Drug News
藥 物 情 報

Issue Number 162

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in April 2023 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

Singapore: PRECEDEX (dexmedetomidine): Increased risk of mortality in critically ill adult intensive care unit patients aged 63.7 years and younger and updates to the Singapore package insert

On 3 April 2023, the Health Sciences Authority (HSA) announced that a Dear Healthcare Professional Letter has been issued by Pfizer Private Limited to inform healthcare professionals of an increased risk of mortality in critically ill adult intensive care unit (ICU) patients aged 63.7 years and younger associated with the use of dexmedetomidine for more than 24 hours.

This finding was from The Sedation Practice in Intensive Care Evaluation (SPICE) III randomised controlled trial that investigated the use of dexmedetomidine as a primary sedative compared with usual care in 3,904 critically ill adult ICU patients. In the study, the exposure to dexmedetomidine was greater than 24 hours with a median duration of treatment of 2.56 days (interquartile range, 1.10 to 5.23) and administration of dexmedetomidine was continued as clinically required for up to 28 days after randomisation.

The Singapore package insert for PRECEDEX has been updated to reflect this new safety concern. It has also been revised to include warnings on hyperthermia/pyrexia and updated information on use in pregnancy and lactation.

In Hong Kong, there are 6 registered pharmaceutical products containing dexmedetomidine. All products are prescription-only medicines. As of the end of April 2023, the Department of Health (DH) had received one case of adverse drug reaction related to dexmedetomidine, but this case was not related to death. Related news was previously issued by European Medicines Agency, and was reported in Drug News Issue No. 149. In light of the above HSA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 4 April 2023. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

The United States: FDA updates prescribing information for all opioid pain medicines to provide additional guidance for safe use

On 13 April 2023, the US Food and Drug Administration (FDA) announced that it is requiring several updates to the prescribing information for both immediate-release (IR) and extended release/long acting (ER/LA) opioid pain medicines. This includes stating for all opioid pain that the risk of overdose increases as the dose increases.

- The updates to IR opioids state these products should not be used for an extended period unless the pain remains severe enough to require them and alternative treatments continue to be inadequate, and that many acute pain conditions treated in the outpatient setting require no more than a few days of an opioid pain medicine. This may include pain occurring with a number of surgical conditions or musculoskeletal injuries.
- The FDA is also updating the approved use for ER/LA opioid pain medicines to recommend they be reserved for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.
- The FDA is also adding a new warning about opioid-induced hyperalgesia (OIH) for both IR and ER/LA opioid pain medicines. This

includes information describing the symptoms that differentiate OIH from opioid tolerance and withdrawal.
- Information in the Boxed Warning, FDA's most prominent warning, for all IR and ER/LA opioid pain medicines will be updated and reordered to elevate the importance of warnings concerning life-threatening respiratory depression, and risks associated with using opioid pain medicines in conjunction with benzodiazepines or other medicines that depress the central nervous system (CNS).
- Other changes are also being required to several sections of the prescribing information, including to the Indications and Usage, Dosage and Administration, and Warnings and Precautions sections. The FDA is also requiring updates to the existing patient Medication Guides to help educate patients and caregivers about these risks.

Recommendations to healthcare professionals:
- In assessing the severity of pain, discuss with the patient the impact of the pain on their ability to function and their quality of life. Assessment of pain should consider both the cause of pain and individual patient factors.
- If the patient's pain is severe enough to require an opioid pain medicine and alternative treatment options are insufficient, prescribe the lowest effective dose of an IR opioid for the shortest duration of time to reduce the risks associated with these products.
- Reserve ER/LA opioid pain medicines only for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.
- For all patients prescribed opioid pain medicines, discuss the availability of naloxone, and consider prescribing it to those at increased risk of overdose.
- Be aware that the symptoms of OIH, a condition where opioids cause an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia), are distinct from opioid tolerance and withdrawal and can be difficult to recognize.
- If a patient is suspected to be experiencing OIH, carefully consider an appropriate decrease in dose of the current opioid pain medicine or safely switching them to a different opioid product, if tolerated. Advise patients about the risk of OIH and tell them to never increase the opioid dosage without first consulting a health care professional, because this could worsen the pain and increase the risk of respiratory depression.

