Drug News
藥 物 情 報

Issue Number 174

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in April 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: GLP-1 receptor agonists: available evidence not supporting link with suicidal and self-injurious thoughts and actions

On 12 April 2024, the European Medicines Agency (EMA) announced that its safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), has concluded that the available evidence does not support a causal association between the Glucagon-Like Peptide-1 receptor agonists (GLP-1) – dulaglutide, exenatide, liraglutide, lixisenatide and semaglutide – and suicidal and self -injurious thoughts and actions.

GLP-1 receptor agonists are used to treat type 2 diabetes and some are also authorised for weight management under certain conditions in adults who are obese or overweight. The review started in July 2023, following case reports of suicidal thoughts and thoughts of self-injury from people using liraglutide and semaglutide medicines, and in November 2023, the committee requested additional data from the marketing authorisation holders for these medicines, namely Ozempic, Rybelsus, Wegovy, Victoza, Saxenda, Xultophy, Byetta, Bydureon, Lyxumia, Suliqua and Trulicity.

Additionally, the committee analysed the results of a recent study, based on a large database of electronic health records, which investigated the incidence of suicidal thoughts in patients with overweight and type 2 diabetes mellitus treated with semaglutide or other non-GLP-1 receptor agonist medicines for diabetes or overweight. The study found no causal association between the use of semaglutide and suicidal thoughts.

Another study was conducted by EMA, based on electronic health records, which examined the risk of suicide-related and self-injury-related events in people with type 2 diabetes mellitus. The results did not support a causal association between the use of GLP-1 receptor agonists and this risk.

After reviewing the available evidence from non-clinical studies, clinical trials, post-marketing surveillance data and the available studies the PRAC considers that no update to the product information is warranted.

The marketing authorisation holders for these medicines will continue to monitor these events closely, including any new publications, as part of their pharmacovigilance activities and report any new evidence on this issue in their Periodic Safety Update Reports (PSURs).

In Hong Kong, there are registered pharmaceutical products containing dulaglutide (4 products), exenatide (1 product), liraglutide (5 products), lixisenatide (2 products) and semaglutide (11 products). All products are prescription-only medicines. As of the end of April 2024, the Department of Health (DH) had received adverse drug reactions with dulaglutide (5 cases), exenatide (2 cases), liraglutide (1 case), lixisenatide (1 case) and semaglutide (7 cases), but these cases were not related to suicidal thoughts or self-injury. Related news were previously issued by the EMA, Health Sciences Authority and United States Food and Drug Administration, and was reported in the Drug News since Issue No. 165, with the latest update reported in Drug News Issue No. 171. The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

The United States: FDA Requires Boxed Warning for T cell Malignancies Following Treatment with BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies

On 18 April 2024, the US Food and Drug Administration (FDA) announced that FDA requires boxed warning for T cell malignancies following treatment with BCMA-directed or CD19-directed autologous chimeric antigen receptor (CAR) T cell immunotherapies.

In November 2023, the Food and Drug Administration (FDA) posted a safety communication to provide information about reports of T cell malignancies including chimeric antigen receptor CAR-positive lymphoma in patients who received treatment with BCMA- or CD19-directed autologous CAR T cell immunotherapies. Reports were received from clinical trials and/or postmarketing adverse event data sources.

Currently approved products in this class include the following:

- Abecma (idecabtagene vicleucel)
- Breyanzi (lisocabtagene maraleucel)
- Carvykti (ciltacabtagene autoleucel)
- Kymriah (tisagenlecleucel)
- Tecartus (brexucabtagene autoleucel)
- Yescarta (axicabtagene ciloleucel)

FDA also listed post-treatment T cell malignancy as a potential signal of serious risk/new safety information for this product class, identified by FDA Adverse Event Reporting System (FAERS) in the July - September 2023 quarterly report. FDA concluded, based on an evaluation of data from postmarketing adverse event and clinical trial reports, that mature T cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusion, and may include fatal outcomes. FDA has determined that the serious risk of T cell malignancies is applicable to all currently approved BCMA-directed and CD19-directed genetically modified autologous CAR T cell immunotherapies. Therefore, in January 2024, FDA initiated class safety labeling changes.

FDA concluded that changes to the Boxed Warning are warranted to highlight the serious risk of T cell malignancies. In addition, FDA has required related updates to other sections of the label (Warnings and Precautions, Postmarketing Experience, Patient Counseling Information and Medication Guide).

Patients and clinical trial participants receiving treatment with these products should be monitored life-long for secondary malignancies. In the event that a new malignancy occurs following treatment with these products, contact the manufacturer to report the event and obtain instructions on collection of patient samples for testing for the presence of the CAR transgene.

