Drug News
藥 物 情 報

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This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in June 2019 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).

Safety Update

Canada: Summary Safety Review - Gentian violet-containing human health products - Assessing the potential risk of cancer

On 12 June 2019, Health Canada announced that it had conducted a health risk assessment on gentian violet-containing products focused on a non-prescription drug product (Gentiane Violet Liquid Topical). The assessment was triggered by the World Health Organization's Codex Alimentarius Commission recommending that regulatory authorities prevent exposure to gentian violet in food because of its potential to cause cancer.

Gentian violet has been used in health products for both humans and animals. In humans, gentian violet has been used to treat infections of the skin. In animals, gentian violet has been used topically for the treatment of surface wounds and eye infections.

Health Canada received 4 Canadian reports of adverse events associated with the use of gentian violet-containing drug products. The reported adverse events include localized skin reactions, pain, discomfort, and local discoloration. Of these 4 reports, 2 involve infants (2 months and 5 months of age). These reports confirm the use of gentian violet to treat oral thrush in infants. Health Canada also identified 50 international reports involving the use of a gentian violet-containing drug product from VigiBase, 4 of which were considered serious. While there have been no Canadian nor international reports of cancer associated with the human use of gentian violet, animal studies show a link between gentian violet and cancer when ingested. It is unknown if applying gentian violet to the skin (topical application) has the same cancer causing effect. Some evidence suggests health products containing gentian violet are being used in infants and breastfeeding mothers. As such, it is possible that when gentian violet is applied to the nipple of the breast and/or used to treat thrush, it may be ingested by infants.

Health Canada's risk assessment of the non-prescription drug product concluded that there is evidence in the scientific literature, based on animal studies, that there is a potential for gentian violet to cause cancer. Although no cases of cancer associated with the use of topical gentian violet were found, oral exposure of gentian violet has been shown in animal studies to cause cancer. Health Canada contacted the manufacturer and notified them of the results of the assessment noting the potential risk of cancer with the use of gentian violet-containing drug products. The manufacturer of Gentiane Violet Liquid Topical voluntarily discontinued the sale of the product in Canada in May 2019, and their heath product drug licence has been cancelled. Consumers are advised to stop using the product and return it to their local pharmacy for proper disposal.

Health Canada has also looked at veterinary drugs that contain gentian violet and manufacturers of the 9 impacted veterinary drug products have agreed to voluntarily discontinue marketing their products in Canada and their drug licence have been cancelled.

In Hong Kong, there are 2 registered pharmaceutical products containing gentian violet (also known as methylrosanilinium chloride), namely Banitore Gentian Violet Solution 1% (HK-46371) which is registered by Hengan Pharmacare Co Ltd, and Onetar Gentian Violet Solution 1% (HK-58334) which is registered by

Unifort (Asia Pacific) Co Limited. All products are for topical use in human. As of 5 July 2019, the Department of Health (DH) had not received any case of adverse drug reaction related to gentian violet. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 13 June 2019, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome

On 19 June 2019, Medicines and Healthcare products Regulatory Agency (MHRA) announced that a clinical trial had shown an increased risk of recurrent thrombotic events associated with rivaroxaban compared with warfarin, in patients with antiphospholipid syndrome and a history of thrombosis. Other DOACs may be associated with a similarly increased risk. The DOACs available are apixaban (Eliquis), dabigatran etexilate (Pradaxa), edoxaban (Lixiana▼), and rivaroxaban (Xarelto▼).

A European Union (EU) review has concluded that use of DOACs in patients with antiphospholipid syndrome could be associated with increased rates of recurrent thrombotic events compared with therapy with a vitamin K antagonist. The level of evidence for an increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome differs among DOACs. However, there is not enough evidence that any DOAC offers sufficient protection in patients diagnosed with established antiphospholipid syndrome, particularly in patients at the highest risk for thromboembolic events (those who test positive for all 3 antiphospholipid tests – lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies). Changes are therefore being made to the product information for these medicines to advise that use of DOACs in these patients with antiphospholipid syndrome is not recommended.

