Drug News
藥 物 情 報

Issue Number 140

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in June 2021 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

Australia: Zostavax vaccine: Safety measures to address risk of infection with the vaccine virus

On 2 June 2021, Therapeutic Goods Administration (TGA) announced that it has required new warnings for Zostavax vaccine to address the risk of fatal disseminated vaccine strain varicella zoster virus infection. A new boxed warning has been added to the Product Information (PI) with information about managing this risk, including pre-screening and risk-based assessment prior to use of the vaccine, and management of suspected cases. A corresponding warning has also been added to the Consumer Medicine Information (CMI) for Zostavax.

The sponsor of Zostavax, Seqirus, is also required to implement the following activities:

- Provide a Patient Alert Card to health professionals to give to each patient receiving Zostavax.
- Provide refrigerator stickers to all providers of Zostavax to place on the fridge in which the medicine is stored.
- Send letters to inform health professionals of the content of the boxed warning statement.
- Update the current Risk Management Plan and Periodic Safety Update Reports to include consideration of this risk.

The TGA has been closely monitoring reports of disseminated vaccine strain varicella zoster infection and has published several safety alerts in response to three deaths related to this condition following vaccination with Zostavax. Investigation of this safety concern has found that the benefits of Zostavax continue to outweigh the risks, but additional risk mitigation is required.

Information for health professionals:
The PI for Zostavax has been updated with the following boxed warning:

- Rarely, disseminated varicella zoster virus (VZV) infection with vaccine (Oka) strain can occur in patients following administration of the live-attenuated Zostavax vaccine. There have been fatal reports of disseminated vaccine-related VZV infection in Australia, including in patients on low dose immunosuppressive medication. The risk increases with the degree of immunosuppression.
- Zostavax is contraindicated in patients with current or recent severe immunocompromising conditions from either a primary or acquired medical condition or medical treatment.
- Careful pre-screening and a risk-based assessment is required prior to administration of any dose of Zostavax. If appropriate, this assessment should include medical specialist consultation and potentially screening for pre-existing antibody to VZV. In such cases, vaccination should be deferred until such advice and/or results have been obtained.
- The Australian Immunisation Handbook contains specific guidance about Zostavax administration in patients who are immunocompromised or have medical conditions that place them at risk of immunocompromise. If uncertain about a person's level of immunocompromise and whether vaccination is safe, do not vaccinate and seek further specialist advice.
- Any patient who experiences a disseminated vesicular (chickenpox-like) rash 2 to 4 weeks after vaccine administration, or who feels unwell or has a fever, should seek medical attention immediately and ensure that their treating health professional is aware of their recent vaccination history.
- If inadvertent vaccination in an immunosuppressed patient has occurred, the patient should be advised regarding the potential for disseminated VZV infection and

the need to seek medical advice should symptoms suggestive of this occur, so that they can be considered for pre-emptive antiviral therapy.
- If a recent Zostavax recipient is suspected of having disseminated VZV infection, the healthcare professional should: conduct appropriate diagnostic testing early in consultation with a clinical microbiologist or infectious diseases physician; where appropriate, initiate appropriate empiric antiviral therapy whilst awaiting test results; where feasible, cease immunosuppression in consultation with their treating specialist.

In Hong Kong, Zostavax For Vaccine (HK-55419) is a pharmaceutical product registered by Merck Sharp & Dohme (Asia) Ltd, and is a prescription-only medicine. As on 5 July 2021, the Department of Health (DH) has received 6 cases of adverse events following immunisation with Zostavax, but none of them involved death. Related news was previously issued by TGA. The current local product insert includes information on "Do not administer Zostavax to individuals who are immunodeficient or immunosuppressed due to disease or therapy, as serious or fatal disseminated vaccine strain varicella-zoster virus disease may occur." In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 2 June 2021 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: Summary Safety Review: Dopamine agonists: Assessing the potential risk of dopamine agonist withdrawal syndrome

On 8 June 2021, Health Canada announced that it reviewed the potential risk of dopamine agonist withdrawal syndrome (DAWS) with the use of the dopamine agonists apomorphine, bromocriptine, cabergoline, pergolide, pramipexole, quinagolide, ropinirole and rotigotine following a manufacturer-initiated Canadian Product Monograph (CPM) update to include DAWS under the Warnings and Precautions section for Mirapex (pramipexole). DAWS may occur after reducing the dose of or stopping some dopamine agonists, and includes symptoms such as apathy, anxiety, depression, fatigue, sweating, panic attacks, insomnia, irritability and pain.

