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

Australia: Removal of prescribing restrictions on ivermectin

On 3 May 2023, the Therapeutic Goods Administration (TGA) announced that prescribing of oral ivermectin for 'off-label' uses will no longer be limited to specialists such as dermatologists, gastroenterologists and infectious diseases specialists from 1 June 2023.

In its final decision published on 3 May 2023, the TGA has removed the restriction through its scheduling in the Poisons Standard because there is sufficient evidence that the safety risks to individuals and public health is low when prescribed by a general practitioner in the current health climate. This considers the evidence and awareness of medical practitioners about the risks and benefits of ivermectin, and the low potential for any shortages of ivermectin for its approved uses. Also, given the high rates of vaccination and hybrid immunity against COVID-19 in Australia, use of ivermectin by some individuals is unlikely to now compromise public health.

However, the TGA does not endorse off-label prescribing of ivermectin for the treatment or prevention of COVID-19. A large number of clinical studies have demonstrated ivermectin does not improve outcomes in patients with COVID-19. The National Covid Evidence Taskforce and many similar bodies around the world, including the World Health Organization, strongly advises against the use of ivermectin for the prevention or treatment of COVID-19.

Ivermectin for oral use is a Prescription Only medicine in the Poisons Standard. It is only approved by the TGA for the treatment of river blindness (onchocerciasis), threadworm of the intestines (intestinal strongyloidiasis), and scabies.

The restriction on ivermectin was introduced in September 2021 because of concerns about the safety of consumers using ivermectin without health advice to treat COVID-19, widespread use of ivermectin instead of approved vaccines and treatments for COVID-19, and potential shortages of the medicine for approved uses.

In Hong Kong, there is one registered pharmaceutical product for human use containing ivermectin, namely Soolantra Cream 10mg/g (HK-64980). This product is registered by Galderma Hong Kong Limited. It is a prescription-only medicine which is indicated for the topical treatment of inflammatory lesions of rosacea in adult patients. Related news was previously issued by TGA. The Department of Health will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

Australia: TGA makes final decision to reduce paracetamol pack sizes

On 3 May 2023, the Therapeutic Goods Administration (TGA) announced its final decision to reduce the maximum size of packs for various paracetamol products.

Each year in Australia around 225 people are hospitalised and 50 Australians die from paracetamol overdose, with rates of intentional overdose highest among adolescents and young adults. This decision aims to reduce the harm from intentional overdose.

From 1 February 2025, new restrictions on paracetamol will:

- reduce the maximum size of packs available for general sale (e.g. supermarkets and convenience stores) from 20 to 16 tablets or

capsules.
- reduce the maximum size of packs available in pharmacies without the supervision of a pharmacist (i.e. 'Pharmacy Only' packs) from 100 to 50 tablets or capsules.
- make other pack sizes of up to 100 tablets or capsules available only under the supervision of a pharmacist ('Pharmacist Only' medicines).

Paracetamol tablets and capsules for both general and Pharmacy Only sale will also be required to be in blister packaging. The maximum size of Pharmacy Only packs of individually wrapped powders or sachets of granules containing paracetamol will also be reduced in line with tablet and capsule packs.

Access to liquid, modified-release and Prescription Only paracetamol is not affected by this decision.

The decision takes into account:
- An independent expert report commissioned by the TGA that examined the incidence of serious injury and death from intentional paracetamol overdose.
- Advice received from the Advisory Committee on Medicines Scheduling.
- Submissions from two rounds of consultation from individuals, and organisations representing consumers, healthcare practitioners and industry.

To further minimise the harm from paracetamol overdose, the TGA is encouraging retailers such as supermarkets to restrict sales to a single pack at a time. The TGA is also encouraging consumers not to stockpile paracetamol in their home and to appropriately store paracetamol and other medicines. To allow manufacturers and retail outlets sufficient time to adjust, the decision takes effect from 1 February 2025.

