Drug News
藥 物 情 報

Issue Number 125

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

US: FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis

On 4 March 2020, the United States (US) Food and Drug Administration (FDA) announced that it is strengthening existing warnings about serious behavior and mood-related changes with montelukast (Singulair and generics), which is a prescription medicine for asthma and allergy.

The FDA is taking this action after a review of available information led it to reevaluate the benefits and risks of montelukast use. Montelukast prescribing information in the US already includes warnings about mental health side effects, including suicidal thoughts or actions; however, many healthcare professionals and patients/caregivers are not aware of the risk. The FDA decided a stronger warning is needed after conducting an extensive review of available information and convening a panel of outside experts, and therefore determined that a *Boxed Warning* was appropriate.

Because of the risk of mental health side effects, the benefits of montelukast may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with other medicines. For allergic rhinitis, also known as hay fever, the FDA has determined that montelukast should be reserved for those who are not treated effectively with or cannot tolerate other allergy medicines. For patients with asthma, the FDA recommends that healthcare professionals consider the benefits and risks of mental health side effects before prescribing montelukast.

Patients and parents/caregivers should stop montelukast and discuss with a healthcare professional right away if they or their child experience behavior or mood-related changes while taking the medicine. These may include: agitation (including aggressive behavior or hostility), attention problems, bad or vivid dreams, depression, disorientation or confusion, feeling anxious, hallucinations (seeing or hearing things that are not really there), irritability, memory problems, obsessive-compulsive symptoms, restlessness, sleepwalking, stuttering, suicidal thoughts and actions, tremor or shakiness, trouble sleeping, uncontrolled muscle movements. They should take montelukast for allergic rhinitis or hay fever only if they cannot tolerate other medicines or they do not work for them. Many other safe and effective allergy medicines are widely available. Talk to their pharmacist or healthcare professional for help deciding which might be best.

Healthcare professionals should consider the risks and benefits of montelukast when deciding to prescribe or continue patients on the medicine. Counsel all patients receiving montelukast about mental health side effects, and advise them to stop the medicine and contact a healthcare professional immediately if they develop any symptoms included but not limited to those listed above. Be aware that some patients have reported neuropsychiatric events after discontinuation of montelukast. Only prescribe montelukast for allergic rhinitis in patients who have an inadequate response or intolerance to alternative therapies.

The FDA reviewed case reports submitted to the FDA, conducted an observational study using data from the FDA's Sentinel System, and reviewed observational and animal studies in the published literature. Given the available information, the FDA also reevaluated the benefits and risks of use of montelukast. The FDA continues to receive reports of mental health side effects reported with montelukast use. Consistent with its prior

evaluations, a wide variety of mental health side effects have been reported, including completed suicides. Some occurred during montelukast treatment and resolved after stopping the medicine. Other reports indicated that mental health side effects developed or continued after stopping montelukast. The Sentinel study, which studied asthma patients 6 years and older, and other observational studies did not find an increased risk of mental health side effects with montelukast compared to inhaled corticosteroids. However, the Sentinel study and the observational studies had some limitations which may affect how the FDA interprets the results. The FDA also reviewed animal studies, which showed that montelukast given orally reaches the brain in rats.

Although new data regarding the risk of mental health side effects with montelukast are limited, the FDA decided to strengthen the warnings by requiring a *Boxed Warning*. Due to the wide availability of alternative safe and effective allergy medicines with long histories of safety, the FDA has reevaluated the risks and benefits of montelukast and has determined it should not be the first choice treatment particularly when allergic rhinitis symptoms are mild. In addition, many healthcare professionals and patients/caregivers are not aware of the risk of mental health side effects despite the existing warnings in the prescribing information.

In Hong Kong, there are 52 registered pharmaceutical products containing montelukast, and all products are prescription-only medicines. As on 6 April 2020, the Department of Health (DH) has received 3 cases of adverse drug reaction (ADR) related to montelukast, of which one case is related to neuropsychiatric events.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 119. The DH issued a letter to remind local healthcare professionals to draw their attention on 20 September 2019. In February 2020, the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the risk of neuropsychiatric reactions of montelukast, including speech impairment and obsessive-compulsive symptoms, and decided to remain vigilant on any related safety updates by other overseas drug regulatory authorities on this issue. In light of the above US FDA's announcement, the DH issued a letter to remind local healthcare professionals to draw their attention on 5 March 2020, and the matter will be further discussed by the Registration Committee.

Singapore: Smecta®: Restriction of treatment of acute diarrhoea to children >2 years of age and adults, and recommendation against use in pregnant and breastfeeding women

On 9 March 2020, the Health Sciences Authority (HSA) of Singapore announced that a Dear Healthcare Professional Letter has been issued by Emerging Pharma to inform healthcare professionals of changes to the use of Smecta® (dioctahedral smectite or diosmectite) in children and in pregnant and breastfeeding women.

