Drug News
藥 物 情 報

Issue Number 155

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

European Union: New measures to minimise risk of meningioma with medicines containing nomegestrol or chlormadinone

On 2 September 2022, the European Medicines Agency (EMA) announced that its human medicines committee (CHMP) has endorsed the recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC), which concluded that the benefits of medicines containing nomegestrol or chlormadinone outweigh the risks, provided new measures are taken to minimise the risk of meningioma.

A meningioma is a tumour of the membranes covering the brain and spinal cord. It is usually benign and is not considered to be a cancer, but due to their location in and around the brain and spinal cord meningiomas can in rare cases cause serious problems.

The CHMP has recommended that medicines containing high-dose nomegestrol (3.75 – 5 mg) or high-dose chlormadinone (5 – 10 mg) should be used at the lowest effective dose and for the shortest duration possible, and only when other interventions are not appropriate. In addition, low- and high-dose nomegestrol- or chlormadinone-containing medicines must not be used by patients who have, or have had, meningioma.

As well as restricting the use of the high-dose medicines, the CHMP has recommended that patients should be monitored for symptoms of meningioma, which can include change in vision, hearing loss or ringing in the ears, loss of smell, headaches, memory loss, seizures and weakness in arms or legs. If a patient is diagnosed with meningioma, treatment with these medicines must be permanently stopped.

The product information for the high-dose medicines will also be updated to include meningioma as a rare side effect.

The CHMP opinion has been sent to the European Commission, which will issue a legally binding decision valid across the EU.

Information for healthcare professionals:

- Meningiomas (single and multiple) have been reported with the use of nomegestrol- or chlormadinone-containing medicines, particularly at high doses and for prolonged time. The risk increases with increasing cumulative doses.
- The use of these medicines at high doses should be restricted to situations where other interventions are considered inappropriate, and they should be used at the lowest effective dose and for the shortest duration.
- Nomegestrol- or chlormadinone-containing medicines are contraindicated in patients with meningioma or a history of meningioma.
- Patients should be monitored for signs and symptoms of meningiomas in line with clinical practice. If a patient is diagnosed with meningioma, treatment with these medicines should be permanently stopped.
- Available evidence suggests that the risk of meningioma decreases after treatment discontinuation of the nomegestrol- or chlormadinone-containing medicine.

In Hong Kong, there is no registered pharmaceutical product containing nomegestrol. There is 1 registered pharmaceutical product (HK-65918) containing chlormadinone in combination with ethinyloestradiol in tablet dose form. The product is a prescription-only medicine. As of the end of September 2022, the Department of Health (DH) had not received any cases of adverse drug reaction

related to chlormadinone. Related news was previously issued by EMA, and was reported in Drug News Issue No. 144 and 153.

In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 11 Jul 2022. 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 starts review of topiramate use in pregnancy and women of childbearing potential

On 2 September 2022, the European Medicines Agency (EMA) announced that its safety committee (PRAC) has started a review of topiramate and the risk of neurodevelopmental disorders in children whose mothers were taking topiramate during pregnancy. Topiramate is a medicine used in the EU for the treatment of epilepsy, prevention of migraine and, in some countries, in combination with phentermine for body weight reduction.

Use of topiramate in pregnant women is known to increase the risk of birth defects. Women with epilepsy who are being treated with topiramate for their seizures are advised to avoid becoming pregnant, and to consult their doctor for advice if they wish to become pregnant. Topiramate must not be used to prevent migraine or control body weight in pregnant women and in women of childbearing potential (women able to have children) who are not using highly effective birth control methods (contraception).

The review was triggered by a recent study which suggested a possible increase in the risk of neurodevelopmental disorders, in particular autism spectrum disorders and intellectual disability, in children whose mothers were taking topiramate during pregnancy.

The study was based on data from several Nordic registries (Denmark, Finland, Iceland, Norway and Sweden), and included information from more than 24,000 children exposed to at least one anti-epileptic medicine before birth. Of these children, 471 were exposed to topiramate alone, including 246 children born to mothers who had epilepsy.

