events associated with dual RAS blockade therapy, than in the general population.

2.2.2. Clinical data

2.2.2.1. VAL-HeFT

The Valsartan Heart Failure Trial (Val-HeFT)[8] was a randomised, placebo-controlled, double-blind, parallel-group trial involving patients at 302 centres in 16 countries. Men and women 18 years old or older with a history and clinical findings of heart failure for at least three months before screening were eligible. Patients had heart failure of New York Heart Association (NYHA) class II, III, or IV and were clinically stable. To be eligible, they had to have been receiving for at least two weeks a fixed-dose drug regimen that could include ACE-inhibitors, diuretics, digoxin, and beta-blockers. In addition, they had to have documented left ventricular dysfunction with an ejection fraction of less than 40% and left ventricular dilatation with an echocardiographically measured short-axis internal dimension at end diastole greater than 2.9cm per square meter of body-surface area. Eligible patients, stratified according to whether or not they were receiving a beta-blocker as background therapy, were randomly assigned to receive oral valsartan or matching placebo. Stratification was performed to ensure the equal distribution of patients receiving these drugs in the two groups. The study was designed with two primary end points: mortality and the combined end point of mortality and morbidity, which 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. Secondary cardiovascular outcomes included the changes from base line to the last available observation after treatment had begun in ejection fraction, NYHA functional class, quality-of-life scores, and signs and symptoms of heart failure. Of the 5010 patients who underwent randomisation, 2511 were assigned to receive valsartan and 2499 to receive placebo, all with background therapy for heart failure. There were no clinically relevant differences in the base-line characteristics of the two groups. At the time of randomisation, 93% of the patients were being treated with ACE-inhibitors.

Regarding the primary endpoints, overall mortality was similar in the two treatment groups. The adjudicated 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

[8] A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure, Cohn et al, N Engl J Med, Vol. 345, No. 23 · December 6, 2001

there were 118 deaths due to heart failure in the valsartan group and 125 in the placebo group). The combined end point of mortality and morbidity was significantly reduced among patients receiving valsartan as compared with those receiving placebo (P=0.009). The benefit appeared early after randomisation and increased throughout the trial. Among the patients in the valsartan group, 723 (28.8%) reached the combined end point, as compared with 801 patients (32.1%) in the placebo group — a 13.2% reduction in risk with valsartan (relative risk (RR)=0.87; 97.5% confidence interval (CI), 0.77 to 0.97). 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 (346 events, or 13.8%) as compared with those receiving placebo (455 events, or 18.2%) (P <0.001). Regarding the secondary end points, the risk of a hospitalisation for heart failure (with censoring of the data for patients who died) was reduced by 27.5% with valsartan (P<0.001). There were 1189 non-adjudicated hospitalisations for heart failure in the placebo group and 923 in the valsartan group (P=0.002). Since hospitalisations for problems other than heart failure were unaffected, the rate of hospitalisations for any cause was reduced similarly — by 250 events, from 3106 in the placebo group to 2856 in the valsartan group (P=0.14). The mean change in ejection fraction from baseline to the last observation was 4.0% in the valsartan group and 3.2% in the placebo group (P= 0.001). More patients in the valsartan group than in the placebo group had improvements in NYHA classification and quality of life, while fewer had worsening.

In a post hoc analysis of the combined end point and mortality in subgroups defined according to baseline treatment with ACE-inhibitors or beta-blockers, valsartan had a favourable effect in patients receiving neither or one of these types of drugs but an adverse effect in patients receiving both types of drugs. Indeed, in patients receiving both an ACE-inhibitor and a beta-blocker at baseline, valsartan had an adverse effect on mortality (P=0.009) and was associated with a trend toward an increase in the combined end point of mortality and morbidity (P=0.10). Among all 366 patients who were not receiving an ACE-inhibitor, whether or not a beta-blocker had been prescribed, there was a significantly lower risk of the combined end point in the valsartan group than in the placebo group (RR=0.56; 95% CI, 0.39 to 0.81), as well as a lower risk of death (RR=0.67; 95% CI, 0.42 to 1.06) compared to the group receiving an ACE-inhibitor (Hazard Ratio (HR)=1.05; 95% CI, 0.92-1.20).

Overall the results showed that valsartan therapy was generally well tolerated. Adverse events leading to the discontinuation of the drug occurred in 249 of the patients receiving valsartan (9.9%) and 181 patients receiving placebo (7.2%) (P <0.001). The adverse events leading to discontinuation and occurring in more than 1%of the patients in the valsartan group included dizziness (in 1.6% of the patients and 0.4% of those in the placebo group; P<0.001), hypotension (1.3% and 0.8%, respectively; P=0.124), and renal impairment (1.1% and 0.2%, P<0.001).

The PRAC noted that the study results showed that valsartan significantly reduced the combined end point of mortality and morbidity and improves clinical signs and symptoms in patients with heart failure, when added to the prescribed therapy, although it also noted that this was driven by the effect on hospital admissions. The PRAC was also concerned by the adverse effect on mortality and morbidity in the subgroup receiving valsartan, an ACE-inhibitor, and a beta-blocker, which raises concern about the potential safety of this specific combination.

2.2.2.2. CHARM-Added

The prospective Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial[9] investigated whether combining candesartan with an ACE-inhibitor improves clinical outcome. The study compared the effect of candesartan with that of placebo among patients with heart failure and reduced left-ventricular ejection fraction. Eligible patients were aged 18 years or older, had left ventricular ejection fraction 40% or lower measured within the past 6 months, NYHA functional class II–IV and treatment with an ACE-inhibitor at a constant dose for 30 days or longer. Patients on ACE-inhibitors were randomly assigned, in a double-blind way, to the candesartan group or the placebo group. The primary outcome was cardiovascular death or unplanned admission to hospital for the management of worsening heart failure. Pre-specified secondary outcomes included a number of combinations of cardiovascular death, admission to hospital for heart failure, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, death (any cause) and development of new diabetes. All deaths were classified as cardiovascular unless an unequivocal non-cardiovascular cause was established. Of the 2548 patients enrolled, 1276 were assigned candesartan and 1272 placebo. The median duration of follow up was 41 months.

A total of 483 (38%) patients in the candesartan group and 538 (42%) in the placebo group experienced the primary outcome of cardiovascular death or admission to hospital for heart failure (unadjusted HR 0.85 [95% CI 0.75–0.96], p=0.011). The annual event rates were 14.1% in the candesartan group and 16.6% in the placebo group. Candesartan reduced cardiovascular mortality and the risk of admission to hospital for heart failure individually, as well as the risk of each of the secondary composite outcomes. There were 302 (24%) cardiovascular deaths in the candesartan group compared with 347 (27%) in the placebo group (unadjusted 0.84 [0.72–0.98], p=0·029). Candesartan also reduced the proportion of patients experiencing a first hospital admission for heart failure after randomisation, the proportion of patients with multiple admissions for heart failure, and the total number of hospital admissions for heart failure. The total number of patients who had myocardial infarction was candesartan 44, placebo 69 (p=0.012); stroke: candesartan 47, placebo 41 (p=0.62); and coronary revascularisation procedures: candesartan 69, placebo 75 (p=0·46). The number of deaths from any cause in the candesartan group was 377 (30%) compared with 412 (32%) in the placebo group (unadjusted HR 0.89 [0.77–1.02], p=0·086). 539 (42%) patients treated with candesartan and 587 (46%) with placebo died from any cause or were admitted for heart failure (unadjusted HR 0.87 [0.78–0.98], p=0.021). In the candesartan group, 852 patients had 2462 hospital admissions for any reason and 858 placebo patients had 2798 admissions (p=0.7 for patients and p=0.023 for admissions). 72 (6%) patients in the candesartan group and 72 (6%) in the placebo group developed new diabetes (unadjusted HR 0.98 [0.70–1.35], p=0·88). Candesartan reduced the risk of cardiovascular death or admission to hospital for heart failure in all predefined subgroups, with no evidence of heterogeneity of treatment effect. In particular, candesartan reduced this risk in patients treated with beta-blockers in addition to an ACE-inhibitor at baseline. Among these patients, 175 (25%) of 702 died in the candesartan group and 195 (27%) of 711 died in the placebo group (HR 0.88 [0·72–1.08], p=0.22). By 6 months, blood pressure was lowered from baseline by 4.6 mm Hg systolic (p=0.007) and 3·0 mm Hg diastolic (p=0.004) more in the candesartan group than in the placebo group.