In Hong Kong, there are registered pharmaceutical products containing buprenorphine (7 products), codeine (356 products), fentanyl (16 products), morphine (16 products), oxycodone (18 products), and tramadol (42 products). These products are drugs under supervised sales or prescription-only medicines. There is no registered pharmaceutical product containing hydrocodone, hydromorphone, and oxymorphone. As of the end of April 2023, the Department of Health (DH) had received adverse drug reaction related to codeine (4 cases), fentanyl (3 cases), morphine (10 cases), oxycodone (4 cases), and tramadol (7 cases). The DH had not received any case of adverse drug reaction related to buprenorphine.

Related news on the safe and appropriate use of opioid analgesics was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 47, with the latest update reported in Drug News Issue No. 131. The DH issued letters to inform local healthcare professionals to draw their attention on 11 September 2013. In February 2015, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that pharmaceutical products which are controlled-release, extended-release or long-acting opioid analgesics (containing hydromorphone, morphine, oxycodone, oxymorphone, tapentadol, fentanyl, buprenorphine and methadone) should include safety information about the risks of addiction, abuse, misuse, overdose and death, and limitations of use in patients with severe pain for which alternative treatment options are inadequate.

In light of the above US FDA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 14 April 2023. The risk of tolerance, dependence, withdrawal symptoms, respiratory depression associated with the use of opioid analgesics, and the risks associated with using opioid analgesics in conjunction with benzodiazepines or other medicines that depress the central nervous system (CNS) are documented in overseas reputable drug references, such as the "Martindale: The Complete Drug Reference" and "AHFS Drug Information". 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.

European Union: Reducing risks to human and animal health from exposure to N-methyl pyrrolidone in veterinary medicines

On 14 April 2023, the European Medicines Agency (EMA) announced that the Committee for Veterinary Medicinal Products (CVMP) recommended new measures to reduce the risks from exposure to the excipient N-methyl pyrrolidone (NMP) for women who may handle NMP-containing veterinary medicines and animals that are given these medicines. The recommendations address inconsistencies in the product information of veterinary medicines containing NMP, which are marketed in many European Union (EU) Member States.

The CVMP recommended that veterinary medicines that expose the user to amounts of NMP above a certain threshold should not be given to animals by pregnant women or by women who may be pregnant. Furthermore, women who are able to have children should exercise caution when using these medicines. This includes wearing personal protective equipment such as gloves, particularly for pour-on and spot-on products, shampoos, sprays and concentrates for oral solutions.

The Committee also recommended that in the absence of studies demonstrating the safe use of veterinary medicines containing NMP in the target animal species during pregnancy, lactation or lay, NMP-containing veterinary medicines should only be given to animals that are pregnant, lactating, in lay or intended for breeding after assessment of the benefits and risks by the treating veterinarian. To assist veterinarians in their decision-making, the product information must specify the precise quantity of NMP contained in these veterinary medicines.

NMP is an excipient used in some veterinary medicines that is classified as a teratogen (a substance that can cause birth defects following exposure during pregnancy) in laboratory animals. There is therefore the possibility that NMP could cause birth defects in children of women who handle or come into contact with NMP-containing medicines during their pregnancy, and in the offspring of animals given these medicines.

More than 1,100 veterinary medicines containing the excipient NMP are available in the EU under various trade names and in different formulations, for use mainly in companion animals and large farm animals. These medicines are available as injections, solutions for infusion, spot-on and pour-on products, shampoos, sheep dips, sprays and concentrates for oral solutions for use in the drinking water of animals or solutions for fish treatment.