The PRAC started reviewing the study results as part of a safety signal assessment in July 2022. The committee will now conduct an in-depth review of the available data on the benefits and risks of topiramate use in pregnant women and women of childbearing potential in the approved indications. The committee will look in particular at the current risk minimisation measures and consider the need for additional measures to minimise the risks of topiramate use in these women.

While the review is ongoing, topiramate should continue to be used according to the authorised product information. Women should discuss any questions or concerns about their topiramate treatment with their doctor or pharmacist. Patients should not stop antiepileptic treatment before speaking with their doctor.

Following this review, the PRAC will give its recommendation as to whether marketing authorisations of topiramate-containing products should be maintained, varied, suspended or revoked. EMA will communicate the PRAC's recommendation once the review has concluded.

In Hong Kong, there are 32 registered pharmaceutical products containing topiramate. All products are prescription-only medicines. As of the end of September 2022, the Department of Health (DH) had received 4 cases of adverse drug reaction related to topiramate, but these cases were not related to neurodevelopmental disabilities in children with prenatal exposure. Related news was previously issued by EMA and Medicines and Healthcare products Regulatory Agency, and was reported in Drug News Issue No. 153. The DH will remain vigilant on the conclusion of the review and any safety updates issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

European Union: Review of pholcodine medicines started

On 2 September 2022, the European Medicines Agency (EMA) announced that it has started a review of medicines that contain pholcodine following concerns that their use may put people at risk of developing anaphylactic reactions (a sudden, severe and life-threatening allergic reaction) to certain medicines called neuromuscular blocking agents (NMBA). Pholcodine is used to treat non-productive (dry) cough in adults and children and NMBAs are used in general

anaesthesia to prevent spontaneous muscle movements to improve operating conditions.

The review was requested by the French medicines agency (ANSM) following preliminary results of a study (ALPHO) carried out in France. The results of the study suggested that taking pholcodine up to 12 months before general anaesthesia may increase the risk of having an NMBA-related anaphylactic reaction. Based on these results ANSM is considering, as a precautionary measure, to suspend the use of pholcodine-containing medicines in France.

The ALPHO study was carried out as a condition to the marketing authorisations of pholcodine-containing medicines following a previous safety review in 2011. At the time, the Agency's Committee for Medicinal Products for Human Use (CHMP) found no firm evidence that use of pholcodine may put people at risk of developing anaphylactic reactions to NMBAs and recommended that a new study (the ALPHO study) should be carried out to investigate this risk in people taking pholcodine.

While ALPHO study was ongoing, in 2021, a study in Australia linked pholcodine's use to an increased risk of anaphylaxis to NMBA muscle relaxants. This led to a recommendation by PRAC to include relevant warnings in the product information of pholcodine-containing medicines.

The PRAC will now review the results of the ALPHO study together with all available data and assess their impact on the benefit-risk balance of pholcodine-containing medicines and issue a recommendation on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the EU. The Agency invites all stakeholders (e.g. healthcare professionals, patients' organisations, the general public) to submit data relevant to this procedure.

In Hong Kong, there are 28 registered pharmaceutical products containing pholcodine. As of the end of September 2022, the Department of Health (DH) had received 1 case of adverse drug reaction related to pholcodine, but this case was not related to anaphylactic reaction. Related news was previously issued by EMA, and was reported in Drug News Issue No. 17 and 26. The DH will remain vigilant on the conclusion of the review and any safety updates issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

China: NMPA's announcement on the revision of package insert of hydroxyethyl-starch solutions for infusion

On 6 September 2022, the National Medical Products Administration (NMPA) announced that in accordance with the evaluation results of adverse drug reaction reports and in order to further ensure the safety of public medication, the NMPA decided to revise the package insert of hydroxyethyl-starch solutions for infusion.

In Hong Kong, there are 4 registered injectable pharmaceutical products containing hydroxyethyl starch. All products are prescription-only medicines. As of the end of September 2022, the Department of Health (DH) had not received any case of adverse drug reaction related to hydroxyethyl starch.

Related news on the adverse drug reactions 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, 104 and 148. The DH also issued letters to inform local healthcare professionals to draw their attention on 17 June 2013 and 15 January 2018.

