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 February 2022 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: Clindamycin capsules and injections: Acute kidney injury

On 3 February 2022, Therapeutic Goods Administration (TGA) announced that a new warning about the nephrotoxic potential of clindamycin capsules and injections has been added to the Australian Product Information (PI). This is not a previously known adverse event associated with this medicine. Health professionals should consider monitoring renal function for certain patients.

Specific clindamycin products in Australia have been approved for the treatment of serious infections caused by susceptible strains of streptococci, pneumococci, staphylococci and anaerobic bacteria. Use should be reserved for penicillin-allergic patients or other patients for whom, in the judgement of the physician, a penicillin is inappropriate. These clindamycin products are marketed under the brand names Dalacin C injections and Dalacin C capsules, as well as various generic brands. Please note that topical clindamycin products are not affected by this issue.

This signal was first identified based on overseas adverse event data and the TGA has evaluated the issue.

The PI documents for Dalacin C injections and Dalacin C capsules have been updated to include the following information:
Section 4.4 Special warnings and precautions for use

- Clindamycin is potentially nephrotoxic. Acute kidney injury including acute renal failure has been reported. Therefore, monitoring of renal function should be considered during therapy of patients with pre-existing renal dysfunction or taking concomitant nephrotoxic drugs and monitoring of renal function should be performed if therapy is prolonged.

Section 4.8 Adverse effects

- Post-marketing experience - renal and urinary disorders: acute kidney injury (frequency not known).

This information will also be incorporated into the PI documents for generic brands.

Acute kidney injury has been reported in Australia. As of 17 November 2021, the TGA has received reports of 5 cases of renal impairment and 5 cases of acute kidney injury associated with systemic clindamycin. There have been no cases of acute renal failure reported in Australia. However, acute renal failure has been reported infrequently overseas.

In Hong Kong, there are registered pharmaceutical products containing clindamycin which are oral capsules (2 products) and injectables (3 products). All products are prescription-only medicines. As of the end of February 2022, the Department of Health (DH) has received one case of adverse drug reaction related to systemic use of clindamycin, but this case was not related to kidney injury. In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 4 February 2022, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: BEOVU (brolucizumab): Risk of intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion

On 3 February 2022, Health Canada announced that an increased incidence of intraocular inflammation,

including retinal vasculitis and retinal vascular occlusion, was observed in patients who received BEOVU 6 mg with every 4 weeks dosing beyond the first 3 doses compared to aflibercept 2 mg every 4 weeks, in neovascular age-related macular degeneration (nAMD) in the MERLIN study. A causal link was observed between the treatment-emergent immune reaction against BEOVU and the BEOVU related retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation (BASICHR0049 study).

After one year of treatment, in a Phase IIIa clinical study (MERLIN), patients with nAMD who received BEOVU 6 mg every 4 weeks maintenance dosing experienced a higher incidence of intraocular inflammation (including retinal vasculitis) and retinal vascular occlusion, when compared with patients who received aflibercept 2 mg every 4 weeks. The incidences of intraocular inflammation and retinal vascular occlusion were also higher than what was previously observed in patients who received BEOVU every 8 or 12 weeks maintenance dosing in the pivotal Phase III clinical studies (HAWK and HARRIER). The interval between two BEOVU doses during maintenance treatment (after the first 3 doses) should not be less than 8 weeks.

In the BASICHR0049 mechanistic study, blood samples were collected from 5 patients with independently confirmed retinal vasculitis and/or retinal vascular occlusion and from 6 control patients who had no signs/symptoms of intraocular inflammation while still receiving BEOVU. In the samples from the 5 patients who experienced retinal vasculitis and/or retinal vascular occlusion, a humoral and cellular immune response against brolucizumab was identified 3 to 5 months after the last BEOVU dose and occurrence of the event. Data showed that there was a presence of high titre anti-drug antibodies (ADAs), with a polyclonal and diverse IgG-driven response against multiple B cell epitopes on the brolucizumab molecule, as well as memory T cell activation induced by unstressed and heat or mechanically-stressed brolucizumab preparations. An increase in in vitro platelet aggregation in the presence of brolucizumab and VEGF-A was also observed. In samples from the control group, ADAs, when present, had lower titres and only marginal responses were detected when inducing T cell activation. In addition, in vitro platelet aggregation was lower compared to patients who had experienced retinal vasculitis and/or retinal vascular occlusion. Taken together with accumulated data regarding the association of treatment-emergent immunogenicity and intraocular inflammation, these results indicate a causal link between the treatment-emergent immune reaction against brolucizumab and the BEOVU related retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation. This finding supports the requirement to discontinue treatment with BEOVU in patients who develop these adverse events.

