Drug News
藥 物 情 報

Issue Number 128

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in June 2020 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

EU: Latest data support continued use of ACE inhibitors and ARB medicines during COVID-19 pandemic

On 9 June 2020, the European Medicines Agency (EMA) of the European Union (EU) announced that recent observational studies of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs, also called sartans) have not shown an effect of these medicines on the risk of becoming infected with severe acute respiratory syndrome coronavirus 2 (the virus causing Coronavirus Disease 2019 (COVID-19)) and do not indicate a negative impact on the outcome for patients with COVID-19 disease.

The EMA therefore reiterates its previous advice that patients should continue to use ACE inhibitors or ARBs as advised by their doctors. Patients with questions or concerns about their treatment should consult a healthcare professional.

ACE inhibitors and ARBs are used for treating patients with high blood pressure, heart problems or kidney disease. In April 2020, media outlets and publications raised concerns about the effects of these medicines in patients with COVID-19. As part of the ongoing monitoring of the safety of medicines, 20 recently published studies on the use of ACE inhibitors and ARBs during the COVID-19 pandemic were reviewed and showed that these concerns are not supported by the latest clinical evidence.

In Hong Kong, there are registered pharmaceutical products containing angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), all products are prescription-only medicines. As on 6 July 2020, the Department of Health (DH) has received 36 cases of adverse drug reaction (ADR) related to agents acting on the renin-angiotensin system (including various ACE inhibitors and ARBs). The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

Canada: Ketamine - Assessing the potential risk of liver and bile duct damage

On 10 June 2020, Health Canada announced that it reviewed the potential risk of liver and bile duct damage with the use of ketamine-containing products after the French regulatory agency (Agence nationale de sécurité du médicament et des produits de santé) published a risk communication and updated product safety information for these products to include the risk of liver and bile duct damage. In Canada, ketamine-containing products are authorized for use by healthcare professionals to make patients unconscious (anesthesia) during surgery or medical procedures.

Health Canada reviewed information from searches of the Canada Vigilance database and international databases of published literature and clinical studies. Health Canada's assessment focused on 19 international epidemiologic studies conducted in many patients and 22 individual patient case reports (21 international and one Canadian) of liver and bile duct damages related to ketamine use.

The review of the 19 epidemiologic studies could not confirm or refute a link between the liver and/or bile duct damages and the use of ketamine due to various study method limitations, such as the presence of confounding factors, possibility of pre-existing liver damage prior to the use of ketamine, or a small number of participants in the study. Of the 22 individual case reports, one report was found to be probably linked to the use of ketamine, 17 reports were found to be possibly

linked; one report was not likely to be linked, and 3 reports did not have enough information to be assessed. Only one of the 22 case reports was from Canada where liver and bile duct damage was found to be possibly linked to the use of ketamine.

Findings from the epidemiologic studies and case reports showed that:

- The use of ketamine products for a few hours to many days may result in some chemical changes in the blood suggesting problems with liver function or the bile flow.
- The use of ketamine products for an extended period of time such as months to years may be linked to liver damage and enlargement of ducts that drain the bile.
- If a patient stops taking ketamine, the damage may be reversed.

Health Canada's review concluded that there is a potential link between the use of ketamine-containing products and damage to the liver and bile duct. If a patient stops taking ketamine, these damages may be reversed. Health Canada will work with manufacturers to update the product safety information of all ketamine-containing products in Canada to inform about this potential risk and advise treatment discontinuation with the first signs of liver or bile duct damage.

In Hong Kong, there are 4 registered pharmaceutical products containing ketamine for human use, all products are prescription-only medicines. As on 6 July 2020, the DH has received 21 cases of ADR related to ketamine, and these cases include liver and bile duct problems such as increase in alkaline phosphatase, hepatotoxicity or biliary dilatation, etc. The risk of abnormal liver function tests and dilated bile duct associated with the use of ketamine is documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference". The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

US: FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems: Update

On 15 June 2020, the United States (US) Food and Drug Administration (FDA) announced an update to its previous Drug Safety Communication about hydroxychloroquine and chloroquine. Based on ongoing analysis and emerging scientific data, the FDA has revoked the emergency use authorization (EUA) to use hydroxychloroquine and chloroquine to treat COVID-19 in certain hospitalized patients when a clinical trial is unavailable or participation is not feasible. The FDA made this determination based on recent results from a large, randomized clinical trial in hospitalized patients that found these medicines showed no benefit for decreasing the likelihood of death or speeding recovery. This outcome was consistent with other new data, including those showing the suggested dosing for these medicines are unlikely to kill or inhibit the virus that causes COVID-19. As a result, the FDA determined that the legal criteria for the EUA are no longer met.