[9] Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin converting enzyme inhibitors: the CHARM-Added trial (McMurray et al., Lancet 2003; 362: 767–71. Published online Sept 1, 2003)

The authors concluded that among patients with heart failure and a low left-ventricular ejection fraction, the addition of candesartan to an ACE-inhibitor decreased the risk of cardiovascular death, and admission to hospital for heart failure. This beneficial effect of candesartan was seen in all pre-specified subgroups of patients, including those treated with beta-blockers and other treatments, with no evidence of treatment heterogeneity and was also seen in patients treated with beta-blockers and ACE-inhibitors.

The PRAC noted the reductions in cardiovascular mortality (absolute risk reduction of 3.6%) and in heart failure hospital admission (absolute risk reduction of 3.8%) for the combination of candesartan and an ACE-inhibitor compared to monotherapy demonstrated by this study, although it was pointed out that mortality from any cause did not differ between both groups. The PRAC considered that the benefits demonstrated in the CHARM-Added trial in patients with heart failure and reduced left-ventricular systolic function suggest that there may be some benefit for the treatment of heart failure if other treatment options have failed, although it was noted that this is the only study performed with dual therapy in heart failure that showed a beneficial effect on both cardiovascular mortality and hospital admissions in heart failure patients. In addition, more patients on candesartan and ACE-inhibitors than on placebo and ACE-inhibitors permanently discontinued study medication because of an adverse event or an abnormal laboratory value: 24% vs. 18% (p=0.0003). Among patients who discontinued study medication, more patients on candesartan and ACE-inhibitors than on placebo and ACE-inhibitors exhibited deterioration of renal function as manifested by doubling of baseline creatinine: 7% vs. 6% (non-significant) and hyperkalaemia (serum potassium concentrations >6 mmol/L) occurred more frequently on candesartan and ACE-inhibitors than on placebo and ACE-inhibitors: 3% vs. 1% (non- significant). In addition, hypotension as adverse event was reported in 5% of patients on candesartan and ACE-inhibitors vs. 4% on placebo and ACE-inhibitor. In patients aged 75 and younger, discontinuation because of hyperkalaemia was reported in 0.8% of patients in the placebo and ACE-inhibitor group and 2.9% of patients on candesartan and ACE-inhibitors. Corresponding figures for patients aged 75 years or older were 1.2% in the placebo and ACE-inhibitor group and 8.5% in the candesartan and ACE-inhibitor group. Nevertheless, the PRAC agreed that the study data indicates that the addition of candesartan to an ACE-inhibitor decreased the risk of cardiovascular death and admission to hospital for heart failure in all pre-specified subgroups of patients and that dual RAS blockade therapy may therefore have a role in selected heart failure patients. The PRAC considered that the higher rates of withdrawals for renal dysfunction and serum potassium in the study group indicate the need for careful monitoring of renal function and serum potassium.

2.2.2.3. VALIANT

The VALsartan In Acute myocardial iNfarcTion (VALIANT)[10] trial was designed to test the hypothesis that treatment with valsartan, an ARB, alone or in combination with captopril, an ACE-inhibitor, would result in better survival than treatment with a proven ACE-inhibitor regimen. The randomised, double-blind trial was conducted at 931 centres in 24 countries. Men and women 18 years of age or older who had had acute myocardial infarction (between 0.5 and 10 days previously) that was complicated by clinical or radiologic signs of heart failure, evidence of left ventricular systolic dysfunction or both were eligible. There were two primary treatment comparisons: valsartan versus captopril, and valsartan plus captopril versus captopril. The trial was designed to enrol approximately 14,500 patients, with follow-up continuing until at least

[10] Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both, Pfeffer et al, N Engl J Med 2003;349:1893-906.

2700 deaths had occurred, providing a power of 86 to 95% to detect a reduction of 15.0 to 17.5% in the risk of death from any cause. For the primary end point (mortality from any cause) and secondary cardiovascular outcomes, the treatment groups were compared on an intention-to-treat basis. A total of 14,703 patients (4909 in the valsartan group, 4885 in the valsartan-and-captopril group, and 4909 in the captopril group) took part in the study. The median duration of follow-up was 24.7 months, for a total of 29,226 cumulative patient-years.

Mortality from any cause and cause-specific mortality were similar in the three treatment groups. A total of 979 patients in the valsartan group (19.9%) died, as did 941 in the valsartan-and-captopril group (19.3%) and 958 in the captopril group (19.5%). The HR for death in the valsartan group as compared with the captopril group was 1.00 (97.5% CI 0.90 to 1.11; P=0.98), and the HR for death in the valsartan-and-captopril group as compared with the captopril group was 0.98 (97.5% CI 0.89 to 1.09; P=0.73). The rate of the secondary end point of death from cardiovascular causes, recurrent myocardial infarction, or hospitalisation for heart failure was also similar in the three groups. The HRs for death from cardiovascular causes and for a hierarchy of composite cardiovascular outcomes generated by adding important nonfatal cardiovascular events (recurrent myocardial infarction, hospitalisation for heart failure, resuscitation from cardiac arrest, and stroke) to death from cardiovascular causes were all similar for the valsartan group as compared with the captopril group and for the valsartan-and-captopril group as compared with the captopril group. A post hoc analysis of the rate of investigator reported hospital admissions for either myocardial infarction or heart failure showed that 919 patients in the valsartan group (18.7%) had a total of 1447 hospitalisations, 834 patients in the valsartan-and-captopril group (17.1%) had a total of 1297 hospitalisations, and 945 patients in the captopril group (19.3%) had a total of 1437 hospitalisations.

The rate of adverse events related to the study treatment differed among groups, with the highest rate occurring in the valsartan-and-captopril group and the lowest rate in the valsartan group. There was a similar pattern in the rates of adverse events leading to a reduction in the dose of a study drug. Clinical reports of hypotension were consistent with the blood-pressure levels in that the frequency of this adverse effect leading to either a reduction in the dose of study medication or the permanent discontinuation of study treatment was highest in the valsartan-and captopril group and lowest in the captopril group. Dose reductions and permanent discontinuations of study medication for renal causes were more frequent in the valsartan and the valsartan and captopril groups. There were no significant differences in the number of patients with a hospitalisation attributed to renal dysfunction (32 in the valsartan group, 30 in the valsartan-and captopril group, and 21 in the captopril group; P=0.14 and P=0.21 for the two comparisons with the captopril group).

The combination of valsartan and captopril was evaluated to determine whether incremental clinical benefits could be achieved with dual RAS blockade therapy but the authors found that this combination regimen did not reduce mortality or the rates of key secondary outcomes in the study population, despite additional lowering of blood pressure and a clear increase in the rate of intolerance to treatment. This finding was in contrast with the results of two recent major trials (Val-HeFT and CHARM-Added) involving patients with heart failure that demonstrated improvements in cardiovascular outcomes with the addition of an ARB to conventional therapy including an ACE-inhibitor. This study, however, differed in terms of the population of patients and the regimens under study. Differences in patterns of cardiovascular risk between patients with stable heart failure and patients with acute myocardial infarction — the latter having higher risks of early death and myocardial infarction than the former — may account for some of the observed differences. In addition, in the heart-failure trials, ARB therapy was added to pre-

existing ACE-inhibitor therapy, and the two treatments were not started concurrently, nor were the doses titrated concurrently. However, the authors considered that the fact that a post hoc analysis showed that combination therapy resulted in an apparent reduction in the cumulative rate of admission for recurrent myocardial infarction or heart failure does at least suggest that this therapy has biologic activity that might result in the observations that have been made in patients with heart failure. Overall, the authors concluded that combining valsartan with captopril increased the rate of adverse events without improving survival.

2.2.2.4. ONTARGET

The ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) was a large scale randomised, double-blind, multicentre, international trial comparing telmisartan 80 mg, ramipril 10 mg, and their combination in the prevention of morbidity and mortality in patients at high risk for cardiovascular events. An analysis of the obtained data was conducted by Yusuf et al[11] with the objective to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg is superior to ramipril 10 mg alone and if (b) telmisartan 80 mg is not inferior to ramipril 10 mg alone in reducing the composite endpoint of cardiovascular death, myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure (heart failure). It was also of primary interest (primary renal endpoint) to compare the concerning the composite endpoint of doubling of serum creatinine, progression to end stage renal disease (ESRD) and all-cause mortality in the subgroup of diabetic nephropathy patients (i.e. diabetic patients with macroalbuminuria assessed as a urinary albumin creatinine ratio [UACR] ≥300 mg/g creatinine at baseline). Progression to ESRD was defined as initiation of dialysis, estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m2, or need for renal transplantation. An additional objective, using an exploratory analysis, was to investigate whether the telmisartan plus ramipril combination is more effective than telmisartan alone for these endpoints.

