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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 July 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 - Propofol-containing products - Assessing the potential risk of prolonged erection of the penis (priapism)

On 12 July 2019, Health Canada initiated a safety review to evaluate the available information regarding the potential risk of priapism with the use of propofol-containing products. These products are used to make a patient relaxed, calm or sleepy (sedation) or unconscious (anesthesia) during surgery or medical procedures.

Priapism is a prolonged, and usually painful, erection of the penis not caused by sexual stimulation. It is a rare, but potentially serious, medical condition. Failure to treat this condition promptly may result in permanent disability, such as the inability to get and keep an erection firm enough for sex (erectile dysfunction).

Health Canada's review was triggered by a Canadian report of priapism in a patient that was sedated with a propofol-containing product for a medical procedure.

Propofol-containing products are prescription drugs which are authorized for sale in Canada and used by health care professionals to make a patient (adult or child) relaxed, calm or sleepy (sedation) or unconscious (anesthesia) during surgery or medical procedures.

Health Canada's review found that there may be a link between propofol-containing products and the risk of priapism.

Health Canada had already approved the addition of

the risk of priapism to the Canadian product information for Diprivan 1%. Health Canada would notify the manufacturers of other propofol-containing products to update the Canadian product safety information to inform Canadians and health care professionals about this potential safety issue.

Health Canada would continue to monitor safety information involving propofol-containing products, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada would take appropriate and timely action if and when any new health risks are identified.

In Hong Kong, there are 8 registered pharmaceutical products containing propofol. All these products are prescription only medicines. As of 5 August 2019, the DH had received 2 cases of adverse drug reactions, but were not related to priapism. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 15 July 2019, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Rivaroxaban (Xarelto▼): reminder that 15 mg and 20 mg tablets should be taken with food

On 17 July 2019, Medicines and Healthcare products Regulatory Agency (MHRA) announced that it had received a small number of reports suggesting lack of efficacy (thromboembolic events) in patients taking 15 mg or 20 mg rivaroxaban on an empty stomach. The MHRA

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reminded patients to take 15 mg or 20 mg rivaroxaban tablets with food.

Clinical trials of rivaroxaban showed that food intake does not affect absorption of 2.5 mg or 10 mg tablets, while absorption of 20 mg tablets was optimal when taken with high-fat, high-calorie meal. For this reason, rivaroxaban 15 mg and 20 mg tablets are to be taken with food.

The MHRA had received a small number of reports of patients taking rivaroxaban 15 mg or 20 mg who experienced a thromboembolic event, which the reporter suspected was due to the patient taking the tablets on an empty stomach.

The section of the Patient Information Leaflet for rivaroxaban 15 mg and 20 mg tablets that advised patients how to take their medicine had been revised to emphasise patients must take rivaroxaban with a meal and the tablets should be swallowed preferably with water.

Healthcare professionals are advised:

- Remind patients to take rivaroxaban 15 mg or 20mg tablets with food.
- For patients who have difficulty swallowing, tablets can be crushed and mixed with water or apple puree immediately before taking; this mixture should be immediately followed by food.
- Rivaroxaban 2.5 mg and 10 mg tablets can be taken with or without food.

In Hong Kong, there are 6 registered pharmaceutical products containing rivaroxaban, namely Xarelto Tab 10mg (HK-57861), Xarelto Tab 20mg (HK-61395), Xarelto Tab 15mg (HK-61396), Xarelto Tablets 20mg (Italy) (HK-65785), Xarelto Tablets 10mg (Italy) (HK-65786) and Xarelto Tablets 15mg (Italy) (HK-65787). All products are registered by Bayer Healthcare Limited, and are prescription-only medicines. As of 5 August 2019, the DH had received 20 cases of adverse drug reaction related to rivaroxaban, but these cases were not related to lack of efficacy. The package insert of the 15mg and 20mg local products already advises patients to take the tablets with food. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

The United Kingdom: Febuxostat (Adenuric): increased risk of cardiovascular death and all-cause mortality in clinical trial in patients with a history of major cardiovascular disease

On 17 July 2019, the MHRA announced that findings from a phase 4 clinical study (the CARES study) in patients with gout and a history of major cardiovascular disease show a higher risk for cardiovascular-related death and for all-cause mortality in patients assigned to febuxostat than in those assigned to allopurinol.

The CARES study (ClinicalTrials.gov NCT01101035) was a phase 4, randomised, double-blind, non-inferiority trial that recruited patients with gout and a history of major cardiovascular disease from the USA, Canada and Mexico. The primary endpoint was time to first occurrence of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and unstable angina with urgent coronary revascularisation. Outcomes analysis was for patients who had received at least 1 dose of the randomly allocated treatment.