Two non-interventional, retrospective United States real-world databases consisting of the IRIS Registry [Study HEORUSV201342] and Komodo Healthcare Map [Study HEORUSV201368], respectively, were evaluated to better understand the incidence of adverse events after initiating treatment with brolucizumab for up to 6 months in patients with nAMD. The results of this retrospective analysis suggest that patients with a history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with BEOVU were more likely to present with similar events after BEOVU injection, as compared to nAMD patients with no history of these conditions. In addition, a higher risk for intraocular inflammation (including retinal vasculitis) and/or retinal vascular occlusion in females has been observed in the 2 retrospective studies as well as in clinical trials (e.g., 5.3% females vs. 3.2% males in the HAWK and HARRIER studies).

Healthcare professionals are advised of the followings:

- Treatment with BEOVU is contraindicated in patients with active intraocular inflammation.
- Patients should not be treated with BEOVU 6 mg at intervals less than 8 weeks beyond the first 3 doses.
- Treatment with BEOVU should be discontinued in patients who develop retinal vasculitis and/or retinal vascular occlusion.
- Based on clinical studies, intraocular inflammation related adverse events, including retinal vasculitis and retinal vascular occlusion, were reported more frequently in female patients treated with BEOVU than in male patients.
- Patients with a history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with BEOVU are at increased risk and should be closely monitored.

The product monograph for BEOVU will be updated to reflect the most recent evidence and the new recommendations.

In Hong Kong, there are 2 registered pharmaceutical products containing brolucizumab, namely Beovu Solution For Injection 6mg/0.05ml (HK-67008) and Beovu Solution for Injection In Pre-filled Syringe 6mg/0.05ml (HK-67009). Both products are registered by Novartis Pharmaceuticals (HK) Limited. They are prescription-only medicines. As of the end of February 2022, the Department of Health (DH) has received 9 cases of adverse drug reaction related to brolucizumab, of which one case was related to retinal vasculitis and another case was related to retinal vasculitis and retinal vein occlusion.

Related news was previously issued by the United Kingdom Medicines and Healthcare products Regulatory Agency and was reported in Drug News Issues No. 147. The DH issued letters to inform local healthcare professionals to draw their attention on 19 January 2022. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Canada: Summary Safety Review: Methadone: Assessing the potential risk of hypoglycemia

On 9 February 2022, Health Canada announced that it reviewed the potential risk of hypoglycemia (low blood sugar) with methadone use. This safety review was triggered by a published case in the United States suggesting that patients using methadone could experience hypoglycemia. Signs and symptoms of hypoglycemia may include shakiness, sweating and irritability. As hypoglycemia gets worse, symptoms may include confusion and loss of consciousness.

Health Canada reviewed the available information from searches of the Canada Vigilance database, the World Health Organization's Adverse Drug Reaction Database, and the published literature. At the time of the review, Health Canada had not received any Canadian reports of hypoglycemia related to methadone use. This safety review looked at 19 international cases of hypoglycemia in adults after methadone use, many of which included incomplete information or described patients who were taking other medications or suffering from medical conditions (kidney disease and/or diabetes) that may contribute to hypoglycemia. Despite these limitations, Health Canada found sufficient evidence to determine a probable link between methadone use and the risk of hypoglycemia in 3 cases and a possible link in 9 cases. An additional 2 cases were unlikely to be linked with methadone use, while the remaining 5 cases did not have enough information to be further assessed. Of the 12 cases linked to methadone use, 5 were reported in patients with kidney disease, 3 in patients with diabetes, and 1 in a patient who had received insulin for an unknown indication in the past. Resolution of hypoglycemia was reported in 11 of these 12 cases, generally following methadone discontinuation or dose reduction.

Health Canada also assessed 6 published studies reporting cases of hypoglycemia after methadone use. These studies had weaknesses in their design, including incomplete data collection, small patient numbers, and the use of other opioids known to cause hypoglycemia at the same time as methadone. Despite these weaknesses, a possible link between the use of methadone and the risk of hypoglycemia was found, including possible biological mechanisms to explain how methadone could lead to hypoglycemia.

Health Canada's review did not identify any trends related to risk factors, duration of use, medical conditions, dose range, or methadone formulation for the development of hypoglycemia following methadone use.

Health Canada's review found a possible link between methadone use and the risk of hypoglycemia. Health Canada will be working with the manufacturers of methadone to update the Canadian product monographs to include the risk of hypoglycemia.

In Hong Kong, there are 2 registered pharmaceutical products containing methadone. These products are prescription-only medicines. As of the end of February 2022, the Department of Health (DH) has received 4 cases of adverse drug reaction related to methadone, but these cases were not related to hypoglycemia. In light of the above Health Canada’s announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 10 February 2022 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

European Union: Advice to postpone use of live vaccines in infants exposed to infliximab during pregnancy or via breastfeeding

On 11 February 2022, European Medicines Agency (EMA) announced that their Pharmacovigilance Risk Assessment Committee (PRAC) informed healthcare professionals on the need to postpone the use of live vaccines in infants who are exposed to infliximab during pregnancy or via breastfeeding.