In Hong Kong, there is one registered pharmaceutical product for veterinary use containing NMP as excipient, namely, Fido's Fre-itch Rinse Concentrate (Vet) (HK-61356). This product is registered by Evergreen Pet Supplies Ltd. It is an over-the-counter medicine. As of the end of April 2023, the Department of Health had not received any case of adverse drug reaction related to NMP. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 17 April 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Singapore: Glypressin (Terlipressin): Serious or Fatal Respiratory Failure and Sepsis/septic shock in Patients with Type 1 Hepatorenal Syndrome

On 21 April 2023, the Health Sciences Authority (HSA) announced that A Dear Healthcare Professional Letter has been issued by Ferring Pharmaceuticals Pte Ltd to inform healthcare professionals of new safety updates regarding the use of terlipressin in patients with type 1 hepatorenal syndrome (type 1 HRS), based on results from the CONFIRM trial.

Terlipressin may cause serious or fatal respiratory failure at a frequency higher than previously known in these patients and may increase their risk of sepsis/septic shock. Terlipressin should be avoided in patients with advanced renal dysfunction [baseline serum creatinine ≥ 442 µmol/L (5.0mg/dL)] and those with Acute-on-Chronic Liver Failure (ACLF) grade 3 and/ or Model for End-Stage Liver Disease (MELD) score ≥ 39, unless the benefit outweighs the risks. Patients with new onset of breathing difficulties or worsening of existing respiratory disease should be stabilised prior to administering the first dose of terlipressin, with close monitoring during treatment. Patients should also be monitored for signs and symptoms

of infection.

The Singapore package insert for Glypressin has been updated to add continuous intravenous (IV) infusion as a method of administration since this method may be associated with lower rates of severe adverse events as compared with IV bolus administration.

In Hong Kong, there are 4 registered pharmaceutical products containing terlipressin. All products are prescription-only medicines. As of the end of April 2023, the Department of Health (DH) had not received any case of adverse drug reaction related to terlipressin. Related news was previously issued by European Medicines Agency and the United Kingdom Medicines and Healthcare products Regulatory Agency, and was reported in the Drug News since Issue No. 147, with the latest update reported in Drug News Issue No.161. The DH issued letters to inform local healthcare professionals to draw their attention on 3 October 2022. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

China: NMPA's announcement on the revision of package insert for Tofacitinib-containing products

On 24 April 2023, the National Medical Products Administration (NMPA) announced that in accordance with the evaluation results of adverse drug reaction reports, and in order to further ensure the public safety of medication use, the NMPA decided to revise the package insert of tofacitinib-containing products (including tofacitinib citrate tablets and tofacitinib citrate sustained-release tablets).

Please refer to the following website in NMPA for details:
https://www.nmpa.gov.cn/xxgk/ggtg/ypshmshxdgg/20230424164231129.html

In Hong Kong, there are 3 registered pharmaceutical products containing tofacitinib. All products are prescription-only medicines. As of the end of April 2023, the Department of Health (DH) had received 9 cases of adverse drug reactions related to tofacitinib. The revised contents in the product insert as stated in the above news is similar to those documented in overseas reputable drug references such as "Martindale: The Complete Drug Reference".

Related news on the adverse drug reactions associated with the use of tofacitinib was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 112, with the latest update reported in Drug News Issue No. 159. The DH had issued letters to inform local healthcare professionals to draw their attention on 29 July 2019, 19 June 2020, 15 June 2021, 2 September 2021 and 31 October 2022.

In December 2019 and December 2021, the Registration Committee of the Pharmacy and Poisons Board had discussed related matters. Currently, the sales pack and/or package insert of registered pharmaceutical products containing tofacitinib should include the relevant safety information on the increased risk of blood clots and death associated with higher dose of tofacitinib (10 mg twice daily), and the risk of thrombosis (including pulmonary embolism and deep vein thrombosis) associated with its use.

As previously reported, the matter will be further discussed by the Registration Committee of the Pharmacy and Poisons Board.

China: NMPA's announcement on the revision of package insert for iodine-containing contrast agents (including meglumine diatrizoate injection, etc.)

On 24 April 2023, the National Medical Products Administration (NMPA) announced that in accordance with the evaluation results of adverse drug reaction reports, and in order to further ensure the public safety of medication use, the NMPA decided to revise the package insert of iodine-containing contrast agents (including Meglumine Diatrizoate Injection, Compound Meglumine Diatrizoate Injection, Iohexol Injection, Iomeprol Injection, Iopamidol Injection, Ioversol Injection, Iodixanol Injection, Iopromide Injection, and Iobitridol Injection).

