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 March 2024 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: PRAC finds no link between mRNA COVID-19 vaccines and postmenopausal bleeding

On 8 March 2023, the 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 postmenopausal bleeding.

Postmenopausal bleeding is commonly defined as vaginal bleeding occurring one year or more after the last menstrual period. Postmenopausal bleeding is always considered abnormal and can be a symptom of serious medical conditions.

Recently, new information emerged from the medical literature as well as post-authorisation data that prompted investigation into postmenopausal bleeding with the two vaccines. The PRAC assessed all available data, including findings from literature, and available post-marketing spontaneous reports of suspected adverse reactions. After careful review, the PRAC considered that the available data do not support a causal association and an update of the product information for either vaccine is not warranted.

The committee will continue to monitor this issue for both Comirnaty and Spikevax through the established safety monitoring practices.

In Hong Kong, there are 3 Comirnaty vaccine products which are registered by Fosun Industrial Co., Limited:

- Comirnaty Dispersion For Injection COVID-19 mRNA Vaccine (Nucleoside Modified) 30 Micrograms/Dose (HK-67665);
- Comirnaty Original/Omicron BA.4-5 Dispersion For Injection COVID-19 mRNA Vaccine (Nucleoside Modified) (15/15 Micrograms)/Dose (HK-67666); and
- Comirnaty Omicron XBB.1.5 Dispersion For Injection COVID-19 mRNA Vaccine (Nucleoside Modified) 30 Micrograms/Dose (HK-68019).

There are 4 Spikevax vaccine products which are registered by Moderna Hong Kong Limited:

- Spikevax Bivalent Original/Omicron BA.4-5 Dispersion For Injection COVID-19 mRNA Vaccine (Nucleoside Modified) (50 Micrograms/50 Micrograms)/ml (HK-67830);
- Spikevax Bivalent Original/Omicron BA.4-5 Dispersion For Injection In Pre-filled Syringe COVID-19 mRNA Vaccine (Nucleoside Modified) 25 Micrograms/25 Micrograms (HK-67831);
- Spikevax XBB.1.5 Dispersion For Injection In Pre-filled Syringe COVID-19 mRNA Vaccine 50 Micrograms/Dose 0.5ml (HK-68081); and
- Spikevax 2023-2024 Formula (XBB.1.5) Suspension For Injection COVID-19 mRNA Vaccine 250 Micrograms/2.5ml (HK-68127).

All products are prescription-only medicines. The Department of Health will remain vigilant on safety update of the products issued by other overseas drug regulatory authorities.

Singapore: Zyrtec-D: Risks of posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome associated with the use of pseudoephedrine

On 18 March 2024, the Health Sciences Authority (HSA) announced that a Dear Healthcare Professional Letter has been issued by GlaxoSmithKline Pte Ltd to inform healthcare

professionals of the risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) associated with the use of pseudoephedrine-containing medicines.

There have been a few overseas cases of PRES and RCVS that have been reported in patients taking pseudoephedrine-containing medicines. Most cases resolved following discontinuation and appropriate treatment.

Healthcare professionals are encouraged to exercise careful discretion when prescribing or dispensing pseudoephedrine-containing medicines, and adhere to the labelled contraindications, warnings and precautions in order to mitigate the risk of occurrence of PRES or RCVS. Patients should be advised to immediately stop using pseudoephedrine -containing medicines and seek medical assistance if signs or symptoms of PRES or RCVS develop. The local package insert of Zyrtec-D (containing cetirizine and pseudoephedrine) will be updated to include further information on these adverse events and measures to reduce the risks.

In Hong Kong, there are 99 registered pharmaceutical products containing pseudoephedrine. All products are pharmacy only medicines. As of the end of March 2024, the Department of Health (DH) had received 2 cases of adverse drug reaction related to pseudoephedrine, but these cases were not related to PRES or RCVS. Related news was previously issued by European Medicines Agency and the United Kingdom Medicines and Healthcare products Regulatory Agency, and was reported in the Drug News since Issue No. 160, with the latest update reported in Drug News Issue No. 172. The DH issued letters to inform local healthcare professionals to draw their attention on 4 December 2023. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Australia: Updated warnings of faricimab (Vabysmo): retinal vasculitis risk

On 20 March 2024, the Therapeutic Goods Administration (TGA) announced that TGA's investigation into the risk of retinal vasculitis and/or retinal occlusive vasculitis in patients being treated with faricimab (Vabysmo) found that stronger warnings regarding this risk were needed in the Product Information (PI) and Consumer Medicine Information (CMI).

TGA's Pharmacovigilance Branch undertook a signal investigation in November 2023 to assess the risk of retinal vasculitis and/or retinal occlusive vasculitis with faricimab. Retinal vasculitis and retinal occlusive vasculitis are serious adverse events that could lead to permanent vision loss and require prompt diagnosis and management.