The main secondary outcome was death from cardiovascular causes, myocardial infarction, or stroke, which was used as the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial. Additional secondary endpoints were the individual components of the primary endpoints, newly diagnosed heart failure, cardiovascular revascularisation procedures, newly diagnosed diabetes, cognitive impairment and cognitive decline, new onset of atrial fibrillation and nephropathy.

The inclusion criteria was defined as male or female patients, 55 years of age or older, and at high risk of developing a major cardiovascular event. Patients were eligible if they had any of the following: coronary artery disease, peripheral arterial disease, previous stroke, transient ischaemic attack or high-risk diabetes. The planned duration of the maintenance period was 3.5 to 5.5 years. A total of 29019 patients were enrolled by 732 centres worldwide. The trial was completed (last patient last seen) on 29 February 2008. A total of 25620 patients were randomised to either the combination of 80 mg telmisartan and 10 mg ramipril daily (n=8502), or 80 mg/day telmisartan (n=8542), or 10 mg/day ramipril (n=8576). 3399 patients (11.7%) were not randomised.

The primary endpoint was defined as the time to first occurrence of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, or hospitalisation for heart failure. At a median follow-up of 56 months, the primary outcome had occurred in 1412 (16.5%) patients in the

[11] Telmisartan, ramipril, or both in patients at high risk for vascular events. ONTARGET, Yusuf et al (ONTARGET Investigators) N Engl J Med. 2008 Apr 10;358(15):1547-59. doi: 10.1056/NEJMoa0801317. Epub 2008 Mar 31.

ramipril group, compared to 1423 (16.7%) patients in the telmisartan group and 1386 (16.3%) patients in the combination-therapy group. The decrease of blood pressure between the inclusion in the trial and the end of the trial were 6.4/4.3 mmHg in the ramipril group, 7.4/5.0 mmHg in the telmisartan group and 9.8/6.3 mmHg in the combination. Compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs. 4.2%, p<0.001) and angioedema (0.1% vs.0.3%, p=0.01) and a higher rate of hypotensive symptoms, and patients given the combination treatment had higher rates of hypotensive symptoms, syncope, renal dysfunction, and hyperkalaemia, with a trend toward an increased risk of renal function requiring dialysis.

Overall, 3068 of the randomised patients (12.0%) died during the study. The incidence of death from all causes was 12.5% in the telmisartan plus ramipril combination group, 11.6% in the telmisartan group, and 11.8% in the ramipril group. The HR for the telmisartan plus ramipril combination versus ramipril was 1.07 (95% CI 0.98, 1.16; p=0.1453). The HR of telmisartan versus ramipril was 0.98 (95% CI 0.90, 1.07; p=0.6378). The predominant reasons for death were cardiovascular death and malignancies in both the telmisartan and ramipril treatment groups. The authors concluded that there is no additional advantage and there is some harm from the combination of telmisartan and ramipril used in full doses in this population, as compared with ramipril alone. The combination of the two drugs was associated with more adverse events without an increase in benefit.

The PRAC concluded that the study did not demonstrate the superiority of the dual RAS blockade therapy in terms of benefit (cardiovascular or renal); on the contrary, a numerically higher rate of all-cause mortality, cardiovascular mortality and of adverse events, such as renal failure, hyperkalaemia and hypotension were associated with the combination use.

As part of the pre-specified analyses of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study, the effects of telmisartan, ramipril and their combination used at full doses, on renal outcomes in a large population at high cardiovascular risk were investigated (Mann et al, 2008)[12] using the data obtained from ONTARGET, as previously described. The primary composite renal outcome was defined as first occurrence of any dialysis, renal transplantation, the doubling of serum creatinine or death, and a secondary renal outcome included any dialysis and doubling of serum creatinine. The number of renal events was increased with the combination therapy for both the primary and secondary endpoints (HR=1.09; 95% CI 1.01-1.18 and HR=1.24; 95% CI 1.01-1.52; respectively). The secondary analyses of dialysis showed that chronic dialysis occurred in a similar frequency in all groups but acute dialysis occurred more frequently in the combination group (HR= 2.19; 95% CI 1.13-4.22). Estimated glomerular filtration rate (eGFR) declined least with ramipril compared with telmisartan (HR= −2.82 [SD 17.2] mL/min/1.73 m² compared to −4.12 [17.4], p<0.0001) or combination therapy (−6.11 [17.9], p<0.0001). The increase in urinary albumin excretion was less with telmisartan (p=0.004) or with combination therapy (p=0·001) than with ramipril. The authors concluded that in patients at high vascular risk, although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes.

Finally, following the early termination of the ALTITUDE study (see below) due to futility and increased harm including an increased risk of stroke, the ONTARGET study investigators decided to use the ONTARGET database to perform a post hoc analysis (Mann et al, 2013)[13] to

[12] Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial, Mann et al 2008, Lancet 2008; 372: 547–53
[13] Dual inhibition of the renin-angiotensin system in high-risk diabetes and risk for stroke and other outcomes: results of the ONTARGET trial, Mann et al, Journal of Hypertension 2013, 31:414–421

investigate the risks of dual RAS blockade therapy on stroke, given that there were a large number of patients with diabetes and chronic kidney disease (CKD) in the ONTARGET study, and information about stroke was collected. The objective of the analysis was to investigate the effect of dual RAS blockade therapy on strokes in people with diabetes both with and without kidney involvement. This post hoc analysis included patients from the ONTARGET study population with diabetes mellitus (DM) (either diagnosis or fasting plasma glucose ≥7mmol/L) plus baseline estimated glomerular filtration rate (eGFR) and baseline albumin to creatinine ratio (UACR) and participants were subdivided into those with or without nephropathy. The primary outcome was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (ischaemic or haemorrhagic) and hospitalisation for congestive heart failure. The composite renal outcome consisted of doubling of serum creatinine and chronic dialysis for more than 2 months.

The ONTARGET diabetic subgroup consisted of 9628 patients (8773 had a DM diagnosis and 855 had fasting plasma glucose ≥7mmol/L and all had baseline eGFR and UACR). CKD was evident in 6465 of the diabetic subgroup meaning 3163 did not have CKD. The group with CKD were more likely to be female, older, have a higher systolic BP, have a history of hypertension, peripheral artery disease or stroke and use diuretics or calcium channel blockers. The authors found no difference in stroke or any other major outcome between dual therapy and monotherapy in patients with or without CKD or in any of the CKD subgroups. However, all adverse events were more frequent in the dual therapy group than in the monotherapy group for both those with CKD and those without. Dialysis-dependent acute kidney injury tended to occur more frequently in those allocated to dual than with monotherapy (HR= 1.55; 95% CI 0.84-2.85), and hyperkalaemia was more frequent in dual therapy (HR= 1.71; 95% CI 1.44-2.02).

The PRAC noted that the results of this post hoc analysis of the ONTARGET data showed no increased risk of stroke or any other of the main outcomes for dual therapy compared to monotherapy. There was an increased frequency of hyperkalaemia, hypotension, syncope and acute dialysis for dual RAS blockade therapy, although an increase in risk was only shown for hyperkalaemia and hypotension.

2.2.2.5. ALTITUDE

The ALTITUDE[14] (The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) study was a placebo-controlled, double-blind, randomised study designed to investigate the effect of aliskiren on top of optimal cardiovascular treatment including an ACE- inhibitor or ARB in a specific population of patients with type 2 diabetes and renal impairment. Nearly half of the patients also had significant cardiovascular disease but patients with uncontrolled hypertension were excluded. The primary objective of this study was to determine whether aliskiren, compared to placebo, would delay the occurrence of cardiovascular and/or renal complications when added to conventional treatment (an ACE-inhibitor or an ARB) in patients with type 2 diabetes at high risk for cardiovascular and renal events. The composite end point consisted of 5 cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, resuscitated sudden death and hospitalisation for heart failure) and 2 renal components (doubling of serum creatinine, end stage renal disease / renal death).