In December 2013 and April 2018, the Registration Committee of the Pharmacy and Poisons Board had discussed related matters. Currently, product inserts of registered pharmaceutical products containing hydroxyethyl starch should include the relevant safety information (hydroxyethyl starch is contraindicated in sepsis, burns, renal impairment and critically ill patients, etc.).

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

Australia: Fluorouracil and capecitabine: DPD deficiency

On 14 September 2022, the Therapeutic Goods Administration (TGA) announced that Product Information (PI) documents for fluorouracil and capecitabine are being updated to expand the existing warning and information about dihydropyrimidine dehydrogenase (DPD) deficiency. Prescribers are advised to consider a reduced starting dose where partial DPD deficiency

is detected.

The TGA is working with the sponsors of fluorouracil and its prodrugs capecitabine and flucytosine to include a new warning in the PI about the potential for severe and potentially life-threatening toxicity in patients with a partial DPD deficiency. The Australian PIs for fluorouracil and capecitabine already included a contraindication for patients with known complete DPD deficiency.

The PIs recommend that special attention be paid to patients' DPD status before therapy or when evaluating patients experiencing fluorouracil-related toxicities.

A review by the TGA, which included advice from the Advisory Committee on Medicines (ACM), found that the Australian PIs for capecitabine and fluorouracil should be updated with advice to reduce the starting dose when partial DPD deficiency is detected. The updated warning for fluorouracil states:

- Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with fluorouracil injection. Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit this toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment. Consideration should be given to applicable clinical guidelines.

The review also found that the capecitabine PIs should include the same warnings about DPD deficiency-related toxicity as the fluorouracil PIs, as well as further information that:

- DPD deficiency-related toxicity usually occurs during the first cycle of treatment or after a dose increase.
- Fatal outcomes have been reported in some cases.
- Laboratory testing for total or partial DPD deficiency should be considered before therapy is initiated or when evaluating patients experiencing related toxicities.

The TGA review followed strengthening of warnings and precautions about DPD deficiency for these products by the European Medicines Agency (EMA). The EMA recommended DPD testing prior to starting treatment and consideration of dose reduction and/or reduced starting dose for those with DPD deficiency. The ACM advised that DPD testing can be a reasonable clinical choice but need not be mandated. The treating team would consider the value of testing for the individual patient, taking into account test availability and cost and the potential for testing to delay treatment.

A review of all adverse event reports submitted to the TGA for fluorouracil, capecitabine and flucytosine up to 20 July 2022 found 11 cases where the reporter noted adverse events were possibly or likely due to DPD deficiency. In most of these cases DPD deficiency was not tested for or confirmed in the affected patients. A total of 6 cases were reported to have had a fatal outcome.

In Hong Kong, there are registered pharmaceutical products containing fluorouracil (4 products) and capecitabine (23 products). All products are prescription-only medicines. There is no registered pharmaceutical product containing flucytosine. As of the end of September 2022, the Department of Health (DH) had received adverse drug reactions related to fluorouracil (102 cases) and capecitabine (70 cases; of which one case was related to DPD deficiency).

Related news was previously issued by the European Medicines Agency (EMA) and United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), and was reported in Drug News Issue No. 113, 125, 126 and 132. The DH issued letters to inform local healthcare professionals to draw their attention on the risk of severe side effects associated with the use of fluorouracil and related medicines (including capecitabine and tegafur) in patients with dihydropyrimidine dehydrogenase deficiency on 18 March 2019.

In June 2021, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the package insert of products containing fluorouracil and capecitabine should include the relevant safety information (including the increased risk of severe and potentially life-threatening toxicity in patients with partial DPD deficiency and consideration for a reduced starting dose in these patients when using parenteral fluorouracil and capecitabine). The DH will remain vigilant on any safety update of the drugs issued by

other overseas drug regulatory authorities.

Australia: Sitagliptin: Safety advisory - low levels of contamination with a nitrosamine impurity

On 16 September 2022, the Therapeutic Goods Administration (TGA) announced that it is investigating potential contamination of sitagliptin medicines with very low levels of a nitrosamine impurity, known as 7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3- a]pyrazine (NTTP).
Sitagliptin is a prescription medicine used to treat type 2 diabetes. It is marketed in Australia under multiple trade names.

