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Review started of combined use of renin-angiotensin system (RAS)-acting agents

The European Medicines Agency has started a review of the risks of combining certain medicines to block separate stages of the renin-angiotensin system (RAS) 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). RAS is a hormone system that controls blood pressure and the volume of fluids in the body, and medicines that act on this system are collectively known as 'RAS-acting agents'.

The review was started due to concerns that combining several RAS-acting agents could increase the risk of hyperkalaemia (high blood potassium levels), low blood pressure and kidney failure, compared with using one RAS-acting agent 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 evidence is based on a number of published studies, including a recent meta-analysis of 33 clinical studies involving over 68,000 patients published in the British Medical Journal[1].

There are three main types of RAS-acting agent: angiotensin receptor blockers (ARBs, sometimes known as sartans), angiotensin converting enzyme inhibitors (ACE inhibitors) and direct renin inhibitors (such as aliskiren).

The current review follows a previous EMA review of medicines containing aliskiren, which concluded in February 2012 that the combination of aliskiren with an ACE inhibitor or ARB could increase the risk of side effects affecting the heart and blood vessels or the kidneys. The EMA's Committee for Medicinal Products for Human Use (CHMP) decided that the combination of aliskiren with an ACE inhibitor or ARB is not recommended in any patient and should be contraindicated in patients with diabetes or moderate to severe kidney impairment, since they are at greater risk.

The European Medicines Agency will evaluate the impact of the latest available evidence on the benefit-risk balance of combining RAS-acting agents in the treatment of hypertension and congestive heart failure.

[1] Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials, Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH, BMJ, 2013 Jan 28; 346:f360. doi: 10.1136/bmj.f360.

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More about the medicines

RAS-acting agents act by blocking different stages of the renin-angiotensin system. ARBs 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 and direct renin inhibitors 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 has been initiated at the request of the Italian Medicines Agency (AIFA), under Article 31 of Directive 2001/83/EC.

The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which will make a set of recommendations. The PRAC recommendation will then be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for all questions concerning medicines for human use, which will adopt a final opinion.