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BY FAX

6 May 2013

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

Dear Dr. LI,

Safety alerts on Medroxyprogesterone, Levothyroxine and Rivaroxaban announced by Singapore HSA

Your attention is drawn to the following drug safety alerts announced by Singapore Health Sciences Authority (HSA):

1. Intramuscular medroxyprogesterone and injection site necrosis and atrophy

HSA informed healthcare professionals on overseas reports of injection site necrosis and atrophy associated with the use of intramuscular (IM) medroxyprogesterone. As of 31 July 2012, a total of 103 medically confirmed global cases of injection site reactions associated with the IM route of administration of medroxyprogesterone were reported to the Pfizer Pte Ltd. (Pfizer). Of these reports, 30.1% were serious and described events such as injection site atrophy, atrophy, skin atrophy, lipoatrophy, injection site necrosis, necrosis, fat necrosis, injection site ulcer, and muscle necrosis. In 44.7% of the cases, there was insufficient information (e.g., site of reaction, dates of onset) to allow a meaningful medical assessment. In 20.4% of the cases, IM medroxyprogesterone injection was reported to be administered at the thigh region instead of the recommended deltoid or gluteal region. There were also 25.2% of cases where the role of IM medroxyprogesterone in the development of injection site necrosis and atrophy could not be ruled out.

HSA is working with Pfizer to further strengthen the warnings in the local package insert for Depo-Provera to include injection site necrosis and skin atrophy as potential injection site reactions. Healthcare professionals are reminded to take into consideration the above safety updates when prescribing IM medroxyprogesterone.

Please refer to HSA's website for details:
http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/Safety_Alerts_2013/intramuscular_medroxyprogesterone.html

In Hong Kong, there are three intramuscularly injectable pharmaceutical products containing medroxyprogesterone registered and are prescription-only medicines. They are indicated for contraceptive use. So far, the Department of Health has not received any related adverse reports in connection with the drug. In view of HSA'a announcement, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

2. Levothyroxine and potential risk of fractures

HSA announced that an increase in the risk of fractures associated with the use of levothyroxine

has been observed in a recent study. Outcomes of the study found that current and recent past levothyroxine use were associated with a significant increased risk of any fractures when compared to remote levothyroxine use. Among current levothyroxine users, a higher risk of any fractures was observed for high (>0.093mg/day) and medium (0.044 to 0.093mg/day) cumulative doses of levothyroxine when compared to low (<0.044mg/day) cumulative doses. Additionally, healthcare professionals should be aware that long-term suppressive doses of levothyroxine therapy has been associated with increased bone resorption and reduced bone mineral density, especially in post-menopausal women.

HSA will further strengthen the local package inserts to include information on the effect of levothyroxine on bone mineral density. Healthcare professionals are advised to take into consideration this safety information when prescribing levothyroxine to their patients and to prescribe the minimum dose necessary to achieve the desired clinical and biochemical response.

Please refer to HSA's website for details:
http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/Safety_Alerts_2013/levothyroxine_and.html

In Hong Kong, there are nine registered pharmaceutical products containing levothyroxine and are prescription-only medicines. They are indicated as replacement therapy in the treatment of thyroid hormone deficiency. So far, the Department of Health has not received any related adverse reports in connection with the drug. In view of HSA'a announcement, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

3. Rivaroxaban (Xarelto) and reports of lack of efficacy in orthopaedic surgery indication

HSA announced that a review of the adverse drug reaction (ADR) reports received by the Netherlands Pharmacovigilance Centre, Lareb, raised a possible signal of lack of efficacy with Xarelto for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery.

As of March 2012, Lareb had received 48 ADR reports related to the use of rivaroxaban. Of these, 31 were reported as serious and the most frequently reported serious ADRs were bleeding events. There were also eight reports of pulmonary embolism (PE) associated with the use of rivaroxaban, which indicated a possible lack of efficacy in certain patients. Of these eight reports, four were confirmed with Computed Tomography (CT) scan. In comparison, the number of PE reports associated with rivaroxaban was disproportionately higher than that for low molecular weight heparin (LMWH) products, which were much more commonly used than rivaroxaban. There were nine PE reports for nadroparin, four for dalteparin, and none for both enoxaparin and tinzaparin. Hence, Lareb has assessed that attention to lack of drug effect manifested through the occurrence of PE is warranted when using rivaroxaban following hip or knee replacement surgery.

HSA continues to monitor for reports of PE associated with rivaroxaban although there is no report of PE locally. Healthcare professionals are advised to monitor their patients for possible lack of efficacy.

Please refer to HSA's website for details:
http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/Safety_Alerts_2013/rivaroxaban__xarelto.html

In Hong Kong, there are three registered pharmaceutical products containing rivaroxaban,

namely Xarelto Tab 10mg (HK-57861), 15mg (HK-61396) and 20mg (61395). They are prescription-only medicines. Xarelto Tab 15mg and 20mg are indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism following an acute DVT in adults. Xarelto Tab 10mg is indicated for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. So far, the Department of Health (DH) had received one adverse report concerning suspected intracranial hemorrhage in connection with rivaroxaban, and no cases on lack of efficacy were received. The DH will keep vigilance on any safety updates of the drug and actions taken by other overseas regulatory authorities for consideration of any action deemed necessary.

Please encourage your members to report any adverse events caused by the drugs to the Pharmacovigilance Unit of Department of Health (tel. no.: 2319 2920, fax: 2186 9845 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 drug safety digest of drug safety news and information issued by Drug Office.

Yours sincerely,

(Ms. Pamela LI)
for Assistant Director (Drug)