Please refer to the following website in NMPA for details:
https://www.nmpa.gov.cn/xxgk/ggtg/ypshmshxdgg/20230424171128191.html

In Hong Kong, there are registered pharmaceutical products which are iodine-containing contrast agents containing iohexol (2 products), iomeprol (4 products), iopamidol (2 products), ioversol (4 products), iodixanol (2 products), iopromide

(2 products), and iobitridol (6 products). All products are prescription-only medicines. There is no registered pharmaceutical product containing meglumine diatrizoate. As of the end of April 2023, the Department of Health (DH) had received adverse drug reaction related to iohexol (1 case), iopamidol (3 cases), iodixanol (3 cases), iopromide (26 cases), and iobitridol (4 cases). The DH had not received any case of adverse drug reaction related to iomeprol and ioversol.

Related news on the adverse drug reactions associated with the use of iodine-containing contrast agents was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 73, with the latest update reported in Drug News Issue No. 149. The DH had issued letters to inform local healthcare professionals to draw their attention on 18 November 2015 and 31 March 2022. In April 2016, the Registration Committee of the Pharmacy and Poisons Board had discussed related matters. Currently, the sales pack labels and/or package inserts of iodine-containing contrast agents should include relevant safety warnings on the risk of hypothyroidism or transient thyroid suppression.

As previously reported, the matter will be further discussed by the Registration Committee of the Pharmacy and Poisons Board .

The United Kingdom: Isotretinoin (Roaccutane): new safety measures to be introduced in the coming months, including additional oversight on initiation of treatment for patients under 18 years

On 26 April 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that the Isotretinoin Expert Working Group (IEWG) of the Commission on Human Medicines (CHM) has made recommendations to strengthen the safety of isotretinoin treatment.

In September 2019, the CHM formed the IEWG to review the safety of isotretinoin, in particular concerns about suspected psychiatric and sexual side effects and whether, in some cases, these continue after use of isotretinoin has been stopped. The IEWG considered all the available evidence, including information from patients and their families, and concluded that gaps in the available evidence meant that it was not possible to say that isotretinoin definitively caused many of the short-term or longer-term psychiatric and sexual side effects. However, the individual experiences of patients and families continue to cause concern and the IEWG emphasised the need for patients to be informed about the risks before starting isotretinoin treatment, for there to be additional oversight of prescribing in young patients under 18, and for patients to be consistently monitored for side effects. Following the review and endorsement by the CHM, the MHRA will be introducing a number of measures to strengthen the safety of isotretinoin.

Isotretinoin should not be used for the treatment of prepubertal acne and is not recommended in children younger than 12 years of age. For patients younger than 18 years of age, there will also be a requirement for two prescribers to jointly agree that the acne is severe enough to justify treatment with isotretinoin and that other standard treatments have been sufficiently tried and were ineffective before isotretinoin is started.

The product information for isotretinoin medicines is being updated with these new requirements and to add new information and warnings regarding psychiatric and sexual disorders. This will include a warning that there have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of isotretinoin. The product information will state that patients, and where applicable their families, must be counselled about the risk of psychiatric side effects and sexual dysfunction prior to prescription of isotretinoin. Patients should have an assessment of their mental health and sexual function prior to treatment and should be monitored during treatment for developing psychiatric or sexual disorders.

Advice for healthcare professionals:

- Isotretinoin is indicated for severe forms of acne resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy.
- Continue to follow strict precautions on prescribing isotretinoin, including the conditions of the isotretinoin Pregnancy Prevention Programme.
- Fully inform patients about the potential risks in addition to the expected benefits before prescribing isotretinoin.
- Assess an individual's mental health before initiation of isotretinoin and monitor regularly for developing or worsening psychiatric disorders.
- Tell patients to seek advice if they feel their mental health or sexual function is affected or

is worsening. Patients with a serious side effect should be told to stop their treatment and seek urgent medical advice.

In Hong Kong, there are 11 registered pharmaceutical products containing isotretinoin. All products are prescription-only medicines. As of the end of April 2023, the Department of Health (DH) had received 2 cases of adverse drug reaction related to isotretinoin, but these cases were not related to psychiatric or sexual side effects.