In total, 8606 type 2 diabetic patients were recruited. Amongst the total population 55.4% had no previous cardiovascular disease history. The median age was 65 years, and the majority of

[14] Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes, Parving et al, N Engl J Med 2012;367:2204-13. DOI: 10.1056/NEJMoa1208799

patients were males (68%) with known diabetes duration of at least 5 years (82%). At the time of randomisation and according to protocol, all patients were treated with either an ACE-inhibitor or an ARB.

A total of 1123 patients experience a primary composite endpoint as previously defined and the HR (aliskiren/placebo) for the primary cardiovascular or renal composite endpoint was 1.09 (95% CI 0.97-1.22), indicating a potential increased risk with aliskiren. A total of 840 patients experienced a secondary composite cardiovascular endpoint. The cardiovascular composite endpoint was defined as the first occurrence of cardiovascular death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, or unplanned hospitalisation for heart failure. The HRs (aliskiren/placebo) were 1.14 (95% CI 0.99-1.30) for the secondary cardiovascular composite endpoint and 1.34 (95% CI 1.01, 1.77, 2-sided p=0.044, with absolute rates of 2.6% (112 events) vs. 2.0% (85 events)) for the non-fatal stroke component within the primary. For the onset of ESRD/renal death 72 (1.7%) of patients in the aliskiren group experienced an adjudicated endpoint vs. 60 (1.4%) in the placebo group with a HR 1.22 (95% CI 0.87-1.72). A total of 343 patients experienced a serious renal failure event (renal failure, renal failure acute, renal failure chronic, renal impairment) defined as serious adverse events. There was a statistically significant difference between treatment groups. Treatment effect adjusted for all specified covariates in a multivariate Cox regression model was: HR (aliskiren vs. placebo) =1.44 (95% CI 1.15-1.81; p=0.0018).

Overall there was an increase in adverse events in the aliskiren group for hypotension, stroke, hyperkalaemia and renal failure all categories. When looking at the stroke incidence, there were more strokes of an ischemic nature whereas the strokes of haemorrhagic nature were less frequent. Furthermore, there was an increase in the ischemic stokes in the aliskiren group as compared to placebo.

In December 2011, the 7th ALTITUDE Data Monitoring Committee (DMC) met to review the second interim efficacy analysis and the accumulated data related to adverse events, laboratory values and physical status. A total of 1123 adjudicated primary outcome events, constituting 69% of the projected total primary outcome events, were tabulated. There were 581 (13.6%) patients treated with aliskiren vs. 542 (12.6%) patients treated with placebo who experienced a primary composite endpoint event. The HR (aliskiren vs. placebo) for the secondary renal outcome was 0.93 (CI 0.76, 1.15) suggesting some potential for minimal renal benefit although the result is heavily impacted by the contribution of doubling of serum creatinine, with 141 patients on aliskiren reaching the endpoint (3.3%) vs. 159 (3.7%) with placebo, HR 0.90 (95% CI 0.71, 1.12). There was an increase in indices of renal impairment in aliskiren treated patients as evidenced by increased rates of ESRD or renal death (72 in aliskiren vs. 60 in placebo) and renal serious adverse events (i.e. renal impairment, renal failure acute, renal failure chronic, renal failure with 201 or 4.7% in aliskiren vs. 142 or 3.3% in placebo; p=0.002). There was also an approximately 50% increase in the incidence of serious adverse events of renal concern within each level of severity in the aliskiren-treated group as compared to placebo. Based on these results, the study was unlikely to demonstrate a benefit from aliskiren treatment added to standard therapy. The results also suggested a higher incidence of the adverse events of non-fatal stroke, renal complications, hyperkalaemia and hypotension after 18-24 months of in this high-risk study population in the aliskiren arm. Given these concerns, the DMC unanimously recommended that all subjects in the ALTITUDE study should cease treatment with aliskiren.

The ALTITUDE study was reviewed by the CHMP in the context of an Article 20 procedure. An ad hoc expert group was consulted and the experts concluded that the interim data from ALTITUDE

raised concerns that the combination of aliskiren with ACE-inhibitors or ARBs may increase the risk in subjects with diabetes and renal disease (eGFR < 60 ml/min) and/or proteinuria, particularly in terms of cerebrovascular and possibly cardiovascular events, hyperkalaemia and progression to end-stage kidney disease. This patient population is frequent among the general hypertension population and the experts were of the view that no group of patients with a positive benefit/risk balance could be identified for the combination treatment. The experts also agreed that the available data suggested that the safety concerns raised for the use of aliskiren in combination with ACE-inhibitors or ARBs apply also to non-diabetic subjects with previous cardiovascular disease or with severe renal impairment.

In its opinion, adopted in February 2012, the CHMP stated that although the study was conducted in patients with diabetes, a large proportion of patients had underlying cardiovascular disease and a sizeable proportion of patients did not have renal disease. The incidence of serious cardiovascular events was of relevance in patients with previous cardiovascular disease. Although the HR increased similarly in patients with and without cardiovascular events, the absolute risk of cardiovascular events on aliskiren was increased versus placebo in patients with previous cardiovascular disease (HR = 1.12, 15.0% and 13.4%) compared to patients without previous cardiovascular disease (HR = 1.16, 7.0% and 6.1%). Among patients with previous cardiovascular events, the highest HR was observed in aliskiren-associated resuscitated sudden death (HR 1.64), and lowest HR was associated with unplanned hospitalisation for heart failure (HR 0.98). The review of cases of stroke, sudden death, and renal serious adverse events, showed a numerical excess of events in the aliskiren group compared to placebo in the ALTITUDE study. The absolute risk of developing a cardiovascular event was greater in diabetic patients with previous cardiovascular events in the aliskiren group and there were concerns regarding the long-term safety profile of aliskiren in combination with ACE-inhibitors or ARBs also in non-diabetic patients with a history of cardiovascular events.

Having reviewed the available data, including other clinical studies and post-marketing data which were considered to confirm the interim results of the ALTITUDE study, the CHMP concluded that the data indicated an increased risk of adverse events including cardiovascular events (hypotension, syncope, stroke, hyperkalaemia) and changes in renal function (including acute renal failure) in patients treated with aliskiren in combination with conventional treatments for hypertension (either an ACE-inhibitor or an ARB), especially in diabetic patients and in patients with impaired renal function. The CHMP therefore recommended the contraindication of the use of aliskiren-containing medicines in combination with ACE-inhibitors or ARBs in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min). Taking into account the post-marketing experience the CHMP also concluded that the combined use of aliskiren with ACE-inhibitors or ARBs is not recommended in the overall patient population.

Having reviewed the study data, the PRAC agreed with the assessment carried out by the CHMP and the conclusions reached in its opinion. The PRAC also considered that the results of the ALTITUDE study are in line with the other available data.

2.2.2.6. Makani et al meta-analysis

The objective of this meta-analysis by Makani et al[15] was to compare the long term efficacy and safety of dual RAS blockade therapy with monotherapy. The study was a systematic review and

[15] Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. Makani et al, BMJ 2013;346:f360

meta-analysis, based on a search of PubMed, Embase and the Cochrane central register of controlled trials to identify trials in humans and published in peer reviewed journals between 1990 and August 2012. Based on the study inclusion criteria, the meta-analysis included randomised controlled trials comparing dual RAS blockade therapy of the RAS (any 2 of ACE-inhibitors, ARBs or aliskiren) with monotherapy, with a sample size of at least 50 patients, with data on either long term efficacy (duration > 1 year) including all-cause mortality, cardiovascular mortality and admissions for heart failure or on safety (duration > 4 weeks) including hyperkalaemia, hypotension, renal impairment and withdrawal due to drug related adverse events. The safety outcomes did not include stroke or myocardial infarction because too few studies reported data on this.

A total of 33 trials were identified which met the inclusion criteria, involving 68 405 patients treated with various combinations of dual RAS blockade therapy (ACE-inhibitor / ARB (22 trials), ACE-inhibitor / aliskiren (3 trials), ARB / aliskiren (7 trials) or ACE-inhibitor or ARB / aliskiren (1 trial)). Mean duration of follow up was 52 weeks, mean patient age was 61 years and mean% male was 71%. The pooled data covered different patient populations: hypertension, heart failure, chronic kidney disease, diabetic nephropathy. On the basis of the quality assessment, 18 of the trials were deemed to be at low risk of bias.