In Hong Kong, Kymriah (tisagenlecleucel) Dispersion For Infusion (HK-66588) is a pharmaceutical product registered by Novartis Pharmaceuticals (HK) Limited. It is a prescription-only medicine. As of the end of April 2024, with regard to tisagenlecleucel, the Department of Health (DH) had received 18 cases of adverse drug reaction, of which 8 cases were reported as malignancies. The other products mentioned in the above FDA's announcement are not registered pharmaceutical products.

Related news was previously issued by FDA and European Medicines Agency, and was reported in Drug News Issue No. 169 and 171. The DH issued letters to inform local healthcare professionals to draw their attention on 24 January 2024. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

European Union: CHMP recommended new contraindications on the co-administration of Reyataz (Atazanavir) with encorafenib and ivosidenib, and with carbamazepine, phenobarbital, and phenytoin

On 26 April 2024, the European Medicines Agency (EMA) announced that the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 25 April 2024, recommending a change to the terms of the marketing authorisation for the medicinal product Reyataz. The marketing authorisation holder for this medicinal product is Bristol-Myers Squibb Pharma EEIG.

The CHMP adopted a change to sections 4.3 and 4.5 of the summary of product characteristics (SmPC) to reclassify drug-drug interactions to new contraindications. The new contraindications are:

- Co-administration with encorafenib and ivosidenib (see section 4.5).

- Co-administration with carbamazepine, phenobarbital, and phenytoin (see section 4.5).

For information, the full contraindications for Reyataz will be as follows:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Reyataz is contraindicated in patients with severe hepatic insufficiency (see sections 4.2, 4.4 and 5.2). Reyataz with ritonavir is contraindicated in patients with moderate hepatic insufficiency (see sections 4.2, 4.4, and 5.2).
- Co-administration with simvastatin or lovastatin (see section 4.5).
- Combination of rifampicin (see section 4.5).
- Combination of the PDE5 inhibitor sildenafil when used for the treatment of pulmonary arterial hypertension (PAH) only (see section 4.5). For co-administration of sildenafil for the treatment of erectile dysfunction see sections 4.4 and 4.5.
- Co-administration with medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows (e.g., quetiapine, lurasidone, alfuzosin, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), lomitapide, and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.5).
- Co-administration with grazoprevir-containing products, including elbasvir/grazoprevir fixed-dose combination (see section 4.5).
- Co-administration with glecaprevir/ pibrentasvir fixed-dose combination (see section 4.5).
- Co-administration with products containing St. John's wort (Hypericum perforatum) (see section 4.5).
- Co-administration with apalutamide, encorafenib and ivosidenib (see section 4.5).
- Co-administration with carbamazepine, phenobarbital, and phenytoin (see section 4.5).

Detailed recommendations for the use of this product will be described in the updated SmPC, which will be published in the revised European public assessment report (EPAR) and made available in all official European Union languages after a decision on this change to the marketing authorisation has been granted by the European Commission.

In Hong Kong, there are 4 registered pharmaceutical products containing atazanavir. All products are prescription-only medicines. As of the end of April 2024, with regard to atazanavir, the Department of Health (DH) had received 2 cases of adverse drug reaction, but these cases were not related to co-administration with encorafenib, ivosidenib, carbamazepine, phenobarbital, and phenytoin. In light of the above EMA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 29 April 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

Singapore: Pseudoephedrine and the rare risk of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)

On 29 April 2024, the Health Sciences Authority (HSA) announced that the European Medicines Agency (EMA) and UK Medicines and Healthcare products Regulatory Agency (MHRA) have completed their safety assessments on the risk of PRES and RCVS associated with pseudoephedrine. Their reviews considered information from post-marketing safety data and advice sought from their pharmacovigilance expert groups. The EMA acknowledged that while PRES and RCVS could lead to serious and life-threatening complications, these are rare conditions that generally resolve with prompt diagnosis and treatment. The MHRA's review noted four reports of suspected PRES or RCVS with pseudoephedrine in the context of over 4 million packets sold in the UK in 2022 alone. Both agencies have contraindicated the use of pseudoephedrine in patients with severe or uncontrolled hypertension or severe renal disease, which are risk factors for PRES and RCVS, and recommended for the addition of warnings on these adverse events to the package inserts (PIs) or patient information leaflets (PILs) of pseudoephedrine-containing products. They have also recommended for healthcare professionals to advise their patients to stop using these products immediately and seek treatment if they develop symptoms of PRES or RCVS.