Elements such as lead occur naturally in soil and trace amounts of these elements can be found in food and water. Naturally occurring diosmectite (the clay from which Smecta® is produced) contains trace amounts of lead too. In compliance with international guideline, the product owner of Smecta® (Ipsen) has conducted a data review and a clinical study which did not find evidence of any actual risk related to lead in adult patients with chronic diarrhoea treated with Smecta® for 5 weeks. Other data developed by Ipsen confirmed the safety profile of Smecta® in the children population with treatment duration of up to 7 days. As a precautionary measure and taking into consideration the lack of data in pregnancy and breastfeeding, Ipsen has decided to restrict the indication of Smecta® for treatment of acute diarrhoea to children 2 years of age and above and in adults, and to recommend against the use of Smecta® in pregnant and breastfeeding women.

In Hong Kong, there are 2 registered pharmaceutical products containing dioctahedral smectite, namely Smecta Sachet (HK-34268) which is registered by Beaufour Ipsen International (Hong Kong) Limited and Monotin Powder 3g/sachet (HK-58612) which is registered by Bright Future Pharmaceuticals Factory. As on 6 April 2020, the DH has not received any case of ADR related to dioctahedral smectite. In light of the above HSA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 20 March 2020. The DH will continue to remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

EU: New testing and treatment recommendations for fluorouracil, capecitabine, tegafur and flucytosine

On 13 March 2020, the European Medicines Agency (EMA) of the European Union (EU) announced that the EMA's safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), has recommended that patients should be tested for the lack of an enzyme called dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with medicines containing fluorouracil given by injection or infusion (drip) and the related medicines capecitabine and tegafur, which are converted to fluorouracil in the body.

As treatment for severe fungal infections with flucytosine (another medicine related to fluorouracil) should not be delayed, testing patients for DPD deficiency before they start treatment is not required.

No pre-treatment testing is needed for patients treated with topical fluorouracil (applied to the skin to treat various skin conditions).

Lack of a working DPD enzyme (up to 8% of the Caucasian population have low levels of a working DPD enzyme, and up to 0.5% completely lack the enzyme), which is needed to break down fluorouracil, causes fluorouracil to build up in the blood. This may lead to severe and life-threatening side effects such as neutropenia (low levels of neutrophils, a type of white blood cells needed to fight infection), neurotoxicity (damage to the body's nervous system), severe diarrhoea and stomatitis (inflammation of the lining of the mouth).

The PRAC assessed the available data and recommended the following measures to ensure the safe use of fluorouracil and fluorouracil-related medicines:

Fluorouracil, capecitabine and tegafur

Testing of patients for DPD deficiency is recommended before starting treatment with fluorouracil injection or infusion, capecitabine and tegafur. This can be done by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations (changes) in the gene for DPD which are associated with an increased risk of severe side effects. Relevant clinical guidelines should be taken into consideration.

Patients with a known complete DPD deficiency must not be given fluorouracil injection or infusion, capecitabine or tegafur, as a complete lack of working DPD puts them at higher risk of severe and life-threatening side effects.

For patients with a partial DPD deficiency, a reduced starting dose of these medicines should be considered; since the effectiveness of a reduced dose has not been established, following doses may be increased if there are no serious side effects. Regular monitoring of fluorouracil blood levels in patients receiving fluorouracil by continuous infusion could improve treatment outcome.

Pre-treatment testing or dose adjustments based on DPD activity are not needed for patients using topical fluorouracil. This is because the level of fluorouracil absorbed through the skin into the body is extremely low, and the safety of topical fluorouracil is not expected to change in patients with partial or complete DPD deficiency.

Flucytosine

Flucytosine is used to treat severe yeast and fungal infections, including some forms of meningitis (inflammation of the membranes that surround the brain and spinal cord). To avoid any delay in starting therapy, pre-treatment testing for DPD deficiency is not required.

Patients with a known complete DPD deficiency must not be given flucytosine, due to the risk of life-threatening side effects.

Patients with a partial DPD deficiency are also at increased risk of severe side effects. In case of side effects, the treating doctor should consider stopping treatment with flucytosine. Testing of DPD activity may also be considered, since the risk of severe side effects is higher in patients with a low DPD activity.

The prescribing information for doctors and patients in the EU will be updated to include the above recommendations.

In Hong Kong, there are 4 registered pharmaceutical products containing fluorouracil, 24 products containing capecitabine and 4 products containing tegafur. All products are prescription-only medicines. There is no registered pharmaceutical product containing flucytosine. As on 6 April 2020, the DH has received 91 cases of ADR related to fluorouracil, 53 cases related to

capecitabine and 1 case related to tegafur. The DH has not received any case of ADR on related to flucytosine.

Related news was previously issued by the EMA and was reported in the Drug News Issue No. 113. The DH issued a letter to inform local healthcare professionals to draw their attention on the EMA's announcement on starting review on screening patients before treatment with fluorouracil, capecitabine, tegafur and flucytosine on 18 March 2019. In light of the above EMA's announcement, the matter will be discussed by the Registration Committee.

