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

Your Ref. **:**
貴處檔號

Our Ref. **:** DH DO PRIE/1-55/1
本局檔號

Tel. No. **:** **3974 4133**
電　話

Fax No. **:** **2803 4962**
圖文傳真

Drug Office
Department of Health
Suites 2002-05, 20/F, AIA Kowloon Tower,
Landmark East, 100 How Ming Street,
Kwun Tong, Kowloon, Hong Kong
香港九龍觀塘巧明街100號
Landmark East 友邦九龍大樓
20樓2002-05室
衞生署藥物辦公室

28th February 2024

To: Certificate holders of registered pharmaceutical products

Dear Sir/Madam,

New Warnings for Statins

On 22nd February 2024, the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (the Committee) considered the latest warnings regarding the risk of myasthenia gravis associated with the use of statins by the drug regulatory authorities of Australia, Canada, the European Union, Singapore, the United Kingdom and the United States, and decided that the sales pack labels and / or package inserts of all registered products containing statins (including atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin) should include the following new safety information (or equivalent) as appropriate:

"Special Warnings and Precautions for use

Myasthenia gravis

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. <Product name/Generic name> should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Undesirable effects

"Myasthenia gravis" is listed as an adverse reaction under "Nervous system disorders" with frequency "Not known", and

"Ocular myasthenia" is listed as an adverse reaction under "Eye disorders" with frequency "Not known"."

You are therefore required to ensure the sales pack labels and / or package inserts of the concerned products registered by your company contain the above safety information to comply with the new requirements. In addition, you are reminded to ensure the sale pack labels and/ or package inserts of the registered statin products already contain the safety information stated in the Annex (or similar wording) as previously endorsed by the Committee. Please submit application for the change of the registered particular(s) to our Office via the online Pharmaceutical Registration System 2.0 (PRS 2.0) at www.drugoffice.gov.hk/prs2-ext/client_authentication.jsp 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 or registration not being renewed by the Committee upon certificate expiry.

For further enquiries on the registration matters of pharmaceutical products, please contact our office at 3974 4175.

Yours faithfully,

(Y. F. YEUNG)
Secretary,
Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee

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

Annex

Safety information previously endorsed by the Pharmacy and Poisons (Registration of Pharmaceutical Substances: Certificate of Clinical Trial/Medicinal Test) Committee

(a) For all statin-containing pharmaceutical products:

(i) "It is recommended that liver function tests should be performed before the initiation of [brand name], and therefore when clinically indicated

(ii) "There have been rare postmarking reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks)."

(iii) "Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors."

(b) For atorvastatin-containing pharmaceutical products:

(i) "Co-administration of strong CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided, lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended. In patients taking telaprevir, concomitant use of atorvastatin should be avoided. The dose of atorvastatin should not exceed 40mg daily when taking with boceprevir and close clinical monitoring is recommended."

(c) For simvastatin-containing pharmaceutical products:

(i) "Restrictions on the use of 80mg dose for simvastatin:

- *Simvastatin 80mg should be used only in patients who have been taking this dose for 12 months or more without evidence of muscle toxicity;*
- *Simvastatin 80mg should not be started in new patients, including patients already taking lower doses of the drug."*

(ii) *"Dose limitations for using simvastatin with certain medicines:*
- *Do not exceed 10mg simvastatin daily with verapamil, diltiazem and other fibrates (except fenofibrate)*
- *Do not exceed 20mg simvastatin daily with amiodarone, amlodipine and ranolazine*
- *Avoid grapefruit juice when taking simvastatin*
- *Patients should be closely monitored when taking fusidic acid with simvastatin. Temporary suspension of simvastatin treatment may be considered."*

(iii) *"Simvastatin is contraindicated with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone), gemfibrozil, ciclosporin and danazol."*

(iv) *"Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥1 g/day."*

(v) *"Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine. Caution should be exercised when prescribing simvastatin with colchicine."*

(d) <u>For lovastatin-containing pharmaceutical products:</u>

(i) *"Lovastatin is contraindicated with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone)."*

(ii) *"The combined use of lovastatin with gemfibrozil or ciclosporin should be avoided."*

(iii) *"The dose of lovastatin should not exceed 20mg daily in patients receiving concomitant medication with danazol, diltiazem, verapamil or dronedarone."*

(iv) *"The dose of lovastatin should not exceed 40mg daily in patients receiving concomitant medication with amiodarone."*

(v) *"Grapefruit juice should be avoided in patients taking lovastatin."*

(vi) *"**Concurrent consumption of red yeast rice***
Consuming red yeast rice or its supplement together with lovastatin should be avoided as it may potentiate the side effects of lovastatin. Seek medical advice before use if you are taking lovastatin. "

(vii) *"**Precaution on pregnancy***
Contraindications
Lovastatin is contraindicated during pregnancy and in nursing mothers.

Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus."

(e) For rosuvastatin-containing pharmaceutical products:

(i) *"The concomitant use with protease inhibitors is not recommended."*

(ii) *"In JUPITER study, there was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c > 6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients."*

(iii) *The safety information related to the drug's effect in Asian patients. Example of wording as follows:*

"Pharmacokinetic studies have demonstrated an increase in exposure to rosuvastatin (or product name of the product) in Asian subjects when compared with Caucasians. Initiation of rosuvastatin (or product name of the product) therapy with 5mg once daily should be considered in Asian patients."

(iv) *"40mg dose of rosuvastatin is contraindicated in Asian patients."*