Infliximab is an anti-inflammatory medicine authorised for the treatment of adults with rheumatoid arthritis (an immune system disease causing inflammation of the joints), Crohn's disease (a disease causing inflammation of the digestive tract), ulcerative colitis (a disease causing inflammation and ulcers in the lining of the gut), ankylosing spondylitis (a disease causing inflammation and pain in the joints of the spine), psoriatic arthritis (a disease causing red, scaly patches on the skin and inflammation of the joints) or psoriasis (a disease causing red, scaly patches on the skin). Infliximab is also authorised in patients aged between 6 and 17 years with severe, active Crohn's disease or severely active ulcerative colitis, when they have not responded to or cannot take other medicines or treatments.

Following treatment during pregnancy, it has been reported that infliximab crosses the placenta and it has been detected in infants up to 12 months after birth. Live vaccines should not be given to infants for 12 months after birth if they have been exposed to infliximab during pregnancy. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier time point if there is a clear clinical benefit for the individual infant.

Infliximab has also been detected at low levels in breast milk, therefore, administration of a live vaccine to a breastfed infant while the mother is receiving the medicine is not recommended unless infant infliximab serum levels are undetectable.

It is important that women treated with infliximab who become pregnant or who breastfeed their infant inform the healthcare professional responsible for vaccination of their infant about their treatment with infliximab.

The Direct healthcare professional communication (DHPC) for infliximab will be forwarded to EMA's human medicines committee, the CHMP. Following the CHMP decision, 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 the EU Member States.

In Hong Kong, there are 3 registered pharmaceutical products containing infliximab. As of the end of February 2022, the Department of Health (DH) has received 15 cases of adverse drug reaction related to infliximab, but these cases are not related to use of live vaccines in infants exposed to infliximab during pregnancy or via breastfeeding. The DH will remain vigilant on any safety update of the drugs issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

European Union: PRAC reviewing cases of period irregularities with mRNA COVID-19 vaccines

On 11 February 2022, European Medicines Agency (EMA) announced that their Pharmacovigilance Risk Assessment Committee (PRAC) is assessing reported cases of heavy menstrual bleeding (heavy periods) and absence of menstruation (amenorrhea) with the COVID-19 vaccines Comirnaty and Spikevax.

The Committee had previously analysed reports of menstrual (period) disorders in the context of the safety summary reports for COVID-19 vaccines approved in the EU and concluded at the time that the evidence did not support a causal link between these vaccines and menstrual disorders.

In view of spontaneous reports of menstrual disorders with both vaccines and of findings from the literature, the PRAC decided to further assess occurrences of heavy periods or amenorrhea following vaccination.

Menstrual disorders are very common and can occur with a wide range of underlying medical conditions as well as from stress and tiredness. Cases of these disorders have also been reported following COVID-19 infection.

Heavy periods may be defined as bleeding characterised by a volume, which may interfere

with the person's physical, social, emotional and material quality of life. Amenorrhea may be defined as the absence of menstrual bleeding for three or more months in a row.

After reviewing the available evidence, the PRAC decided to request an in-depth evaluation of all available data, including reports from spontaneous reporting systems, clinical trials and the published literature. At this stage, it is not yet clear whether there is a causal link between the COVID-19 vaccines and the reports of heavy periods or amenorrhea. There is also no evidence to suggest that COVID-19 vaccines affect fertility.

EMA will communicate further when more information becomes available.

In Hong Kong, the above products are not registered pharmaceutical product under the Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). The Department of Health will remain vigilant on any safety update of the product issued by other overseas drug regulatory authorities.

European Union: EMA starts safety review of Janus kinase inhibitors for inflammatory disorders

On 11 February 2022, European Medicines Agency (EMA) announced that their Pharmacovigilance Risk Assessment Committee (PRAC) has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis).

The review was prompted by the final results from a clinical trial (study A3921133) of the JAK inhibitor Xeljanz (tofacitinib). The results showed that patients taking Xeljanz for rheumatoid arthritis and who were at risk of heart disease were more likely to experience a major cardiovascular problem (such as heart attack, stroke or death due to cardiovascular disease) and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors. The study also showed that compared with TNF-alpha inhibitors, Xeljanz was associated with a higher risk of death due to any cause, serious infections and blood clots in the lungs and in deep veins (venous thromboembolism VTE).

In addition, preliminary findings from an observational study involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of major cardiovascular problems and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.

In the treatment of inflammatory disorders, Olumiant and other JAK inhibitors work in a similar way to Xeljanz. PRAC will therefore carry out a review to determine whether these risks are associated with all JAK inhibitors authorised in the EU for the treatment of inflammatory disorders and whether the marketing authorisations for these medicines should be amended.

Some measures to minimise these risks are already in place for Xeljanz as a result of a review finalised in 2020, which analysed the interim results of study A3921133. In addition, the product information for Xeljanz was further updated in 2021 to reflect the increased risk of major cardiovascular problems and cancer observed after the release of additional data from this study.

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; and 2 products containing baricitinib, namely Olumiant Tablets 2mg (HK-65663) and Olumiant Tablets 4mg (HK-65664) which are registered by Eli Lilly Asia, Inc. All products are prescription-only medicines.