UK: Esmya (ulipristal acetate): suspension of the licence due to risk of serious liver injury

On 18 March 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that, on 9 March 2020, the EMA started a review of Esmya following a new case of liver failure requiring liver transplant. This case occurred despite the patient and physician having adhered to measures that were put in place following a previous review to minimise the risk of liver injury, namely measuring liver function before and during treatment, and stopping treatment immediately in case of raised liver enzyme levels. This case is the fifth case of liver injury requiring liver transplant reported worldwide in women receiving Esmya.

To protect public health, marketing authorisations for all ulipristal acetate 5mg products for uterine fibroids will be suspended in the UK for the duration of the review. Patients currently taking Esmya for uterine fibroids should stop taking the medicine and no new patients should start treatment. The MHRA will communicate the recommendations of the review once finalised.

The MHRA has issued a recall of Esmya from pharmacies, wholesalers, and patients.

Since authorisation and to 18 March 2020, the MHRA has received 19 suspected ADR reports of liver disorders with the use of Esmya in the UK. None report liver transplant or death. Approximately 2,865 treatment courses of Esmya were dispensed in the UK in 2019.

The emergency contraceptive ellaOne also contains ulipristal acetate (single dose, 30mg). There are no concerns with this medicine at this time.

Healthcare professionals are advised:

- Contact patients currently being treated with Esmya as soon as possible and stop their treatment; discuss alternative treatment options for uterine fibroids as appropriate.
- Do not start any new patients on Esmya.
- Advise recent users to seek immediate medical attention if they develop signs and symptoms of liver injury (nausea, vomiting, malaise, right hypochondrial pain, anorexia, asthenia or jaundice).
- Perform liver function tests 2–4 weeks after stopping Esmya as recommended in the product information.

In Hong Kong, Esmya (ulipristal acetate) Tablets 5mg (HK-62553) is a pharmaceutical product registered by Orient Europharma Co. Ltd, and is a prescription-only medicine. As on 6 April 2020, the DH has not received any case of ADR related to Esmya.

Related news on the previous review of Esmya was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 98, 100, 103, 106 and 114. The DH issued a letter to inform local healthcare professionals to draw their attention on the risk of serious liver injury on 12 February 2018. In December 2018, the Registration Committee discussed the matter, and decided that the sales pack or package insert of the product should include the relevant safety information.

Related news on the recent review of Esmya was previously issued by the EMA and the HSA. The DH issued a letter to remind local healthcare professionals to draw their attention on 16 March 2020.

On 20 March 2020, the DH endorsed Orient Europharma Co. Ltd to voluntarily recall Esmya Tablets 5mg (HK-62553) from patients due to the potential risk of liver injury. Press release was posted on the Drug Office website on 20 March 2020 to alert the public of the product recall.

The DH will remain vigilant on the conclusion of the review and safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

UK: Tofacitinib (Xeljanz▼): new measures to minimise risk of venous thromboembolism and of serious and fatal infections

On 18 March 2020, the MHRA announced new measures to minimise risk of venous thromboembolism and of serious and fatal infections of tofacitinib.

In 2019, interim results from the ongoing study A3921133 prompted a European review into the benefits and risks of tofacitinib. Study A3921133 included patients aged 50 years or older with rheumatoid arthritis and an increased risk of cardiovascular disease. While the review was ongoing, the MHRA advised healthcare professionals of the potential risk of venous thromboembolism and temporary contraindications for the 10mg twice-daily dose of tofacitinib in patients with risk factors for pulmonary embolism.

Following the conclusion of the review, the interim contraindications communicated in May 2019 have been replaced with the measures outlined below. Venous thromboembolism is an uncommon reaction with tofacitinib treatment (up to 1 in 100 patents). Study A3921133 showed an increased risk of pulmonary embolism in this population with tofacitinib 5mg twice daily compared with tumor necrosis factor (TNF) inhibitors and an even greater risk with 10mg twice-daily. Incidence rates for deep vein thrombosis were also increased with tofacitinib. Risks of pulmonary embolism were further increased in patients with risk factors for venous thromboembolism.

In an ongoing extension trial to assess use of tofacitinib in ulcerative colitis, cases of pulmonary embolism and deep vein thrombosis were also observed in patients using tofacitinib 10mg twice-daily who had underlying venous thromboembolism risk factors.

New recommendations include:
- For any dose and in any indication, exercise caution when considering tofacitinib in patients who have known risk factors for venous thromboembolism, in addition to their underlying disease.
- Maintenance treatment for ulcerative colitis at the 10mg twice-daily dose is not recommended in patients with known risk factors for venous thromboembolism, unless there is no suitable alternative treatment.

Risk factors for venous thromboembolism include previous venous thromboembolism, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Other venous thromboembolism risk factors that should be considered include age, obesity (body-mass index $\geq$30 kg/m^2), diabetes, hypertension, and smoking status.