The TRAPS study was an investigator-sponsored, randomised, open-label, multicentre study with blinded endpoint adjudication. Outcomes with rivaroxaban were compared with warfarin in patients with antiphospholipid syndrome and a history of thrombosis, and at high risk for thromboembolic events (patients who persistently tested positive for all 3 antiphospholipid tests). The trial was terminated prematurely after the enrolment of 120 patients due to an excess of thromboembolic events among patients in the rivaroxaban arm. Mean follow-up was 569 days. In the study, 59 patients were randomly assigned to rivaroxaban 20 mg (15 mg dose for patients with creatinine clearance <50 ml/min) and 61 to warfarin (INR 2.0–3.0). Thromboembolic events occurred in 12% of patients assigned to receive rivaroxaban (4 cases of ischaemic stroke and 3 of myocardial infarction). No thromboembolic events were reported in patients assigned to receive warfarin. Major bleeding events occurred in 4 patients (7%) in the rivaroxaban group and 2 patients (3%) in the warfarin group. No deaths were reported.

Available data for apixaban, edoxaban and dabigatran etexilate are more limited than for rivaroxaban because there have been no completed clinical trials of these products in patients with antiphospholipid syndrome. However, available data suggest these other DOACs may be associated with a similarly increased risk of recurrent thrombotic events as with use of rivaroxaban. One investigator-sponsored research study is ongoing to study rates of thrombosis in patients with antiphospholipid syndrome on apixaban (ASTRO-APS). The final results are not yet available.

Healthcare professionals are advised:

- DOACs are not recommended in patients with antiphospholipid syndrome, particularly high-risk patients (those who test positive for all 3 antiphospholipid tests — lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies).
- Review whether continued treatment with a DOAC is appropriate for patients diagnosed with antiphospholipid syndrome, particularly high-risk patients, and consider switching to a vitamin K antagonist such as warfarin.

In Hong Kong, there are registered pharmaceutical products containing apixaban (2 products), dabigatran etexilate (3 products), edoxaban (3 products) and rivaroxaban (6 products), and all products are prescription-only medicines. As of 5 July 2019, the DH had received cases of adverse drug reaction related to apixaban (19 cases), dabigatran etexilate (12 cases), edoxaban (13 cases) and rivaroxaban (18 cases). In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 20 June 2019, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued

On 19 June 2019, the MHRA announced that diabetic ketoacidosis had been reported in patients with type 2 diabetes on a combination of a GLP-1 receptor agonist and insulin who had doses of concomitant insulin rapidly reduced or discontinued. Exenatide (Bydureon, Byetta), liraglutide (Victoza, Saxenda▼, Xultophy▼ [combination product with insulin]), and dulaglutide (Trulicity▼) are glucagon-like peptide-1 (GLP-1) receptor agonists (also known as GLP-1 mimetic therapies). GLP-1 receptor agonists are not substitutes for insulin.

Serious and life-threatening cases of diabetic ketoacidosis have been reported in association with exenatide, liraglutide, and dulaglutide, particularly after rapid reduction or discontinuation of concomitant insulin. An EU review of these reports concluded that the cases could be attributed to abrupt discontinuation or dose reduction of insulin while initiating GLP-1 receptor agonist therapy, resulting in a poor glycaemic control. This review did not identify euglycaemic diabetic ketoacidosis as a safety concern specific to treatment with GLP-1 receptor agonist therapies. A few cases in the review reported reactions suggestive of euglycaemic diabetic ketoacidosis; however, these were attributed to concomitant use of sodium-glucose co-transporter-2 inhibitor (SGLT2) medicines, which are known to be associated with euglycaemic diabetic ketoacidosis.

When GLP-1 receptor agonist therapy is added to existing treatment with insulin, a reduction in the dose of insulin may be considered to reduce the risk of hypoglycaemia. A stepwise approach to insulin dose adjustment is recommended, taking into account a patient's glucose levels and individual insulin requirements. The Summaries of Product Characteristics and Patient Information Leaflets for exenatide, liraglutide, and dulaglutide are being updated to note that a stepwise approach is recommended for insulin dose reduction and to advise that blood glucose self-monitoring is necessary when adjusting the dose of insulin, particularly during initiation of GLP-1 receptor agonist therapy.