As of the end of February 2022, the Department of Health (DH) has received 8 cases of adverse drug reaction related to tofacitinib, of which one case was related to lung cancer, 3 cases were related to deep vein thrombosis, one case was related to pneumonia, one case was related to herpes zoster disseminated, one case was related to cellulitis and one case was related to disseminated tuberculosis. As of the end of February 2022, the DH has received 3 cases of adverse drug reaction related to baricitinib, of which one case was related to deep vein thrombosis.

Related news on the risk of blood clots and death of tofacitinib was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issues Nos. 112, 115, 117, 120, 121, 125, 128, 136, 138, 143 and 147. The DH issued letters to inform local healthcare professionals to draw their attention on 29 July 2019 and 19 June 2020. In December 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, 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).

Related news on the risk of serious heart-related problems and cancer of tofacitinib was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issues Nos. 136, 137, 138, 140, 143, 144 and 147. The DH issued letters to inform local healthcare professionals to draw their attention on 15 June 2021. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Related news on the risk of blood clots of baricitinib was previously issued by the United Kingdom Medicines and Healthcare products Regulatory Agency and Health Canada, and was reported in Drug News Issues Nos. 125 and 143. The current local product inserts already contain safety information on the risk of venous thromboembolism.

As the review is ongoing, the DH will remain vigilant on its final conclusions and recommendations and any safety update issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

Australia: SGLT2 inhibitors approved for T2DM only

On 15 February 2022, Therapeutic Goods Administration (TGA) announced that sodium glucose co-transporter 2 (SGLT2) inhibitor products are approved for use in the management of type 2 diabetes mellitus (T2DM). They are not approved for use in type 1 diabetes (T1DM). Prescribers are reminded of the risk of diabetic ketoacidosis (DKA) with the off-label use of these medicines.

SGLT2 inhibitors improve glycaemic control in patients with T2DM by reducing renal glucose reabsorption. Through inhibition of SGLT2 in these patients, excess glucose is excreted in the urine. Due to continued local and international post-marketing reports of off-label use of SGLT2 inhibitors, the TGA is reminding health professionals that these products are approved for use in the management of T2DM only. They are not approved for use in patients with T1DM.

This applies to the SGLT2 inhibitors empagliflozin, dapagliflozin, ertugliflozin and canagliflozin marketed in Australia.

The current Product Information (PI) for these medicines has not changed, and still includes lengthy warnings regarding the increased risk of DKA with SGLT2 inhibitor use in T1DM.

In 2021, the TGA received 6 reports of off-label use with SGLT2 inhibitors in T1DM patients. Of these, 3 were associated with DKA, indicating that off-label prescribing of SGLT2 inhibitors in T1DM continues. The TGA considers that the seriousness of the risk of DKA requires an updated reminder for prescribers about the risks of off-label use of SGLT2 inhibitors in T1DM patients.

Prescribers are again reminded that SGLT2 inhibitors should be used according to the PI, and T1DM is not an approved indication for these medicines.

In Hong Kong, there are 23 registered pharmaceutical products containing SGLT2 inhibitors, including empagliflozin (10 products), dapagliflozin (5 products), ertugliflozin (4 products) and canagliflozin (4 products). All products are prescription-only medicines. As of the end of February 2022, the Department of Health (DH) has received 3 cases of adverse drug reaction of DKA related to SGLT2 inhibitors: empagliflozin (1 case), dapagliflozin (1 case) and canagliflozin (1 case).

Related news on the risk of DKA of SGLT2 inhibitors was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issues Nos. 67, 74, 76, 105 and 125. The DH issued letters to inform local healthcare professionals to draw their attention on 19 March 2020.

Currently, the package insert of locally registered pharmaceutical products containing SGLT2

inhibitors should include safety information on the risk of DKA, and the drugs should not be used for treatment of patients with T1DM. The DH will remain vigilant on any safety update of the drugs issued by other overseas drug regulatory authorities.

The United Kingdom: Hydroxychloroquine and chloroquine - increased risk of cardiovascular events when used with macrolide antibiotics; reminder of psychiatric reactions

On 15 February 2022, Medicines and Healthcare products Regulatory Agency (MHRA) announced that an observational study in patients with rheumatoid arthritis has shown that co-administration of azithromycin with hydroxychloroquine is associated with an increased risk of cardiovascular events and cardiovascular mortality.

An observational retrospective study published in August 2020 compared records of adverse events in patients initiated on hydroxychloroquine alone with those in patients initiated on sulfasalazine alone for rheumatoid arthritis. The same study compared severe adverse events associated with use of hydroxychloroquine plus azithromycin with those associated with use of hydroxychloroquine plus amoxicillin. The study showed that in a short-term period (up to 30 days) after first use of hydroxychloroquine treatment in combination with azithromycin there was an increased risk of angina or chest pain, heart failure, and cardiovascular mortality compared with the combination of hydroxychloroquine and amoxicillin. No excess risk of severe adverse events was identified in the short-term period of hydroxychloroquine alone (compared with sulfasalazine), but longer-term use past 30 days was associated with increased cardiovascular mortality. Although the mechanism of the observed effects was not examined in detail by the study, it has been proposed that events could be caused by cumulative effects of hydroxychloroquine and azithromycin on the QT interval, potentiating arrhythmias and cardiac death, or through other additive cardiotoxic effects more generally.