Overall 57% of patients prematurely discontinued trial treatment and 45% of patients did not complete all trial visits; 6,190 patients were followed for a median of 32 months. The median duration of exposure was 728 days for patients in febuxostat group (n=3,098) and 719 days in allopurinol group (n=3,092). The primary MACE endpoint occurred at similar rates in the febuxostat and allopurinol treatment groups (10.8% versus 10.4% of patients, respectively; hazard ratio 1.03, 95% confidence interval [CI] 0.87–1.23).

In secondary analysis, the incidence of cardiovascular deaths was higher in the group assigned to febuxostat than in the group assigned to allopurinol (4.3% versus 3.2%, respectively; hazard ratio 1.34, 95% CI 1.03–1.73). The incidence of all-cause mortality was also higher in patients assigned to febuxostat than in those assigned to allopurinol (7.8% versus 6.4% respectively; hazard ratio 1.22, 95% CI 1.01–1.47), which was mainly driven by the higher rate of cardiovascular deaths in the febuxostat group.

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A European Union (EU) review of the findings of the CARES study and their impact on the safety of febuxostat recommended avoiding febuxostat in patients with a history of major cardiovascular disease. A letter had been sent to relevant healthcare professionals. The Summary of Product Characteristics and Patient Information Leaflet was being updated to reflect the CARES study results.

Healthcare professionals are advised:

- Avoid treatment with febuxostat in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options are appropriate.
- Note the clinical guidelines for gout, which recommend treatment with febuxostat only when allopurinol is not tolerated or contraindicated.

Patients taking febuxostat are advised to contact their healthcare professional if they are concerned about their medicine.

In Hong Kong, there are 2 registered pharmaceutical products containing febuxostat, namely Feburic Tablets 80mg (HK-61185) and Feburic Tablets 120mg (HK-61186). Both products are registered by Astellas Pharma Hong Kong Company Limited, and are prescription-only medicines. As of 5 August 2019, the DH had received one case of adverse drug reaction related to febuxostat, but this case was not related to death. Related news was previously issued by the United States Food and Drug Administration, and was reported in the Drug News Issue Nos. 97 and 112. The DH issued letters to inform local healthcare professionals to draw their attention on 22 Feb 2019. In June 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and noted that the package insert of the local products had already included the relevant safety information. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Singapore: Risk of non-melanoma skin cancer associated with use of hydrochlorothiazide

On 24 July 2019, Health Sciences Authority (HSA)

announced that it had issued a letter, in consultation with its Product Vigilance Advisory Committee, to update healthcare professionals on the outcome of its review regarding the risk of non-melanoma skin cancer (NMSC) associated with hydrochlorothiazide (HCTZ) use. The HSA was working with the companies to strengthen the local package inserts of HCTZ-containing products to warn of the potential risk of the NMSC.

In Hong Kong, there are 97 registered pharmaceutical products containing hydrochlorothiazide, and all products are prescription-only medicines. As of 5 August 2019, the DH had received 3 cases of adverse drug reaction related to hydrochlorothiazide, but these cases were not related to skin cancer. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue Nos. 109, 111 and 113. The DH issued letters to inform local healthcare professionals to draw their attention on 15 Nov 2018. In April 2019, the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the matter, and decided that the DH to be vigilant on any related safety updates by other overseas drug regulatory authorities. In light of the above HSA's announcement, the matter will be further discussed by the Registration Committee.

European Union: Updated restrictions for Gilenya: multiple sclerosis medicine not to be used in pregnancy

On 26 July 2019, European Medicines Agency (EMA) announced that the multiple sclerosis medicine Gilenya (fingolimod) must not be used in pregnant women and in women able to have children but not using effective contraception. If a woman becomes pregnant while using Gilenya, the medicine must be stopped and the pregnancy will have to be closely monitored. This is because the active substance in Gilenya, fingolimod, can harm the unborn baby and may cause birth defects.

To minimise this risk, women able to have children must have a pregnancy test before starting treatment with Gilenya to ensure they are not pregnant, and must use effective contraception during treatment and for two months after stopping

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the medicine.

These recommendations follow a review triggered by reports suggesting that the risk of birth defects in infants who have been exposed to Gilenya during pregnancy is twice as high as the 2 to 3% risk observed in the general population. The most frequently reported birth defects in infants exposed to Gilenya were those affecting the heart, kidneys, bones and muscles.