Tofacitinib is known to increase the risk of serious and fatal infections such as pneumonia, cellulitis, herpes zoster, and urinary tract infections. Existing advice contraindicates use of tofacitinib in patients with active infections, and advises healthcare professionals to consider the benefits and risks in patients with recurrent infections, a history of serious or opportunistic infection, or travel to areas of endemic mycoses, and in those who have underlying conditions that may predispose them to infection.

Study A3921133 showed incidence of non-fatal serious infections to be higher in patients with rheumatoid arthritis receiving tofacitinib than in those receiving a TNF inhibitor. The risk of serious infections and fatal infections was further increased in older patients aged 65 years or older, as compared to younger patients (aged 50–64 years).

Healthcare professionals are advised only to use tofacitinib in patients older than age 65 years if there is no alternative treatment.

Healthcare professionals are advised:

<u>Venous thromboembolism risk</u>
- Tofacitinib is associated with a dose-dependent increased risk of serious venous thromboembolism.
- Use caution in any patients with known risk factors for venous thromboembolism in addition to the underlying disease.
- In patients with ulcerative colitis who have known risk factors for venous thromboembolism in addition to the underlying disease, use of 10mg twice-daily tofacitinib for maintenance treatment is not recommended unless no suitable alternative treatment is available.
- Do not exceed the recommended dose of 5mg twice-daily (or 11mg prolonged-release once-daily) for rheumatoid arthritis or 5mg twice-daily for psoriatic arthritis in any patients.

<u>Vigilance for events and actions if they occur</u>
- Inform patients of the signs and symptoms of

venous thromboembolism before they start tofacitinib and advise them to seek prompt medical help if they develop signs such as a painful swollen leg, chest pain, or shortness of breath.
- Discontinue tofacitinib treatment permanently if signs of venous thromboembolism occur.

Infection risk
- Tofacitinib increases the risk of serious and fatal infections, with rates of infections greater in older patients.
- Only consider use of tofacitinib in patients older than 65 years if no suitable alternative treatment is available.

In the interim analysis of study A3921133 in patients with rheumatoid arthritis, mortality within 28 days of last treatment was increased in patients treated with tofacitinib compared with those treated with TNF inhibitors. Mortality was mainly due to cardiovascular events, infections, and malignancies.

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 on 6 April 2020, the DH has received 5 cases of ADR related to tofacitinib, of which one case is related to deep vein thrombosis and 3 cases are related to infections (pneumonia, cellulitis and disseminated tuberculosis).

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, 115, 117, 120 and 121. The DH issued a letter to inform local healthcare professionals to draw their attention on 29 July 2019. In December 2019, the Registration Committee discussed the matter, and decided that the sales pack or package insert of tofacitinib should include the relevant safety information. The current local package insert of the tofacitinib products also include caution on serious infections in the elderly population. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

UK: Baricitinib (Olumiant▼): risk of venous thromboembolism

On 18 March 2020, the MHRA announced the risk of venous thromboembolism of baricitinib.

In April 2017, clinical trial findings showed an imbalance in cases of deep vein thrombosis and pulmonary embolism with baricitinib treatment compared with placebo. The exposure-adjusted incidence rate for venous thromboembolism was 0 for placebo compared with 1.3 events per 100 patient-years of exposure for baricitinib 4mg. However, at the time a causal link could not be fully established due to the presence of confounding factors. Based on the data, a warning was added to recommend that baricitinib be used with caution in patients with risk factors for deep vein thrombosis and pulmonary embolism and that if patients experience signs of venous thromboembolism, treatment should be temporarily interrupted and patients should be evaluated promptly.

Following findings of an increased risk of pulmonary embolism in an ongoing study with another Janus kinase (JAK) inhibitor, tofacitinib, a recent European cumulative review reassessed the evidence for risk with baricitinib. The advice has now been updated to recommend discontinuation of baricitinib if clinical signs of venous thromboembolism occur.

Cumulatively, there have been 102 cases of venous thromboembolism events reported post-marketing worldwide since marketing. Some of these reports contained more than one thromboembolic event and within these cases there were 63 events of pulmonary embolism and 51 events of deep vein thrombosis. Cumulatively, as of 31 July 2019, there have been an estimated 95,100 patients exposed to baricitinib and 42,800 patient years of exposure. There was no consistent pattern in time to onset of venous thromboembolism (where provided) but most cases occurred between 6–12 months after initiation.

In one case, the patient continued baricitinib treatment after experiencing a deep vein thrombosis. It was later reported that the patient had a recurrent venous thromboembolism and subsequently a pulmonary embolism. Baricitinib treatment was then permanently discontinued.

Upadacitinib (Rinvoq▼) was recently approved for use in the EU. Deep venous thrombosis and pulmonary embolism events have been reported in patients taking upadacitinib. Like tofacitinib and baricitinib, upadacitinib should be used with

caution in patients at high risk for venous thromboembolism. If features of deep venous thrombosis and pulmonary embolism occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Healthcare professionals are advised:

- Clinical trial data show a greater frequency of venous thromboembolism events with baricitinib compared with placebo – deep vein thrombosis and pulmonary embolism events are considered to be uncommon with baricitinib (up to 1 in 100 patients).
- Use caution if considering baricitinib in patients with additional risk factors for deep vein thrombosis and pulmonary embolism, such as prior medical history of venous thromboembolism, surgery, immobilisation, older age, and obesity.
- Discontinue baricitinib treatment permanently if clinical features of venous thromboembolism occur.
- Advise patients undergoing treatment with baricitinib to seek urgent medical attention if they experience a painful swollen leg, chest pain, or shortness of breath.

