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PRAC recommends against combined use of medicines affecting the renin-angiotensin (RAS) system

Recommendation will now be considered by CHMP for final opinion

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the risks of combining different classes of medicines that act on the renin-angiotensin (RAS) system, 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.

The PRAC has advised that combining medicines from any two of these classes should not be recommended, and in particular that patients with diabetes-related kidney problems (diabetic nephropathy) should not be given an ARB with an ACE-inhibitor. Where such combination (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 PRAC recommendation will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP) which will adopt the Agency's final opinion.

The RAS system is involved in maintaining water and salt (electrolyte) balance in the body, and hence in controlling blood pressure, and 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), while some are also used in certain kidney disorders to help reduce loss of protein in the urine. In order to achieve greater control, such medicines have been given in combination, but 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 worsening of kidney function compared with using one of these medicines alone, and might not have the anticipated beneficial effects.

This 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 on the heart, circulation and kidneys, and was therefore not recommended in any patient



and should be contraindicated in patients with diabetes or moderate to severe kidney impairment, who are at greater risk.

The PRAC supported the conclusions of the previous review. In addition, it found evidence from several large studies in patients with various pre-existing heart and circulatory disorders, or with type 2 diabetes, that combination of an ARB with an ACE-inhibitor was associated with an increased risk of hyperkalaemia, 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.

Further details of the review and the evidence behind it, as well as recommendations for patients and healthcare professionals, will be made available at the time of the CHMP opinion.

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 direct renin inhibitors (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.

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

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