Advice to the Patients

- They must not take the multiple sclerosis medicine Gilenya if they are pregnant or if they are able to have children but not using effective contraception.
- This is because Gilenya may harm the unborn baby if used during pregnancy. If they use Gilenya during pregnancy, their children could be at higher risk of birth defects, in particular those affecting the heart, kidneys, bones and muscles.
- They must use effective contraception while taking Gilenya. If they are taking Gilenya and are planning to have a baby, they should talk to the doctor first. Before trying for a baby, they must stop taking Gilenya and wait for at least two months. During these two months, they must still use contraception.
- If they do become pregnant while taking Gilenya, they should tell the doctor straight away. Their doctor will stop the Gilenya treatment and carry out extra tests to monitor the pregnancy.
- The doctor will talk to the patients about the risk before starting and during treatment with Gilenya, and will give the patients a card with information on why they should not become pregnant while taking Gilenya, and what they should do to avoid becoming pregnant while taking this medicine.
- If they are female patients able to have children and just starting treatment with Gilenya, they will first need to have a pregnancy test to make sure that they are not pregnant.
- If they have any questions about Gilenya or the risks it poses to the unborn child, they should talk to their doctor, nurse or pharmacist.

Advice to the Healthcare Professionals

- Due to the risk of congenital malformations in fetuses exposed to fingolimod in utero, Gilenya is now contraindicated in pregnant women and in women of childbearing potential not using effective contraception.
- For women of childbearing potential, ensure that:
 - i) patients are informed of the risk of harmful effects to the fetus associated with fingolimod treatment;
 - ii) a negative pregnancy test result is available before treatment initiation;
 - iii) effective contraception is used during treatment and for 2 months after treatment discontinuation;
 - iv) fingolimod treatment is stopped 2 months before planning a pregnancy.
- If a woman becomes pregnant during treatment, Gilenya must be discontinued and the patient should be given medical advice about the risk of harmful effects to the fetus. The pregnancy should be closely monitored, and ultrasonography examinations should be performed.

These updated recommendations follow a review of available data triggered by post-marketing reports suggesting that infants born to mothers treated with fingolimod during pregnancy have a two-fold increased risk of major congenital malformations compared with the rate observed in the general population (which is 2-3 %, according to EUROCAT - the European network of population-based registries for the epidemiological surveillance of congenital anomalies).

The most frequently reported major malformations in infants exposed to fingolimod in utero are congenital heart diseases (such as atrial and ventricular septal defects, tetralogy of Fallot), renal abnormalities and musculoskeletal abnormalities.

In Hong Kong, Gilenya Hard Capsules 0.5mg (HK-61192) is a pharmaceutical product registered by Novartis Pharmaceuticals (HK) Limited, and is a prescription-only medicine. As of 5 August 2019, the DH had received 5 cases of adverse drug reaction related to fingolimod, but these cases were not related to birth defects. In light of the above EMA's announcement, the DH issued letters to

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inform local healthcare professionals to draw their attention on 29 July 2019; and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

United States: Xeljanz, Xeljanz XR (tofacitinib): Drug Safety Communication - Due to an Increased Risk of Blood Clots and Death with Higher Dose

On 26 July 2019, the United States Food and Drug Administration (FDA) announced that it had approved new warnings about an increased risk of blood clots and of death with the 10 mg twice daily dose of Xeljanz, Xeljanz XR (tofacitinib), which is used in patients with ulcerative colitis. In addition, the approved use of tofacitinib for ulcerative colitis would be limited to certain patients who are not treated effectively or who experience severe side effects with certain other medicines. The FDA approved these changes, including adding the most prominent Boxed Warning, after reviewing interim data from an ongoing safety clinical trial of tofacitinib in patients with rheumatoid arthritis (RA) that examined a lower and this higher dose of the medicine.

Tofacitinib works by decreasing the activity of the immune system; an overactive immune system contributes to RA, psoriatic arthritis (PsA), and ulcerative colitis. Tofacitinib was first approved in 2012 to treat adult patients with RA who did not respond well to the medicine methotrexate. When FDA first approved tofacitinib in 2012, FDA required a post-marketing clinical trial in patients with RA on background methotrexate, to evaluate the risk of heart-related events, cancer, and infections. The trial is studying two different doses of tofacitinib (5 mg twice daily, which is the currently approved dose for RA, and a higher, 10 mg twice daily dosage) in comparison to a tumour necrosis factor (TNF) blocker. In RA, the body attacks its own joints, causing pain, swelling, and loss of function. An interim analysis of the trial's results found an increased occurrence of blood clots and of death in patients treated with tofacitinib 10 mg twice daily compared to patients treated with tofacitinib 5 mg twice daily or a TNF blocker. In 2017, the FDA approved the medicine to treat patients with a second condition that causes joint

pain and swelling, PsA, who did not respond well to methotrexate or other similar medicines. In 2018, the FDA approved tofacitinib to treat ulcerative colitis, which is a chronic, inflammatory disease affecting the colon.

Advice to the Patients

- Patients should tell the health care professionals if they have a history of blood clots or heart problems, and any other questions or concerns.
- Stop taking tofacitinib and seek emergency medical attention right away if they experience any unusual symptoms, including those that may signal a blood clot such as:
 - Sudden shortness of breath
 - Chest pain that worsens with breathing
 - Swelling of a leg or arm
 - Leg pain or tenderness, or red or discolored skin in the painful or swollen leg or arm
- Do not stop taking tofacitinib without first talking to the healthcare professional, as doing so can worsen the patients' condition.