In Hong Kong, there are 5 registered pharmaceutical products containing hydroxychloroquine, and all products are prescription-only medicines. There is no registered pharmaceutical product containing chloroquine. As on 6 July 2020, the DH has received 4 cases of ADR related to hydroxychloroquine, but these cases are not related to heart rhythm problems. The DH has not received any case of ADR related to chloroquine.

Related news on the risk of heart rhythm problems associated with the use of hydroxychloroquine and chloroquine was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 126 and 127. Adverse effects and precautions about heart rhythm problems associated with the use of hydroxychloroquine and chloroquine are documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference". The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

Canada: Xeljanz and Xeljanz XR (tofacitinib) and Jakavi (ruxolitinib) - Janus Kinase (JAK) inhibitors - Assessing the potential risk of blood clots in the deep veins (venous thromboembolic events)

On 18 June 2020, Health Canada announced that it reviewed the potential risk of venous thromboembolic events (VTE), including blood clots in the veins of the legs and arms (deep vein thrombosis) and blood clots in the lungs (pulmonary embolism), linked with the use of

Janus Kinase (JAK) inhibitors. This review was triggered by early results from an ongoing safety study for Xeljanz (tofacitinib).

Given that there were already serious warnings for VTE in the product safety information for Olumiant (baricitinib), another JAK inhibitor, the safety review focused on the safety findings of the other JAK inhibitors marketed in Canada at the time of the review, Xeljanz and Xeljanz XR (tofacitinib) and Jakavi (ruxolitinib).

The safety review found that an ongoing safety study for Xeljanz showed an increased risk of blood clots in the lungs and death when the drug was taken at a high dose of 10 mg twice a day. This study is being conducted in patients 50 years of age or older with rheumatoid arthritis and at least one cardiovascular risk factor.

Health Canada's assessment focused on 51 cases (8 Canadian and 43 international) of VTE in people taking Xeljanz/Xeljanz XR. Of the 51 cases, 38 were found to be possibly linked to Xeljanz/Xeljanz XR, 3 were not likely to be linked and 10 cases did not have enough information to be assessed. Among the 51 cases, there were 2 deaths possibly linked to the use of Xeljanz/Xeljanz XR. The patients described in the case reports also had inflammatory diseases that may increase the risk of VTE. Health Canada also assessed 8 Canadian cases of VTE in patients taking Jakavi. Of the 8 cases, 3 cases showed a possible link to Jakavi. Among the 8 cases, there was one death, but the report did not contain enough information to link the death to the use of Jakavi. The patients described in the case reports also had blood disorders that may increase the risk of VTE. The information available from the published literature did not provide case reports or information that linked VTE with the use of Xeljanz/Xeljanz XR and/or Jakavi.

Health Canada's review has concluded that there is a link between the risk of VTE and the use of Xeljanz. The review has concluded that Xeljanz/Xeljanz XR should be avoided in patients at increased risk of thrombosis and it should be discontinued in patients with signs of thrombosis. Xeljanz should be used at the lowest dose that works well and for the shortest duration in patients with ulcerative colitis. The product safety information for Xeljanz/Xeljanz XR in Canada has been updated to include this new safety information. Health Canada's review also found a possible link between Jakavi and VTE. Health Canada will be working with the manufacturer to update the product safety information for Jakavi in Canada to include the risk of VTE.