Health Canada reviewed information from Canadian and international databases of reported adverse reactions, as well as from the scientific literature. Health Canada reviewed 23 case reports (2 Canadian and 21 international) of DAWS in patients treated with dopamine agonists. The 21 international cases included 5 cases reported to the Canada Vigilance database, and 16 that were only available through the scientific literature. Three cases of DAWS were found to be probably linked to the use of pramipexole, 5 cases were possibly linked, and 2 cases (1 Canadian) could not be further assessed due to insufficient information. One case was found to be probably linked with the use of quinagolide. Five cases were found to be possibly linked with the use of ropirinole, and 2 cases could not be further assessed due to insufficient information. One case of DAWS was found to be possibly linked to the use of bromocriptine and pramipexole taken together. Two cases, 1 with cabergolide and pergolide taken together and the other with pramipexole and ropirinole taken together, could not be further assessed due to lack of information. In 2 cases (1 Canadian), patients were taking pramipexole, ropinirole and rotigotine separately at different times. For these cases, a probable link was found with the use of pramipexole and a possible link was found with the use of ropirinole. The use of rotigotine and the risk of DAWS could not be further assessed due to missing information.

Health Canada's review of the available information has established a link between the use of pramipexole, quinagolide or ropinirole and the risk of DAWS. The CPM for pramipexole has been updated to include a warning on the risk of DAWS. Health Canada will work with the manufacturers of quinagolide and ropinirole to update their CPMs to also include a warning about this safety issue.

At this time, there is not enough information to establish a link between apomorphine, bromocriptine, cabergoline, pergolide or rotigotine and DAWS. As a precaution, Health Canada will work with the manufacturers of these products to include the potential risk of DAWS in their CPMs to raise awareness among healthcare professionals that DAWS has been observed for other members of the dopamine agonist drug class, and encourage reporting of this potential safety issue.

In Hong Kong, there are registered pharmaceutical products containing apomorphine (3 products), bromocriptine (5 products), cabergoline (1 product), pramipexole (13 products), quinagolide (3 products), ropinirole (12 products)

and rotigotine (4 products). All products are prescription-only medicines. There is no registered pharmaceutical product containing pergolide. As on 5 July 2021, the DH has not received any case of adverse drug reaction related to the above dopamine agonists. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 9 June 2021 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

European Union: Conclusion of signal of sinus bradycardia with Veklury

On 11 June 2021, the European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended a change to the product information for Veklury (remdesivir) to include sinus bradycardia (heart beats more slowly than usual) as an adverse reaction of unknown frequency for this medicine.

The committee reviewed all the available data on rare reported cases of bradycardia in patients who received Veklury as well as data from clinical trials and the scientific literature. The PRAC concluded that a causal relationship between the use of the medicine and this adverse event is at least a reasonable possibility and recommended a change in the product information to raise awareness among healthcare professionals. The majority of events of sinus bradycardia resolved a few days after the treatment with Veklury was discontinued.

In Hong Kong, there is one registered pharmaceutical product containing remdesivir, namely Veklury Powder for Concentrate for Solution for Infusion 100mg (HK-66766). The product is registered by Gilead Sciences Hong Kong Limited, and is a prescription-only medicine. The product is indicated for SARS-CoV-2 Infection and is conditionally approved with very limited safety, efficacy, and quality data for public health emergency to satisfy local unmet medical need and the registration status is subjected to be reviewed by the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee.

As on 5 July 2021, the DH has received one case of adverse drug reaction related to remdesivir, and this case is related to hypotension.

Related news on the safety signal of sinus bradycardia in patients taking remdesivir was previously issued by EMA, and was reported in the Drug News Issue No. 136. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 15 June 2021 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

European Union: PRAC concludes review of signal of increased risk of major cardiovascular events and cancer with Xeljanz

On 11 June 2021, EMA announced that the PRAC has recommended an update to the product information for Xeljanz (tofacitinib) to include a new recommendation for its use. The committee has concluded its review of a safety signal regarding major adverse cardiovascular events and cancer (excluding non-melanoma skin cancer). The evidence is gathered from a recent study (A3921133) on this medicine conducted in patients who were 50 years of age or older with at least one additional cardiovascular risk factor. The PRAC is reminding healthcare professionals to carefully evaluate a patient's individual benefit-risk profile when deciding to prescribe or continue the treatment with Xeljanz (tofacitinib).

Xeljanz (tofacitinib) is used to treat adults with moderate to severe rheumatoid arthritis (inflammation of the joints), psoriatic arthritis (red, scaly patches on the skin with inflammation of the joints) and ulcerative colitis (inflammation and ulcers of the colon and rectum).

Final results from a recently completed study (A3921133) showed an increased risk of major adverse cardiovascular events and cancer in some patients, compared with TNF-alpha inhibitors (other medicines for rheumatoid arthritis). The PRAC is therefore advising healthcare professionals that Xeljanz (tofacitinib) should only be used in patients over 65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors, if no suitable treatment alternative is available.

