Drug News
藥 物 情 報

Issue Number 118

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

US: FDA review finds no increased risk of prostate cancer with Parkinson's disease medicines containing entacapone (Comtan, Stalevo)

On 13 August 2019, the United States (US) Food and Drug Administration (FDA) announced that its review of additional data found no increased risk of prostate cancer with the use of entacapone to treat Parkinson's disease. The FDA conducted this review after an earlier trial suggested this possible risk. As a result, its recommendations for using Comtan (entacapone) and Stalevo (a combination of entacapone, carbidopa, and levodopa) will remain the same in the prescribing information.

The FDA alerted the public in March 2010 that it was aware of a clinical trial suggesting a possible increased risk of prostate cancer with the entacapone component of Stalevo. The FDA subsequently required the Stalevo manufacturer, Novartis, to conduct a study to further evaluate this potential risk. The FDA also studied this issue independently using data from the Department of Veterans Affairs healthcare system. Based on these additional studies, the FDA concluded that entacapone use is not associated with an increased risk of prostate cancer.

Healthcare professionals should follow standard prostate cancer screening recommendations for patients. Patient and caregivers should continue to take their medicine as prescribed and talk to their healthcare professionals if they have any questions or concerns.

In Hong Kong, there are 12 registered pharmaceutical products containing entacapone, and all products are prescription only medicines. As of 5 September 2019, the Department of Health (DH) has not received any case of adverse drug reaction (ADR) related to entacapone. Related news was previously issued by the US FDA, and was reported in the Drug News Issue No. 6. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

UK: Carfilzomib (Kyprolis▼): reminder of risk of potentially fatal cardiac events

On 19 August 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that anti-cancer therapy with carfilzomib has been associated with cases of cardiac arrest, cardiac failure, and myocardial infarction, including in patients without pre-existing cardiac disorders.

As included in the Summary of Product Characteristics in the UK, carfilzomib has been associated with new or worsening cardiac failure, decreased ejection fraction, pericarditis, atrial fibrillation, tachycardia, myocardial ischaemia, and myocardial infarction. Death due to cardiac arrest has occurred within a day of carfilzomib administration and fatal outcomes have also been reported following cardiac failure and myocardial infarction.

The MHRA recently received a report from a Coroner following death by cardiac arrest of a man given carfilzomib, cyclophosphamide, and dexamethasone in a clinical trial. The Pharmacovigilance Expert Advisory Committee of the Commission on Human Medicines considered

the safety profile for carfilzomib and risks of cardiac reactions. The Committee advised that warnings about risks in the product information of carfilzomib are clear but emphasised the need for prescribers to be reminded of the risk.

Since 2013 and up to July 2019, 5 cases of cardiac failure, 5 of arrhythmia, 3 of cardiac arrest, 2 of pericarditis, 2 of left ventricular failure, and 5 of myocardial infarction, of which 6 were fatal (including the Coroner's case), have been reported in the UK in post-marketing settings and in clinical trials in patients administered carfilzomib. Some of the patients in these cases did not report pre-existing cardiac disorders.

Healthcare professionals are advised:

- Cases of cardiac arrest, cardiac failure, and myocardial infarction, including fatal cases, have been reported in patients receiving anti-cancer therapy with carfilzomib – not all cases occurred in patients with a pre-existing cardiac disorder.
- Monitor patients for signs and symptoms of cardiac disorders before and during treatment with carfilzomib.
- Stop carfilzomib if severe or life-threatening cardiac events occur. Restarting treatment may be considered at a lower dose once the condition is controlled and the patient is functionally stable.

In Hong Kong, there are 2 registered pharmaceutical products containing carfilzomib, namely Kyprolis for Injection 60mg/vial (HK-64828) and Kyprolis for Injection 30mg/vial (HK-65431). Both products are registered by Amgen Hong Kong Limited, and are prescription only medicines. As of 5 September 2019, the DH has received 16 cases of ADR related to carfilzomib, of which 2 cases are related to heart failure and one case is related to cardiac dysfunction. Special warnings about the risk of cardiac disorders and precautions for use are included in the product insert of the above local products. In light of the above MHRA's announcement, the DH issued a letter to remind local healthcare professionals to draw their attention on 20 August 2019. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

EU: New measures to avoid potentially fatal dosing errors with methotrexate for inflammatory diseases

On 23 August 2019, the European Medicines Agency (EMA) of the European Union (EU) announced that it has recommended new measures to prevent serious and potentially fatal errors with the dosing of methotrexate for treating inflammatory diseases such as rheumatoid arthritis, psoriasis and Crohn's disease. The recommendations result from a review of reports that patients are using methotrexate incorrectly despite previous measures to prevent errors.

For inflammatory conditions, methotrexate must be used just once a week. Using methotrexate more frequently than intended can result in serious side effects. The review found that the error in dosing frequency can occur at any step from prescribing the medicine to the patient taking it.

