Recommendation against combined use of medicines affecting the Renin-Angiotensin (RAS) system

30.04.2014 | Circular Number P09/2014

Information on the Renin Angiotensin System (RAS) and medicinal products

The Renin Angiotensin System (RAS) is a hormone system that controls blood pressure and the volume of fluids in the body. The RAS system is involved in maintaining water and salt (electrolyte) balance in the body, and hence in controlling blood pressure.

Medicines affecting this system (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.

Angiotensin-II-Receptor Blockers (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.

Angiotensin-Converting-Enzyme-inhibitors (ACE inhibitors) (benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril or zofenopril).

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 are used mainly 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.

RAS-acting agents have been authorised in the European Union (EU) including Malta through central and national approval procedures and are widely available under a variety of trade names. Products, which have an authorisation to be placed on the market in Malta, can be identified at **www.maltamedicineslist.com** by searching the active ingredients mentioned above.

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Information from European Medicines Agency about the safety concern

In order to achieve greater control, such medicines from each of the three types are sometimes given in combination. The review was started due to concerns that combining several RAS-acting agents could increase the risk of side-effects, including low blood pressure and worsening of kidney function compared with using one of these medicines alone, and might not have the anticipated beneficial effects.

Following a thorough review, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (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 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. 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.

For more information visit www.ema.europa.eu

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on medications affecting the RAS. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority ADR form, which can be downloaded from **www.medicinesauthority.gov.mt/adrportal** and sent to **postlicensing.medicinesauthority@gov.mt** or online at or to the marketing authorisation holder or their local representatives.

Prof. John J Borg PhD (Bristol)
Post-licensing Director

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

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