A national review of safety data by the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines considered these data. The review recommended that the product information for hydroxychloroquine and systemic azithromycin medicines should be amended to include new warnings and advice on these risks. Due to the similar safety profiles, the risks seen with concurrent use of hydroxychloroquine and azithromycin are considered to apply to concurrent use of hydroxychloroquine and other systemic macrolide antibiotics (clarithromycin or erythromycin) and to use of chloroquine with systemic macrolide antibiotics. As such, the review recommended that similar warnings should also be added to the product information for chloroquine and for systemic clarithromycin or erythromycin. These warnings are not being introduced for topical macrolide products, as these products are used at lower doses and with very limited potential for systemic exposure, and do not list cardiovascular events as potential adverse effects associated with their use.

Hydroxychloroquine and chloroquine have been previously associated with psychiatric reactions, including reports of depression, anxiety, hallucinations, and psychosis. In November 2020, a European safety review recommended updates to the warnings for hydroxychloroquine and chloroquine medicines to include a range of reported psychiatric reactions, including rare cases of suicidal behaviour. The review noted that when psychiatric events occurred, they were typically within the first month of treatment. Events have been reported in patients with no previous history of psychiatric disorders. Information about these reactions have been added to the Summary of Product Characteristics and Patient Information Leaflets for hydroxychloroquine and chloroquine.

Advice for healthcare professionals:

- An observational study has shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events (including angina or chest pain and heart failure) and cardiovascular mortality.
- Carefully consider the benefits and risks before prescribing systemic azithromycin or other systemic macrolide antibiotics (erythromycin or clarithromycin) to patients being treated with hydroxychloroquine or chloroquine.
- If there is a clinical need to prescribe systemic macrolide antibiotics with hydroxychloroquine or chloroquine, use caution in patients with risk factors for cardiac events and follow advice in the product information for each medicine.

- Be vigilant for psychiatric reactions associated with hydroxychloroquine or chloroquine, especially in the first month of treatment; events have been reported in patients with no prior history of psychiatric disorders.

In Hong Kong, there are 5 registered pharmaceutical products containing hydroxychloroquine. All products are prescription-only medicines. There is no registered pharmaceutical product containing chloroquine. As of the end of February 2022, the Department of Health (DH) has received 4 cases of adverse drug reaction related to hydroxychloroquine, but these cases were not related to cardiac and psychiatric reactions. The DH has not received any case of adverse drug reaction related to chloroquine.

Related news on the risk of heart rhythm problems associated with the use of hydroxychloroquine and chloroquine (particularly in combination with other drugs that have similar effects on the heart, such as the antibiotic azithromycin) was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issues Nos. 126, 127 and 128.

Related news on the risk of psychiatric disorders associated with the use of hydroxychloroquine and chloroquine was previously issued by European Medicines Agency, and was reported in Drug News Issues No. 133. The DH issued letters to inform local healthcare professionals to draw their attention on 30 November 2020.

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

Singapore: Mavenclad (cladribine) – risk of serious liver injury and recommendations for liver function monitoring

On 16 February 2022, Health Sciences Authority (HSA) announced that a Dear Healthcare Professional Letter had been issued by Merck Pte Ltd to inform healthcare professionals of adverse events of liver injury following treatment with Mavenclad (cladribine) and recommendations for liver function monitoring of patients on Mavenclad. Liver injury, including serious cases and cases leading to discontinuation of treatment, has been reported in patients treated with Mavenclad. A recent review of available safety data has concluded an increased risk for liver injury following treatment with Mavenclad. Healthcare professionals are advised to take a detailed patient history of the underlying liver disorders or episodes of liver injury with other medicines before treatment initiation and to assess the patient's liver function tests prior to initiation of therapy in year 1 and year 2. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction, healthcare professionals are advised to promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with Mavenclad as appropriate.

In Hong Kong, there is 1 registered pharmaceutical product containing cladribine. The product is a prescription-only medicine. As of the end of February 2022, the Department of Health (DH) has not received any cases of adverse drug reaction related to cladribine.

Related news was previously issued by the European Medicine Agency and was reported in Drug News Issues No. 147. The DH issued letters to inform local healthcare professionals to draw their attention on 15 January 2022. As previously reported, the DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities and consider if any further action deemed necessary.

Australia: Safety advisory: Careful assessment and screening for immunocompromise essential before administration of Zostavax

On 17 February 2022, Therapeutic Goods Administration (TGA) announced that it has published previous safety advice about avoiding the use of Zostavax vaccine in immunocompromised patients but continues to receive reports of such cases. This is a reminder that careful assessment and screening for immunocompromise is essential before administration of Zostavax, with resources to assist in the process.