The TGA has set an acceptable intake (AI) limit for NTTP of 37 nanograms (ng) per day. Australian sponsors of sitagliptin products have reported that some sitagliptin products in the Australian market contain levels of NTTP that are higher than this limit. This issue also affects sitagliptin products supplied overseas.

To prevent a shortage of sitagliptin, the TGA is temporarily allowing supply of sitagliptin medicines containing NTTP that exceed the AI limit. The TGA has assessed that an intake of up to 246 ng NTTP per day does not pose a health concern based on short-term exposure compared with the risks for patients that cannot access their sitagliptin medicines. The risks of not taking sitagliptin as prescribed, is greater that the risk associated with this impurity.

Consumers are advised to continue to take their sitagliptin medicines as prescribed. Patients should not stop taking their sitagliptin medicines unless instructed to by their health professional.

Nitrosamines are a group of compounds which can damage DNA. They are commonly found in low levels in a variety of foods, including smoked and cured meats, dairy products, vegetables, in some drinking water, and in air pollution. Long-term exposure, over years, can increase an individual's risk of developing cancer.

The additional risk that would be posed by the trace levels of NTTP being detected in sitagliptin is likely to be very low. However, the presence of nitrosamine impurities is generally considered unacceptable for a medicine. The actual health risk depends on the medicine and dose taken and will vary from person to person.

Nitrosamine impurities have also been found in other medicines. They were first identified in 'sartan' medicines in 2018. Medicines affected by nitrosamine impurities in Australia include 'sartan' blood pressure medicines in 2018, metformin and ranitidine products in 2019, varenicline products and rifampicin products in 2021, and quinapril products in 2022.

Health professionals should be aware that NTTP may be present at very low levels in sitagliptin products supplied in Australia. However, there is no reason to stop prescribing sitagliptin as the benefits continue to far outweigh the risk posed by this impurity.

The TGA has reviewed results reported by Australian sponsors of sitagliptin medicines on the ARTG that are available on the market. It continues to work with its international regulatory partners and sitagliptin medicine sponsors to respond to this issue and will determine whether other actions are required.

In Hong Kong, there are 12 registered pharmaceutical products containing sitagliptin. All products are registered by Merck Sharp & Dohme (Asia) Ltd (MSD), and are prescription-only medicines. As of the end of September 2022, the Department of Health (DH) had received 8 cases of adverse drug reaction related to sitagliptin. None of them is concluded to be related to the presence of 7-Nitroso-3-(trifluoromethyl)-5, 6, 7, 8- tetrahydro [1,2,4]triazolo-[4,3- a]pyrazine (NTTP). The DH has been contacting MSD to follow up on the impact of the local marketed products; and will remain vigilant on the development of the issue and any safety update of the drugs issued by overseas drug regulatory authorities for consideration of any action deemed necessary.

Canada: Summary Safety Review - Xeljanz/ Xeljanz XR (tofacitinib), Olumiant (baricitinib) and Rinvoq (upadacitinib) - Janus Kinase (JAK) Inhibitors

On 16 September 2022, Health Canada announced that it reviewed the available information from searches of the Canada Vigilance databasea, international databases, scientific literature, as well as clinical and observational studies related to the risks of serious heart-related problems, blood clots, cancer and death with Xeljanz/Xeljanz XR,

Olumiant and Rinvoq.

The final findings from the clinical research study linked Xeljanz/Xeljanz XR to higher risks of serious heart-related problems, cancer and death, and confirmed the initial findings of an increased risk of blood clots from 2019. These risks have already been reflected in the CPM of Xeljanz/Xeljanz XR. Health Canada also looked at the interim findings from a 2021 observational study with Olumiant, which showed increased rates of serious heart-related problems and blood clots with its use. Given the similar mechanisms of action and indications for Xeljanz/Xeljanz XR, Olumiant and Rinvoq, Health Canada considers that they may have similar risks. Overall, the findings are supportive of the need for precautionary measures with the use of JAK inhibitors for inflammatory conditions.

Health Canada's current review found that a drug class effect for the risks of serious heart-related problems, blood clots, cancer and death with JAK inhibitors used for the treatment of chronic inflammatory diseases cannot be excluded at this time.