Sections 4.4 and 4.8 of the Vabysmo PI were updated to reflect the additional safety information and a Dear Health Care Professional letter was sent to ophthalmologists who prescribe intravitreal injections. The CMI was updated to reflect the changes.

Additional warnings added to the Australian PI:
4.4 Special warnings and precautions for use
Retinal Vasculitis and/or Retinal Occlusive Vasculitis: Retinal vasculitis and/or retinal occlusive vasculitis, typically in the presence of intraocular inflammation, have been reported with the use of Vabysmo in the postmarketing setting. Discontinue treatment with Vabysmo in patients who develop these events. Patients should be instructed to report any change in vision without delay (see section 4.8).

4.8 Adverse effects (undesirable effects)
Postmarketing Experience: Rare cases of retinal vasculitis and/or retinal occlusive vasculitis have been spontaneously reported in the postmarketing setting. Retinal vasculitis and retinal occlusive vasculitis have also been reported in patients treated with intravitreal therapies.

A search of TGA's Adverse Events Management System database on 19 December 2023 for 'faricimab' and reaction terms 'vasculitis' and 'retinal vasculitis' returned 3 related adverse event reports.

Health professionals should be alert to the updated warnings and should inform patients and carers of the potential retinal vasculitis and/or retinal occlusive vasculitis risk associated with faricimab use.

In Hong Kong, there is one registered pharmaceutical product containing faricimab, namely Vabysmo Solution For Intravitreal Injection 6mg/0.05ml (HK-67656). The product is registered by Roche Hong Kong Limited. It is a prescription-only medicine. As of the end of March

2024, the Department of Health (DH) had received 5 cases of adverse drug reaction related to faricimab, but these cases were not related to retinal vasculitis or retinal occlusive vasculitis. In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 21 March 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

The United States: FDA approves safety labeling changes regarding DPD deficiency for fluorouracil injection products

On 21 March 2024, the US Food and Drug Administration (FDA) announced that it approved safety labeling changes for fluorouracil injection products.

The FDA became aware of additional safety information regarding the risk of serious adverse reactions related to fluorouracil use in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. Revisions have been made to the Highlights of Prescribing Information and sections 5 (Warnings and Precautions) and 17 (Patient Counseling Information) of the full prescribing information to provide information about these risks. In addition, a new subsection 12.5 (Pharmacogenomics) has been added to section 12 (Clinical Pharmacology).

In Hong Kong, there are 3 registered pharmaceutical products which are fluorouracil injectable products. All products are prescription-only medicines. As of the end of March 2024, the Department of Health (DH) had received 108 cases of adverse drug reaction related to fluorouracil, but these cases were not related to DPD deficiency.

Related news was previously issued by European Medicines Agency, the United Kingdom Medicines and Healthcare products Regulatory Agency and Australia Therapeutic Goods Administration, and was reported in the Drug News since Issue No. 113, with the latest update reported in Drug News Issue No. 155. The DH issued letters to inform local healthcare professionals to draw their attention on 18 March 2019.

In June 2021, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the labelling of fluorouracil injectable products should include safety information regarding the increased risk of toxicity in patients with DPD deficiency. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

European Union: Synapse Labs Pvt. Ltd: Re-examination confirms suspension of medicines over flawed studies

On 22 March 2024, the European Medicines Agency (EMA) announced that its human medicines committee, the Committee for Medicinal Products for Human Use (CHMP) confirmed its recommendation to suspend or not grant the marketing authorisations of a number of generic medicines tested by Synapse Labs Pvt. Ltd, a contract research organisation (CRO) located in Pune, India on 21 March 2024. This confirmation concludes the re-examination requested by the applicants and marketing authorisation holders for some of the medicines concerned.

The CHMP adopted its initial recommendation in December 2023, after a good clinical practice (GCP) inspection which showed irregularities in study data and inadequacies in study documentation and in the computer systems and procedures to manage study data. This raised serious concerns about the data from bioequivalence studies conducted at the CRO. Such studies are carried out to show that a generic medicine releases the same amount of active substance in the body as the reference medicine.

For the majority of the medicines tested by Synapse Labs on behalf of European Union (EU) companies, the CHMP concluded that supporting data were lacking or insufficient to show bioequivalence and therefore recommended suspending the marketing authorisations of these medicines. For a small number of the medicines, sufficient supporting data were available to demonstrate bioequivalence; marketing authorisations for these medicines were maintained and ongoing marketing authorisation applications could continue.

As a result of the CHMP's initial opinion and re-examination, the recommendation to suspend medicines for which adequate bioequivalence data are lacking is confirmed. To lift the suspension, companies must provide alternative data demonstrating bioequivalence. Medicines for which ongoing marketing authorisation applications rely solely on data from Synapse Labs

will not be granted authorisation in the EU. An updated list of the medicines affected by the procedure is available on EMA's website.