Related news was previously issued by MHRA, and was reported in the Drug News since Issue No. 96, with the latest update reported in Drug News Issue No. 133. The DH issued letters to inform local healthcare professionals to draw their attention on 27 October 2017.

Currently, the sales pack or package insert of locally registered isotretinoin-containing products should include warnings on suicide, suicidal attempts and sexual dysfunction including erectile dysfunction and decreased libido.

In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 27 April 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections and increased mortality

On 26 April 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced new risk minimisation measures for Janus kinase (JAK) inhibitors used to treat chronic inflammatory disorders, consistent with the measures introduced for tofacitinib (Xeljanz) in 2020 and 2021. This advice affects abrocitinib (Cibinqo), baricitinib (Olumiant), upadacitinib (Rinvoq) and filgotinib (Jyseleca) when used for chronic inflammatory disorders.

In 2020, the results of a clinical safety trial in patients with rheumatoid arthritis aged 50 years or older with at least one cardiovascular risk factor (Study A3921133) found that tofacitinib was associated with an increased risk of major adverse cardiovascular events (MACE, defined as death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke), malignancies, venous thromboembolism (VTE), and serious and fatal infections, compared with tumour necrosis factor (TNF)-alpha inhibitors (etanercept or adalimumab). The tofacitinib product information and educational materials were updated at this time. Given the findings, MHRA advised that tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable treatment alternatives.

Following the findings for tofacitinib, a broader review was conducted by the European Medicines Agency in 2022, looking at all JAK inhibitors indicated for inflammatory diseases. As well as the results of study A3921133 for tofacitinib, the review considered the preliminary findings of a multi-database observational cohort study of baricitinib (Olumiant) treatment (study B023), which also suggested an increased risk of major cardiovascular events (incidence rate ratio (IRR) 1.92; 95% CI 1.27 to 2.91) and VTE (IRR 1.34; 95% CI 0.84 to 2.14) in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.

The latest review looked at the available mechanistic and safety data for each of the 5 JAK inhibitors approved as treatments for inflammatory conditions. The review concluded that the effects could be considered a class effect, while acknowledging that the extent to which the findings of study A3921133 applied to all JAK inhibitors was dependent on the similarities of each treated population in terms of the presence of risk factors.

The MHRA reviewed the recommendations together with information relevant to the use of these medicines in the United Kingdom and sought independent advice from the Pharmacovigilance Expert Advisory Group of the United Kingdom's Commission on Human Medicines. Following this review, changes are being made to the product information for all JAK inhibitor medicines authorised for inflammatory diseases to note the updated risk characterisation and expanded risk minimisation measures.

Based on the data assessed, some updates to the existing warnings for tofacitinib were recommended and these will be implemented for

all JAK inhibitors included in the review. The advice across the class of medicines on the need for caution in use in patients with risk factors for VTE was updated to include VTE risk factors, which are distinct from the cardiovascular and malignancy risk factors mentioned elsewhere. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorders.

In the previous update to the tofacitinib product information, it was advised that tofacitinib should only be used in current or past smokers if no suitable treatment alternatives are available, as current or past smoking were identified as predictive factors for development of MACE and malignancies. Further analysis of this risk factor in participants of study A3921133 found that more than 90% of tofacitinib-treated patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively. The warnings on MACE and malignancy for all JAK inhibitors have therefore been updated from past smoking to specify long-time past smoking as a risk factor, in addition to current smoking.

Post-hoc analyses of study A3921133 showed that a history of atherosclerotic cardiovascular disease (a composite of coronary artery disease, cerebrovascular disease, or peripheral artery disease) is a risk factor for MACE. Therefore, the warning on MACE for all JAK inhibitors is being updated to include history of atherosclerotic cardiovascular disease as a risk factor.

Increased all-cause mortality is being added as a risk for patients 65 years of age and older.

Where possible, lower doses are recommended for patients with risk factors for these serious side effects.