In Hong Kong, there are 746 registered pharmaceutical products containing paracetamol. As of the end of May 2023, the Department of Health (DH) had received 50 cases of adverse drug reaction related to paracetamol, of which 11 cases were related to overdose/intentional misuse in dosing frequency.

Currently, the sales pack label of locally registered paracetamol-containing products should include advice against using more than the recommended dose and against using more than one product containing paracetamol. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Australia: Live vaccines: what are the contraindications?

On 4 May 2023, the Therapeutic Goods Administration (TGA) announced that health professionals are reminded that live vaccines should not be given to people who are significantly immunocompromised or pregnant. This is particularly the case for the herpes zoster vaccine Zostavax and the Japanese encephalitis vaccine Imojev as incorrect use continues to be reported. While not all reports of inadvertent use are associated with an adverse event, this safety alert provides a timely reminder to healthcare professionals considering live vaccinations for patients.

If health professionals are uncertain about the degree of immunocompromise in a patient, do not give them a live vaccine and seek specialist advice. Detailed information to manage these patients, including tools to assess the severity of immunocompromise, are available from the Australian Immunisation Handbook.

People who are significantly immunocompromised should not receive live vaccines due to the risk of unchecked infection. People who are immunocompromised include those who:
- are receiving high-dose immunosuppressive therapy, including biologic or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs or tsDMARDs) or oral corticosteroids (≥20 mg per day of prednisolone equivalent dose).
- are receiving chemotherapy or radiation.
- have malignancies related to the immune system such as lymphoma, leukaemia or Hodgkin disease, even if they are not receiving active treatment.
- have AIDS or symptomatic HIV.
- have similar immunocompromising conditions due to a disease or treatment.

In general, pregnant women should not receive live vaccines and should be advised not to become pregnant within 28 days of receiving a live vaccine.

As with all vaccines, live vaccines are contraindicated in anyone who has had a severe allergic reaction to a previous dose of the same

vaccine or from a different vaccine containing a component of the live vaccine, such as albumin.

Zostavax is contraindicated in people with current or recent severe immunocompromising conditions from a medical condition or treatment. The TGA has published previous safety advisory on this issue.

Imojev, the live vaccine, should not be given to children under 9 months of age and is contraindicated in immunocompromised individuals and women who are pregnant or breastfeeding.

In Hong Kong, there are registered pharmaceutical products which are live vaccines, including Zostavax For Vaccine (HK-55419) which is registered by Merck Sharp & Dohme (Asia) Ltd, and Imojev Japanese Encephalitis Vaccine (HK-62787) which is registered by Sanofi Hong Kong Limited. Both products are prescription-only medicines. As of the end of May 2023, the Department of Health (DH) had received 6 cases of adverse events following immunisation with Zostavax. The DH has not received any case of adverse events following immunisation related to Imojev.

Related news on the use of Zostavax in immunocompromised patients was previously issued by TGA, and was reported in the Drug News since Issue No. 140, with the latest update reported in Drug News Issue No. 148. The DH issued letters to inform local healthcare professionals to draw their attention on 2 June 2021. In December 2021, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided to keep vigilant on any update from other health authorities on the matter.

The current local product insert of Zostavax and Imojev includes safety advice on the use of the vaccine in patients with immune deficiency and in pregnancy. The risks and precautions associated with the use of live vaccines in immunocompromised patients and in pregnancy are also documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference". The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

Australia: Important safety information for Janus kinase (JAK) inhibitors

On 11 May 2023, the Therapeutic Goods Administration (TGA) announced that a large post-marketing rheumatoid arthritis safety study of the Janus kinase (JAK) inhibitor tofacitinib found an increased risk of major cardiovascular problems, such as heart attack and stroke, cancer, blood clots, serious infections and death, as compared with tumour necrosis factor (TNF) inhibitors. Based on the results of this study, a class-wide boxed warning and strengthened precautions about these risks have been added to the Australian Product Information documents for JAK inhibitors used to treat chronic inflammatory conditions.