Some of the medicines that have been recommended for suspension may be of critical importance (e.g., due to a lack of available alternatives) in some EU Member States. National authorities will assess the situation and can postpone the suspension of these medicines for a maximum of two years in the interest of patients. Companies have to submit the required bioequivalence data for these medicines within one year.

The CHMP's recommendation will now be sent to the European Commission which will issue a legally binding decision in due course.

Among the 103 drug ingredients/combinations of drug ingredients recommended for suspension by EMA, submission of bioequivalence data is required for 11 drug ingredients (namely, carbamazepine, gabapentin, lacosamide, oxcarbazepine, phenytoin, primidone, topiramate, zonisamide, clindamycin, digoxin and methotrexate) for registration of pharmaceutical product in Hong Kong.

Currently, there are registered pharmaceutical products containing carbamazepine (6 products), gabapentin (26 products), lacosamide (6 products), oxcarbazepine (6 products), phenytoin (5 products), topiramate (26 products), clindamycin (81 products), digoxin (4 products) and methotrexate (10 products). These products are not manufactured by the companies marketing the related products as listed by EMA. In addition, the bioequivalence study of these products submitted for registration were not conducted by Synapse Labs Pvt. Ltd. There is currently no registered pharmaceutical product containing primidone and zonisamide.

Related news was previously issued by EMA, and was reported in Drug News Issue No. 165. The Department of Health will remain vigilant on safety update on this matter issued by other overseas drug regulatory authorities.

Canada: Ezetrol (ezetimibe) and the risks of drug-induced liver injury and severe cutaneous adverse reactions

On 27 March 2024, Health Canada announced that Ezetrol (ezetimibe) may cause drug-induced liver injury (DILI) and severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilic and systemic symptoms (DRESS).

The Market Authorization Holder conducted a review of international safety data and the scientific literature and identified 42 post-marketing cases of DILI in patients taking Ezetrol, including a Canadian case of liver injury associated with ezetimibe monotherapy. There was sufficient evidence to suggest a causal association between ezetimibe monotherapy and DILI. Therefore, the current recommendation to consider performing liver function tests at the initiation of, or during treatment with, Ezetrol in combination with a statin or fenofibrate has been expanded to include Ezetrol monotherapy.

The review also identified rare cases of SCARs in patients taking Ezetrol. There was sufficient evidence to suggest at least a reasonable possibility of a causal association with some cases of SJS, TEN, and DRESS.

Healthcare professionals are advised to:

- Consider performing liver function tests at the initiation of Ezetrol, whether administered as monotherapy or in combination with a statin or fenofibrate, and subsequently as required.
- Instruct patients to immediately contact a healthcare professional if they experience symptoms of liver injury. Liver function should be evaluated if liver injury is suspected.
- Instruct patients to stop taking Ezetrol and to seek immediate medical help if they experience symptoms of SCARs.

The Canadian Product Monograph (CPM) for Ezetrol has been updated to include warnings about these serious adverse reactions. Health Canada will work with the manufacturers of generic versions of ezetimibe to update their respective CPMs.

In Hong Kong, there are 21 registered pharmaceutical products containing ezetimibe. All products are prescription-only medicines. As of the end of March 2024, with regard to ezetimibe, the Department of Health (DH) had received 6 cases of adverse drug reaction, of which one case was reported as acute hepatitis. All of the 6 cases were not related to SCARs. In light of the above Health

Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 28 March 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

Canada: Summary Safety Review: Amiodarone: Assessing the potential risk of primary graft dysfunction following heart transplantation

On 27 March 2024, Health Canada announced that it reviewed the potential risk of primary graft dysfunction (PGD) following heart transplantation with the pre-transplant use of amiodarone. The safety review was triggered by a labelling update in the United Kingdom.

Health Canada reviewed information provided by the manufacturers, and from searches of the Canada Vigilance database and the scientific literature. At the time of the review, Health Canada had not received any Canadian reports of PGD related to the pre-heart transplant use of amiodarone. Health Canada reviewed 7 international cases of PGD in patients taking amiodarone before heart transplantation. In all 7 cases, the role of amiodarone could not be determined due to insufficient clinical information about factors that could have contributed to the risk of PGD, such as the use of other medications and patient medical conditions. Health Canada also reviewed 6 articles published in the scientific literature. While these studies had a number of weaknesses, including the presence of confounders (other factors that may have contributed to the occurrence of PGD) and bias (conscious or unconscious influencing of a study and its results), overall the evidence reviewed was sufficient to support an increased risk of PGD in patients taking amiodarone before heart transplantation.