The meta-analysis results were presented as RRs with 95% CI, and stratified by trials with patients with heart failure vs. patients without heart failure. Dual RAS blockade therapy was shown to be associated with an increased risk of hyperkalaemia (RR=1.55; 1.32-1.82), hypotension (RR=1.66; 1.38-1.98), and renal failure (RR=1.41; 1.09-1.84). According to the authors, efficacy and safety results were consistent in cohorts with and without heart failure when dual RAS blockade therapy was compared with monotherapy, except for all-cause mortality (higher in the cohort without heart failure) and renal failure (significantly higher in the cohort with heart failure).

Data for the evaluation of all-cause mortality were available from 7 trials with a total of 56,824 patients. Overall, 3,314 of 21,638 patients (15.3%) died in the dual therapy group compared with 5,286 of 35,186 patients (15%) in the monotherapy group. When compared with monotherapy alone, dual therapy was not associated with any significant benefit for all-cause mortality (RR 0.97, 95% CI 0.89-1.06) or cardiovascular mortality (RR 0.96, 95% CI 0.88-1.05) and mortality was increased in the non-heart failure group, (RR 1.07, 95% CI 1.00 – 1.14). However, compared with monotherapy, dual therapy was associated with an 18% reduction in admissions to hospital for heart failure (RR 0.82, 95% CI 0.74-0.92), especially in the heart failure group (RR 0.77, 95% CI 0.68 – 0.88). With regard to adverse events, dual therapy was associated with a significant increased risk of all adverse events of interest, with a 55% increased risk of hyperkalaemia (P<0.001), a 66% increased risk of hypotension (P<0.001), a 41% increased risk of renal failure (P=0.01), and a 27% increased risk of withdrawal due to adverse events (P<0.001) in the whole analysis. These increased risks were consistent for patients with or without heart failure, except for renal failure where the risk was significantly increased in the heart failure group (RR 2.19 95% CI 1.82 – 2.65). There were no consistent patterns across the various combinations of dual RAS blockade therapy in term of the increase in risks of adverse events.

The PRAC noted that the authors themselves acknowledged a number of methodological limitations mainly due to the heterogeneity of the included studies, stating that “the results are subject to limitations inherent to any meta-analysis based on pooling of data from different trials with different duration, doses of drugs, definitions for safety outcomes, and patient groups.

Analysis of safety events is also prone to several biases since the data vary in each study for quality, incidence, severity, and adjudication. The reporting may also be influenced by expectations of the investigators, sponsors, and patients". Nevertheless, the authors concluded that although dual RAS blockade therapy seems to have beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy. The authors stated that the benefit-risk ratio argues against the use of dual RAS blockade therapy.

The PRAC considered the Makani et al meta-analysis to be a comprehensive analysis of dual RAS blockade therapy, focused on a well-defined objective and performed using an appropriate search strategy. Study outcomes were generally well defined and consistent across studies, except for hypotension which varied from 'symptomatic hypotension to evidence of low blood pressure'. Renal failure was the only renal endpoint, so the authors may have underestimated renal events with dual RAS blockade therapy by not including renal impairment. The meta-analysis included a large number of patients and despite not all patients contributing data to all outcomes, the number in the analysis for each outcome was still large. The mean age of patients across the studies was in line with the epidemiology of hypertension and most chronic cardiovascular conditions, although a skew towards men (mean percentage male was 71%) was noted. The PRAC agreed that the results showed no benefit of dual RAS blockade on all-cause mortality or cardiovascular mortality compared to monotherapy and in fact mortality was higher in the heart failure group. Admissions for heart failure were significantly reduced by dual therapy, especially in patients with heart failure, in line with other studies which have shown dual therapy is beneficial in this condition, so this result was not unexpected and is offset by an increased risk of adverse events. The data however clearly demonstrates that patients on dual RAS blockade therapy were significantly more at risk of hyperkalaemia, hypotension, renal failure and withdrawal due to drug related events. Patients with heart failure being treated with dual RAS blockade therapy were significantly more likely to have renal failure. The PRAC however noted that a criticism of the meta-analysis is that a high proportion of patients were taking diuretics and the resulting salt and water depletion may have increased susceptibility to adverse events.

Despite the inclusion of many low quality trials and a statistical indication of heterogeneity, a large number of patients were included in this review, and these findings are consistent with other trials examining dual RAS blockade. The vast majority were patients at high cardiovascular risk, only a few thousands were in the indication of uncomplicated hypertension. However, cardiovascular risk factors can be found widely in patients treated with aliskiren, ACE-inhibitors, and ARBs including uncomplicated hypertension. Of note, although large numbers of other ARBs and ACE-inhibitors were included in the study, there was an over-representation by telmisartan, candesartan, and ramipril, however, no bias caused by overrepresented drugs could be seen and the PRAC considered a class effect for RAS-acting agents to be evident. The PRAC concluded that the benefit of reduced hospital admissions for heart failure was offset by the significantly increased risk of hyperkalaemia, hypotension, renal failure and drug withdrawal with dual therapy generally, while a neutral effect on outcome was shown.

2.2.2.7. VA NEPHRON-D

The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D)[16] study was a multicentre, double-blind, randomised, controlled study designed to test the efficacy of the combination of losartan (an ARB) with lisinopril (an ACE-inhibitor), as compared with standard treatment with losartan alone, in slowing the progression of proteinuric diabetic kidney disease. The primary end point was the first occurrence of a defined decline in eGFR, end stage renal disease (ESRD), or death. The secondary renal end point was the first occurrence of a decline in eGFR or ESRD. Patients who reached the primary end point on the basis of eGFR continued to receive study medications until the occurrence of ESRD or death. Tertiary end points included cardiovascular events (myocardial infarction, stroke, or hospitalisation for congestive heart failure), the slope of change in eGFR, and the change in albuminuria at 1 year. Safety outcomes were all-cause mortality, serious adverse events, hyperkalaemia, and acute kidney injury. A total of 4346 patients were screened, 1648 were enrolled, and 1448 underwent randomisation (724 in each group). Baseline characteristics in the two groups were similar.

In October 2012, the data and safety monitoring committee recommended that the study treatment be stopped, primarily on account of safety concerns due to increased rates of serious adverse events, hyperkalaemia, and acute kidney injury in the combination-therapy group as compared with the monotherapy group, along with low conditional power (<5% for the observed trend) to detect a treatment effect on the primary end point. The data and safety monitoring committee concluded that the absolute risk of serious adverse events appeared to be greater than the potential benefit of reducing primary end-point events, even if the hypothesised treatment effect emerged later in follow-up. The sponsor accepted the recommendation and instructed the executive committee to stop the study treatment. At study closure, the median patient follow-up was 2.2 years.

Regarding the primary endpoint, there were 152 primary end-point events in the monotherapy group (21.0%) and 132 in the combination-therapy group (18.2%). The overall event rate was 10.8 events per 100 person-years of follow-up in the monotherapy group and 9.5 events per 100 person-years of follow-up in the combination-therapy group. The composition of first events was as follows: in the monotherapy group, 78 patients had a change in eGFR, 23 had ESRD, and 51 died; in the combination-therapy group, 59 patients had a change in eGFR, 18 had ESRD, and 55 died. The risk of the primary end point did not differ significantly between the two groups. There was also no significant difference in the HRs among pre-specified subgroups.

Regarding the secondary endpoint, there were 101 secondary end-point events (a decline in eGFR or ESRD) in the monotherapy group (14.0%) and 77 events in the combination-therapy group (10.6%). The overall event rate was 7.2 events per 100 person-years of follow-up in the monotherapy group and 5.5 events per 100 person-years of follow-up in the combination-therapy group. There was no significant between-group difference in mortality or ESRD, though the number of ESRD events was small.

Regarding the tertiary endpoints, there was no significant difference in the rate of cardiovascular events between the two groups. The number of patients with myocardial infarction was higher and the number of patients with congestive heart failure was lower in the combination-therapy group than in the monotherapy group, but the differences were not significant. The rate of

[16] Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy, the VA NEPHRON-D Investigators, N Engl J Med 2013; 369:1892-1903 November 14, 2013DOI: 10.1056/NEJMoa1303154

stroke was the same in the two groups. There was no significant difference in treatment effect on the decline in eGFR (P=0.17).