These new warnings for baricitinib, tofacitinib and upadacitinib follow a TGA review of a randomised safety trial called the ORAL Surveillance Study. This trial compared the safety of tofacitinib at two doses (5 mg twice daily and 10 mg twice daily) to TNF inhibitors in around 4,300 patients with rheumatoid arthritis. Patients were followed for an average of four years. To be enrolled, they had to be aged 50 years or older and have at least one cardiovascular risk factor. The final results of the study found a higher incidence of major adverse cardiovascular events, malignancies (particularly lung cancer, lymphoma and non-melanoma skin cancer), thromboembolic events, serious infections and death due to any cause with tofacitinib compared to TNF inhibitors.

The TGA considers the findings of this study relevant to the other JAK inhibitors baricitinib and upadacitinib as they share similar mechanisms of action to tofacitinib. As such a class-wide update has been made to the Product Information and the Consumer Medicines Information across all approved chronic inflammatory indications.

If health professionals are treating patients taking JAK inhibitors for chronic inflammatory conditions, please be aware of these risks and discuss them with their patients. Consider the benefits and risks for each individual before initiating or continuing therapy. Periodic skin examination is recommended for patients taking these medicines, particularly those with risk factors for skin cancer. Patients should also be regularly re-evaluated to assess for changes in their venous thromboembolism risk.

The current Product Information safety updates for baricitinib (Olumiant), tofacitinib (Xeljanz) and upadacitinib (Rinvoq) include a new boxed warning with the information below:

The product should only be used if no suitable treatment alternatives are available in patients:

- with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers).
- with malignancy risk factors (e.g. current malignancy or history of malignancy).
- who are 65 years of age and older.

See section 4.4 Special warnings and precautions for use: Mortality, Major adverse cardiovascular events, Thrombosis, Malignancy, Infections and Use in the elderly.
Section 4.4 Special warnings and precautions for use has been updated in Mortality, Major adverse cardiovascular events, Thrombosis, Malignancy and Use in the elderly.

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.; and 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. All products are prescription-only medicines.

As of the end of May 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 and one case was related to cytomegalovirus colitis).

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. 162. The DH 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 or package insert of tofacitinib products should include safety information about increased risk of blood clots and death with higher dose (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 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 States: FDA updating warnings to improve safe use of prescription stimulants used to treat ADHD and other conditions

On 11 May 2023, the US Food and Drug Administration (FDA) announced that, to address continuing concerns of misuse, abuse, addiction and overdose of prescription stimulants, FDA is requiring updates to the Boxed Warning and other information to ensure the prescribing information is made consistent across the entire class of these medicines.

Prescription stimulants are used to treat attention deficit/hyperactivity disorder (ADHD), binge-eating disorder and uncontrollable episodes of deep sleep called narcolepsy. Examples of common prescription stimulants include Adderall (amphetamine/dextroamphetamine), Concerta (methylphenidate), Dexedrine (dextroamphetamine) and Ritalin (methylphenidate).

The current prescribing information for some prescription stimulants does not provide up to date warnings about the harms of misuse and abuse, and particularly that most individuals who misuse prescription stimulants get their drugs from other family members or peers. Further, individuals who are prescribed stimulants are often faced with requests to share their medication. Sharing these

medicines with others can lead to development of substance use disorder and addiction in those with whom these drugs are shared.

Prescription stimulants can be an important treatment option for disorders for which they are indicated. However, even when prescribed to treat an indicated disorder, their use can lead to misuse or abuse. Misuse and abuse, also called nonmedical use, can include taking your own medicine differently than prescribed or using someone else's medicine. For this reason, sharing prescription stimulants with those for whom they are not prescribed is an important concern and a major contributor to nonmedical use and addiction. Misuse and abuse of prescription stimulants can result in overdose and death, and this risk is increased with higher doses or unapproved methods of taking the medicine such as snorting or injecting.