In Hong Kong, there are 3 registered pharmaceutical products containing tofacitinib, namely Xeljanz Tablets 5mg (HK-63303), Xeljanz XR Extended Release Tablets 11mg (HK-66141) and Xeljanz Tablets 10mg (HK-66833). All

products are registered by Pfizer Corporation Hong Kong Limited, and are prescription-only medicines. As on 5 July 2021, the DH has received 8 cases of adverse drug reaction related to tofacitinib, of which one case is related to lung cancer.

Related news on the risk of serious heart-related problems and cancer of tofacitinib was previously issued by various overseas drug regulatory authorities, was reported in the Drug News Issue No. 136, 137 and 138. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 15 June 2021 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Australia: Sertraline and microscopic colitis

On 23 June 2021, TGA announced that the Product Information (PI) documents for sertraline have been updated to include microscopic colitis as a potential adverse effect of unknown frequency based on post -marketing experience.

Microscopic colitis is now included in the list of 'Gastrointestinal disorders' in the 'Adverse effects (Post-marketing experience)' section in Australian sertraline PI documents. Microscopic colitis is a type of inflammatory bowel disease. It is characterised by non-bloody, watery diarrhoea. Other symptoms may include faecal urgency, incontinence and nocturnal episodes. There are two different types of microscopic colitis - lymphocytic colitis and collagenous colitis. They present with the same symptoms but differences are found on histological examination. Diagnosis requires a biopsy.

Similar information about microscopic colitis has been added to product information in Europe based on a recommendation from the EMA after reviewing pharmacovigilance data and the medical literature.

In Australia, to 20 May 2021, there are six cases of microscopic colitis suspected to be related sertraline reported to the TGA and included in the Database of Adverse Event Notifications (DAEN). Of these, five were described as lymphocytic colitis and one as collagenous colitis.

Diarrhoea is listed as a very common adverse reaction associated with sertraline and occurs in at least 10% of people who start taking the medicine. If diarrhoea is severe or prolonged, microscopic colitis should be taken into consideration.

In Hong Kong, there are 20 registered pharmaceutical products containing sertraline, and all products are prescription-only medicines. As on 5 July 2021, the DH has received 2 cases of adverse drug reaction related to sertraline, but these cases are not related to microscopic colitis. In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 23 June 2021, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Australia: Updated contraception advice for tamoxifen

On 23 June 2021, TGA announced that the recommended duration of contraception after finishing tamoxifen treatment has been extended from two months to nine months. This means women should continue their contraception and not become pregnant for at least nine months after tamoxifen therapy has ended.

Tamoxifen is contraindicated in pregnancy and the possibility of pregnancy should be excluded before treatment is started. Women of child-bearing potential should be advised to use barrier or other non-hormonal contraceptive methods if they are sexually active, both during treatment and for nine months after treatment has ended. Women should be informed about the potential risks to the foetus, should they become pregnant while taking tamoxifen or within nine months of finishing treatment.

The Australian pregnancy category for tamoxifen remains unchanged - Category B3. A small number of reports of spontaneous abortions, birth defects and foetal deaths have occurred after women have taken tamoxifen, although no causal relationship has been established.

This change is based on the United States Food and Drug Administration guidance for genotoxic pharmaceuticals which recommends a minimum contraception period of six months plus five elimination half-lives after cessation of therapy.

In Hong Kong, there are 13 registered pharmaceutical products containing tamoxifen, and all products are prescription-only medicines. As on 5 July 2021, the DH has received 10 cases of

adverse drug reaction related to tamoxifen, but these cases are not related to abortions, birth defects and foetal deaths. In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 23 June 2021, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: Summary Safety Review: Kadcyla (trastuzumab emtansine): Assessing the potential risk of tumor lysis syndrome

On 24 June, 2021, Health Canada announced that it reviewed the potential risk of tumor lysis syndrome with the use of Kadcyla. The review was triggered by reports of suspected tumor lysis syndrome in patients using Kadcyla that were provided by the manufacturer.

Tumor lysis syndrome is a potentially life-threatening condition that can occur during cancer treatment. When cancer cells are killed by the cancer treatment, they release their contents (salts and proteins) into the blood. When cancer cells break down faster than the kidneys can remove these substances from the blood, it can cause changes to the chemical balance in the blood, which may result in damage to organs, most commonly the kidneys, heart and brain.

Health Canada reviewed information received from the manufacturer, as well as information from searches of the Canada Vigilance Database, international databases and published literature. Health Canada reviewed 17 cases (10 Canadian and 7 foreign) of tumor lysis syndrome in patients treated with Kadcyla. Of the 17 cases, 4 Canadian cases were found to be unlikely linked to the use of Kadcyla. The remaining 13 cases (6 Canadian and 7 foreign) did not have enough information in the reports for further review. It was difficult to establish a link between tumor lysis syndrome and Kadcyla use due to missing information or the presence of other contributing factors (chemotherapy treatment and underlying medical conditions) in the 17 cases. At the time of the review, Health Canada did not find any reports in the scientific literature to support a link between tumor lysis syndrome and Kadcyla use.