Advice for healthcare professionals:

- An increased incidence of malignancy, MACE, serious infections, VTE and mortality, when compared to those treated with TNF-alpha inhibitors, has been observed in trials of patients with rheumatoid arthritis with certain risk factors when treated with some JAK inhibitors, particularly tofacitinib.
- Following a review, these risks are considered class effects across JAK inhibitors used for chronic inflammatory disorders and therefore it is advised to avoid prescribing these medicines unless there are no suitable alternatives in patients with the following risk factors: age 65 years or older; current or past long-time smoking; other risk factors for cardiovascular disease or malignancy.
- Use caution if prescribing in patients with risk factors for VTE other than those listed above.
- Where applicable, use lower doses in patients with risk factors.
- The incidence of non-melanoma skin cancer in the study was also higher with tofacitinib than with a TNF inhibitor, therefore carry out periodic skin examinations in all patients on JAK inhibitor medicines to check for signs of skin malignancy.
- Inform patients of these risks and key signs and symptoms that could warrant urgent medical attention.

In Hong Kong, there are 3 registered pharmaceutical products containing tofacitinib, namely Xeljanz Tablets 5mg (HK-63303), Xeljanz XR Extended Release Tablets 11mg (HK-66141) and Xeljanz Tablets 10mg (HK-66833) which are registered by Pfizer Corporation Hong Kong Limited; 2 products containing baricitinib, namely Olumiant Tablets 2mg (HK-65663) and Olumiant Tablets 4mg (HK-65664) which are registered by Eli Lilly Asia, Inc.; 2 products containing upadacitinib, namely Rinvoq Prolonged-Release Tablets 15mg (HK-66872) and Rinvoq Prolonged-Release Tablets 30mg (HK-67512) which are registered by Abbvie Limited; and 3 products containing abrocitinib, namely Cibinqo Tablets 100mg (HK-67658), Cibinqo Tablets 200mg (HK-67659) and Cibinqo Tablets 50mg (HK-67660) which are registered by Pfizer Corporation Hong Kong Limited. All products are prescription-only medicines. There is no registered pharmaceutical product containing filgotinib.

As of the end of April 2023, the Department of Health (DH) had received adverse drug reaction related to tofacitinib (9 cases; of which 2 cases were related to cancer, 3 cases were related to deep vein thrombosis, one case was related to disseminated tuberculosis, one case was related to cellulitis, one case was related to pneumonia and one case was related to herpes zoster disseminated), baricitinib (3 cases; of which one case was related to deep vein thrombosis and one case was related to pneumocystis jirovecii pneumonia) and upadacitinib (6 cases; of which 4 cases were related

to herpes zoster, one case was related to cytomegalovirus colitis). The DH had not received any case of adverse drug reaction related to abrocitinib.

Related news on the risk of blood clots, serious heart-related problems, cancer and serious infections of JAK inhibitors was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 112, with the latest update reported in Drug News Issue No. 159. The DH had issued letters to inform local healthcare professionals to draw their attention on 29 July 2019, 19 June 2020, 15 June 2021, 2 September 2021 and 31 October 2022.

In December 2019, the Registration Committee of the Pharmacy and Poisons Board (the Committee) discussed the matter on the risk of blood clots and death associated with the use of tofacitinib, and decided that the sales pack and/or package insert of registered pharmaceutical products containing tofacitinib should include safety information on the increased risk of blood clots and death associated with higher dose of tofacitinib (10 mg twice daily).

In December 2021, the Committee discussed the matter on the risk of venous thromboembolic events (including deep vein thrombosis and pulmonary embolism) associated with the use of JAK inhibitors (tofacitinib, baricitinib and ruxolitinib), and decided that the sales pack and/or package insert of these products should include the relevant safety information.

As previously reported, the matter will be further discussed by the Committee.

The United Kingdom: Nitrofurantoin: reminder of the risks of pulmonary and hepatic adverse drug reactions

On 26 April 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that healthcare professionals prescribing nitrofurantoin should be alerted to the risks of pulmonary and hepatic adverse drug reactions and advise patients to be vigilant for the signs and symptoms in need of further investigation.