FDA is requiring the Boxed Warning, FDA's most prominent warning, to be updated and FDA is adding other information to the prescribing information for all prescription stimulants. FDA is adding information that patients should never share their prescription stimulants with anyone, and the Boxed Warning information will describe the risks of misuse, abuse, addiction and overdose consistently across all medicines in the class. The Boxed Warning also will advise heathcare professionals to monitor patients closely for signs and symptoms of misuse, abuse and addiction. FDA is also requiring updates to the existing patient Medication Guides to help educate patients and caregivers about these risks.

Healthcare professionals should assess patient risk of misuse, abuse and addiction before prescribing stimulant medicines. Counsel patients not to share their prescribed stimulant with anyone else. Educate patients and their families on these serious risks, proper storage of the medicine and proper disposal of any unused medicine. Throughout treatment, regularly assess and monitor them for signs and symptoms of nonmedical use, addiction and potential diversion, which may be evidenced by more frequent renewal requests than warranted by the prescribed dosage.

FDA reviewed the medical literature published from January 2006 to May 2020 on misuse and abuse, also called nonmedical use, of prescription stimulants and associated adverse events. Overall, the most common source of prescription stimulants for nonmedical use in the general population came from friends or family members, with estimates generally ranging from 56 percent to 80 percent, usually provided for free. Nonmedical use from their own prescription accounted for approximately 10 percent to 20 percent of people who report having used stimulants nonmedically in the past year. Less commonly reported sources included drug dealers or strangers accounting for 4 percent to 7 percent of people who report having used stimulants nonmedically in the past year, and the internet accounting for 1 percent to 2 percent.

FDA review found that nonmedical use has remained relatively stable over the past two decades, despite the increasing number of prescription stimulants dispensed. However, the past-year prevalence of nonmedical use of these medicines varies across specific subpopulations and is highest in the following groups: young adults ages 18 to 25 (estimates ranged from 4.1 percent to 7.5 percent), college students (4.3 percent), and adolescents and young adults diagnosed with ADHD (estimates ranged from 14 percent to 32 percent). According to the available data, people who use prescription stimulants for nonmedical reasons have a higher risk of developing a substance use disorder than those who do not. The most serious harms were more commonly observed with nonmedical use by a non-oral route such as snorting or injecting.

In Hong Kong, there are registered pharmaceutical products containing methylphenidate (25 products) and lisdexamfetamine (3 products). All products are prescription-only medicines. There is no registered pharmaceutical product containing amphetamine or dextroamphetamine. As of the end of May 2023, the Department of Health (DH) had received 2 cases of adverse drug reaction related to methylphenidate, of which one case was related to intentional overdose. The DH had not received any case of adverse drug reaction related to lisdexamfetamine. In light of the above FDA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 12 May 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

European Union: Fluoroquinolone antibiotics: reminder of measures to reduce the risk of long-lasting, disabling and potentially irreversible side effects

On 12 May 2023, the European Medicines Agency

(EMA) announced that its safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), is reminding healthcare professionals that the use of fluoroquinolone antibiotics, given by mouth, injection or inhalation, is restricted due to the risk of disabling, long-lasting and potentially irreversible side effects.

These restrictions were introduced in 2019 following an European Union (EU)-wide review of these very rare, but serious side effects. An EMA funded study has shown that although the use of fluoroquinolone antibiotics has reduced, these medicines may still be prescribed outside of their recommended uses.

Restrictions on the use of fluoroquinolone antibiotics mean that they should not be used:

- to treat infections that might get better without treatment or are not severe (such as throat infections);
- to treat non-bacterial infections, e.g., non-bacterial (chronic) prostatitis;
- for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.

Importantly, fluoroquinolones should be avoided in patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic. They should be used with special caution in the elderly, patients with kidney disease and in those who have had an organ transplantation because these patients are at a higher risk of tendon injury. Since the use of a corticosteroid with a fluoroquinolone also increases this risk, combined use of these medicines should be avoided.