The GLP-1 receptor agonists lixisenatide (Lyxumia) and semaglutide (Ozempic▼) are also authorised for use in the United Kingdom (UK). Lixisenatide and semaglutide were not subject to the EU review. At the time of publication, the MHRA has not received any UK reports of diabetic ketoacidosis in association with lixisenatide and semaglutide. However, the theoretical risk of diabetic ketoacidosis when changes are made to insulin dose cannot be excluded.

Up until the end of May 2019, the MHRA's Yellow Card Scheme has received 26 reports of diabetic ketoacidosis, and 10 reports of reactions relating to ketone body formation (increased blood ketones, ketonuria) in patients taking exenatide, liraglutide, and dulaglutide. This corresponds to a UK estimated exposure to these 3 medicines of about 2 million patient-years of treatment between 2007 and 2018. In around a third of the UK cases reported, insulin was either discontinued or the dose was rapidly reduced at initiation of the GLP-1 receptor agonist. In the remaining cases, it is difficult to establish the role of these agents due to possible precipitating factors for diabetic ketoacidosis, such as other medicines or underlying conditions. Although nausea and vomiting may be considered adverse drug reactions of GLP-1 receptor agonists, these are also well-known symptoms of diabetic ketoacidosis and should be taken seriously when initiating GLP-1 receptor agonists and adjusting insulin doses. Many of the cases of diabetic ketoacidosis and related reactions

occurred within 2 weeks of initiation of GLP-1 receptor agonists. Nausea and vomiting were commonly co-reported reactions.

Inform patients of the signs and symptoms of diabetic ketoacidosis (nausea, vomiting, abdominal pain, excessive thirst, increased frequency of urination, difficulty breathing, confusion, unusual fatigue, or sleepiness) and the need for urgent medical attention if they occur.

Healthcare professionals are advised:
- Serious and life-threatening cases of diabetic ketoacidosis have been reported in association with exenatide, liraglutide, and dulaglutide, particularly after discontinuation or reduction of concomitant insulin.
- Blood glucose self-monitoring is necessary when adjusting the dose of insulin, particularly when GLP-1 receptor agonist therapy is initiated and insulin is reduced.
- If the insulin dose is to be reduced, a stepwise approach is recommended.
- Discuss with patients the risk factors for and signs and symptoms of diabetic ketoacidosis and advise them to seek immediate medical advice if these develop.

In Hong Kong, there are registered pharmaceutical products containing exenatide (3 products), liraglutide (3 products), dulaglutide (2 products) and lixisenatide (5 products), and all products are prescription-only medicines. There is no registered pharmaceutical product containing semaglutide. As of 5 July 2019, the DH had received cases of adverse drug reaction related to exenatide (2 cases), liraglutide (1 case), dulaglutide (4 cases) and semaglutide (1 case). The DH had not received any case of adverse drug reaction related to lixisenatide. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 20 June 2019, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Taiwan: Announcement on the amendments of the guiding principle of the drug products containing the valproates for the usage in female

On 24 June 2019, the Taiwan Food and Drug Administration announced that in light of the recent review from overseas regarding the valproates for epilepsy, migraine, or bipolar disorder treatment, on the risk of foetal developmental disorder or birth defect, in women with child-bearing potential, it made the decision to amend the guidance in relation to the drug use in female patients.

In Hong Kong, there are 10 registered pharmaceutical products containing valproic acid and/or valproate, and all products are prescription-only medicines. As of 5 July 2019, the DH had received 9 cases of adverse drug reaction related to valproic acid or valproate, but these cases are not related to adverse effects of foetal developmental disorder, or a pregnant woman bearing a child with birth defect.

Related news on the recent review of valproate was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since the Issue No. 90, with the latest update in Issue No. 107. The DH issued letters to inform local healthcare professionals to draw their attention on 12 Feb 2018.