In Hong Kong, there are 2 registered pharmaceutical products containing tofacitinib, namely Xeljanz Tablets 5mg (HK-63303) and Xeljanz XR Extended Release Tablets 11mg (HK-66141) which are registered by Pfizer Corporation Hong Kong Limited; 4 products containing ruxolitinib, namely Jakavi Tab 20mg (HK-61972), Jakavi Tab 5mg (HK-61973), Jakavi Tab 15mg (HK-61974) and Jakavi Tablets 10mg (HK-66148) which are registered by Novartis Pharmaceuticals (HK) Limited; and 2 products containing baricitinib, namely Olumiant Tablets 2mg (HK-65663) and Olumiant Tablets 4mg (HK-65664) which are registered by Eli Lilly Asia, Inc. All products are prescription-only medicines.

As on 6 July 2020, the DH has received 7 cases of ADR related to tofacitinib, of which 3 cases are related to deep vein thrombosis. The DH has received 17 cases of ADR related to ruxolitinib, but these cases are not related to deep vein thrombosis or pulmonary embolism. The DH has not received any case of ADR related to baricitinib.

Related news on the risk of blood clots of tofacitinib was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 112, 117 and 125. The DH issued a letter to inform local healthcare professionals to draw their attention on 29 July 2019. In December 2019, the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the matter, and decided that the sales pack or package insert of tofacitinib should include the relevant safety information.

Related news on the risk of blood clots of baricitinib was previously issued by the United Kingdom Medicines and Healthcare products Regulatory Agency, and was reported in the Drug News Issue No. 125. The current local product inserts already contain safety information on the risk of venous thromboembolism.

In light of the risk of venous thromboembolic events associated with the use of ruxolitinib in the above Health Canada's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 19 June

Safety Update

2020, and the matter will be discussed by the Registration Committee.

Australia: Water for injection and haemolysis

On 24 June 2020, the Therapeutic Goods Administration (TGA) of Australia announced that health professionals are reminded that water for injection can cause haemolysis resulting in patient harm, including death, if large quantities are inadvertently administered intravenously without being rendered isotonic.

Water for injection, which is hypotonic, is indicated for dissolving or diluting injectable therapeutic substances for parenteral administration (where water is a suitable solvent). It is contraindicated for intravenous (IV) administration if it is not adjusted to isotonicity by the addition of suitable solutes.

The TGA is aware of international reports of mix-ups between 1 litre bags of water for injection and other 1 litre bags, including sodium chloride 0.9% and glucose 5%.

As with any therapeutic goods, water for injection products should always be used in strict accordance with all instructions for using the product. All registered injection products in Australia with a volume of 100 mL or more are required to include a statement on the label if the injection is hypotonic, hypertonic or isotonic.

Always carefully check the label to ensure there is no confusion between water for injection and other IV bags.

In Hong Kong, there are 11 registered pharmaceutical products containing only water for injection for human parenteral administration, and all products are prescription-only medicines. As on 6 July 2020, the DH has not received any case of ADR related to water for injection. Healthcare professionals should check the product label carefully and follow the product instructions accordingly.

Drug Recall

DH endorsed batch recall of Truxima Concentrate for Solution for Infusion 100mg/10ml (HK-66443) and 500mg/50ml (HK-66444)

On 29 June 2020, the DH endorsed a licensed medicine wholesaler, Kerry Pharma (Hong Kong) Limited (Kerry), to recall one batch each of Truxima Concentrate for Solution for Infusion 100mg/10ml (HK-66443) and 500mg/50ml (HK-66444) from the market due to misprinting of registration number on both products and wrong expiry date on the 100mg/10ml product. The products are registered in Hong Kong by Celltrion Healthcare Hong Kong Limited and distributed by Kerry.

The affected batches:

<u>For 100mg/10ml</u>
Registration Number: HK-66443 (misprinted as HK-66444)
Batch No.: 9C3C028
Manufacturing date: 2019-05-18
Expiry date: 2022-05-17 (misprinted as 2023-05-17)

<u>For 500mg/50ml</u>
Registration Number: HK-66444 (misprinted as HK-66443)
Batch No.: 9C8C103
Manufacturing date: 2019-06-07
Expiry date: 2023-06-06

The DH received notification from Kerry that, as informed by the manufacturer, the Hong Kong registration number for the above products were mistakenly swapped in the affected batches; the expiry date of the 100mg/10ml product was also wrongly printed. Although the quality of the products would not be affected by this misprinting, Kerry is recalling the affected batches from the market.