The MHRA has received a Coroner's report following the death of a patient who experienced acute pulmonary damage and respiratory failure after being treated with nitrofurantoin for a urinary tract infection for a 10-day course. The Coroner raised concerns about the known risk of acute pulmonary damage following nitrofurantoin treatment and the need to highlight this to healthcare professionals and patients.

The potential for acute pulmonary damage with nitrofurantoin is well-documented in the product information for nitrofurantoin. The Summary of Product Characteristics (SmPC) states that acute, subacute and chronic pulmonary adverse reactions have been observed in patients treated with nitrofurantoin. Symptoms of acute pulmonary reactions usually include fever, chills, cough, chest pain, dyspnoea, pulmonary infiltration with consolidation or pleural effusion on chest X-ray, and eosinophilia. For subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form.

Information from published studies on the frequency or severity of pulmonary adverse drug reactions in association with acute use of nitrofurantoin is limited. A precise estimate of frequency of these pulmonary adverse drug reactions and the frequency of fatal outcomes cannot be made, but evidence from observational studies suggests that the pulmonary adverse drug reactions in association with acute use of nitrofurantoin are infrequent.

If symptoms of pulmonary damage occur, nitrofurantoin should be discontinued immediately. The Patient Information Leaflet (PIL) advises patients that lung adverse reactions may occur and that patients should consult a doctor immediately if they notice symptoms of a lung reaction. Close monitoring of pulmonary conditions is advised for patients receiving long-term therapy (especially elderly people). Patients and carers should be reminded about the symptoms of pulmonary damage and the need to seek prompt medical advice if they experience these symptoms.

Following advice from the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines, Marketing Authorisation Holders for these medicines have been requested to strengthen the wording in the United Kingdom SmPC and PIL. These updates will include the advice that healthcare professionals should be vigilant for respiratory symptoms in patients taking nitrofurantoin, for any duration, and promptly investigate these symptoms, as they may indicate a pulmonary reaction.

Safety Update

MHRA also reminds healthcare professionals of the risk of hepatic adverse drug reactions and clarify advice on the frequency of monitoring. Nitrofurantoin can rarely cause hepatic reactions, including cholestatic jaundice, chronic active hepatitis, autoimmune hepatitis, and hepatic necrosis. Events with a fatal outcome have been reported. Nitrofurantoin should be discontinued immediately if hepatitis occurs.

The onset of hepatitis may be gradual and may not have obvious symptoms at first. It is important to monitor patients periodically for changes in biochemical tests that could indicate hepatic dysfunction and for clinical signs or symptoms of liver abnormality, especially in patients taking long -term nitrofurantoin. When scheduling periodic monitoring, take into account relevant local guidance, as well as any pre-existing conditions that might mask the symptoms of a hepatic reaction and the patient's ability to recognise symptoms and seek advice in the event of a hepatic reaction. This periodic monitoring may be an opportunity to remind patients about the possible symptoms of hepatic reactions and to remind them to seek medical advice if they experience these symptoms.

Advice for healthcare professionals:

- Advise patients and caregivers to be vigilant for new or worsening respiratory symptoms while taking nitrofurantoin and promptly investigate any symptoms that may indicate a pulmonary adverse reaction.
- Pulmonary reactions may occur with short- or long-term use of nitrofurantoin, and increased vigilance for acute pulmonary reactions is required in the first week of treatment.
- Patients receiving long-term therapy, for example for recurrent urinary tract infections, should be closely monitored for new or worsening respiratory symptoms, especially if elderly.
- Immediately discontinue nitrofurantoin if new or worsening symptoms of pulmonary damage occur.
- Be vigilant for symptoms and signs of liver dysfunction in patients taking nitrofurantoin for any duration, but particularly with long-term use, and monitor patients periodically for signs of hepatitis and for changes in biochemical tests that would indicate hepatitis or liver injury.
- Use caution when prescribing nitrofurantoin in patients with pulmonary disease or hepatic dysfunction, which may mask the signs and symptoms of adverse reactions.
- Advise patients to read carefully the advice in the PIL about symptoms of possible pulmonary and hepatic reactions and to seek medical advice if they experience these symptoms.

