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

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圖文傳真

Drug Office
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衞生署藥物辦公室

9th September 2024

To: Certificate holders of registered pharmaceutical products

Dear Sir/Madam,

New Warnings for Metformin

The Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (the Committee) under the Pharmacy and Poisons Board has considered, in its meeting on 5th September 2024, the latest warnings related to the risk of vitamin B12 deficiency associated with metformin and the advice for monitoring patients at risk 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 metformin should include the following new safety information (or equivalent [Note 1]) as appropriate:

> ***"Special Warnings and Precautions for use***
> *Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.*

[Note 1] Related safety information with other wording in accordance with reputable references and/or approved package inserts from drug regulatory authorities of reference countries may also be accepted on a case-by-case basis.

Undesirable effects

'Vitamin B12 decrease/deficiency' is listed as an adverse reaction under 'Metabolism and nutrition disorders' with frequency 'Common'."

or

"Warnings and Precautions

Vitamin B12 Deficiency

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 measurements at 2- to 3-year intervals in patients on <Product name/Generic name> and manage any abnormalities."

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 metformin products already contain the safety information stated in the Annex (or equivalent [see Note 1 above]) as previously endorsed by the Committee. Please submit application for the change of the registered particular(s) to the Drug 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 the Drug 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

For all metformin-containing pharmaceutical products:

(a) The recommendations on the use of metformin in patients with reduced kidney function. Example of wording as follows:

"Posology and method of administration

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

For pharmaceutical products containing metformin in immediate-release formulations:

GFR (mL/min)	***Total maximum daily dose (to be divided into 2-3 daily doses)***	***Additional considerations***
60-89	*3000 mg*	*Dose reduction may be considered in relation to declining renal function.*
45-59	*2000 mg*	*Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin.* *The starting dose is at most half of the maximum dose.*
30-44	*1000 mg*	
<30	-	*Metformin is contraindicated.*

For pharmaceutical products containing metformin in extended-release formulations:

GFR (mL/min)	***Total maximum daily dose***	***Additional considerations***
60-89	*2000 mg*	*Dose reduction may be considered in relation to declining renal function.*
45-59	*2000 mg*	*Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin.* *The starting dose is at most half of the maximum dose.*
30-44	*1000 mg*	
<30	-	*Metformin is contraindicated.*

(b) The safety information related to the precautions for metformin use with iodinated contrast agents. Example of wording as follows:

"Special Warnings and Precautions for use

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable."