Drug News
藥 物 情 報

Issue Number 152

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in June 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: EMA recommends withdrawal of marketing authorisation for amfepramone medicines

On 10 June 2022, European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended the withdrawal of European Union (EU) marketing authorisations for amfepramone obesity medicines.

The recommendation follows a review which found that measures to restrict the use of these medicines for safety reasons have not been sufficiently effective. It found that the medicines were being used for longer than the recommended maximum period of 3 months, thereby potentially increasing the risk of serious side effects, such as pulmonary arterial hypertension (high blood pressure in the arteries of the lungs) and dependency. The medicines were also being used in patients with a history of heart disease or psychiatric disorders, increasing their risk of heart and psychiatric problems. In addition, there was evidence of use during pregnancy, which could pose risks to the unborn baby.

The review considered all available information relating to these concerns, including data from two studies on the use of amfepramone medicines in Germany and in Denmark. In addition, the PRAC received advice from a group of experts, comprising endocrinologists, cardiologists and a patient representative.

The PRAC considered introducing further measures to minimise the risk of side effects but could not identify any that would be sufficiently effective. The PRAC therefore concluded that the benefits of amfepramone medicines do not outweigh their risks and recommended that the medicines be removed from the market in the EU.

Information for healthcare professionals:

- EMA is recommending the withdrawal of the EU marketing authorisations for amfepramone-containing medicines for the treatment of obesity.
- A review of available data has found that amfepramone medicines continue to be used outside the current risk minimisation measures included in the product information.
- Inappropriate use may increase the risk of serious adverse effects, including cardiovascular disease, pulmonary arterial hypertension, dependency and psychiatric disorders, as well as harmful effects if used during pregnancy.
- There is limited efficacy of a short-term treatment as patients usually regain weight following cessation of treatment.
- Healthcare professionals should advise patients about other treatment options.

The PRAC recommendation will now be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a position.

In Hong Kong, there is one registered pharmaceutical product containing amfepramone, namely Dipropion Capsules 75mg (HK-64796). The product is registered by Jean-Marie Pharmacal Co Ltd. It is a prescription-only medicine. As of the end of June 2022, the Department of Health (DH) had not received any case of adverse drug reaction related to amfepramone. As the PRAC recommendation will now be sent to the CMDh for consideration, the DH will remain vigilant on any safety update of the drug issued by EMA and other overseas drug regulatory authorities for consideration of any action deemed necessary.

European Union: PRAC finds no link between mRNA COVID-19 vaccines and absence of menstruation

On 10 June 2022, European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that there was insufficient evidence to establish a causal association between the COVID-19 vaccines Comirnaty and Spikevax and cases of absence of menstruation (amenorrhoea). Absence of menstruation may be defined as no bleeding for a period of 90 days or more.

The PRAC assessed all the available data, including findings from the literature and cases of amenorrhea reported to EudraVigilance after the administration of Comirnaty and Spikevax. Overall, the PRAC considered that the available data does not support causal association and an update of the product information for either vaccine.

The PRAC will continue to carefully monitor this issue and has requested the marketing authorisation holders to include it in the next periodic safety update reports for Comirnaty and Spikevax.

In Hong Kong, the above products are not registered pharmaceutical products 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). Related news was previously issued by EMA and was reported in Drug News Issue No. 148. The Department of Health will remain vigilant on any safety update of the product issued by other overseas drug regulatory authorities.

European Union: Xalkori - Vision disorders, including risk of severe visual loss, need for monitoring in paediatric patients

On 10 June 2022, European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) discussed a direct healthcare professional communication (DHPC) containing important information for Xalkori (crizotinib). This DHPC informs healthcare professionals of the risk of ocular toxicity, severe visual loss and the need for monitoring in paediatric patients with Xalkori.

Xalkori is a cancer medicine used to treat adults with a type of lung cancer called non-small cell lung cancer (NSCLC), when the disease is advanced. Xalkori has been studied in children from 6 to 18 years of age as a monotherapy for the treatment of relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) that is ALK positive or patients with unresectable, recurrent, or refractory ALK positive inflammatory myofibroblastic tumour (IMT).

Vision disorders have been reported in 61% of paediatric patients treated with crizotinib in clinical trials for these indications.

Vision disorders and ocular toxicity are more challenging to detect in children. Young patients may not report or notice changes in vision without specific questioning of symptoms and examinations. Paediatric patients should be monitored for ocular toxicity, including the risk of severe vision loss. They should receive a baseline ophthalmologic examination prior to starting Xalkori with follow-up examinations. Healthcare professionals are advised to inform patients and caregivers of the symptoms and remind them to contact their doctor if any of these symptoms develop. Any visual symptoms should be referred to an eye specialist.

Healthcare professionals are also advised to consider a dose reduction of Xalkori for patients who develop Grade 2 ocular disorders. If Grade 3 and 4 ocular disorders occur, treatment with the medicine should be discontinued permanently, unless another cause is identified.

The product information and the educational material for patients and caregivers have been updated with instructions/recommendations in children about the risk of ocular toxicity, including severe vision loss.

The DHPC for Xalkori 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 holders, 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 2 registered pharmaceutical products containing crizotinib, namely Xalkori Cap 250mg (HK-61968) and

Xalkori Cap 200mg (HK-61969). Both products are registered by Pfizer Corporation Hong Kong Limited. They are prescription-only medicines. As of the end of June 2022, the Department of Health (DH) had received 28 cases of adverse drug reaction related to crizotinib, but these cases were not related to vision disorders. The above registered products are currently indicated for treatment in adults only and the risk of visual disorders is included in the current product information. The DH will remain vigilant on any safety update of the drug issued by EMA and other overseas drug regulatory authorities for consideration of any action deemed necessary.

The United Kingdom: Metformin and reduced vitamin B12 levels - new advice for monitoring patients at risk

On 20 June 2022, Medicines and Healthcare products Regulatory Agency (MHRA) announced that decreased vitamin B12 levels, or vitamin B12 deficiency, is now considered to be a common side effect in patients on metformin treatment, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors.

Patients with a vitamin B12 deficiency can be asymptomatic or they can present with symptoms of megaloblastic anaemia or neuropathy or both. Other symptoms of low vitamin B12 levels may include mental disturbance (depression, irritability, cognitive impairment), glossitis (swollen and inflamed tongue), mouth ulcers, and visual and motor disturbances. It is important for patients with anaemia or neuropathy caused by vitamin B12 deficiency to be diagnosed and treated as soon as possible to avoid the development of permanent symptoms.

Decreased vitamin B12 levels is a known consequence of long-term treatment with metformin. The mechanism is currently thought to be multifactorial, comprising altered intestinal motility, bacterial overgrowth, and reduced uptake of vitamin B12 within the small intestine (or a combination of these factors).

The known adverse drug reaction of vitamin B12 deficiency was recently reviewed for the brand leader Glucophage (metformin) within Europe with input from the MHRA. After this review, MHRA has agreed that the product information for medicines containing metformin should be updated. The current literature suggest that the frequency of this adverse drug reaction is higher than previously thought. The Glucophage product information for healthcare professionals and patients has now been updated to state that vitamin B12 deficiency is a common adverse drug reaction, and may affect up to 1 in 10 people who take it. The product information has also been updated to note that the risk of this adverse reaction occurring increases with increasing metformin dose and treatment duration and in patients with risk factors known to cause vitamin B12 deficiency. The updated product information also includes new advice to healthcare professionals to test vitamin B12 levels in those presenting with anaemia or neuropathy and that periodic vitamin B12 monitoring should be considered in patients with risk factors for vitamin B12 deficiency. The product information for other medicines containing metformin will also be updated including fixed-dose combination products containing metformin.

Risk factors for vitamin B12 deficiency are wide ranging. They include: baseline vitamin B12 levels at the lower end of the normal range; conditions associated with reduced vitamin B12 absorption (such as elderly people and those with gastrointestinal disorders such as total or partial gastrectomy, Crohn's disease and other bowel inflammatory disorders, or autoimmune conditions); diets with reduced sources of vitamin B12 (such as strict vegan and some vegetarian diets); concomitant medication known to impair vitamin B12 absorption (including proton pump inhibitors or colchicine); genetic predisposition to vitamin B12 deficiency, such as intrinsic factor receptor deficiency (Imerslund-Gräsbeck syndrome) and transcobalamin II deficiency.

Advice for healthcare professionals:

- Metformin can commonly reduce vitamin B12 levels in patients, which may lead to vitamin B12 deficiency.
- The risk of low vitamin B12 levels increases with higher metformin dose, longer treatment duration, and in patients with risk factors for vitamin B12 deficiency.
- Test vitamin B12 serum levels if deficiency is suspected (for example, in patients presenting with megaloblastic anaemia or new-onset neuropathy) and follow current clinical guidelines on investigation and management of vitamin B12 deficiency.
- Consider periodic vitamin B12 monitoring in patients with risk factors for vitamin B12

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deficiency.

- Administer corrective treatment for vitamin B12 deficiency in line with current clinical guidelines; continue metformin therapy for as long as it is tolerated and not contraindicated.

In Hong Kong, there are 118 registered pharmaceutical products containing metformin. All products are prescription-only medicines. As of the end of June 2022, the Department of Health (DH) had received 19 cases of adverse drug reaction related to metformin, but these cases were not related to vitamin B12 deficiency. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 21 June 2022, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Batch recall of Rocephin for Injection 1G IV Sterile Powder

On 30 June 2022, the Department of Health (DH) endorsed a licensed wholesaler, Roche Hong Kong Limited (Roche), to recall one batch (batch number B0746B02) of Rocephin for Injection 1G IV Sterile Powder (Hong Kong Registration number HK-20190) from the market due to a potential quality defect of the product.

The DH received notification from Roche that the overseas packaging unit of Roche had detected pinholes in some of the 10ml Water for Injection ampoules attached to the product. The pinholes were considered melting defects during the production of the ampoules. As a precautionary measure, Roche voluntarily recall the affected batch from the market. DH's investigation is continuing.

The above product, containing ceftriaxone, is a prescription medicine used for treatment of infections. According to Roche, the affected batch has been supplied to private hospitals, private doctors and re-exported to Macau.

As of the end of June 2022, the DH had not received any adverse drug reaction report related to the affected product. A notice was posted on the Drug Office website on 30 June 2022 to alert the public of the product recall. The DH will closely monitor the recall.

Drug Incident

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

On 24 June 2022, the Department of Health (DH) conducted an operation against the sale of a slimming product, namely VSlimming Herbal, which was found to contain undeclared controlled drug ingredients, including a banned drug ingredient. During the operation, a 57-year-old man was arrested by the Police for suspected illegal sale and possession of Part 1 poisons and unregistered pharmaceutical product.

Acting upon intelligence, a sample of the above suspected unregistered pharmaceutical product was purchased from a retail store in Sham Shui Po for analysis. Test results from the Government Laboratory revealed that the oral capsules included in the sample contained sibutramine and spironolactone, both of which 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, pharmaceutical products containing sibutramine have been banned in Hong Kong because of an increased cardiovascular risk. Spironolactone is a prescription drug used in the management of heart failure and should only be used under supervision of a doctor. Side effects include headaches, gastrointestinal disturbance, hyponatraemia (abnormally low blood sodium level) and hyperkalaemia (elevated blood potassium level).

A press release was posted on the Drug Office website on 24 June 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,
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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.