As a precautionary measure, Health Canada is working with the manufacturers to update and align these risks in the CPMs for JAK inhibitors indicated for chronic inflammatory diseases. Health Canada will communicate these updates to healthcare professionals and the public through a Health Product Risk Communication and Public Advisory. Health Canada will continue to monitor safety information involving Xeljanz/Xeljanz XR, Olumiant and Rinvoq, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action should new health risks be identified.

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 30mg (HK-67512) and Rinvoq Prolonged-Release Tablets 15mg (HK-66872) which are registered by Abbvie Limited. All products are prescription-only medicines.

As of the end of September 2022, the Department of Health (DH) had 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 September 2022, the DH had received 3 cases of adverse drug reaction related to baricitinib, of which one case was related to deep vein thrombosis. As of the end of September 2022, the DH had received 6 cases of adverse drug reaction related to upadacitinib, of which one case was related to lung inflammation, 4 cases was related to herpes zoster and one case was related to cytomegalovirus colitis.

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 No. 112, 115, 117, 120, 121, 125, 128, 136, 138, 143, 147 and 148. 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 the 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 No. 136, 137, 138, 140, 143, 144, 147 and 148. 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 various overseas drug regulatory authorities, and was reported in Drug News Issues No. 125, 143 and 148. The current local product inserts already include safety information on the risk of venous thromboembolism.

The DH will remain vigilant on any safety updates issued by overseas drug regulatory authorities for consideration of any action deemed necessary.

The United Kingdom: Methylphenidate long-acting (modified-release) preparations: caution if switching between products due to differences in formulations

On 26 September 2022, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that prescribers and dispensers should use caution if switching patients between different long-acting formulations of methylphenidate (Concerta XL, Medikinet XL, Equasym XL, Ritalin LA, and generics) as different instructions for use and different release profiles may affect symptom management.

A recent European procedure looked at differences between Medikinet XL and other long-acting formulations of methylphenidate and the impact on safety and efficacy when switching to and from products. This procedure concluded that caution is advised if long-acting formulations of methylphenidate are used interchangeably due to the differences between formulations in frequency of dosing, administration with food, and plasma drug concentration achieved. These updates will be made to the United Kingdom Summary of Product Characteristics for Medikinet XL. MHRA has considered this, together with the safety data for all long-acting methylphenidate medicines, and agree with this position. MHRA also considered reports and queries from patients, carers and healthcare professionals in the United Kingdom regarding concerns of lack of effect and increased adverse effects when switching between long-acting formulations of methylphenidate. MHRA sought the views of the Paediatric Medicines Expert Advisory Group of the Commission on Human Medicines on these concerns.

MHRA is alerting healthcare professionals to the need to use caution when prescribing or dispensing long-acting methylphenidate preparations and to adequately counsel patients as required. MHRA will continue to monitor safety information and will seek to introduce this wording in other long-acting methylphenidate formulations as appropriate.

All long-acting methylphenidate preparations include an immediate-release component as well as a modified-release component. This means methylphenidate is released in two phases (biphasic). This allows for rapid onset of action and a slower extended release, avoiding the need to take further doses during the day to maintain effect. It is possible that several formulations will need to be tried before one is found that suits an individual. The biphasic-release profiles of these products are not all equivalent and contain different proportions of the immediate-release and modified-release components. The differing time–action profiles provided by long-acting formulations of methylphenidate allow clinicians to target specific periods of the day that are particularly relevant for a patient, facilitating individualisation of attention deficit hyperactivity disorder (ADHD) treatment. Transferring to another formulation can result in changes in symptom management at key time periods during the day.

The response to methylphenidate varies greatly from patient to patient and therefore the doctor will need to increase or decrease a dose to find one that suits the patient (dose-finding phase). A number of long-acting methylphenidate preparations are available, and they differ from each other in several aspects, including: their available dose strengths; the ratio of immediate-release and modified-release methylphenidate; mechanism of release; pharmacokinetics; plasma concentration-time profiles and bioavailability; their dependence on the presence or absence of food at the time of ingestion. Due to these differences, changing preparations means that the dose may have to be adjusted to avoid the potential for overdose or underdose.