Health Canada's review of the available information could not confirm a link between the use of Kadcyla and the risk of tumor lysis syndrome in Canada. At the time of this review, Health Canada found the available information for Kadcyla related to this risk in Canada too limited to warrant regulatory action. Health Canada has asked the manufacturer for additional information about the risk of tumor lysis syndrome related to the use of Kadcyla in Canada and in other jurisdictions, and will review this information to determine if any measures are needed at that time.

In Hong Kong, Kadcyla Powder For Concentrate For Solution For Infusion 160mg (HK-63486) and Kadcyla Powder For Concentrate For Solution For Infusion 100mg (HK-63487) are registered pharmaceutical products containing trastuzumab emtansine. Both products are registered by Roche Hong Kong Limited, and are prescription-only medicines. As on 5 July 2021, the DH has received 29 cases of adverse drug reaction related to trastuzumab emtansine, but these cases are not related to tumor lysis syndrome. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

The United States: Coronavirus (COVID-19) Update: Moderna and Pfizer-BioNTech COVID-19 vaccines: increased risks of myocarditis and pericarditis

On 25 June 2021, The US Food and Drug Administration (FDA) announced revisions on the patient and provider fact sheets for the Moderna and Pfizer-BioNTech COVID-19 vaccines regarding the suggested increased risks of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the tissue surrounding the heart) following vaccination. For each vaccine, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) has been revised to include a warning about myocarditis and pericarditis and the Fact Sheet for Recipients and Caregivers has been revised to include information about myocarditis and pericarditis. This update follows an extensive review of information and the discussion by Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices meeting on Wednesday. The data presented at this meeting reinforced the FDA's decision to revise the fact sheets and further informed the specific revisions. The warning in the Fact Sheets for Healthcare Providers Administering Vaccines notes that reports of adverse events suggest increased risks of myocarditis and pericarditis, particularly following the second dose and with onset of symptoms within a few days after

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vaccination. Additionally, the Fact Sheets for Recipients and Caregivers for these vaccines note that vaccine recipients should seek medical attention right away if they have chest pain, shortness of breath, or feelings of having a fast-beating, fluttering, or pounding heart after vaccination.

In Hong Kong, the above products are not registered pharmaceutical products under the Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). Related news was previously issued by the EMA and Health Canada. The DH issued letters to inform local healthcare professionals to draw their attention on 28 June 2021. The DH will remain vigilant on safety update of the product issued by other overseas drug regulatory authorities.

Drug Recall

Recall of three batches of Losartan-Teva Tablet 50mg

On 30 June 2021, the DH endorsed a licensed drug wholesaler, Teva Pharmaceutical Hong Kong Limited (Teva), to recall three batches (batch numbers: 0480918, 0681118, and 0760120) of Losartan-Teva Tablet 50mg (Hong Kong Registration Number: HK-58863) from the market as a precautionary measure due to the presence of an impurity in the product.

The DH received today notification from Teva of the finding by the overseas manufacturer of the product that the active pharmaceutical ingredient of the above batches contain a higher than accepted level of azido impurity. According to Teva, the three affected batches have been imported and supplied in Hong Kong. As a precautionary measure, Teva is voluntarily recalling those batches from the market.

Azido impurity is considered a mutagen that can cause a change in the DNA of a cell and may increase the risk of cancer, although the risk for the azido impurity to cause cancer in humans is unknown. Overseas drug regulatory authorities have been reviewing the safety impact of azido impurity found in medicinal products. The DH will closely monitor the development of the issue and any safety updates regarding the drug issued by overseas drug regulatory authorities for consideration of any action deemed necessary.

The above product is a prescription medicine used to lower blood pressure. According to Teva, the affected batches have been supplied to clinics of the DH, private clinics and community pharmacies. As on 5 July 2021, the DH has not received any adverse reaction reports in connection with the product. Press release was posted the Drug Office website on 30 June 2021 to alert the public of the product recall.

Drug Incident

Public urged not to buy or consume slimming products with undeclared banned ingredient

On 23 June 2021, the DH appealed to members of the public not to buy or consume a slimming product named 2WEEKS as it was found to contain an undeclared and banned Western drug ingredient that might be dangerous to health.

Acting upon intelligence, a local seller was found offering for sale the above slimming product via a social media platform. A sample of the product was obtained for analysis and the Government Laboratory's results confirmed that the sample contained sibutramine, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138). The DH's investigation is continuing.

Sibutramine was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of increased cardiovascular risk.

Press release was posted on the Drug Office website on 23 June 2021 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 $50,000 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: Adverse Drug Reaction and Adverse Event Following Immunization Unit,
Drug Office, Department of Health,
Room 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wanchai, Hong Kong

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.