The new measures to prevent errors include restricting who can prescribe these medicines, making warnings on the packaging more prominent and providing educational materials for patients and healthcare professionals. In addition, to help patients follow the once-weekly dosing, methotrexate tablets will be provided in blister packs and not in bottles (or tubes). The measures were agreed after consultation with patients and healthcare professionals.

Information for patients

- If they are taking methotrexate for rheumatoid arthritis, psoriasis or Crohn's disease, they must take it just once a week.
- Take the methotrexate medicine on the same day every week.
- Follow the instructions on the packaging of the methotrexate medicine.
- They will receive a patient card with the methotrexate tablets (or oral liquid). Read it carefully because it tells them how to take the medicine.
- Show their patient card to any new healthcare professional who treats them so that new healthcare professionals know that they take their methotrexate medicine once a week.
- See their doctor at once if they get a sore throat, fever, mouth ulcers, diarrhoea,

vomiting, skin rashes, bleeding or unusual weakness. These can be signs of taking too much methotrexate.
- Always attend their scheduled clinic visits and blood test appointments to make sure that the methotrexate medicine is working and that it is not causing any concern.
- If they are not sure about how to take the methotrexate medicine or they have any questions about it, talk to their doctor or pharmacist.

Healthcare professionals should follow these recommendations:
- Methotrexate for inflammatory conditions is intended for use just once a week. Serious side effects including fatalities have occurred when methotrexate is taken more often.
- Only physicians with expertise in using methotrexate medicines should prescribe them.
- Healthcare professionals who prescribe or dispense methotrexate for inflammatory conditions should:
  - read the educational materials for oral methotrexate medicines;
  - ensure that they are familiar with the latest changes to the summaries of product characteristics for methotrexate medicines used for inflammatory conditions;
  - give clear instructions to the patient (or carer) about once-weekly dosing;
  - check carefully that the patient (or carer) understands that the medicine must be used once a week, and do this each time a new prescription is issued or the medicine is dispensed;
  - decide together with the patient (or carer) on which day of the week the patient uses methotrexate;
  - counsel the patient (or carer) about signs of methotrexate overdose and give instructions to promptly seek medical advice in case of suspected overdose.

In Hong Kong, there are 18 registered pharmaceutical products containing methotrexate (including 6 products in oral form and 12 parenteral products). All these products are prescription only medicines. As of 5 September 2019, the DH has received 39 cases of ADR related to methotrexate, but they were not reported to be related to dosing errors. Related news was previously issued by the EMA, and was reported in the Drug News Issue No. 102. In light of the above EMA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 26 August 2019. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

US: FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease

On 28 August 2019, the US FDA announced that it has received reports that the use of Mavyret (a fixed-dose combination of glecaprevir and pibrentasvir), Zepatier (a fixed-dose combination of elbasvir and grazoprevir), or Vosevi (a fixed-dose combination of sofosbuvir, velpatasvir, and voxilaprevir) to treat chronic hepatitis C in patients with moderate to severe liver impairment has resulted in rare cases of worsening liver function or liver failure. All these medicines contain a hepatitis C virus protease inhibitor and are not indicated for use in patients with moderate to severe liver impairment. In most patients, symptoms resolved or new onset worsening of liver function improved after stopping the medicine. These medicines have been widely used and are safe and effective in patients with no or mild liver impairment.

In many of the reported cases, liver failure occurred in patients who had signs and symptoms of moderate to severe liver impairment (Child-Pugh B or C) or other serious liver problems and should not have been treated with these medicines. In some cases, patients were reported to have no cirrhosis or compensated cirrhosis with mild liver impairment (Child-Pugh A) despite having evidence of decreased platelets at baseline or an increase in the pressure within the portal vein that carries blood from the digestive organs to the liver. In addition, some cases had other significant pre-existing risk factors such as liver cancer, alcohol abuse, or serious medical illnesses associated with serious liver problems. These factors may have contributed to clinical worsening of liver function or liver

failure during treatment with these hepatitis C medicines. In most cases, liver failure or decompensation typically occurred within the first 4 weeks of starting treatment. The FDA will continue to monitor this safety concern and will communicate any new information to the public if it becomes available.

Healthcare professionals should continue to prescribe Mavyret, Zepatier, or Vosevi as indicated in the prescribing information for patients without liver impairment or with mild liver impairment (Child-Pugh A). Assess severity of liver disease at baseline and closely monitor for signs and symptoms of worsening liver function such as increases in liver enzymes, jaundice, ascites, encephalopathy, and variceal hemorrhage. Assessment of baseline liver disease and close monitoring are especially important in those with pre-existing significant liver problems or risk factors, such as hepatocellular carcinoma or alcohol abuse, which can also contribute to clinical worsening of liver function or liver failure during treatment. Discontinue these medicines in patients who develop signs and symptoms of liver decompensation or as clinically indicated.