Serious adverse events occurred in more patients in the combination-therapy group than in the monotherapy group. The rate of serious adverse events was 98 events per 100 person-years in the combination-therapy group versus 82 events per 100 person-years in the monotherapy group. The proportion of serious adverse events attributed to study medication by the site investigators was higher in the combination-therapy group than in the monotherapy group. Acute kidney injury was the main reason for the higher rate of serious adverse events in the combination-therapy group, with 190 acute kidney injury events in 130 patients in the combination-therapy group (12.2 events per 100 person-years) as compared with 105 acute kidney injury events in 80 patients in the monotherapy group (6.7 events per 100 person-years). The HR with combination therapy was 1.7 (1.3 to 2.2).The rate of hyperkalaemia in the combination-therapy group was more than double the rate in the monotherapy group. After randomisation, there were 139 total events in 104 patients (98 events in the combination-therapy group [6.3 events per 100 person-years] and 41 events in the monotherapy group [2.6 events per 100 person-years]). The HR for hyperkalaemia with combination therapy was 2.8 (1.8 to 4.3).

The authors concluded that combination therapy with an ARB and an ACE-inhibitor, as compared with monotherapy, was associated with an increased risk of serious adverse events (acute kidney injury and hyperkalaemia) and did not provide a significant benefit with respect to the primary end point (renal-disease progression or death), mortality, or cardiovascular disease. The authors considered that these results were generally consistent with those of ONTARGET and ALTITUDE, which showed increased harm and no cardiovascular or renal benefit with dual RAS blockade therapies. Monotherapy with ACE-inhibitors or ARBs slows the progression of proteinuric diabetic nephropathy but has not been shown to slow the progression of non-proteinuric kidney disease. The authors had hypothesised that the benefit in slowing the progression of kidney disease would outweigh the risks of hyperkalaemia and acute kidney injury associated with more intensive blockade of RAS. However, the significant increase in risk overshadowed a non-significant trend toward a benefit with respect to the primary and secondary end points. As compared with monotherapy, combination therapy was associated with 17 more serious adverse events per 100 person-years. The risk of hyperkalaemia was more than twice as high in the combination-therapy group as in the monotherapy group. Acute kidney injury events primarily accounted for the increased rates of serious adverse events with combination therapy. In conclusion, the authors stated that the study results show that the use of combination therapy with an ACE-inhibitor and an ARB in patients with proteinuric diabetic kidney disease does not provide an overall clinical benefit.

The PRAC reviewed the results from the prematurely terminated VA NEPHRON-D study and also contacted the study authors to obtain clarifications on some aspects of the study. In particular, it was clarified that the decision to discontinue the study was driven by the review of overall safety and the benefit-risk ratio of continuing the study. The authors also stated that although 15.6% of the patients had a history of congestive heart failure, the ejection fraction was not known for most individuals and the study did therefore not provide any evidence regarding a cardiovascular indication for combination therapy. The PRAC agreed that the study demonstrated that dual RAS blockade therapy does not convey clinical benefits in patients with diabetic nephropathy, as the treatment failed to reduce mortality or cardiovascular events over time compared to monotherapy and was instead associated with 17 more serious adverse events per 100 person-years including hyperkalaemia and acute kidney injury. The PRAC considered that the results

were in line with those obtained from the ONTARGET and ALTITUDE studies and confirmed the need to restrict the use of dual RAS blockade therapy in patients with diabetic nephropathy.

2.2.3. Spontaneous reports

A number of MAHs submitted overviews and analyses of solicited and unsolicited individual case safety reports (ICSR), including from clinical studies and from post-marketing data, where the events of interest were reported for their products together with another RAS-acting agent. It was noted that such data was not available for all substances.

In cases where the patient was on a concomitant therapy, the adverse events reported were mainly those that would be expected with dual RAS blockade therapy (including hypotension with or without pre-syncope, stroke, hyperkalaemia and changes in renal function (including acute renal failure)). The most frequent events in patients treated with dual RAS blockade therapy were events of the underlying disease as the majority of the ICSRs involved patients who presented risk factors in the form of their medical condition or medical history such as hypertension, diabetes or heart failure (which are in themselves risk factors for renal impairment), chronic kidney disease or acute renal failure and/or concomitant medication.

It is difficult to establish to what extent dual RAS blockade therapy contributed towards the adverse reactions compared to pre-existing risk factors, based on the available information. The PRAC therefore concluded that given the inherent limitations of spontaneous case report (such as possible reporting bias and lack of adequate denominator information) and in light of the large body of data available from randomised clinical trials, detailed discussions on spontaneous reports would not provide meaningful additional information.

2.2.4. Guidelines

The PRAC also noted a number of guideline providing recommendations on the use of dual RAS blockade therapy in hypotension and heart failure:

The 2013 ESH/ESC Guidelines for the management of arterial hypertension, which specifies that "*the only combination that cannot be recommended on the basis of trial results is that between two different blockers of the RAS*". This recommendation is based on the results of ONTARGET and ALTITUDE studies (Mann et al. 2008, Yusuf et al. (ONTARGET investigators) 2008, Parving et al. 2012). The guideline further states that "*The combination of two antagonists of the RAS is not recommended and should be discouraged*", with the statement being labelled as a class III level recommendation (defined as "*Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful*", to be worded as "*Is not recommended*"), supported by level A evidence ("*Data derived from multiple randomized clinical trials or meta-analyses*").

The 2012 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure advises that "*The addition of an ARB (or renin inhibitor) to the combination of an ACE-inhibitor AND a mineralocorticoid antagonist is NOT recommended because of the risk of renal dysfunction and hyperkalaemia*" in patients with symptomatic (NYHA class II–IV) systolic heart failure, with the statement being labelled as a class III level recommendation supported by level C evidence ("*Consensus of opinion of the experts and/or small studies, retrospective studies, registries*").

The 2013 ACCF/AHA Guideline for the Management of Heart Failure advises that the combination treatment of ARBs and ACE-inhibitors can be used to treat heart failure with EF<40% (NHYA

class II-IV) if there are still heart failure symptoms despite optimal standard therapy with ACE-inhibitors and beta-blockers, especially in patients for whom an aldosterone antagonist is not indicated or tolerated. It also advises that "*the routine combined use of an ACE-inhibitor, ARB and aldosterone antagonist is potentially harmful*" and is not recommended.

The NICE guideline on management of chronic heart failure in adults in primary and secondary care (2010) recommends to "*Seek specialist advice before offering second-line treatment to patients with heart failure due to left ventricular systolic dysfunction*". Specialist advice is also recommended if considering combination therapy with an ARB for a patient remaining symptomatic despite optimal treatment with an ACE-inhibitor and a beta-blocker, especially if the patient has mild to moderate heart failure (NYHA class II-IV).

2.2.5. Consultation of the Scientific Advisory Group in Cardiovascular Issues (SAG CVS)

The PRAC also requested further advice from the Scientific Advisory Group in Cardiovascular Issues (SAG CVS) and a meeting was convened on 11 February 2014. The experts were asked, based on their clinical experience and in light of the recent meta-analysis by Makani et al and the premature termination of the VA NEPHRON-D study due to safety concerns, to discuss dual RAS blockade therapy using ARBs and ACE-inhibitors. In particular, the experts were asked whether any patients groups benefiting from dual RAS blockade therapy could be identified, what kind of monitoring and treatment stopping criteria should be applied, whether periodic reviews of effectiveness should be conducted and whether treatment should be initiated under specialist supervision. The experts were requested to consider the safety and efficacy of dual RAS blockade therapy in the subgroups of patients with non-diabetic nephropathy, patients with diabetic nephropathy and patients with heart failure.

Following the discussion, the experts were of the opinion that a relatively small subgroup of patients with heart failure may benefit from dual RAS blockade therapy: a modest reduction in heart failure hospital admissions may be achieved in patients not sufficiently responding to the standard heart failure therapy including ACE-inhibitor plus a loop diuretics plus a beta-blocker, and intolerant to MRA, provided that treatment is prescribed by a specialist and carefully monitored. The exception would be for those heart failure patients with both diabetes and nephropathy, for whom dual RAS blockade therapy is not recommended, due to the demonstrated adverse events and the lack of robust evidence of benefits in patients with diabetic nephropathy.