In Hong Kong, Olumiant Tablets 2mg (HK-65663) and Olumiant Tablets 4mg (HK-65664) are registered pharmaceutical products containing baricitinib. Both products are registered by Eli Lilly Asia, Inc. (Eli Lilly), and are prescription-only medicines. As on 6 April 2020, the DH has not received any case of ADR related to baricitinib. The current local product inserts already contain safety information on the risk of venous thromboembolism. In February 2020, Eli Lilly submitted an application for updating the local product inserts to include the discontinuation of baricitinib if clinical signs of venous thromboembolism occur. The DH will continue to work with the company to update the relevant product information and remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

There is no registered pharmaceutical product containing upadacitinib.

UK: SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness

On 18 March 2020, the MHRA announced that sodium-glucose co-transporter 2 (SGLT2) inhibitor treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than urine.

A detailed European review in 2016 confirmed diabetic ketoacidosis, including euglycaemic diabetic ketoacidosis, as a rare risk for the SGLT2 inhibitor class of medicines. The review recommended healthcare professionals should inform patients on SGLT2 inhibitors of the risks of diabetic ketoacidosis and counsel them on risk factors and actions to take in case of signs and symptoms. Due to the risk of diabetic ketoacidosis, recommendations were added to the product information of these medicines to interrupt SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious medical illnesses and to not restart treatment until the patient's condition has stabilised.

In 2019 a new European review assessed reports of peri-operative diabetic ketoacidosis in patients taking SGLT2 inhibitors. The review recommended warnings be updated to include routine monitoring of ketones in patients hospitalised for surgery or acute illness. This approach aims to help identify patients who are at risk of developing (or are already in the early stages of) diabetic ketoacidosis, so that prompt corrective measure can be applied.

Testing of ketones in blood is recommended, rather than measuring ketone bodies in urine. The basis for this recommendation is that SGLT2 inhibitors may diminish the excretion of ketone bodies in the urine, thereby making urine measurement of ketone bodies less reliable than blood testing. The current Joint British Diabetes Society Inpatient Care Group national guideline for the management of diabetic ketoacidosis (2013) already recommends the use of blood ketone tests based on the measurement of β-hydroxybutyrate.

The review of the evidence did not identify a specific type of surgery as being linked to an increased risk of peri-operative diabetic ketoacidosis. In addition, there was insufficient evidence to make specific recommendations concerning peri-operative management such as a specific time-point to stop or restart SGLT2 inhibitor treatment or management of food intake and insulin use.

Diabetic ketoacidosis is a serious complication of

diabetes caused by low insulin levels. The 2016 EU review was triggered by rare cases of diabetic ketoacidosis in patients taking SGLT2 inhibitors for type 2 diabetes. In several reports of diabetic ketoacidosis assessed by the review, blood glucose levels were only moderately elevated. Therefore, updates to the product information advised healthcare professionals to test for raised ketones in patients taking SGLT2 inhibitors with signs and symptoms of ketoacidosis, even if plasma glucose levels are near-normal. The review recommended interrupting SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious illnesses and to not restart treatment until the patient's condition has stabilised. However, the advice did not specifically instruct prescribers to check or monitor ketones. Healthcare professionals were also advised to avoid restarting treatment with a SGLT2 inhibitor in patients who experienced diabetic ketoacidosis during use, unless another cause for the ketoacidosis was identified and resolved.

Healthcare professionals are advised:

- Interrupt SGLT2 inhibitor treatment in patients who are hospitalised for major surgical procedures or acute serious medical illnesses.
- Monitor ketones during this period – measurement of blood ketone levels is preferred to urine.
- Restart treatment with the SGLT2 inhibitor once ketone values are normal and the patient's condition has stabilised.

In Hong Kong, there are 23 registered pharmaceutical products containing SGLT2 inhibitors, including canagliflozin (4 products), dapagliflozin (5 products), empagliflozin (10 products) and ertugliflozin (4 products). All products are prescription-only medicines. As on 6 April 2020, the DH has received 3 cases of ADR of diabetic ketoacidosis related to SGLT2 inhibitors: dapagliflozin (1 case), canagliflozin (1 case) and empagliflozin (1 case).

Related news on the risk of diabetic ketoacidosis of SGLT2 inhibitors was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 67, 74, 76 and 105. In February 2017, the Registration Committee discussed the matter, and decided that the package insert of products containing SGLT2 inhibitors should include safety information on the risk of diabetic ketoacidosis.

In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 19 March 2020, and the matter will be discussed by the Registration Committee.

