

**NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF
DIRECTIVE 2001/83/EC**

FAX NUMBER –44 20 75237051

This notification is an official referral under Article 31 of Directive 2001/83/EC to the PRAC made by Italy – AIFA:

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| Active substances | Angiotensin Receptor Blockers (ARBs) Angiotensin Converting Enzyme Inhibitors (ACEis) Direct Renin Inhibitors (aliskiren) |
| Marketing Authorisation Holders in the referring Member State | Various |

A signal regarding the safety of dual blockade of the renin-angiotensin system (RAS), raised by a recently published meta-analysis by Makani¹ on dual RAS blockade achieved through the concomitant use of angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEis) or direct renin inhibitors (aliskiren), was discussed at PRAC meeting in April 2013. Results from 33 randomised controlled trials with 68.405 patients (mean age 61 years, 71% men) and mean duration of 52 weeks were included. The authors showed that dual blockade was 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 blockade was compared with monotherapy except for all-cause mortality, which was higher in the cohort without heart failure (P=0.04 v P=0.15), and renal failure shown to be significantly higher in the cohort with heart failure (P<0.001 v P=0.79). In addition, dual blockade of the RAS (compared with monotherapy) was not associated with a clinical benefit in reducing all-cause mortality (relative risk [RR] = 0.97; 95%CI 0.89-1.06) and cardiovascular mortality (RR= 0.96; 0.88-1.05), but was associated with a reduction in admissions to hospital for heart failure (RR=0.82, 0.74-0.92). The authors therefore concluded that dual blockade of the renin-angiotensin system was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy and failed to reduce mortality.

Following a review conducted by the European Medicines Agency on aliskiren-containing medicines (primarily based on data from the ALTITUDE trial), in the context of a procedure under Article 20 of Regulation (EC) No 726/2004 for aliskiren-containing products, it was concluded that these medicinal product should be contraindicated in patients with diabetes or moderate to severe renal impairment who take ACEis or ARBs. This contraindication was implemented the SmPC of aliskiren medicinal products. In addition, a warning that advised that the combination of aliskiren with an ACEi or ARB is not recommended in all other patients (EMA/CHMP/112042/2012) was also included. Indeed, results from the “Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints” (ALTITUDE), showed that the risks of renal impairment, low blood pressure (hypotension), and high potassium blood levels (hyperkalaemia) in a group of patients taking aliskiren plus an ARB or ACEi increased versus a group of patients taking placebo plus an ARB or ACEi.

Concerns about the safety of combination treatment with an ACEi and an ARB, particularly in patients with left ventricular dysfunction had already been identified in a previous meta-analysis² Hypotension, worsening kidney function, and an increase in serum potassium were the most worrying adverse events. However, in the context of heart failure the incidence of these side effects should be balanced with the effect of dual blockade on cardiovascular endpoints. However, the increased risk of adverse events may lead to discontinuation on ACEi + ARB combination therapy compared with ACEi alone.

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.

The conclusion of Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)² also highlighted the danger of dual inhibition of the renin-angiotensin system, reporting an increased risk of acute dialysis and hyperkalaemia in patients prescribed ACEis and ARBs together.

In a recent meta-analysis of trials in chronic kidney disease⁴ dual RAS blockade was associated with an increased risk of hyperkalemia and hypotension, but there was no effect on doubling of the serum creatinine, hospitalization or mortality relative to monotherapy.

Recently, the U.S. Veterans Affairs Cooperative Study “Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D)” was terminated early based on a greater number of observed acute kidney injury events and hyperkalaemia in the dual blockade therapy group (ARB/ACEi: losartan/lisinopril) compared to patients receiving an ARB plus placebo⁵.

Having considered the new available evidence from the scientific literature, given the seriousness of the signals of harm associated with the dual blockade of RAS, through the concomitant use of any substances from the ACEi, ARBs and direct renin inhibitors (aliskiren) classes, AIFA considers that it is in the interest of the Community to refer the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) and requests that it gives its recommendation under Article 31 of Directive 2001/83 on whether any other regulatory measures should be taken on the marketing authorisations of the above mentioned substances.

Date

17.04.2013

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

⁵ National PBM Bulletin, February 12 2013: Dual Renin-Angiotensin Adolsterone System Blockade in Diabetic Nephropathy and Increased Adverse Events. U.S. Department of Veterans Affairs Health Administration (VHA), Pharmacy Benefit Management Services (PBM), Medical Advisory Panel (MAP), and Center for Medication Safety (VA MEDSAFE). Available at: <http://www.pbm.va.gov/vamedsafe/nationalpbmbulletin/DualRenin-AngiotensinAldosteroneSystemBlockadeandImpairedRenalFu.pdf>