All patients for whom Zostavax is considered should be assessed for immunocompromise prior to vaccination. Do not administer Zostavax if the immune status of the patient is unclear. Zostavax is contraindicated in patients with current or recent severe immunocompromising conditions from either a primary or acquired medical condition or medical treatment. Fatalities due to disseminated disease with vaccine (Oka) strain varicella zoster virus (VZV) have followed administration of

Zostavax to immunocompromised patients. The risk of disseminated VZV infection with vaccine (Oka) strain increases with the degree of immunosuppression.

Assessing immunocompromise can be complex. A screening checklist to identify patient contraindications prior to vaccination is available in the Australian Immunisation Handbook. Assessment before vaccination can include consulting a medical specialist and screening for pre-existing antibody to VZV. Defer vaccination until advice and results have been obtained.

An immunosuppressed patient who has been inadvertently vaccinated with Zostavax should be informed of the potential for developing disseminated VZV infection. Any patient who experiences a disseminated vesicular (chickenpox-like) rash 2 to 4 weeks after vaccine administration, or who feels unwell or has a fever, should seek medical attention immediately and tell the doctor they have received Zostavax.

If a recent Zostavax recipient is suspected of having disseminated varicella-zoster virus infection, the health professional should:

- conduct appropriate diagnostic testing early in consultation with a clinical microbiologist or infectious diseases physician.
- where appropriate, initiate appropriate empiric antiviral therapy while awaiting test results
- where feasible, cease immunosuppression in consultation with their treating specialist.

The TGA has received three reports of fatal cases of disseminated VZV infection involving the vaccine (Oka) strain following Zostavax administration. Two of the three deaths arose from medication errors involving the administration of Zostavax to immunocompromised patients. The third death was in an immunocompetent patient.

The TGA has published safety advisories about avoiding the use of Zostavax in people who are immunocompromised and has required the sponsor to undertake several risk mitigation activities. Despite these activities, the TGA has received five reports of Zostavax administration in immunocompromised patients since 1 July 2021. In all five cases Zostavax was given to patients were subsequently identified to be receiving concurrent immunosuppressive therapies. Neither disseminated VZV infection or death have been reported in any of these cases. Expert advice provided by the Advisory Committee on Vaccines on 1 December 2021 acknowledged the main area of difficulty was not likely a lack of awareness that Zostavax should not be given to immunocompromised patients, but rather the complexity of around the assessment and definition of 'immunocompromise'.

In Hong Kong, Zostavax For Vaccine (HK-55419) is a pharmaceutical product registered by Merck Sharp & Dohme (Asia) Ltd. The product is a prescription-only medicine. As of the end of February 2022, the Department of Health (DH) has received 6 cases of adverse events following immunisation with Zostavax, but none of them involved death. Related news was previously issued by TGA and was reported in Drug News Issue No. 140. 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 includes information on “Do not administer Zostavax to individuals who are immunodeficient or immunosuppressed due to disease or therapy, as serious or fatal disseminated vaccine strain varicella-zoster virus disease may occur.” The DH will remain vigilant on any safety update of the product issued by other overseas drug regulatory authorities.

Australia: Ipilimumab and serous retinal detachment

On 18 February 2022, Therapeutic Goods Administration (TGA) announced that treatment with ipilimumab has been linked to the rare yet serious adverse event of serous retinal detachment. The amount of photoreceptor degeneration and loss of vision can be minimised by early diagnosis and treatment.

Ipilimumab is a human monoclonal antibody that binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and boosts the response of the immune system to cancer cells. It is marketed in Australia as Yervoy.

Ipilimumab is indicated as monotherapy for the treatment of patients with melanoma; in combination with nivolumab for the treatment of melanoma, renal cell carcinoma and malignant pleural mesothelioma; and in combination with nivolumab and 2 cycles of platinum doublet

chemotherapy for the treatment of non-small cell lung cancer.

As ipilimumab upregulates the immune system, autoimmune-like side effects may result in ocular changes that include serous retinal detachment. Visual acuity may decrease when the macula becomes detached, and consequently the patient may notice a distortion of images. Without prompt treatment, total retinal detachment and blindness may occur.

Warnings about serous retinal detachment and transient vision loss have been incorporated in Section 4.4 of the PI for ipilimumab as follows:
'In the post-marketing setting, cases of Vogt-Koyanagi-Harada syndrome and serous retinal detachment have been reported (see Section 4.8 Adverse effects).
For ipilimumab-related uveitis, iritis, serous retinal detachment or episcleritis, topical corticosteroid eye drops should be considered as medically indicated. Transient vision loss has been reported in patients with ipilimumab-related ocular inflammations.
Other clinically significant immune-related adverse reactions, including some with fatal outcome, have been observed across clinical trials of ipilimumab in combination with nivolumab investigating various doses across tumour types (see Section 4.8 Adverse effects). These include rare cases of myotoxicity. Cases of Vogt-Koyanagi-Harada syndrome and serous retinal detachment have been reported post-marketing (see Section 4.8 Adverse effects). Transient vision loss has been reported in patients with ipilimumab-related ocular inflammations. Refer to the Product information for nivolumab.'