In Dec 2014, the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the findings of a previous review of European Medicines Agency (EMA) on the risk of valproate products in pregnancy and had decided that warnings and precautions on the risk of pregnancy should be included in valproate products. In December 2018, the Registration Committee decided that for valproate-containing products indicated for the treatment of epilepsy, migraine, or bipolar disorder in women with child-bearing potential, the actual sales label and/or package insert of the products should include the relevant warnings of the risk. Subsequently, on 21 June 2019, the Registration Committee issued letters to request the Certificate Holders of the relevant registered pharmaceutical products to implement risk minimization measures, to provide the healthcare professionals and the patients with educational materials regarding the relevant risk of the drug, and to reinforce the message of the risk of teratogenicity or foetal developmental disorder.

The DH will keep vigilant on safety updates of

valproate from other overseas drug regulatory authorities.

Canada: Opdivo (nivolumab) and Yervoy (ipilimumab) used alone, or in combination - Assessing the potential risk of Hemophagocytic Lymphohistiocytosis (HLH)

On 24 June 2019, Health Canada announced that it had completed a safety review of the risk of Hemophagocytic Lymphohistiocytosis (HLH - a condition where a large number of immune cells attack and destroy other blood cells) associated with the use of Opdivo (nivolumab) and/or Yervoy (ipilimumab) following reports of HLH published in medical literature. The review concluded that there may be a link between the use of these products and the development of HLH.

HLH is a life-threatening overreaction of the immune system where a large number of immune cells attack and destroy other blood cells. HLH is characterized by a large release of certain proteins by immune cells in the blood (referred to as a "cytokine storm" or "cytokine release syndrome"), as well as the accumulation of activated immune cells (lymphocytes and macrophages) in organs and tissues.

In the safety review, the Health Canada found that:
- The use of Opdivo and Yervoy (alone or in combination) is known to cause a range of immune-related side effects.
- At the time of the review, Health Canada had received 1 Canadian report of a cancer patient who developed HLH after treatment with Opdivo, in combination with Yervoy. This report was considered serious and involved death.
- Health Canada also looked at 21 international reports of HLH following treatment with Opdivo and Yervoy, either used alone or in combination. All reports were considered serious, and 6 of the 21 involved death.
- Health Canada could not confirm whether the use of Opdivo or Yervoy was the cause of the reported deaths in the Canadian or the international reports.
- Health Canada also looked at the scientific and medical literature. The articles reviewed suggest that there may be a link between the use of drugs that are in the PD-1 inhibitors class (such as Opdivo), and the development of HLH.
- Health Canada's assessment could not rule out a link between Opdivo and Yervoy and the development of HLH.

Health Canada would work with the manufacturer to determine the appropriate changes to the product safety information; and encouraged consumers and healthcare professionals to report any adverse reactions related to the use of this, or other health products. It would continue to monitor safety information involving Opdivo and Yervoy, to identify and assess potential harms.

In Hong Kong, there are 2 registered pharmaceutical products containing nivolumab, namely OPDIVO CONCENTRATE FOR SOLUTION FOR INFUSION 40MG/4ML (HK-64231) and OPDIVO CONCENTRATE FOR SOLUTION FOR INFUSION 100MG/10ML (HK-64232); and 2 registered products containing ipilimumab, namely YERVOY CONCENTRATE FOR SOLUTION FOR INFUSION 50MG/10ML (HK63494) and YERVOY CONCENTRATE FOR SOLUTION FOR INFUSION 200MG/40ML (HK-63495); which are registered by Bristol-Myers Squibb Pharma (HK) Ltd, and are prescription-only medicines.

As of 5 July 2019, the DH had received 48 cases of adverse drug reaction for nivolumab and 12 cases for ipilimumab, but none of them were related to HLH. The DH will keep vigilant on the further safety updates from the other overseas drug regulatory authorities.

Canada: Summary Safety Review - Systemic fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin and norfloxacin)

On 27 June 2019, Health Canada announced that it had carried out a safety review of the potential risk of aortic aneurysm and aortic dissection with the use of fluoroquinolones. The safety review was triggered by published studies, including one study conducted in Canada.