The study, which evaluated data from the primary care setting in six European countries (Belgium, France, Germany, the Netherlands, Spain and the United Kingdom) between 2016 and 2021, suggests that the measures taken to restrict the use of these medicines as a result of the EU-wide review had a modest impact.

A direct healthcare professional communication (DHPC) will now be sent to healthcare professionals in the EU. The DHPC will emphasize the need to limit the use of these medicines to a last-line treatment in patients who have no alternative therapeutic options and only after a careful assessment of the benefits and risks for individual patients.

Information for healthcare professionals:

- Findings of a study commissioned by EMA (EUPAS37856) suggest that fluoroquinolones continue to be prescribed outside of their recommended uses.
- EMA also notes that the study was subject to limitations and that caution should therefore be used when interpreting its data.
- Healthcare professionals are reminded of the outcome of an EU-wide review of inhaled and systemic quinolone and fluoroquinolone antibiotics that was conducted in 2018 by EMA. This review led to significant restrictions on the use of these medicines due to the risk of rare but long-lasting (up to months or years), serious, disabling and potentially irreversible adverse reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses).
- These adverse reactions can be limited by restricting the use of fluoroquinolones to a last -line treatment in patients who have no alternative therapeutic options and only after a careful assessment of the benefits and risks for individual patients.
- Particular caution should be taken when prescribing fluoroquinolones in older patients, those with renal impairment, solid organ transplantation or on systemic corticosteroids as the risk of some adverse reactions (e.g. tendonitis, tendon rupture) are higher in these patients. Concomitant treatment with a fluoroquinolone and a corticosteroid should be avoided.
- Patients should be informed of the risks associated with fluoroquinolones prior to initiating treatment, including the potentially long-lasting and serious nature of these side effects, and advised to stop treatment and speak with their doctor at the first signs or symptoms of these adverse reactions.
- Fluoroquinolone treatment should be discontinued, and alternative treatment should be considered at the first sign of tendon pain or inflammation or of symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness, so as to prevent development of potentially irreversible adverse reactions.

In Hong Kong, there are registered pharmaceutical products containing systemic fluoroquinolones for use in human, including ciprofloxacin (53 products), levofloxacin (47 products), moxifloxacin (7 products), norfloxacin (3 products), ofloxacin (15 products) and prulifloxacin (one product). All products are prescription-only medicines.

As of the end of May 2023, the Department of Health (DH) had received adverse drug reaction related to ciprofloxacin (one case), levofloxacin (13 cases; of which 3 cases were related to tendinitis and/or neuropathy), moxifloxacin (one case) and ofloxacin (4 cases; all cases were related to suicide/suicide attempt). The DH had not received any case of adverse drug reaction related to norfloxacin and prulifloxacin.

Related news on the risk of musculoskeletal, nervous and psychiatric adverse reactions associated with the use of fluoroquinolones was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 25, with the latest update reported in Drug News Issue No. 124. The DH issued letters to inform local healthcare professionals to draw their attention on 8 November 2011, 16 August 2013, 13 May 2016, 11 July 2018 and 8 October 2018.

In June 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the sales pack labels and/or package inserts of locally registered pharmaceutical products containing fluoroquinolones for systemic use should contain safety information about the risk of disabling and potentially irreversible serious adverse reactions (including tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects). The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

European Union: Gavreto: measures to minimise increased risk for tuberculosis

On 12 May 2023, the European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) discussed a direct healthcare professional communication (DHPC) containing important information on Gavreto (pralsetinib). This DHPC aims to inform healthcare professionals of the increased risk of tuberculosis and measures to minimise this risk, which was identified following a post-marketing review.

In the European Union (EU), Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged-during-transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

Tuberculosis, mostly extrapulmonary, has been reported in patients receiving this medicine. An investigation of global safety data for Gavreto identified nine cases of tuberculosis in patients, of which the majority (7/9) occurred in tuberculosis-endemic regions.

Before starting treatment, patients should be evaluated for active and inactive (latent) tuberculosis, as per local recommendations. In patients with active or latent tuberculosis, standard antimycobacterial therapy should be initiated before treatment with Gavreto is started.