Health Canada's review found a possible link between the pre-heart transplant use of amiodarone and the risk of PGD. Health Canada will work with the manufacturers to update the Canadian Product Monograph of amiodarone-containing products to include the risk of PGD following heart transplantation.

In Hong Kong, there are 8 registered pharmaceutical products containing amiodarone. All products are prescription-only medicines. As of the end of March 2024, the Department of Health (DH) had received 2 cases of adverse drug reaction related to amiodarone, but these cases were not related to PGD. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 28 March 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

Canada: Summary Safety Review: Ibrance (palbociclib): Assessing the potential risk of venous thromboembolism

On 27 March 2024, Health Canada announced that it reviewed the potential risk of venous thromboembolism (VTE) with the use of Ibrance. The safety review was triggered by the 2020 publication of a study that found a higher risk of VTE with the use of cyclin-dependent kinase inhibitors (CDKIs), a class of drugs to which Ibrance belongs.

Venous thromboembolism, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a condition where a blood clot forms in a vein blocking the flow of blood through parts of the body. Deep vein thrombosis is a blood clot in a deep vein of the body, usually in the legs. A PE occurs when a DVT dislodges and travels to the lung artery, blocking blood flow and oxygen to the lungs. If not treated quickly, VTE can lead to disability and death.

At the time of the review, the Canadian Product Monograph (CPM) for the other CDKIs, Verzenio (abemaciclib) and Kisqali (ribociclib), included warnings for the risk of VTE, but not the CPM for Ibrance.

Health Canada reviewed information provided by the manufacturer and from the scientific literature. Health Canada reviewed 7 randomized controlled trials (RCTs) involving Ibrance, which included 8,793 patients. The majority (>95%) of these patients had early or metastatic breast cancer. Analysis of data across the 7 RCTs showed a higher risk of VTE with Ibrance treatment. Specifically, in the more relevant trials in metastatic breast cancer patients, VTE was reported in 3.4% of patients treated with Ibrance plus an endocrine therapy (medicine that either blocks the effects or interferes with the production of estrogen in the body), compared with 1.9% of patients treated with the endocrine therapy alone. The evidence reviewed supports a probable link between the risk of VTE and the use of Ibrance. This finding is consistent with the VTE findings for

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the other CDKIs marketed in Canada.

Health Canada's review of the available information concluded that there is a probable link between the use of Ibrance and the risk of VTE. Health Canada is working with the manufacturer to update the CPM for Ibrance to include the risk of VTE.

In Hong Kong, there are registered pharmaceutical products containing palbociclib (6 products), abemaciclib (3 products) and ribociclib (one product). All products are prescription-only medicines. As of the end of March 2024, the Department of Health (DH) had received adverse drug reaction related to palbociclib (145 cases) and ribociclib (26 cases), but these cases were not related to VTE. With regard to abemaciclib, the DH had received 17 cases of adverse drug reaction, of which one case was reported as VTE and one case was reported as PE.

Currently, the product insert of the locally registered abemaciclib-containing products include safety information about the risk of VTE. The current registered product insert of palbociclib- and ribociclib-containing products do not include the relevant information. In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 28 March 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

Drug Recall

Further Recall of Mecotuss Cap and Lyhexine Cap

On 26 March 2024, the Department of Health (DH) endorsed a licensed manufacturer, Meyer Pharmaceuticals Ltd (Meyer), to recall all batches of Mecotuss Cap (HK-35597) and Lyhexine Cap (HK-37207) from the market as a precautionary measure due to potential stability issue.

Following the batch recall of the above two products on 26 January 2024, further investigations conducted by Meyer revealed that the two products when storing under high temperature and humidity may have stability issue but would not be harmful to users. As a precautionary measure, Meyer is voluntarily recalling all the batches of these two products from the market.

The above two products are over-the-counter medicines used for the relief of cold and cough symptoms. According to Meyer, the products have been supplied to local private doctors, pharmacies and medicine companies.

As of the end of March 2024, the DH had not received any adverse reaction reports in connection with the above products. The DH will closely monitor the recall.

Drug Incident

Public urged not to buy or consume slimming product with undeclared controlled and banned drug ingredient

On 21 March 2024, the Department of Health (DH) appealed to the public not to buy or consume a slimming product with a Korean name (please refer to the photo in the press release), as it was found to contain an undeclared controlled and banned drug ingredient.

Acting upon a public complaint, the DH obtained a sample of the above product via a social media platform for analysis. Test results from the Government Laboratory revealed that the sample contained sibutramine, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138). The DH's investigation is continuing.

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

A press release was posted in the Drug Office website on 21 March 2024 to alert the public of the drug incident.

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

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

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

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

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

Useful Contact

Drug Complaint:

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

Adverse Drug Reaction (ADR) Reporting:

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

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

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