The above products, containing rituximab, are prescription medicines used in the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukemia. According to Kerry, the products have been supplied to private doctors.

Patients who have used the above products should seek advice from their healthcare professionals if in doubt.

As on 6 July 2020, the DH has not received any adverse reaction report in connection with the products. A notice was posted on the Drug Office website on 29 June 2020 to alert the public of the

Drug Recall

products recall.

Drug Incident

Public urged not to buy or consume slimming product with undeclared Western drug ingredient sibutramine

On 8 June 2020, the DH appealed to the public not to buy or consume a slimming product named Leisure Slimming Capsule as it was found to contain an undeclared and banned drug ingredient that might be dangerous to one's health.

Acting upon intelligence, a sample of the above product was purchased via a social media network platform for analysis. The test result from the Government Laboratory revealed that the sample contained the banned drug ingredient sibutramine.

Sibutramine is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138), which was once used as an appetite suppressant. Since November 2010, pharmaceutical products containing sibutramine have been banned in Hong Kong because of an increased cardiovascular risk.

Members of the public who have purchased the above product should stop consuming it immediately. They should consult healthcare professionals for advice if feeling unwell after consumption.

Weight control should be achieved through a balanced diet and appropriate exercise. The public should consult healthcare professionals before using any medication for weight control. They may visit the website of the Drug Office of the DH for "Health messages on overweight problem and slimming products" and "Information on slimming products with undeclared Western drug ingredients" for more information.

Press release was posted on the Drug Office website on 8 June 2020 to alert the public of the drug incident.

Regulation of Advanced Therapy Products

The Pharmacy and Poisons (Amendment) Bill 2019 was passed by the Legislative Council on 17 July 2020 and published in the Gazette as the Pharmacy and Poisons (Amendment) Ordinance 2020 on 24 July 2020. The purpose of the amendments is to regulate Advanced Therapy Products.

Advanced Therapy Products are innovative medical products based on genes, cells and tissues. They may offer great medical potential for benefiting patients. At the same time, due to their complicated nature and our limited knowledge and experience, the risks and long-term side effect of ATPs need to be carefully managed. In view of the high risks associated with the rapid scientific advancement, the new Amendment Ordinance is to introduce a clear regulatory framework on the clinical research and therapeutic use of ATPs in order to safeguard public health and facilitate their development. For details of the Pharmacy and Poisons (Amendment) Ordinance 2019, please refer to the letter to the healthcare professionals and the Gazette at the following link.

https://www.drugoffice.gov.hk/eps/upload/eps_news/40893/EN/1/DH%20Letter_HCP_20200724_en.pdf

The provisions of the Amendment Ordinance will come into operation on a day appointed by the Secretary for Food and Health by a notice published at the Gazette about one year later.

Advice to Health Professionals

Advice on handling of medicines in Telemedicine

It has come to our attention that Telemedicine (the practice of medicine over a distance, in which interventions, diagnoses, therapeutic decisions, and subsequent treatment recommendations are based on patient data, documents and other information transmitted through telecommunication systems) has become a more common practice of the medical profession in Hong Kong. In fact, the Medical Council of Hong Kong issued an Ethical Guidelines on Practice of Telemedicine in December 2019 to provide guidance to medical practitioners.

While the term “telemedicine” embraces a wide spectrum of activities, please be reminded that the supply of medicines should be in accordance with the relevant legislation which imposes restrictions

Advice to Health Professionals

on the sale and supply of medicines in Hong Kong, such as the Dangerous Drugs Ordinance, Cap. 134, Antibiotics Ordinance, Cap. 137 and Pharmacy and Poisons Ordinance, Cap. 138 and the relevant Code of Practice and Guidelines.

Further, the prescribers are advised to ensure the integrity of the medicines being delivered so that no mix up occurs as well as to ensure that the quality of the medicines being delivered are not adversely affected by temperature or humidity during their delivery.

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: ***Undesirable Medical Advertisements and Adverse Drug Reaction Unit,***
Drug Office, Department of Health,
Suites 2002-05, 20/F, AIA Kowloon Tower,
Landmark East, 100 How Ming Street,
Kwun Tong, Kowloon

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.