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DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG REGISTRATION AND IMPORT/EXPORT CONTROL DIVISION
3/F., Public Health Laboratory Centre,
382 Nam Cheong Street, Kowloon, Hong Kong

BY FAX

18 February 2016

Dr. Donald LI
President
Hong Kong Academy of Medicine
(Fax Number: 2505 5577)

Dear Dr. LI,

Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency's (MHRA) announcement regarding monitoring of blood electrolytes is essential in patients coprescribed a potassium-sparing diuretic and an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) for heart failure.

Spironolactone is indicated in patients with congestive heart failure. It is a competitive aldosterone antagonist that increases sodium excretion while reducing potassium loss at the distal renal tubule. This mechanism of action means that hyperkalaemia can occur, particularly in patients with impaired renal function. Spironolactone should not be used in patients with severe renal impairment or pre-existing hyperkalaemia.

ACEi are mainly indicated in patients with hypertension or heart failure. ARBs are indicated in hypertension and some are also indicated in heart failure. Recognised side effects of treatment with an ACEi or ARB include renal dysfunction and an increase in serum potassium. Risk factors for hyperkalaemia, such as renal insufficiency and diabetes mellitus, are more common in patients who require treatment with ACEi or ARB. Dehydration may also increase the risk of renal dysfunction leading to hyperkalaemia. Hyperkalaemia has been estimated to occur in between 1 in 100 and 1 in 1000 patients who take an ACEi or ARB.

A recent coroner's case reported to MHRA described a case of fatal hyperkalaemia in a patient with heart failure, diabetes, and chronic renal failure who was being treated with several medicines including spironolactone. A low-dose ACEi was subsequently added for treatment of increased blood pressure. A few days later, the patient was admitted to hospital with severe hyperkalaemia and acute-on-chronic renal failure and subsequently died.

Healthcare professionals are advised of the following:

- Concomitant use of spironolactone with ACEi or ARB is not routinely recommended because of the risks of severe hyperkalaemia, particularly in patients with marked renal impairment.
- Use the lowest effective doses of spironolactone and ACEi or ARB if coadministration is considered essential.
- Regularly monitor serum potassium levels and renal function.
- Interrupt or discontinue treatment in the event of hyperkalaemia.

Please refer to the MHRA's website for details:

https://www.gov.uk/drug-safety-update/spironolactone-and-renin-angiotensin-system-drugs-in-heart-failure-risk-of-potentially-fatal-hyperkalaemia

In Hong Kong, there are 9 registered pharmaceutical products containing spironolactone, 153 ACEi products (including 1 containing cilazapril, 43 containing enalapril maleate, 45 containing lisinopril, 8 containing perindopril arginine, 15 containing perindopril erbumine, 13 containing ramipril, 16 containing captopril, 2 containing imidapril hydrochloride, 3 containing trandolapril, 3 containing benazepril hydrochloride and 4 containing zofenopril calcium), and 258 ARB products (including 20 containing candesartan, 80 containing valsartan, 4 containing azilsartan, 2 containing eprosartan, 63 containing losartan, 23 containing telmisartan, 52 containing irbesartan, 14 containing olmesartan). All these are prescription only medicines. So far, the Department of Health (DH) has received one adverse drug reaction case on spironolactone, but it was not related to hyperkalemia due to co-administration of spironolactone and ACEi/ARB. DH will remain vigilant on any safety updates of the drugs combination and actions taken by other overseas regulatory authorities for consideration of any action deemed necessary. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours sincerely,

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for Assistant Director (Drug)