EU: No change is needed in use of direct oral anticoagulants following EMA-funded study

On 27 March 2020, the EMA announced that no change to the conditions of use of the direct oral anticoagulants (DOACs) Eliquis (apixaban), Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban) is needed following a review of the results of a European study of real-world data for these medicines.

The study, commissioned by the EMA and using real-world data from Denmark, France, Germany, Spain, the Netherlands and the UK, assessed the risk of serious bleeding with these 3 medicines when used to prevent blood clotting in patients with non-valvular atrial fibrillation (irregular rapid contractions of the heart) and compared this with other oral anticoagulants called vitamin K antagonists (VKAs).

The results were reviewed by the EMA's human medicines committee, Committee for Medicinal Products for Human Use (CHMP), in consultation with the PRAC, and were compared with data from other similar studies and in the published literature.

The EMA's review concluded that the pattern of serious bleeding seen in patients taking Eliquis, Pradaxa and Xarelto was similar to that seen in the clinical trials on which the authorisation of the medicines were based. The data were not sufficient to allow robust conclusions to be drawn on comparisons between the 3 medicines.

The study also looked at whether the use of the medicines in clinical practice was in line with the authorised uses and took into account existing contraindications, warnings and advice on interactions with other medicines. The EMA concluded that no changes to the product information were warranted, as the data did not provide robust evidence of a high level of non-adherence to the authorised product information.

The study results provided further data on the known increased risk of bleeding in older patients (>75 years). The companies marketing these

DOAC medicines will be asked to further explore the issue and to investigate whether changes to the recommended doses could be beneficial for these patients.

Information for patients:

- A study was carried out on the use of the anticoagulant medicines Eliquis (apixaban), Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban). These medicines prevent blood clots in a number of situations, including in patients with non-valvular atrial fibrillation. Blood clots can cause serious problems when they occur in important organs such as the lungs and brain. However, because these medicines prevent clotting, bleeding in various parts of the body can be an unwanted side effect.
- The study looked at bleeding in patients with non-valvular atrial fibrillation (irregular rapid contractions of the heart) treated with one of the 3 medicines and compared with other anticoagulant medicines such as warfarin.
- The EMA has reviewed the results of the study and concluded that the risk of bleeding with the medicines was as expected. The study did not show that there was a high level of incorrect use of the medicines.
- The EMA recommends that Eliquis, Pradaxa and Xarelto can continue to be used in the same way as they are now by patients and healthcare professionals and there is no need to change the current advice for these medicines.
- Based on the study results, which show that older patients (>75 years) are at greater risk of bleeding, the EMA will ask the companies marketing these medicines to explore the issue and investigate whether changes to the dosing recommendations for older patients could be beneficial for these patients.
- If they have any questions about their medicines, talk to their doctor or pharmacist.

Information for healthcare professionals:

- A retrospective, non-interventional study using European databases was carried out in 6 countries to assess the risk of major bleeding associated with use of DOACs when compared to VKAs, in patients with non-valvular atrial fibrillation. The study had been proposed following a workshop held by the EMA in 2015 on the clinical use of DOACs.
- Overall, the new data confirm the bleeding patterns of DOACs versus VKA already observed in clinical trials and described in the product information of the medicines. The benefit-risk balance remains positive for all three DOACs investigated (apixaban, dabigatran, rivaroxaban) within the authorised indications. Comparable results were found in similar studies conducted in Canada and the US.
- The study also looked at adherence with sections 4.1, 4.3, 4.4, and 4.5 of the summary of product characteristics for the medicines in the EU. The EMA concluded that the data did not provide robust evidence of a high level of non-adherence to the authorised product information.
- There was an observation of increased risk of bleeding in older patients (>75 years). Further studies are needed to explore the issue and to determine whether there are differences in risk between individual DOACs. The data were not sufficient to recommend dosage changes in this population. The companies marketing these medicines will be asked to explore the issue and to carry out an analysis to determine whether modification of the dosing recommendations could be beneficial for older patients.

In Hong Kong, there are registered pharmaceutical products which are direct oral anticoagulants containing apixaban (2 products), dabigatran etexilate (3 products) and rivaroxaban (7 products), and all products are prescription-only medicines. As on 6 April 2020, the DH has received ADR related to apixaban (25 cases), dabigatran etexilate (12 cases) and rivaroxaban (19 cases). The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

EU: Recommendations to restrict use of fosfomycin antibiotics

On 27 March 2020, the EMA has recommended that fosfomycin medicines given by infusion (drip) into a vein should only be used to treat serious infections when other antibiotic treatments are not suitable. Fosfomycin medicines given by mouth can continue to be used to treat uncomplicated bladder infections in women and adolescent girls. They can also be used to prevent infection in men who undergo a procedure whereby a tissue sample is taken from their prostate (biopsy).

The EMA further recommends that fosfomycin medicines given by mouth to children (under 12 years of age) and intramuscular formulations (fosfomycin medicines for injection into a muscle) should no longer be used as there are insufficient data available to confirm their benefits to patients.