Based on their clinical experience, the Makani et al publication and current clinical guidelines, and given the absence of supporting data, the experts considered that dual RAS blockade therapy should not be used for treatment of hypertension, in patients with diabetes and nephropathy nor in patients with evidence of previous vascular disease and nephropathy. Some experts indicated that dual RAS blockade therapy might be prescribed in (younger) patients with nephropathy and severe proteinuria without co-morbidities, although other experts indicated that the benefit of dual RAS blockade therapy in such patients was not clearly demonstrated.

The experts were of the opinion that dual RAS blockade therapy should be initiated by specialists and that patients should remain under regular specialist monitoring during treatment, as intermittent acute hyperkalaemia or renal dysfunction may occur. The monitoring should include regular blood pressure checks in view of the risk of hypotensive events caused by the dual RAS blockade therapy. It is appreciated that monitoring may be done by specialised nurses under specialist supervision. An example of the frequency and the type of monitoring is given in the

2012 ESC G*uidelines for the diagnosis and treatment of acute and chronic heart failure*. However, it was recognised that this level of monitoring may not always be feasible for patients living in remote areas or outside big cities.

The experts agreed that treatment with the second added RAS-acting agent should be interrupted whenever hyperkalaemia or renal dysfunction occurs. The physician may consider resuming dual RAS blockade therapy after one to two weeks, once the condition leading to the adverse reaction has been resolved and the potassium levels have been confirmed to be back to baseline values. In patients with severe hyperkalaemia, it may be necessary to interrupt treatment with both RAS-acting agents for 2 or 3 days.

The experts also considered that patients may need additional ad-hoc assessment in case of intercurrent illness (vomiting, diarrhoea, fever, which may cause dehydration, renal failure and hyperkalaemia) during treatment or if there is another change in the patient's condition. Healthcare professionals should be made aware of this through the inclusion of recommendations on how to address these events in the product information.

The education of patients was also considered very important and the experts recommended that specific guidance should be included in the package leaflet, including information on the need for medical consultation in conditions described in the previous paragraph.

2.2.6. Overall discussion on efficacy

The PRAC considered that the available efficacy data indicates that dual RAS blockade therapy does not provide significant benefit in the general patient population, although there is evidence to suggest that some selected patient subpopulations may benefit from this dual RAS blockade therapy. In particular, although no clear and consistent benefits in reducing stroke, all-cause mortality or cardiovascular mortality were demonstrated except for in one trial which also demonstrated benefit of dual RAS blockade therapy in heart failure patients in terms of cardiovascular mortality (CHARM-added), a number of trials in heart failure patients have shown that the addition of a second RAS-acting agent may reduce hospital admissions for heart failure in patients with heart failure, which is considered a meaningful clinical endpoint (VALIANT and Val-HeFT, CHARM-Added). Dual RAS blockade therapy may have beneficial effects on certain surrogate endpoints (including lowering of albuminuria in patients with renal disease) but this effect is either not supported or even contradicted by trials on major renal outcome data, including ONTARGET, ALTITUDE and VA NEPHRON-D and is therefore considered uncertain. The PRAC therefore concluded that dual RAS blockade therapy should not be routinely used in the treatment of heart failure and is not recommended in the general population although it may benefit certain patients who remain symptomatic while receiving monotherapy or who cannot otherwise use alternative therapies, including potentially patients with diabetic nephropathy. This was supported by the SAG CVS experts, who considered that some patients with heart failure may benefit from dual RAS blockade therapy.

2.2.7. Overall discussion on safety

The PRAC was of the opinion that there is considerable evidence from large clinical trials and meta-analyses, in particular from the Makani et al meta-analysis, ONTARGET (Yusuf et al.2008), ALTITUDE (Parving et al.2012) and the recently prematurely terminated VA NEPHRON-D trial (the VA NEPHRON-D Investigators, 2013), which conclusively demonstrates that dual RAS blockade therapy through the combined use of ACE-inhibitors, ARBS or aliskiren is associated with an increased risk of adverse

events, including hypotension, hyperkalaemia and renal failure compared to monotherapy, in particular in patients with diabetic nephropathy. This is of particular concern, as these patients and patients with renal impairment are already particularly prone to developing hyperkalaemia. The PRAC noted that these conclusions were supported by the available post-marketing data and the conclusions of the SAG CVS experts and agreed that dual RAS blockade therapy through the combined use of ACE-inhibitors, ARBS or aliskiren is not recommended.

2.3. Risk minimisation activities

The PRAC was of the opinion that the concerns identified during this procedure with regard to the safety and the lack of efficacy of dual RAS blockade therapy can adequately be managed through changes to the product information, including instructions that treatment should only occur under specialist supervision and be subject to frequent close monitoring of renal function, electrolytes and blood pressure, as described in the next paragraph, without the need for additional risk minimisation measures.

2.4. Changes to the product information

The PRAC considered that there was a need to implement changes to the product information of all the RAS-acting agents involved in the procedure, in order to reflect the available information and adequately manage the concerns identified during this procedure with regard to the safety and the lack of efficacy of dual RAS blockade therapy. Because the concerns observed in association with dual RAS blockade therapy were considered to be a class issue, the PRAC harmonised the changes to the product information to the extent possible, although in order to respect the existing wording and treatment recommendations and the structure already in place in the existing PI documents, a full harmonisation of the relevant sections of the product information was not possible. In particular, candesartan and valsartan are also authorised in the treatment of heart failure and a specific wording was therefore agreed for these two substances. The PRAC therefore agreed on the following five sets of changes to the product information, to be implemented as relevant for each marketing authorisation: for all ACE-inhibitors, for all ARBs except candesartan and valsartan, for candesartan specifically, for valsartan specifically and for aliskiren. The corresponding changes for the package leaflets of all the products involved in the procedure were also defined and agreed.

The PRAC considered that the data demonstrates that dual RAS blockade therapy is not recommended in the general population. However, because of the possibility of benefit of this therapy in certain patient subgroups, including potentially in patients with diabetic nephropathy, the PRAC decided against the introduction of a contra-indication and instead introduced a warning in *Section 4.4 – Warnings and precautions* of the SmPC to state that dual RAS blockade therapy through the combined use of ACE-inhibitors, ARBs or aliskiren is not recommended and, if considered absolutely necessary, should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. The PRAC however clearly specified, based on data from the ONTARGET and VA NEPHRON-D studies that ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. Related information was also introduced in S*ection 4.5 – Interaction with other medicinal products and other forms of interaction*.

The PRAC was also of the opinion that the additional data reviewed confirmed the need for the contraindication regarding the concomitant use of ACE-inhibitors or ARBs with aliskiren-containing products in patients with diabetes mellitus or renal impairment. This contraindication was already agreed in the context of the previous review on aliskiren-containing products, on the basis of the

ALTITUDE study data. The PRAC considered that it should be also be implemented in *Section 4.3 – Contraindication* of the product information of ARBs and ACE-inhibitors.

The PRAC also considered it important to reflect the source of the data supporting the changes made to the product information. As the concerns regarding the lack of efficacy and the adverse events identified in association with dual RAS blockade therapy were considered to be class effects, the PRAC was of the view that the data was of relevance to all ACE-inhibitors and ARBs and that it was therefore justified to introduce brief descriptions of the ONTARGET, VA NEPHRON-D and ALTITUDE studies in *Section 5.1 – Pharmacodynamic properties* of the SmPC of all ACE-inhibitors and ARBs, including for products for which the active substance was not investigated in these studies.

The PRAC also recommended that for ARB and ACE-inhibitor-containing products specifically mentioning that they can be used alone or in combination with other antihypertensive agents, these statements should be accompanied by cross-references to Sections 4.3, 4.4, 4.5 and 5.1.

For candesartan- and valsartan-containing products, which are also authorised in the treatment of heart failure, additional information was agreed upon to reflect the fact that the available data suggests that dual RAS blockade therapy may be of benefit in some patients with symptomatic heart failure. In *Section 4.1 – Therapeutic indications* of the SmPC, the heart failure indication was revised to allow dual RAS blockade therapy through add-on therapy to ACE-inhibitors when other treatment options cannot be used. *Section 4.2 – Posology and method of administration* of the SmPC was revised in line with the indication and in addition, a special warning was added for candesartan and valsartan under the heading "*Heart failure*" in Section 4.4, to reinforce the risk of adverse events and the need for specialist supervision.

The package leaflet was updated accordingly to reflect the changes proposed to the SmPC. The proposed amendments to the product information are attached to this report.