Patients should be aware that the risk of serious liver injury is rare. However, they should contact their healthcare professional right away if they develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools as these may be signs of liver injury. If they have liver impairment or other pre-existing risk factors that can worsen liver function such as a history of alcohol abuse, they should talk with their healthcare professional about the benefits and risks of the medicine.

In Hong Kong, Maviret Tablets (HK-65653) is registered by Abbvie Limited, Zepatier Tablets (HK-65571) is registered by Merck Sharp & Dohme (Asia) Ltd, and Vosevi Tablets (HK-65775) is registered by Gilead Sciences Hong Kong Limited. All products are prescription only medicines. As of 5 September 2019, the DH has received 5 cases of ADR related to glecaprevir/ pibrentasvir, of which one case is related to alanine aminotransferase increased and hyperbilirubinaemia. In light of the above FDA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 29 August 2019. The DH will continue to remain vigilant on safety update of the drugs issued by the FDA and other overseas drug regulatory authorities for consideration of any action deemed necessary.

UK: Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping

On 30 August 2019, the MHRA announced that new data have confirmed that the risk of breast cancer is increased during use of all types of HRT, except vaginal estrogens, and have also shown that an excess risk of breast cancer persists for longer after stopping HRT than previously thought. Prescribers of HRT should discuss the updated total risk with women using HRT at their next routine appointment.

Systemic HRT is taken orally or applied under or via the skin (as gels or patches [transdermal]) for the relief of vasomotor or related symptoms of the menopause. For women with an intact uterus, progestogen is normally added to estrogen for the prevention of adverse endometrial effects such as hyperplasia and cancer.

On 29 August 2019, a new meta-analysis of participant data from the Collaborative Group on Hormonal Factors in Breast Cancer was published in The Lancet. The analysis included 108,647 cases of breast cancer in prospective studies. The study included long-term follow-up of women who did not use HRT and those who discontinued HRT, mostly in the early 2000s. Among women with complete information, mean HRT duration was 10 years in current users and 7 years in past users.

Key findings of the study include:

- All forms of systemic HRT are associated with a significant excess incidence of breast cancer, irrespective of the type of estrogen or progestogen or route of delivery (oral or transdermal).
- There is little or no increase in risk with current or previous use of HRT for less than 1 year; however, there is an increased risk with

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HRT use for longer than 1 year.

- Risk of breast cancer increases further with longer duration of HRT use.
- Risk of breast cancer is lower after stopping HRT than it is during current use, but remains increased in ex-HRT users for more than 10 years compared with women who have never used HRT.
- Risk of breast cancer is higher for combined estrogen-progestogen HRT than estrogen-only HRT.
- For women who use HRT for similar durations, the total number of HRT-related breast cancers by age 69 years is similar whether HRT is started in her 40s or in her 50s.
- The study found no evidence of an effect on breast cancer risk with use of low doses of estrogen applied directly via the vagina to treat local symptoms.

Healthcare professionals are advised:

- A new meta-analysis of more than 100,000 women with breast cancer has shown that some excess risk of breast cancer with systemic HRT persists for more than 10 years after stopping; the total increased risk of breast cancer associated with HRT is therefore higher than previous estimates.
- Prescribers of HRT should inform women who use or are considering starting HRT of the new information about breast cancer risk at their next routine appointment.
- Only prescribe HRT to relieve post-menopausal symptoms that are adversely affecting quality of life and regularly review patients using HRT to ensure it is used for the shortest time and at the lowest dose.
- Remind current and past HRT users to be vigilant for signs of breast cancer and encourage them to attend for breast screening when invited.

In Hong Kong, HRT products are registered pharmaceutical products. As of 5 September 2019, the DH has not received any case of ADR related to the drugs. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 2 September 2019. The Drug Office will remain vigilant on safety updates of the drugs by other overseas health regulatory authorities.

Drug Incident

DH urged public not to buy or use topical product with undeclared controlled ingredient betamethasone dipropionate

On 16 August 2019, the DH appealed to the public not to buy or use a topical product (no English name on the package, Chinese name: 百植坊皮膚膏) as it was found to contain an undeclared controlled drug ingredient.

Acting on a public complaint, the DH purchased a sample of the above product via a social media platform for analysis. Test results from the Government Laboratory revealed that the product contained betamethasone dipropionate, which is a Part 1 poison controlled under the Pharmacy and Poisons Ordinance (Cap. 138).

Betamethasone dipropionate is a steroid substance for treating inflammatory skin disorders. Inappropriate or excessive application of steroids could cause skin problems and body-wide side effects such as moon face (facial swelling), high blood pressure, high blood sugar, skin atrophy, adrenal insufficiency and osteoporosis. Products containing betamethasone dipropionate should only be used under a doctor's directions and supplied by a pharmacy under the supervision of a registered pharmacist upon a doctor's prescription.

Press release was posted on the Drug Office website on 16 August 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 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.

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

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Adverse Drug Reaction (ADR) Reporting:

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

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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.