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## Restriction of combined use of medicines affecting the renin-angiotensin system (RAS)

On 23 May 2014 the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) endorsed restrictions on combining different classes of medicines that act on the renin-angiotensin system (RAS), a hormone system that controls blood pressure and the volume of fluids in the body.

These medicines (called RAS-acting agents) belong to three main classes: angiotensin-receptor blockers (ARBs, sometimes known as sartans), angiotensin-converting enzyme inhibitors (ACE-inhibitors) and direct renin inhibitors such as aliskiren. Combination of medicines from any two of these classes is not recommended and, in particular, patients with diabetes-related kidney problems (diabetic nephropathy) should not be given an ARB with an ACE-inhibitor.

Where combination of these medicines (dual blockade) is considered absolutely necessary, it must be carried out under specialist supervision with close monitoring of kidney function, fluid and salt balance and blood pressure. This would include the licensed use of the ARBs candesartan or valsartan as add-on therapy to ACE-inhibitors in patients with heart failure who require such a combination. The combination of aliskiren with an ARB or ACE-inhibitor is strictly contraindicated in those with kidney impairment or diabetes.

The CHMP opinion confirmed recommendations made by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) in April 2014, following assessment of evidence from several large studies in patients with various pre-existing heart and circulatory disorders, or with type 2 diabetes. These studies found that combination of an ARB with an ACE-inhibitor was associated with an increased risk of hyperkalaemia (increased potassium in the blood), kidney damage or low blood pressure compared with using either medicine alone. Furthermore, no significant benefits from dual blockade were seen in patients without heart failure and benefits were thought to outweigh risk only in a selected group of patients with heart failure in whom other treatments were unsuitable. This broad review of evidence relating to all RAS-acting agents supported the conclusions of a previous EMA review relating specifically to medicines containing aliskiren.<sup>1</sup>

The CHMP opinion was forwarded to the European Commission, which issued final decisions valid throughout the EU in September 2014.

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<sup>1</sup> European Medicines Agency recommends new contraindications and warnings for aliskiren-containing medicines. Available at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2012/02/news\\_detail\\_001446.jsp&mid=WCOb01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001446.jsp&mid=WCOb01ac058004d5c1)



## Information to patients

- RAS-acting agents are medicines acting on a hormone system that helps to control blood pressure and the amount of fluid in the body. They are used to treat conditions like high blood pressure or heart failure (when the heart cannot pump blood around the body as well as it should). These medicines can be of three different classes known as ARBs, ACE inhibitors and direct renin inhibitors (the last represented by the medicine aliskiren).
- RAS-acting agents from two different classes have sometimes been combined for an increased effect. However, a review of the latest evidence has suggested that in most patients such combination does not increase the benefits, and may increase the risks of low blood pressure, increased potassium in the blood and possible damage to the kidney.
- Combining RAS-acting agents is therefore no longer recommended. In particular, patients who have kidney problems related to diabetes should not be given an ARB with an ACE inhibitor (use of either of these types of medicine with aliskiren is already prohibited in patients with diabetes or kidney problems).
- In a small number of patients (mostly with heart failure) there may still be a medical need to combine two classes of these medicines. When this is considered absolutely necessary, it will be carried out under specialist supervision with close monitoring of kidney function, fluid and salt balance and blood pressure.
- Patients currently taking a combination of these medicines, or who have any concerns or questions, should discuss their medication with their doctor at their next regular appointment.

## Information to healthcare professionals

- On the basis of current evidence, dual RAS blockade therapy through the combined use of ACE-inhibitors, ARBs or aliskiren is not recommended in any patient. In particular, ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy, and existing contraindications on the use of aliskiren with either an ARB or an ACE inhibitor in patients with diabetes mellitus or moderate to severe renal impairment ( $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$ ) are confirmed.
- In individual cases where combined use of an ARB and ACE inhibitor is considered absolutely essential, it must be carried out under specialist supervision with close monitoring of renal function, electrolytes and blood pressure.
- Such supervised use would include the licensed use of candesartan or valsartan as add-on therapy to ACE inhibitors in patients with heart failure. However, in patients with chronic heart failure, dual blockade should be limited to those intolerant to mineralocorticoid antagonists and with persistent symptoms despite other optimal therapy.

These recommendations are based on a detailed review of the available data, including clinical trials, meta-analyses and publications, as well as advice from a group of experts on cardiovascular medicine.

- There is considerable evidence from large clinical trials such as ONTARGET<sup>1</sup>, ALTITUDE<sup>2</sup> and VA NEPHRON-D<sup>3</sup> and from meta-analyses such as that of Makani<sup>4</sup> (involving over 68,000 patients) demonstrating that dual RAS blockade 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 with monotherapy, in particular in patients with diabetic

nephropathy. This is of particular concern, as these patients and patients with renal impairment are already prone to developing hyperkalaemia.

- Available efficacy data indicate that such dual blockade does not provide significant benefit in the general patient population, although some selected patient sub-populations may possibly benefit. In patients with heart failure there is some evidence that the addition of a second RAS-acting agent may reduce hospital admissions.
- The existing contraindication on 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 m<sup>2</sup>), which is based on the ALTITUDE study data, was confirmed in the light of the additional data reviewed.

The product information for all RAS-acting agents has been amended accordingly.

#### References.

1. Yusuf S, Teo KK, Pogue J, et al. (ONTARGET Investigators). Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med.* 2008; 358(15): 1547-59.
2. Parving HH, Brenner BM, McMurray JJ, et al. (ALTITUDE Investigators). Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med.* 2012; 367(23): 2204-13.
3. Fried LF, Emanuele N, Zhang JH, et al. (VA NEPHRON-D Investigators). Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med.* 2013; 369(20): 1892-1903.
4. Makani H, Bangalore S, Desouza KA, et al. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *BMJ.* 2013; 346: f360. doi: 10.1136/bmj.f360.

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#### More about the medicine

RAS-acting agents work by blocking different stages of the renin-angiotensin system (RAS).

ARBs (containing the active substances azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan or valsartan) block receptors for a hormone called angiotensin II. Blocking the action of this hormone allows blood vessels to widen and helps to reduce the amount of water re-absorbed by the kidneys, thereby reducing blood pressure in the body.

ACE-inhibitors (benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril or zofenopril) and the direct renin inhibitor aliskiren block the actions of specific enzymes involved in the production of angiotensin II in the body (ACE-inhibitors block angiotensin-converting enzyme, while renin inhibitors block an enzyme called renin).

RAS-acting agents have been authorised in the European Union (EU) through central and national approval procedures and are widely available in the EU under a variety of trade names.

## **More about the procedure**

The review of RAS-acting agents was initiated at the request of the Italian Medicines Agency (AIFA), under Article 31 of Directive 2001/83/EC.

A review of these data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). As some RAS-acting agents have been centrally authorised, the PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's final opinion. The CHMP opinion was then forwarded to the European Commission, which confirmed it and issued final decisions, valid throughout the EU, on 4 and 9 September 2014.

## **Contact our press officers**

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