PHARMACY AND POISONS BOARD
HONG KONG
香港藥劑業及毒藥管理局

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25th February 2016

To: Certificate holders of
registered pharmaceutical products

Dear Sirs / Madams,

New Safety Warnings for Combined Use of Medicines affecting the Renin-Angiotensin System

On 18th February 2016, the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (the Committee) considered the latest overseas recommendations on the risks for combined use of medicines affecting the renin-angiotensin system (RAS), and decided that the sales pack labels and/or package inserts of pharmaceutical products containing RAS-acting agents, including angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, and direct renin inhibitors (full list of affected products in Annex I), should include the new safety warnings as detailed in Annex II.

You are therefore required to review and revise, if necessary, the sales pack labels and/or package inserts of the concerned products registered by your company to ensure that the products comply with the above requirements. The revised sales pack labels and/or package inserts should be submitted to the Committee for approval within 2 months from the date of this letter. Failing to comply with the above requirements may result in de-registration of the products by the Committee.

If you have any enquiries on the above issue, please contact the Drug Office duty officer at 2319 8458.

Yours sincerely,

(Clive CHAN)
Secretary,
Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee

c.c. 7-15/3, Product Files
SM/CC

Annex I

List of the Affected Products

(a) **Angiotensin-receptor blockers (ARBs):**

Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, etc..

(b) **Angiotensin-converting enzyme inhibitors (ACEIs):**

Benzaepril, captopril, cilazapril, enalapril, imidapril, lisinopril, perindopril, ramipril, trandolapril, zofenopril, etc.

(c) **Direct renin inhibitors:**

Aliskiren

Annex II

New Safety Warnings:

(a) For products containing ARBs or ACEIs:

Contraindication

The concomitant use of [BRAND NAME] with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual 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.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Interaction with other medicinal products and other forms of interaction

Clinical trial data has shown that dual blockade of the RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and

decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

(b) For products containing <u>aliskiren:</u>

Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone-system (RAAS)

Hypotension, syncope, stroke, hyperkalaemia and decreased renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the RAAS by combining aliskiren with an ACE-inhibitor or an angiotensin II receptor blocker is therefore not recommended. If dual 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.

Interaction with other medicinal products and other forms of interaction

Clinical trial data has shown that dual blockade of the RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, stroke, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.