The DHPC for Gavreto will be forwarded to EMA's Committee for Medicinal Products for Human Use (CHMP). When adopted, the DHPC will be disseminated to healthcare professionals by the marketing authorisation holders, according to an agreed communication plan, and published on the Direct healthcare professional communications page and in national registers in EU Member States.

In Hong Kong, there is one registered pharmaceutical product containing pralsetinib, namely Gavreto Capsules 100mg (HK-67499). The product is registered by Cstone Pharm (HK) Holding Limited. It is a prescription-only medicine. As of the end of May 2023, the Department of Health (DH) had received 2 cases of adverse drug reaction related to pralsetinib, but these cases were not related to tuberculosis. 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.

Singapore: High-dose vitamin B6 and risk of peripheral neuropathy

On 15 May 2023, the Health Sciences Authority (HSA) announced the risk of peripheral neuropathy associated with the use of high-dose vitamin B6.

Vitamin B6 is a water-soluble vitamin that comprises different related compounds such as pyridoxine, pyridoxal, pyridoxamine and pyridoxal 5'-phosphate (PLP). The majority of vitamin B6

supplements contain the biologically inactive form, pyridoxine, which is converted by the body into the biologically active form, PLP. PLP functions as an important co-enzyme in various metabolic processes and neurotransmitter synthesis.

Peripheral neuropathy has been reported following chronic high-dose (>100mg/day) consumption of vitamin B6. Healthcare professionals may consider reviewing the dose and duration of vitamin B6 intake (including over-the-counter health supplements) by patients who present with symptoms of peripheral neuropathy.

While peripheral neuropathy is a known safety concern with vitamin B6, the exact mechanism of this adverse event has not been fully elucidated. Postulated mechanisms include the saturation of enzymes leading to accumulation of free pyridoxine and subsequent neurotoxicity, aldehyde toxicity through elevated PLP concentration, the formation of reactive intermediates and competitive inhibition of PLP-dependent enzymes.

The precise-dose response relationship of vitamin B6 causing peripheral neuropathy and the threshold for duration of use have also not been clearly established. Evidence from literature on vitamin B6 -related neuropathy is largely based on case reports, case series and small clinical studies, where the vitamin B6 dosage and duration of use ranged from <50mg to >10g, and three days to ten years, respectively. However, limitations were noted in some studies, such as the absence of a physician's assessment or clinical neurological assessment, and potential confounding by the patient's susceptibility to develop neuropathies (e.g., drug, alcohol and nutritional status).

To date, HSA has received one local adverse event report in 2020 regarding non-serious severe neuralgia in a 65-year-old Chinese male who took a vitamin B6-containing product. There were no further details on the dose and duration of vitamin B6 consumption in the report. The local package inserts of therapeutic products that provide a vitamin B6 daily dose exceeding 100mg are in the process of being strengthened to include warnings on peripheral neuropathy.

While the effect of peripheral neuropathy usually occurs when vitamin B6 is consumed in high doses and/or over long duration, the mechanism of the adverse event, precise dose-response relationship, and threshold for duration of use have not been clearly established. Healthcare professionals may consider reviewing the dose and duration of vitamin B6 intake (including over-the-counter health supplements) by patients who present with symptoms of peripheral neuropathy.

In Hong Kong, there are registered pharmaceutical products containing vitamin B6 substances, including pyridoxine and pyridoxal. As of the end of May 2023, the Department of Health (DH) had received 8 cases of adverse drug reaction related to pyridoxine, but these cases were not related to peripheral neuropathy. The DH had not received any case of adverse drug reaction related to pyridoxal.