In Hong Kong, there are 5 registered pharmaceutical products containing nitrofurantoin. All products are prescription-only medicines. As of the end of April 2023, the Department of Health (DH) had received one case of adverse drug reaction related to nitrofurantoin, which was related to pulmonary embolism.

The risk of pulmonary reactions and hepatotoxicty with relevant precautions associated with the use of nitrofurantoin is documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference". The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

Drug Recall

Batch recall of Epiduo Forte 0.3%/2.5% Gel (15g)

On 12 April 2023, the Department of Health (DH) endorsed a licensed drug wholesaler, Galderma Hong Kong Limited (Galderma), to recall one batch (batch number: 359448) of Epiduo Forte 0.3%/2.5% Gel, 15g bottle (Hong Kong registration number: HK-66483) from the market due to potential quality issue.

The DH received notification from Galderma that the overseas manufacturer of the product reported that, during stability testing, the assay of one of the active ingredients, benzoyl peroxide, in the above batch was found to be a bit higher than the labelled content, which may reflect a quality issue. As a precautionary measure, Galderma is voluntarily recalling the affected product from the market.

The above product, containing adapalene and benzoyl peroxide, is a prescription medicine used for the cutaneous treatment of acne vulgaris. According to Galderma, the affected batch has been supplied to private hospitals, private doctors and re-exported to Macau.

Drug Recall

As of the end of April 2023, the DH had not received any adverse reaction reports in connection with the affected batch of product. A notice was posted in the Drug Office website on 12 April 2023 to alert the public of the product recall. The DH noted that the recall was completed.

Recall 3 batches of Omezole 20 Cap 20mg (Enteric-coated)

On 25 April 2023, the Department of Health (DH) endorsed a licensed drug wholesaler Hovid Limited (Hovid), to recall 3 batches (batch number: CC07689, CB09638 & CC04545) of Omezole 20 Cap 20mg (Enteric-coated) (Hong Kong Registration Number: HK-49585) from the market because the product's label does not match with the registered one.

In the course of routine market surveillance by the DH, it was found that the name and address of the manufacturer on the label of the above product was different from the registered label, which rendered the product unregistered. Since supply of unregistered pharmaceutical product contravene the Pharmacy and Poisons Regulations (Cap. 138A), Hovid voluntarily recalls the product from the market. DH's investigation is continuing.

The above product, containing omeprazole, is a pharmacy-only medicine used for treatment of gastric ulcer and gastro-oesophageal reflux syndrome. According to Hovid, the product has been supplied to DH clinics, private hospitals, local private doctors, local pharmacies and re-exported to Macau.

As of the end of April 2023, the DH had not received any adverse reaction reports in connection with the above batches of product. A notice was posted in the Drug Office website on 25 April 2023 to alert the public of the product recall. The DH will closely monitor the recall.

Drug Incident

Woman arrested for suspected illegal sale and possession of slimming product with undeclared controlled and banned drug ingredient

On 20 April 2023, the Department of Health (DH) conducted an operation against the sale of a slimming product, namely Bellissimo Instant Premix Coffee & Chocolate Drinks, which was found to contain an undeclared and banned drug ingredient. During the operation, a 39-year-old woman was arrested by the Police for the suspected illegal sale of a Part 1 poison and an unregistered pharmaceutical product.

Acting upon intelligence, a sample of the above product was purchased via an internet website for analysis. Test results from the Government Laboratory revealed that the sample contained sibutramine, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138). The DH's investigation is continuing.

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

A press release was posted in the Drug Office website on 20 April 2023 to alert the public of the drug incident.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap. 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap. 137) and the maximum penalty is a $50,000 fine and one year's imprisonment for each offence.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

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

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.

Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/

Useful Contact

Drug Complaint:

Tel: 2572 2068
Fax: 3904 1224
E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920
Fax: 2319 6319
E-mail: adr@dh.gov.hk
Link: http://www.drugoffice.gov.hk/adr.html

Post: Adverse Drug Reaction and Adverse Event Following Immunization Unit,
Drug Office, Department of Health,
Room 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wanchai, Hong Kong

The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.