Switching between different preparations may result in concerns from patients and parents or caregivers. No single formulation meets the requirements of all patients with ADHD and the unique characteristics of each agent should be matched to the individual needs of the patient. Switching between formulations with differing pharmacokinetics can also be associated with differences in adverse events or patient experiences of effectiveness in both paediatric and adult patient groups. Frequent switching between different products should be avoided. Once a patient is established on a product, prescribers may wish to maintain them on that specific product. In such cases, prescribing by specifying brand or manufacturer may be appropriate. Changes to medication should only be made in the context of individual review and should be communicated to patients, who should be advised to report any changes to their symptoms or development of side

effects.

Advice to healthcare professionals:

- Caution should be used if long-acting formulations of methylphenidate are to be used interchangeably due to the differences between formulations in dosing frequency, administration with food, amount and timing of the modified-release component, and overall clinical effect.
- Follow specific dosage recommendations for each formulation.
- If considering a switch to another long-acting preparation: consult with the patient (and their parent or caregiver if relevant) to discuss the reasons for this and the possible changes they may experience in symptom management and side effects (and what to do if these occur); consider patient preferences such as their individual needs, dose frequency, possible side effects, or other issues related to the patient's condition; reiterate the instructions for use for the newly prescribed formulation, especially whether it should be taken with or without food.
- Clinical guidance advises to prescribe these long-acting formulations of methylphenidate by specifying brand name or by using the generic drug name and name of the manufacturer.

In Hong Kong, there are 26 registered pharmaceutical products containing methylphenidate. Nineteen of them are modified-release preparations, including Medikinet CR Modified-release Capsules 40mg (HK-65756), Medikinet CR Modified-release Capsules 10mg (HK-65757), Medikinet CR Modified-release Capsules 20mg (HK-65758) and Medikinet CR Modified-release Capsules 30mg (HK-65759). All products are prescription-only medicines. As of the end of September 2022, the Department of Health (DH) had received 2 cases of adverse drug reaction related to methylphenidate, but these cases were not related to switching between different preparations. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 27 September 2022, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

European Union: New recommendations for terlipressin-containing medicines in the treatment of hepatorenal syndrome

On 30 September 2022, the European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) recommended new measures to reduce the risk of respiratory failure and sepsis when using terlipressin-containing medicines in people with type 1 hepatorenal syndrome (HRS-1).

The new measures include adding to the product information a warning to avoid terlipressin-containing medicines in patients with advanced acute-on-chronic liver disease or advanced kidney failure. Patients with breathing problems should receive treatment to manage their condition before starting terlipressin. During and after treatment, patients should be monitored for signs and symptoms of respiratory failure and infection. In addition, healthcare professionals can consider giving terlipressin-containing medicines as a continuous infusion into the vein as an alternative to giving it by bolus injection as this may reduce the risk of severe side effects.
The recommendations follow the PRAC's review of available data, including results from a clinical trial involving patients with HRS-1 which suggested that patients who were treated with terlipressin-containing medicines were more likely to experience and die from respiratory disorders within 90 days after the first dose than those who were given placebo. Although respiratory failure is a known side effect of terlipressin, the frequency of respiratory failure seen in the study was higher (11%) than previously reported in the product information. In addition, the study reported sepsis in 7% of patients in the terlipressin arm compared with none in the placebo group.

There were limitations to the data, such as differences in how terlipressin was used in the clinical trials compared to clinical practice. After considering these limitations together with other available data and consulting an expert group composed of healthcare professionals with expertise in the field of hepatorenal syndrome, PRAC concluded that new measures are needed to ensure that the benefits of terlipressin-containing medicines continue to outweigh the risks.

Information for healthcare professionals:

- A higher than previously known risk of respiratory failure has been reported when using terlipressin-containing medicines for the treatment of HRS-1. In addition, a new risk of sepsis has been identified with the use of terlipressin-containing medicines for HRS-1.