Related news was previously issued by Australia Therapeutic Goods Administration, and was reported in the Drug News Issue No. 156. The DH issued letters to inform local healthcare professionals to draw their attention on 5 October 2022. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

The United Kingdom: Direct-acting oral anticoagulants (DOACs): paediatric formulations; reminder of dose adjustments in patients with renal impairment

On 25 May 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that risk minimisation materials are available to support the safe use of new paediatric formulations of rivaroxaban (Xarelto) and dabigatran etexilate (Pradaxa). In addition, the MHRA asks healthcare professionals to consult the current advice to ensure that all patients with renal impairment receive an appropriate dose of DOAC medicines. Available DOACs include the direct factor Xa inhibitors apixaban (Eliquis), edoxaban (Lixiana), and rivaroxaban (Xarelto), and the direct thrombin inhibitor dabigatran etexilate (Pradaxa).

With regards to the dosing and restrictions to the use of DOACs by renal function, the advice relating to paediatrics is as follows: Dosing of DOACs for children is based on body weight. For use of rivaroxaban in children aged younger than 1 year, renal function should be determined using serum creatinine. Rivaroxaban is not recommended in children younger than 1 year with serum creatinine results above 97.5th percentile. For all other children, the glomerular filtration rate should be determined. In paediatric patients with a

glomerular filtration rate lower than 50mL/min/1.73m^2 treatment with rivaroxaban is not recommended (1 year and older) and use of dabigatran is contraindicated. Advice relating to adults is as follows: Exposure to DOACs is increased in patients with renal impairment and it is therefore important that patients receive an appropriate dose adjusted for renal function. Renal function in adults should be assessed by calculating creatinine clearance (CrCl) using the Cockcroft-Gault formula. Patients with renal impairment should be reviewed regularly to ensure ongoing efficacy and safety, with dosing adjusted as required.

Healthcare professionals are advised:

- for paediatric use of these medicines, counsel parents and caregivers about the reconstitution and dosing of dabigatran granules and rivaroxaban granules to reduce the risk of medication errors; highlight the new instructions for use and other educational materials to support safe use in children
- ensure all patients with renal impairment receive an appropriate DOAC dose and monitor renal function during treatment to ensure dose remains appropriate
- report suspected adverse drug reactions associated with DOACs, including thromboembolic or haemorrhagic events

In Hong Kong, there are registered pharmaceutical products containing apixaban (4 products), dabigatran etexilate (3 products), edoxaban (3 products) and rivaroxaban (11 products), and all products are prescription-only medicine. While the MHRA announcement did not highlight any specific adverse event, as of the end of May 2023, the Department of Health (DH) had received cases of adverse drug reaction related to apixaban (60 cases), dabigatran etexilate (21 cases), edoxaban (29 cases) and rivaroxaban (27 cases). The package inserts of all the above products have already included relevant information about dosage adjustments in patients with renal impairment.

Amongst the above registered pharmaceutical products, one product containing rivaroxaban, namely, Xarelto Granules for Oral Suspension 1mg/mL (HK-67498) is for paediatric use; its package insert has already included information about the relevant dosing advice for children. For all the other registered products containing apixaban, dabigatran etexilate, edoxaban and rivaroxaban, they are for adults only. Furthermore, their package inserts have already included information about patients with renal impairment shall receive an appropriate dose of DOAC medicines.

In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 29 May 2023. The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

The United Kingdom: Febuxostat: updated advice for the treatment of patients with a history of major cardiovascular disease

On 25 May 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that caution is required if prescribing febuxostat in patients with pre-existing major cardiovascular disease, particularly, in those with evidence of high urate crystal and tophi burden or those initiating urate-lowering therapy.

In July 2019, the MHRA advised healthcare professionals to avoid febuxostat treatment in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options were appropriate. This followed a review of the findings from a phase 4 clinical trial (the CARES study) in patients with gout and a history of major cardiovascular disease. The CARES study showed a higher risk for cardiovascular-related death and for all-cause mortality in patients assigned to febuxostat than in those assigned to allopurinol.