Advice to the Healthcare Professionals

- Healthcare professionals should discontinue tofacitinib and promptly evaluate patients with symptoms of thrombosis.
- Counsel patients about the risks and advise them to seek medical attention immediately if they experience any unusual symptoms, including those of thrombosis listed above.
- Reserve tofacitinib to treat ulcerative colitis for patients who have failed or do not tolerate tumor necrosis factor (TNF) blockers.
- Avoid tofacitinib in patients who may have a higher risk of thrombosis.
- When treating ulcerative colitis, use tofacitinib at the lowest effective dose and limit the use of the 10 mg twice daily dosage to the shortest duration needed.

In Hong Kong, Xeljanz Tablets 5mg (HK-63303) and Xeljanz XR Extended Release Tablets 11mg (HK-66141) are registered pharmaceutical products containing tofacitinib. Both products are registered by Pfizer Corporation Hong Kong Limited, and are prescription-only medicines. As of 5 August 2019, the DH had received 3 cases of adverse drug reaction related to tofacitinib, but these cases were

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not related to blood clots. Related news was previously issued by various drug regulatory authorities, and was reported in the Drug News Issue No. 112. In light of the recent FDA's announcement, the DH issued letters to inform

local healthcare professionals to draw their attention on 29 July 2019; and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

DH endorsed batch recall of HOSPIRA DOCETAXEL INJECTION 20MG / 2ML

On 17 July 2019, the DH endorsed a licensed drug wholesaler, PFIZER CORPORATION HONG KONG LIMITED (PFIZER), to recall one batch (batch number: DC11805C) of HOSPIRA DOCETAXEL INJECTION 20MG/2ML (Hong Kong Registration number: HK-60801) from the market because of a potential quality issue.

The DH received notification from PFIZER that during routine stability testing of the above product, the manufacturer found that the level of an impurity of the above batch may exceed the acceptable level at the end of shelf-life. Although the testing result indicated that the batch was still within specification, PFIZER recalled the batch of product as a precautionary measure. According to the preliminary investigation by the manufacturer, other batches are not affected by the issue.

The above product, containing docetaxel, is a prescription medicines used for the treatment of various cancers. According to PFIZER, the affected batch of product has been supplied to a few private doctors.

As of 5 August 2019, the DH has 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 17 July 2019 to alert the public of the product recall.

DH endorsed batch recall of SLITone Ultra oral solution

On 26 July 2019, the DH endorsed a licensed drug wholesaler, KSENA HEALTHCARE LTD (KSENA), to recall 18 batches (batch numbers: from 000918049957 to 000918049974) of SLITone Ultra oral solution from the market because of product mix-up during the packaging process.

The DH received notification from KSENA that, the manufacturer had reported the above batches of product may contain another product after investigating into a complaint. The above product contains liquid allergen extracts and is used for the treatment of allergic disease. The product was prepared for the treatment of individual patients; and with oral liquids containing specific allergen extracts that are packed as required by the medical practitioners. Each box (containing 90 small bottles of oral liquid) has a unique batch number. It was found that the above batches of the product may contain bottles of oral liquid with different allergen extracts. According to the manufacturer, such mix-up was introduced during the packaging process. As a precautionary measure, KSENA recalled all 18 batches of the product.

The above product is not a registered pharmaceutical product in Hong Kong but was imported for the treatment of particular patients by registered medical practitioners. As of 5 August 2019, no report of adverse events in relation to the use of the above products was received. A notice was posted on the Drug Office website on 26 July 2019 to alert the public of the product recall.

Drug Incident

Man arrested for suspected illegal sale of unregistered pharmaceutical product

On 25 July 2019, the DH and the Police conducted

a joint operation, during which a 62-year-old man was arrested for suspected illegal sale of an unregistered pharmaceutical product and Part 1 poison.

Drug Incident

Acting upon intelligence, the DH purchased a sample of a topical product named Xingfuhuli Plant Essential Oil at a retail stall in Ap Lei Chau for analysis. Test results from the Government Laboratory revealed that the sample contained diclofenac, which is a Part 1 poison controlled under the Pharmacy and Poisons Ordinance (Cap 138).

Diclofenac is a non-steroidal anti-inflammatory drug which can be used topically to relieve pain. It should

be supplied at pharmacies under the supervision of a registered pharmacist. Inappropriate use of diclofenac may cause erythema and dermatitis. Pharmaceutical products should be used under the advice of healthcare professionals.

Press release was posted on the Drug Office website on 25 July 2019 to alert the public of the drug incident.

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 accordance 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.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

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,
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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.