- Terlipressin-containing medicines should be avoided in patients with advanced renal dysfunction (serum creatinine ≥ 442µmol/l (5.0 mg/dl)) and in patients with acute-on-chronic liver failure grade 3 and/or model for end-stage liver disease (MELD) score ≥39 MELD score, unless the benefits outweigh the risks.
- Patients with new onset of breathing difficulties or worsening of existing respiratory disease should be stabilized before treatment with terlipressin-containing medicines and should be closely monitored during treatment. If patients develop respiratory symptoms, a dose reduction of human albumin should be considered, if applicable. If symptoms are severe or do not resolve, terlipressin should be discontinued.
- Patients should be closely monitored for symptoms of infection.
- In addition, healthcare professionals can consider giving terlipressin-containing medicines as a continuous intravenous infusion as an alternative to bolus injection, as continuous infusion may reduce the risk of severe adverse events compared to bolus injection.

In Hong Kong, there are 4 registered pharmaceutical products containing terlipressin. All products are prescription-only medicines. As of the end of September 2022, the Department of Health (DH) had not received any case of adverse drug reaction related to terlipressin. Related news was previously issued by EMA and was reported in Drug News Issue No. 147. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 3 October 2022, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

European Union: Imbruvica (ibrutinib): new risk minimisation measures, including dose modifications, due to the increased risk for serious cardiac events

On 30 September 2022, the European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) discussed a direct healthcare professional communications (DHPC) containing important information for Imbruvica (ibrutinib).

This DHPC aims to inform healthcare professionals about an increased risk of fatal and serious cardiac arrhythmias and cardiac failure with the use of ibrutinib.

Patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of cardiac events including sudden fatal cardiac events.

The PRAC advises that a clinical evaluation of cardiac history and function should be performed before starting a treatment with ibrutinib. In patients with risk factors for cardiac events, benefits and risks should be assessed before initiating treatment with the medicine and alternative treatment may be considered. Patients should be carefully monitored during treatment for signs of deterioration of cardiac function and be clinically managed. Ibrutinib should be withheld for any new onset or worsening of grade 2 cardiac failure or grade 3 cardiac arrhythmias. Treatment may be resumed as per new dose modification recommendations.

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

In Hong Kong, there are 4 registered pharmaceutical products containing ibrutinib, namely Imbruvica Capsules 140mg (HK-64088), Imbruvica Capsules 140mg (HK-65397), Imbruvica Tablets 140mg (HK-67062) and Imbruvica Tablets 280mg (HK-67063). All products are registered by Johnson & Johnson (Hong Kong) Ltd. They are prescription-only medicines. As of the end of September 2022, the Department of Health (DH) had received 28 cases of adverse drug reaction related to ibrutinib, of which 6 cases were related to atrial fibrillation and one case was related to heart failure.

Related news on the risk of ventricular tachyarrhythmia associated with the use of ibrutinib was previously issued by the United Kingdom Medicines and Healthcare products Regulatory Agency and Health Canada, and was reported in

Safety Update

Drug News Issues No. 94 and 105. The DH issued letters to inform local healthcare professionals to draw their attention on 16 August 2017. In December 2017, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the package insert of ibrutinib-containing products should include safety information on the risk of ventricular tachyarrhythmia.

Related news on the risk of cardiac arrhythmias and cardiac failure associated with the use of ibrutinib was previously issued by Health Canada, and was reported in Drug News Issues No. 154.

The current package insert of the above 4 local ibrutinib-containing products include safety information on the risk of cardiac arrhythmia (including atrial fibrillation, atrial flutter and ventricular tachyarrhythmia) and cardiac failure. 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.

Drug Incident

Public urged not to buy or consume virility product containing undeclared controlled ingredients

On 28 September 2022, the Department of Health (DH) urged the public not to buy or consume a virility product named "HE ABSOLUTE KING" as it was found to contain an undeclared controlled ingredient.

Acting upon intelligence, the DH earlier purchased a sample of the above product via a social media platform for analysis. Test results from the Government Laboratory revealed that the sample contained tadalafil, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138).

The DH's investigation is continuing.

Tadalafil is used for treatment of erectile dysfunction and should only be used under the advice of a medical doctor. Side effects of tadalafil include low blood pressure, headaches, vomiting, dizziness and transient vision disturbances. It may interact with some drugs (such as nitroglycerin for treatment of angina) and cause a decrease in blood pressure to dangerous levels. Improper use of tadalafil may pose serious health risks, especially for patients with heart problems.

A press release was posted on the Drug Office website on 28 September 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.