HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

RECOMMENDATION TO RESTRICT THE COMBINED USE OF MEDICINES AFFECTING THE RENIN-ANGIOTENSIN (RAS) SYSTEM

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. These medicines, which are called RAS-acting agents, belong to three classes:

1. Angiotensin-receptor blockers (ARBs) for example candesartan, telmisartan, valsartan, losartan, olmesartan and irbesartan*,
2. Angiotensin-converting enzyme inhibitors (ACE inhibitors) for example captopril, enalapril, lisinopril, ramipril, perindopril and zofenopril*,
3. Direct renin inhibitors such as aliskiren*, which is the only authorised substance in its class.

The PRAC has advised that combining medicines from any two of these classes should not be recommended, and in particular that patients with diabetic nephropathy should not be given an ARB with an ACE-inhibitor. Where such a combination (known as dual blockade) is considered absolutely necessary, it must be carried out under specialist supervision with close monitoring of kidney function, electrolyte balance and blood pressure. This recommendation also extends to 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 patients with renal impairment or diabetes mellitus.

The benefit-risk of the individual RAS-acting agents used as monotherapy or as combination therapy with antihypertensive agents from other classes such as beta blockers were not considered within the scope of this review and any issues identified apply only to dual RAS blockade therapy.

The PRAC reviewed the totality of the available data, including clinical trials, meta-analysis and publications. It was of the opinion that there is considerable evidence from these, in particular the Makani et al meta-analysis[1], ONTARGET (Yusuf et al. 2008)[2], ALTITUDE (Parving et al. 2012)[3] and the prematurely terminated VA NEPHRON-D trial (the VA NEPHRON-D Investigators, 2013)4, which demonstrate 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 to monotherapy. The Makani et al meta-analysis reinforces conclusions from individual studies, that the likely benefits from dual blockade are limited to a reduction in hospital admissions for heart failure among people with pre-existing heart failure, and highlights some important safety concerns associated with dual therapy. Based on the totality of the evidence, the PRAC has recommended that dual therapy should be restricted to limited situations under specialist supervision after careful consideration of the likely risks and benefits.

Following this review, harmonised implementation of these recommendations into product information has begun in order to reflect the available information and adequately manage the concerns identified with regards to dual RAS blockade therapy and the overall conclusion that dual blockade of the renin angiotensin system with an ACE inhibitor plus an angiotensin receptor blocker (ARB) has only a limited place in treatment e.g. in a selected group of symptomatic patients with heart failure and reduced left ventricular function in whom other treatments are unsuitable.

Section 4.4 of the Summary of Product Characteristics (SmPC) is in the process of being updated for all products accordingly to highlight that dual RAS blockade through the combined use of ACE-inhibitors, ARBs or aliskiren is not recommended and if, considered absolutely necessary, should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. It will be clearly specified however that ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

Advice to Healthcare Professionals

- The benefit risk balance of RAS-acting agents remains favourable when used in line with the updated recommendations.
- Dual blockade of the renin angiotensin system with an ACE inhibitor plus an angiotensin receptor blocker (ARB) has only a limited place in treatment for example, in a selected group of symptomatic patients with heart failure and reduced left ventricular function in whom other treatments are unsuitable.
- The combined use of ACE-inhibitors, ARBs or aliskiren increases the risk of adverse events such as hyperkalaemia, hypotension and renal impairment compared to use of these medicines alone.

- Dual blockade of the RAS system is therefore generally not recommended and should not be used in patients with diabetic nephropathy.
- If dual RAS blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
- In patients with diabetes mellitus or renal impairment (GFR < 60ml/min), the concomitant use of ACE inhibitors or ARBs with aliskiren-containing products is contraindicated.

Key Message
Dual blockade of the renin angiotensin system with an ACE inhibitor plus an angiotensin receptor blocker (ARB) has only a limited place in treatment such as in a selected group of symptomatic patients with heart failure and reduced left ventricular function with the necessary monitoring and specialist supervision. Combined use of ACE inhibitors, ARBs or aliskiren is associated with an increased risk of adverse events, including hypotension, hyperkalaemia and renal failure compared to monotherapy.

**Products currently authorised in Ireland include Atacand, Blopress (candesartan), Micardis (telmisartan), Diovan (valsartan), Co-Diovan (valsartan and hydrochlorothiazide), Cozaar (losartan), Aprovel (irbesartan), Omesar (olmesartan), Omesar Plus (olmesartan and hydrochlorothiazide), Konverge (olmesartan and amlodipine), Konverge Plus (olmesartan, amlodipine, hydrochlorothiazide), Captor (captopril), Innovace (enalapril), Zestril (lisinopril), Zestoretic (lisinopril and hydrochlorothiazide), Zofenil (zofenopril), Tritace (ramipril), Coversyl (perindopril), Rasilez (aliskiren), Rasilez HCT (aliskiren and hydrochlorothiazide), Rasilamlo (aliskiren and amlodipine). Generics of some products are also available. Further details are available at www.hpra.ie*

References

1. Makani H, et al. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ. 2013; 346: f360.

2. Yusuf S, et al. Telmisartan, ramipril or both in patients at high risk for vascular events. N Engl J Med 2008; 358:1547-59.

3. Hans-Henrik Parving, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012; 367:2204-2213.

4. VA Nephron-D Investigators. Combined Angiotensin Inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013; 369:1892-1903.

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IRISH MEDICINES BOARD NAME CHANGE

Effective from 1 July 2014, the Irish Medicines Board (IMB) is changing its name to the Health Products Regulatory Authority (HPRA). First established in 1966, the National Drugs Advisory Board (NDAB) later became the IMB in 1996. However over the last 18 years, its regulatory remit has expanded to include other health products as well as a number of health related functions. In addition to medicines, the organisation now has a role in regulating a range of areas including:

- Medical devices,
- Controlled drugs,
- Blood components,
- Tissues and cells,
- Human organs for transplantation,
- Cosmetic products,
- Use of animals for scientific purposes.

The new name is considered to clearly reflect the wider scope of work, functions and responsibilities across the health products sector. At the same time, it is intended to build on the IMB's heritage and reputation as a professional, progressive and science driven public sector organisation.

While the name has changed, the mission of the HPRA remains the same: To protect and enhance public and animal health through the regulation of medicines, medical devices and other health products. The organisation remains committed to working on behalf of patients and the public to ensure heath products are as safe as possible and do what they are intended to do. The new logo will be seen on all HPRA documents from 1 July 2014.

Please note that in addition to the name change, the imbpharmacovigilance@imb.ie email address will change to medsafety@hpra.ie. While the new email address will not become operational until 1 July, the existing email address will remain in use for a transitional period after that date, but please do update your internal systems/records to reflect these changes, as necessary.

Further information on the name change has been circulated to stakeholders and is available from the HPRA website (www.hpra.ie), including details of current and replacement topic-based and departmental email addresses.