These recommendations follow a review by the CHMP of the safety and effectiveness of these antibiotics.

The review aimed to determine the place of fosfomycin in the treatment of infections, taking into account the latest available evidence. It concluded that:

- Fosfomycin given into a vein should only be used for treating certain serious infections such as those affecting the heart, lungs, blood and brain or those that are difficult to treat such as complicated infections of the abdomen, urinary tract or of the skin and soft tissue.
- Fosfomycin, for use by mouth, can continue to be used for treating uncomplicated cystitis in women and adolescent girls. Fosfomycin granules (which contain fosfomycin trometamol) can also continue to be used in men undergoing biopsy of the prostate. The EMA asked companies for further data to justify the continued use of oral medicines containing fosfomycin trometamol and fosfomycin calcium.
- Intramuscular fosfomycin and fosfomycin granules for children (2 g) should be suspended as there is no clear evidence that they are sufficiently effective for their currently authorised uses.

Information for patients:

- Fosfomycin antibiotics given into a vein will now only be used to treat serious infections when other antibiotic treatments are not suitable. These include infections affecting the heart, lungs, blood, brain, abdomen, urinary tract and skin and soft tissue.
- Fosfomycin given as granules dissolved in water and taken by mouth will continue to be used in women and adolescent girls to treat uncomplicated infections of the bladder, and in men who are having a tissue sample taken from their prostate (biopsy).
- Some fosfomycin medicines (medicines given by injection into a muscle and granules for children) will soon no longer be available as there is no evidence that they work well enough.
- If the patients have any questions about their treatment, they should speak to their doctor or pharmacist.

Information for healthcare professionals:

The EMA has made recommendations for the use of different formulations of fosfomycin:

Fosfomycin for intravenous use

Intravenous fosfomycin should now only be used for the treatment of the following serious infections when other antibiotic treatments are not suitable: complicated urinary tract infections, infective endocarditis, bone and joint infections, hospital-acquired pneumonia including ventilator-associated pneumonia, complicated skin and soft tissue infections, bacterial meningitis, complicated intra-abdominal infections, bacteraemia possibly associated with any of the infections listed above.

Fosfomycin for oral use

The 3 g granules for oral suspension (fosfomycin trometamol) and oral capsules (fosfomycin calcium) can continue to be used for acute, uncomplicated cystitis in women and adolescent girls. In order for fosfomycin calcium preparations to remain authorised, the EMA has asked for further information on the benefits and risks to improve the evidence-base behind its use. Fosfomycin trometamol can also continue to be used prophylactically in men undergoing transrectal prostate biopsy. The EMA has asked for further information to support dosage recommendation of this indication.

Fosfomycin is no longer indicated in the EU for use for urinary tract infections in children and the paediatric formulation (2 g granules) will therefore be suspended from the market.

Fosfomycin for intramuscular use

As the evidence supporting the use of intramuscular fosfomycin medicines is not sufficient, these products will also be suspended in the EU.

The product information for medicines containing fosfomycin in the EU will be updated as required to take these recommendations into account.

In Hong Kong, there are two registered pharmaceutical products containing fosfomycin as oral granules, namely Monurol Paediatric Sachets

Safety Update

2g (HK-43158) and Monurol Sachets 3g (HK-43159). As on 6 April 2020, the DH has not received any case of ADR related to fosfomycin.

In light of the EMA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 30 March 2020, and the matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed recall of three batches of Metformin-Teva 500mg Tablets (HK-60334)

On 11 March 2020, the DH endorsed a licensed wholesale dealer, the International Medical Company Ltd, to recall three batches of Metformin-Teva 500mg Tablets (HK-60334) from the market due to the potential presence of an impurity in the product. The affected batches are 16532717, 16532817 and 16532917.

The DH received notification from the wholesale dealer that the manufacturer suspected that the above product might contain the impurity *N*-nitrosodimethylamine (NDMA) based on laboratory testing. The DH then collected samples of the product for analysis. Results from the Government Laboratory confirmed that the samples contained NDMA. As a precautionary measure, the wholesale dealer is voluntarily recalling all available batches of the above product from the market.

The DH noted that NDMA is classified as a probable human carcinogen based on results from laboratory tests and overseas drug regulatory authorities have been reviewing the safety impact of NDMA found in some medicinal products including metformin.

The above product containing metformin is a prescription medicine used for the treatment of diabetes mellitus. According to the wholesale dealer, the product has been supplied to local private doctors and pharmacies.

Patients who are taking the above product should not stop taking the medicine, but should seek advice from their healthcare professionals as soon as possible for appropriate arrangements.

As on 6 April 2020, the DH has not received any adverse reaction report in connection with the product. Press release was posted on the Drug Office website on 11 March 2020 to alert the public of the product recall.

Overall situation related to detection of NDMA in metformin

As on 6 April 2020 in Hong Kong, there are 124 registered pharmaceutical products containing metformin. All products are prescription-only medicines.