2.5. Communication plan

Regarding the communication of the procedure outcome, the PRAC defined the following key elements to be considered by member states wishing to communicate nationally:

Key elements for communication at national level

- Dual renin angiotensin system (RAS) blockade therapy through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of adverse reactions, such as hyperkalaemia, low blood pressure and worsening of kidney function, compared to the use of these medicines alone.
- Dual RAS blockade therapy is not recommended.
- In particular dual RAS blockade therapy should not be used in patients with diabetic nephropathy.
- If dual RAS blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
- In patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2), the concomitant use of ACE-inhibitors or angiotensin II receptor blockers with aliskiren-containing products is contraindicated.

- Valsartan and candesartan remain authorized for treatment of heart failure in combination with ACE-inhibitors in selected patients who cannot use other heart failure treatments. As recommended above, treatment should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
- Patients currently on dual RAS blockade therapy are recommended to discuss their treatment with their doctor at the next scheduled appointment.

Further information

RAS-acting agents are used particularly in the treatment of hypertension (high blood pressure) and congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body).

The referral under Article 31 of Directive 2001/83/EC was initiated following the publication of a recent meta-analysis (Makani et al. BMJ. 2013 Jan 28;346:f360) of 33 clinical studies involving over 68,000 patients. This meta–analysis raised the concern that combining two drugs that affect the renin-angiotensin system could increase the risk of hyperkalaemia, hypotension and kidney failure, compared with using one such medicine alone. In addition, using multiple RAS-acting agents may not be more beneficial than a single RAS-acting agent in terms of reducing overall mortality.

The PRAC examined clinical trial data from a number of large studies including:

ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes) and ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints).

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

ALTITUDE was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both.

Taken together these studies showed that the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of side effects, such as hyperkalaemia, low blood pressure and worsening of kidney function, compared to the use of these medicines alone. These adverse reactions contributed to the conclusion that dual RAS blockade therapy is not recommended and in particular that it should not be used in patients with diabetic nephropathy. Furthermore, no significant benefits from dual RAS blockade therapy with regard to overall mortality, cardiovascular and renal events were seen in patients without heart failure and benefits were thought to outweigh the risk only in a selected group of patients with heart failure in whom other treatments are unsuitable.

2.6. Overall benefit-risk assessment

The PRAC reviewed the totality of the available data, including clinical trials, meta-analysis and publications, the MAHs' responses as well as the report from the Scientific Advisory Group in Cardiovascular Issues (SAG CVS). The PRAC was of the opinion that there is considerable evidence from large clinical trials and meta-analyses, in particular from the Makani et al meta-analysis, ONTARGET, ALTITUDE and the recently prematurely terminated VA NEPHRON-D trial, which conclusively demonstrates that dual RAS blockade therapy through the combined use of ACE-inhibitors, ARBS or aliskiren is associated with an increased risk of adverse events, including hypotension,

hyperkalaemia and renal failure compared to monotherapy, in particular in patients with diabetic nephropathy. This is of particular concern, as these patients and or patients with renal impaired are already particularly prone to developing hyperkalaemia.

The PRAC considered that the available efficacy data indicates that dual RAS blockade therapy does not provide significant benefit in the general patient population, although there is evidence to suggest that some selected patient subpopulations may benefit from this dual RAS blockade therapy. In particular, a number of trials in heart failure patients have shown that the addition of a second RAS-acting agent may reduce hospital admissions for heart failure in patients with heart failure, which is considered a meaningful clinical endpoint (VALIANT and Val-HeFT, CHARM-Added). The PRAC therefore concluded that dual RAS blockade therapy should not be routinely used in the treatment of heart failure and is not recommended in the general population although it may benefit certain patients who remain symptomatic while receiving monotherapy or who cannot otherwise use alternative therapies, including potentially patients with diabetic nephropathy. Treatment should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

The PRAC acknowledged that for some substances, very little data on dual RAS blockade therapy is available and that data does not exist for every possible combination of dual RAS blockade therapy. However, the PRAC considered that the overall available data strongly suggests that the concerns identified with regard to safety and the lack of efficacy are a class effect and therefore considered that the conclusions of the review apply to all active substances involved in the procedure.

The PRAC was of the opinion that the concerns identified during this procedure with regard to the safety and the lack of efficacy of dual RAS blockade therapy could be adequately managed through changes to the product information, without the need for additional risk minimisation measures. The PRAC therefore concluded that the product information of all RAS-acting agents should be revised to reflect the identified risks and provide guidance to prescribers and patients. A warning was introduced to state that dual RAS blockade therapy through the combined use of ACE-inhibitors, ARBs or aliskiren is not recommended and, if considered absolutely necessary, should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. The PRAC however clearly specified, based on data from the ONTARGET and VA NEPHRON-D studies that ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. The PRAC was also of the opinion that the contraindication based on the ALTITUDE study data regarding the concomitant use of ACE-inhibitors or ARBs with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) was confirmed by the additional data reviewed and that it should also be implemented in the product information of ARBs and ACE-inhibitors. The PRAC also considered it important to reflect the source of the data supporting the changes made to the product information. The PRAC therefore introduced brief descriptions of the ONTARGET, VA NEPHRON-D and ALTITUDE studies in the product information of all ACE-inhibitors and ARBs, including for products for which the active substance was not investigated in these studies to reflect the available knowledge in the therapeutic area. For candesartan- and valsartan-containing products, which are also authorised in the treatment of heart failure, additional information was agreed upon to reflect the fact that the available data suggests that dual RAS blockade therapy in combination with an ACE-inhibitor may be of benefit in certain patients who cannot use other heart failure treatments, provided that they are used under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

The PRAC concluded that the benefit-risk balance of RAS-acting agents remains favourable, including in the context of dual RAS blockade therapy, subject to the agreed revisions to the product information.

3. Overall conclusion and grounds for the recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC initiated by Italy following the emergence of new evidence on the efficacy and safety of dual RAS blockade therapy through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren, to determine whether any regulatory measures should be taken on the marketing authorisations of the products involved in this procedure;
- The PRAC reviewed the totality of the available data, including clinical trials, meta-analysis and publications, the MAHs' responses as well as the report from the Scientific Advisory Group in Cardiovascular Issues;
- The PRAC was of the view that there is considerable evidence, in particular from the ONTARGET, ALTITUDE and VA NEPHRON-D trials which conclusively demonstrates that dual RAS blockade therapy through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with an increased risk of adverse events, including hypotension, hyperkalaemia and renal failure compared to monotherapy;
- The PRAC considered that the available efficacy data indicates that dual RAS blockade therapy does not provide significant benefit in the general patient population although certain patient subpopulations may benefit from treatment, provided that it occurs only under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure;
- The PRAC was of the opinion that the concerns identified with regard to safety and the lack of additional efficacy of dual RAS blockade therapy are a class effect and that the conclusions of the review therefore apply to all the active substances involved in this procedure;
- The PRAC was of the opinion that the concerns identified with regard to the safety and the lack of additional efficacy of dual RAS blockade therapy can be adequately managed through changes to the product information, without the need for additional risk minimisation measures.

The PRAC, as a consequence, concluded that the benefit-risk balance of the RAS-acting agents identified in the Annexes A / Annex I remains favourable, provided that their product information is revised to reflect the concerns associated with dual RAS blockade therapy. Having considered the matter, the PRAC therefore recommended the variation of the marketing authorisations for RAS-acting agents.

The divergent position is appended to the PRAC recommendation.

Appendix 1

Divergent position to PRAC recommendation

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

For renin-angiotensin system (RAS)-acting agents

Procedure number: EMEA/H/A-31/1370

Divergent statement

Based on the presented evidence in their totality, I agree with the PRAC recommendation to update the product information of the medicinal products belonging to the class of ACE-inhibitors, ARBs and direct renin inhibitor (aliskiren) to include wording reflecting new evidence of risks associated with the use of RAS dual blockade, through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren.

However, based on the results of the large randomised, controlled trials ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes), I am not in agreement with the implementation of a strong warning for patients with diabetic nephropathy as a risk minimisation measure.

Indeed in these patients, the studies have shown no significant beneficial effect of RAS dual blockade on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension has been observed compared to monotherapy.

I therefore consider that a contraindication is the best risk minimisation measure to avoid the risk of renal impairment, hypotension and hyperkalaemia in patients with diabetic nephropathy.

PRAC member expressing a divergent opinion:

Carmela Macchiarulo (IT)	10 April 2014	Signature: …….....