A further trial has now been concluded on the cardiovascular safety of febuxostat, the FAST study. The FAST study was conducted in patients in the United Kingdom (UK), Denmark, and Sweden who had at least one cardiovascular risk factor and had already been treated with allopurinol for a median duration of 6 years; additionally, serum urate levels were controlled with dose-optimised allopurinol before randomisation. The FAST study concluded that febuxostat was non-inferior to allopurinol therapy with respect to the primary cardiovascular endpoint, and, unlike the CARES study results, that long-term use was not associated with an increased risk of death or cardiovascular death compared to allopurinol.

Following a review of the FAST study findings and advice from the Pharmacovigilance Expert

Safety Update

Advisory Group of the Commission on Human Medicines, the product information for febuxostat has been updated to include the results. The product information retains the warning for cardiovascular disorders and now advises that treatment of patients with pre-existing major cardiovascular diseases with febuxostat should be exercised cautiously.

In particular, treatment should be exercised cautiously in patients with pre-existing major cardiovascular diseases with evidence of high urate crystal and tophi burden or those initiating urate lowering therapy. Prescribing clinicians should titrate febuxostat appropriately to minimise gout flares following initiation, thus minimising additional inflammation.

The MHRA also notes that clinical guidelines for gout, which has been updated since the time of the FAST study publication, state that allopurinol should be offered as first-line treatment to people with gout who have major cardiovascular disease (for example, previous myocardial infarction or stroke, or unstable angina).

As such, febuxostat treatment of chronic hyperuricaemia in patients with pre-existing major cardiovascular diseases should be exercised cautiously, with particular caution in patients with evidence of high urate crystal and tophi burden or those initiating urate lowering therapy.

Healthcare professionals are advised:

- in patients with pre-existing major cardiovascular diseases, febuxostat therapy should be used cautiously, particularly in those with evidence of high urate crystal and tophi burden or those initiating urate-lowering therapy
- following initiation of febuxostat, prescribers should titrate the febuxostat dose to minimise gout flares and inflammation
- note that clinical guidelines for gout recommend that allopurinol should be offered as first-line treatment for people with gout who have major cardiovascular disease
- report suspected adverse drug reactions associated with febuxostat

In Hong Kong, there are 10 registered pharmaceutical products containing febuxostat and all are prescription-only medicines. As of the end of May 2023, the Department of Health (DH) had received 5 cases of adverse drug reaction with febuxostat, of which one case was related to stroke. Related news regarding the cardiovascular risk and mortality was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 97, with the latest update reported in Drug News Issue No. 117. The DH issued letters to inform local healthcare professionals to draw their attention on 22 February 2019. In June 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and it is noted that the package insert of the local products had included relevant cardiovascular risk information. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 29 May 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

Drug Recall

Batch recall of three allopurinol-containing products

On 5 May 2023, the Department of Health (DH) endorsed a licensed drug wholesaler, Welldone Pharmaceuticals Limited (Welldone), to recall three allopurinol-containing products namely Tospan Allopurinol Tablets 300mg (HK-66537) with batch number 22D00 2022-027, Willipo Allopurinol Tablets 300mg (HK-66538) with batch number 22D00 2022-026 and Eformat Allopurinol Tablets 300mg (HK-66534) with batch number 22D00 2022-025 from the market due to a quality issue.

In the course of routine market surveillance by the DH, sample of the above allopurinol-containing product was collected from Welldone for analysis. Testing result from the Government Laboratory showed that the sample failed the dissolution test, which might affect the efficacy of the products. Welldone thus voluntarily recalled the products from the market. DH's investigation is continuing.

The above products, containing allopurinol, are prescription-only medicines indicated mainly for hyperuricaemia and gout. According to Welldone, the products have been supplied to local pharmacies and re-exported to Macau.

As of the end of May 2023, the DH had not received any adverse reaction reports in connection with the above products. A notice was posted in the

Drug Recall

Drug Office website on 5 May 2023 to alert the public of the product recall. The DH noted that the recall was completed.

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

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

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

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.
Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

Useful Contact

Drug Complaint:

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

Adverse Drug Reaction (ADR) Reporting:

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

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

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