The following has been added to Section 4.8 of the PI in Post-marketing experience:
'Eye disorders: Serous retinal detachment'.

It is important for physicians, ophthalmologists and patients to be aware of this possible adverse reaction because without appropriate treatment, many retinal detachments progress to involve the central retina and may lead to loss of vision.

In Hong Kong, there are 2 registered pharmaceutical products containing ipilimumab, namely Yervoy Concentrate For Solution For Infusion 50mg/10ml (HK-63494) and Yervoy Concentrate For Solution For Infusion 200mg/40ml (HK-63495); which are registered by Bristol-Myers Squibb Pharma (HK) Ltd, and are prescription-only medicines.

As of the end of February 2022, the Department of Health (DH) has received 41 cases of adverse drug reactions related to ipilimumab, but these cases are not related to serous retinal detachment. In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 19 February 2022. The DH will keep vigilant on any further safety updates from the other overseas drug regulatory authorities.

Australia: Administer vinca alkaloids by intravenous infusion only

On 24 February 2022, Therapeutic Goods Administration (TGA) announced that unintended intrathecal injection of vinca alkaloids can result in fatal outcomes. To prevent this, the Product Information (PI) for vincristine, vinblastine and vinorelbine products has been changed to ensure these medicines are always given intravenously and by no other route.

Warnings that these products are for intravenous administration only are being included in the 'Dose and method of administration' section (4.2) and 'Special warnings and precautions for use' section (4.4) of the PI for these medicines. Below is a summary of the information that is being incorporated:
'Syringes should not be used for administration of vinca alkaloids. Preparation must be by dilution in small volume intravenous bags (the "minibag" technique), rather than in a syringe, to protect against accidental administration via the spinal route. Vinca alkaloids should be prepared for intravenous use only. Fatal if given by any other route.'

Any mention of 'injecting' is being replaced by 'infusing' throughout the PI documents for all 3 medicines.

To 1 February 2022, there have been 3 cases of administration error of vinca alkaloids by the intrathecal route, including one death, reported to the TGA and included in its Database of Adverse Event Notifications.

In Hong Kong, there are 13 registered pharmaceutical products containing vincristine (4 products), vinblastine (2 products) and vinorelbine (7 products) which are injectables. All

products are prescription-only medicines. As of the end of February 2022, the Department of Health (DH) has received adverse drug reaction related to vincristine (90 cases), vinblastine (3 cases) and vinorelbine (3 cases), but these case were not related to medication errors in relation to unintended intrathecal injection. Related news was previously issued by the United States Food and Drug Administration, and was reported in Drug News Issue No. 135. The DH issued letters to inform local healthcare professionals to draw their attention on 18 January 2021. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

European Union: Hydroxyethyl-starch solutions for infusion recommended for suspension from the market

On 25 February 2022, European Medicines Agency (EMA) announced that the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) adopted Pharmacovigilance Risk Assessment Committee's (PRAC) recommendation of suspending the marketing authorisations for hydroxyethyl-starch (HES) solutions for infusion across the European Union.

On 11 February 2022, EMA's safety committee, PRAC, recommended that the marketing authorisations for HES solutions for infusion should be suspended across the European Union. These products were authorised as an addition to other treatments for plasma volume replacement following acute (sudden) blood loss.

The safety of HES solutions for infusion was reviewed by EMA in 2013, and a number of restrictions and measures to minimise the risk of kidney injury and death in certain patients (those critically ill, with burn injuries or with sepsis, a bacterial infection in the blood) were put in place at the time.

As a result of a review conducted in 2018, the use of HES solutions for infusion was further restricted to accredited hospitals, and healthcare professionals prescribing or administering the medicines had to be trained in their appropriate use. Additionally, further warnings were introduced in the product information to remind healthcare professionals that these medicines must not be used in patients with sepsis or kidney impairment or in other vulnerable patients such as the critically ill. These measures were put in place to ensure that HES solutions for infusion were not used in patients who were at increased risk of harm. Companies marketing HES solutions for infusion were also requested to conduct a drug utilisation study to check whether these restrictions were adhered to in clinical practice, and to submit the results of this study to EMA.

The PRAC reviewed the results from this study, which show that HES solutions for infusion are still being used outside the recommendations included in the product information. The Committee concluded that the further restrictions introduced in 2018 have not sufficiently ensured that the medicines are used safely, and that HES solutions continue to be used in certain groups of patients in whom serious harm has been demonstrated.

Since adherence to the set of measures agreed in 2018 was a condition for the safe use of HES solutions for infusion, and the study has shown this has not happened, the benefits of these medicines are no longer considered to outweigh their risks. The PRAC explored the possibility of introducing additional measures to ensure HES solutions are used according to the product information but concluded that there were no other measures, or combination of measures, that would be feasible and sufficient to protect patients.