Related news on the detection of NDMA in metformin products was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 122 and 124. The DH issued a letter to inform local healthcare professionals to draw their attention on 6 December 2019. The DH has contacted the certificate holders of all registered metformin products for follow up on the local impact of the issue, and collected samples of metformin-containing products in the local market for analysis. When there are any health risks identified and posed to the public, a press statement will be issued as soon as possible. Please find update information at Drug Office's website (www.drugoffice.gov.hk).

As on 6 April 2020, the DH has received 17 cases of ADR related to metformin. None of them is concluded to be related to the presence of NDMA. The DH will remain vigilant on the development of the issue and any safety update of the drug issued by overseas drug regulatory authorities for consideration of any action deemed necessary.

Patients who are taking metformin-containing products should not stop taking the medicines, but should seek advice from their healthcare professionals for proper arrangement.

DH endorsed recall of Esmya Tablets 5mg (HK-62553)

On 20 March 2020, the DH endorsed a licensed wholesale dealer, Orient Europharma Co Ltd, to voluntarily recall a pharmaceutical product, Esmya Tablets 5mg (HK-62553) from patients due to the potential risk of liver injury.

The DH has been monitoring the safety of Esmya

Drug Recall

since December 2017, when the EMA started a review on Esmya following reports of serious liver injury, and healthcare professionals have been alerted to the risk. Following the EMA's further recommendation on 13 March 2020 that women taking Esmya and its generic products for uterine fibroids should stop taking it, the DH has also issued a letter to healthcare professionals informing them about the EMA's announcement.

Based on the latest EMA recommendation, Orient Europharma Co Ltd decided to recall the affected product from patients as a precautionary measure.

The product concerned, containing 5mg ulipristal acetate, is a prescription medicine used for the treatment of uterine fibroids. According to Orient Europharma Co Ltd, the product has been supplied to the Hospital Authority, private hospitals, local private doctors and pharmacies. Some products have also been exported to Macao.

People who are taking the above product should stop using the medicine and consult their healthcare professionals for appropriate arrangements.

As on 6 April 2020, the DH has not received any adverse reaction report in connection with the product. Press release was posted on the Drug Office website on 20 March 2020 to alert the public of the product recall.

Drug Incident

Woman arrested for illegal sale of unregistered pharmaceutical products

On 10 March 2020, the DH conducted an operation against the sale of unregistered pharmaceutical products, during which a 29-year-old woman was arrested by the Police for the illegal sale of unregistered pharmaceutical products and Part 1 poisons.

Acting upon a public complaint, two types of pharmaceutical products for asthma and pain relief were found being offered for sale via a social media platform. The products were labelled in Japanese and do not bear Hong Kong pharmaceutical product registration numbers.

The product for asthma relief is believed to contain tulobuterol (with three strengths of 0.5mg, 1mg and 2mg, and all labelled with "sawai") while the product for pain relief is believed to contain ibuprofen (labelled with "EVE QUICK"). Both ingredients are Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap. 138).

Tulobuterol is a bronchodilator and its side effects include palpitations, arrhythmias, headaches and tremors. Ibuprofen is a non-steroidal anti-inflammatory pain killer and its side effects include nausea, gastrointestinal discomfort and peptic ulcers. Products containing the above ingredients should only be supplied by a pharmacy under the supervision of a registered pharmacist or upon the advice of a medical practitioner.

People who have purchased the above products should stop using them and consult healthcare professionals for advice if in doubt or feeling unwell after use. Press release was posted on the Drug Office website on 10 March 2020 to alert the public of the drug incident.

Public urged not to buy or consume liquids for e-cigarettes with undeclared nicotine content

On 13 March 2020, the DH appealed to the public not to buy or consume two liquids intended for use with electronic nicotine delivery systems, commonly known as e-cigarettes, as they were found to contain undeclared nicotine.

Acting upon a public complaint, the DH purchased samples of two liquid products for e-cigarettes, namely "火器小辣条 2.0" and "ammo 雾化烟弹" at a retail store in Sham Shui Po for analysis. Test results from the Government Laboratory revealed that both samples contained nicotine, which is a Part 1 poison controlled under the Pharmacy and Poisons Ordinance (Cap. 138).

An operation was conducted against the above retail store on 13 March 2020. During the operation, two men aged 61 years and 32 years were arrested by the Police for suspected illegal sale and possession of Part 1 poisons and unregistered pharmaceutical products.

According to the Ordinance, nicotine-containing e-cigarette products are classified as pharmaceutical products requiring registration with the Pharmacy and Poisons Board of Hong Kong before they can be sold in Hong Kong.

Drug Incident

Smokers are advised to quit smoking for their own health and that of others. They are encouraged to make use of smoking cessation services through the DH's Integrated Smoking Cessation Hotline (1833 183). Information on smoking cessation can also be obtained from the DH's Tobacco and Alcohol Control Office website (www.taco.gov.hk).

Press release was posted on the Drug Office website on 13 March 2020 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: ***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.