An aortic dissection is a tear of the inside lining of the aorta, the major blood vessel that carries blood from the heart to the rest of the body. An aortic aneurysm is a balloon-like bulge in the wall of the

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aorta. A rupture of the aneurysm can cause bleeding and, in the most serious cases, may lead to death. Patients with an aortic aneurysm frequently do not show any symptoms and the aneurysm may not be diagnosed until it ruptures. Both aortic dissection and ruptured aneurysm can cause severe pain and death. While a tear and bulge can occur in any artery, they are most common in the aorta. High blood pressure (hypertension) and the build-up of plaques inside arteries (atherosclerosis) are major risk factors for aortic dissections and/or aneurysms

At the time of the review, Health Canada received 28 international published reports, and 4 Canadian reports of aortic aneurysms and dissections with the use of fluoroquinolones. Of the Canadian reports, 3 were further assessed as they met the criteria defined for the review. One report showed a possible link between aortic aneurysm and the use of levofloxacin. The other 2 cases could not be assessed due to insufficient information.

Health Canada also looked at the scientific literature and focused on 4 published studies. Although there were limitations to these studies, they showed an approximately two-fold increased risk of aortic aneurysm and dissection in patients treated with fluoroquinolones, including one Canadian study.

The review has concluded that there may be a link between the use of systemic fluoroquinolones (given by mouth, by injection, or by inhalation) and aortic aneurysm and dissection. Given the frequent use of fluoroquinolones in Canada and the information reviewed, these side effects are considered rare.

Health Canada recommended that the product safety information for all systemic fluoroquinolone products be updated to include information about this rare but serious adverse effect. In addition, it will inform Canadians and healthcare professionals of this new safety information; and is working with the manufacturers to update the product safety information of all systemic fluoroquinolone products marketed in Canada.

In Hong Kong, there are 180 registered pharmaceutical products containing fluoroquinolones which are oral preparations or injectables for use in human, including ciprofloxacin (79 products), levofloxacin (60 products), moxifloxacin (6 products), norfloxacin (6 products), ofloxacin (28 products) and prulifloxacin (1 product). All products are prescription-only medicines. As of 5 July 2019, the DH had received 6 cases of adverse drug reaction related to levofloxacin and 1 case related to moxifloxacin, but these cases are not related to aortic aneurysm and dissection.

Related news related to aortic aneurysm and aortic dissection was previously issued by various overseas drug regulatory authorities; and was reported in the Drug News Issue Nos. 109 and 110. The DH issued letters to inform local healthcare professionals to draw their attention on 15 Nov 2018. In June 2019, the Registration Committee of the Pharmacy and Poisons Board decided that the sales pack labels and/or package inserts of registered pharmaceutical products containing fluoroquinolones for systemic use should be updated and include the warnings for the risk of aortic aneurysm and dissection. The DH will keep vigilant on other safety updates from other overseas drug regulatory authorities.

Drug Recall

DH endorsed batch recall of Maalox Plus Tablet (HK-01550)

On 28 June 2019, the DH endorsed a licensed drug wholesaler, SANOFI-AVENTIS HONG KONG LTD (Sanofi), to recall one batch (batch number: U319) of Maalox Plus Tablet (HK-01550) each box containing 40 tablets from the market because of mislabeling of the manufacturing date on the outer sales pack.

The DH received notification from Sanofi that the repackaging company in Singapore mislabeled the manufacturing date of the product to MFG 08/2108 instead of MFG 08/2018. According to the preliminary investigation by the manufacturer,

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other batches are not affected by the issue. Other information on the label of this batch is also correct.

The above product, containing aluminium hydroxide, magnesium hydroxide and simeticone, is a non-prescription medicine used for the treatment of gastro-intestinal disease. According to Sanofi, the affected batch of product has been supplied to the private hospitals and doctors. As of 5 July 2019, the DH had not received any adverse reaction report in connection with the affected batch of the product. A notice was posted on the Drug Office website on 28 June 2019 to alert the public of the product recall.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap. 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap. 137) and the maximum penalty is a $30,000 fine and one year's imprisonment for each offence.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordnance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.
Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 3904 1224

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920

Fax: 2319 6319

E-mail: adr@dh.gov.hk

Link: http://www.drugoffice.gov.hk/adr.html

Post: ***Pharmacovigilance Unit,***
Drug Office, Department of Health,
Rm 1856, 18/F, Wu Chung House,
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The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.