In view of the serious risks that certain patient populations are still exposed to, the PRAC therefore recommended the suspension of the marketing authorisations for HES solutions for infusion in the European Union.

The PRAC recommendation was sent to the CMDh, which adopted its position on 23 February 2022. As the CMDh position was adopted by majority vote, it will now be sent to the European Commission, which will take an EU-wide legally binding decision in due course.

In Hong Kong, there are 4 registered pharmaceutical products containing hydroxyethyl starch, namely Voluven Infusion 6% (HK-50474) and Volulyte 6% Solution for Infusion (HK-58087) which are registered by Fresenius Kabi Hong Kong Limited; and Tetraspan 6% Solution for Infusion (HK-56978) and Tetraspan 10% Solution for Infusion (HK-56979) which are registered by B. Braun Medical (HK) Ltd. All products are prescription-only medicines. As of the end of February 2022, the Department of Health (DH) has not received any case of adverse drug reaction

related to hydroxyethyl starch.

Related news on the increased risks of kidney injury and death associated with the use of hydroxyethyl starch was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issues No. 44, 48, 50, 99, 102, 103 and 104. The DH issued letters to inform local healthcare professionals to draw their attention on 17 June 2013 and 15 January 2018.

In December 2013, the Registration Committee of the Pharmacy and Poisons Board decided that products containing hydroxyethyl starch should contain the relevant safety information (hydroxyethyl starch is contraindicated in sepsis, burns, renal impairment or renal replacement therapy, critically ill patients, etc., and in patients undergoing open heart surgery in association with cardiopulmonary bypass the use of hydroxyethyl starch is not recommended due to the risk of excess bleeding).

As previously reported, the DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary. The information will be provided to the Registration Committee of the Pharmacy and Poisons Board for further consideration in view of latest recommendation issued by EMA.

Australia: Donepezil and cardiac conduction disorders

On 28 February 2022, Therapeutic Goods Administration (TGA) announced that cardiac conduction disorders have been reported in patients receiving donepezil. The Product Information (PI) documents for this medicine are being updated to advise caution in patients with known QTc prolongation or a family history of this condition. Additionally, caution is advised in patients also receiving other drugs that affect the QTc interval, or who have certain types of cardiac disease or electrolyte disturbances. As these adverse effects can be severe and potentially life threatening, clinical monitoring may be required.

Donepezil is marketed in Australia as Aricept and various generic brands. The following warning has been added to 'Cardiovascular conditions' in the 'Special warnings and precautions for use' section (4.4) of the Aricept PI for donepezil:
'Cases of QTc interval prolongation and Torsades de Pointes have been reported for donepezil (see sections 4.4 and 4.8). Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring may be required. Examples include: Class IA antiarrhythmics (e.g. disopyramide); Class III antiarrhythmics (e.g. amiodarone, sotalol); Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline); Other antipsychotics (e.g. phenothiazine derivatives, pimozide, ziprasidone); Certain antibiotics (e.g. clarithromycin, erythromycin, moxifloxacin)'

In the 'Adverse effects' section (4.8) of the Aricept PI for donepezil, 'electrocardiogram QT interval prolonged' and 'polymorphic ventricular tachycardia including Torsades de Pointes' have been added to the post-marketing experience list.

The PI updates are based on evidence published in the literature and from post-market adverse event data in Australia and internationally. To 5 January 2022, there have been 18 cases of atrioventricular block, atrioventricular block complete, atrioventricular block second degree, bundle branch block, bifascicular block or Torsades de Pointes associated with donepezil reported to the TGA and included in its Database of Adverse Event Notifications.

Health professionals should be aware of any pre-existing or family history of cardiac disease, significant electrolyte changes and relevant drug interactions when prescribing donepezil for a patient. The cardiac conduction disorders caused by donepezil can be potentially life threatening, so monitoring of cardiac function may be required in at-risk individuals or where this adverse event is suspected.

In Hong Kong, there are 37 registered pharmaceutical products containing donepezil. All products are prescription-only medicines. As of the end of February 2022, the Department of Health (DH) has not received any case of adverse drug reaction related to donepezil. In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 1 March 2022 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Incident

Public urged not to buy or consume slimming products with undeclared controlled ingredients

On 25 February 2022, the Department of Health (DH) appealed to the public not to buy or consume two slimming products, namely Million Burning and the other with a Japanese name (please refer to photo 2 in the press release), as they were found to contain undeclared controlled drug ingredients.

Acting upon intelligence, samples of the above products were purchased earlier via a social media platform for analysis. Test results from the Government Laboratory revealed that the sample of Million Burning contained sibutramine and the sample of the other product (please refer to photo 2 in the press release) contained frusemide. Both ingredients are Part 1 poisons 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, products containing sibutramine have been banned in Hong Kong because of an increased cardiovascular risk. Frusemide is a diuretic used in the treatment of high blood pressure, heart failure and oedema. Common adverse effects include feeling thirsty, dizziness, headaches and fast or irregular heartbeat.

Press release was posted on the Drug Office website on 25 February 2022 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/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.