To date, HSA has not received any local adverse event report of PRES or RCVS associated with pseudoephedrine despite its long history and

widespread use. In March 2024, one of the product registrants issued a Dear Healthcare Professional Letter to notify healthcare professionals about the risks of PRES and RCVS associated with the use of pseudoephedrine. HSA will work with the product registrants to strengthen the warnings on PRES and RCVS and their related symptoms in the PIs or PILs of pseudoephedrine-containing products registered locally.

Healthcare professionals are advised to take note of the advisories by the EMA and MHRA. They may also consider counselling their patients on symptoms that require immediate medical attention to facilitate the prompt detection of PRES and RCVS symptoms and the necessary medical intervention. These include sudden onset of severe headache, nausea, vomiting, visual disturbances, seizures and altered mental status.

In Hong Kong, there are 99 registered pharmaceutical products containing pseudoephedrine. All products are pharmacy only medicines. As of the end of April 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 HSA, EMA and MHRA, and was reported in the Drug News since Issue No. 160, with the latest update reported in Drug News Issue No. 173. 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 .

The United Kingdom: Finasteride reminder of the risk psychiatric side effects and of sexual side effects (which may persist after discontinuation of treatment)

On 29 April 2024, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that a patient alert card is being introduced for men taking finasteride to help raise awareness of the risk of psychiatric side effects and sexual dysfunction, including the potential for sexual dysfunction to persist after treatment has stopped. Healthcare professionals are reminded to monitor patients for both psychiatric and sexual side effects.

MHRA completed a safety review into finasteride following concerns from patients regarding a lack of awareness of these side effects amongst patients and healthcare professionals. A previous Drug Safety Update for finasteride was issued in 2017, however at the time the potential for persistence of some of the side effects were not widely known. MHRA recently reviewed the available evidence, including Yellow Card reports, published scientific literature and actions by other regulators, and this was considered by the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines. The PEAG noted that the product information for finasteride contains information regarding the potential for persistent sexual side effects after discontinuation with finasteride and depression and suicidal ideation. However, these side effects are not well known by prescribers and patients and therefore a Drug Safety Update article was recommended.

The PEAG also recommended inclusion of a patient card inside the pack. The card aims to increase awareness of the side effects including depression, suicidal thoughts and sexual dysfunction, and to advise patients on what to do if they experience these adverse effects. The patient card will be introduced this year.

Since the first report was received in November 1992, MHRA has received 426 Yellow Card reports up until 5 April 2024 of finasteride (both 1mg and 5mg formulations) and sexual dysfunction, including reports of erectile dysfunction (inability to get and maintain an erection) and decreased sex drive. In almost half of these reports, the outcome was recorded as ‘not recovered’ or ‘not resolved’.

Since the first report was received in February 1993, MHRA has received 281 reports of finasteride and depressed mood disorders and suicidal and self-injurious behaviours, up until 5 April 2024.

Advice for healthcare professionals:

- finasteride has been associated with depression, suicidal thoughts and sexual dysfunction
- patients have reported that sexual dysfunction (including decreased libido and erectile dysfunction) has persisted even after treatment was stopped
- before prescribing finasteride, ask patients if they have a history of depression or suicidal ideation
- advise patients to stop finasteride 1mg (Propecia) for male pattern hair loss

immediately if they develop depression or suicidal thoughts and to contact their doctor as soon as possible
- advise patients prescribed finasteride 5mg (Proscar) for benign prostatic hyperplasia to consult their doctor for further medical advice as soon as possible if they develop depression or suicidal thoughts
- monitor patients for psychiatric and sexual side effects
- a patient card will be introduced in all finasteride packs, which will highlight the risk of sexual side effects and psychiatric side effects reported with finasteride to increase awareness among patients and prescribers

In Hong Kong, there are 31 registered pharmaceutical products containing finasteride. All products are prescription-only medicines. As of the end of April 2024, with regard to finasteride, the Department of Health (DH) had received 5 cases of adverse drug reaction, of which 2 cases were reported as decreased libido, erectile dysfunction and depression.

Related news on the risk of psychiatric side effects and of sexual side effects associated with the use of finasteride was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 91, with the latest update reported in Drug News Issue No. 159. The DH issued letters to inform local healthcare professionals to draw their attention on 25 May 2017 and 20 January 2023. In September 2017, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the sales pack label and/or package insert of finasteride-containing products should include the relevant safety information. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

The United Kingdom: Montelukast: reminder of the risk of neuropsychiatric reactions

On 29 April 2024, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that healthcare professionals prescribing montelukast should be alert to the risk of neuropsychiatric reactions in all patients including children and adolescents. Reported neuropsychiatric reactions include sleep disorders, hallucinations, anxiety and depression, as well as changes in behaviour and mood. Healthcare professionals should advise patients and their caregivers to be alert to these risks and seek medical advice as soon as possible if neuropsychiatric reactions occur.

To increase awareness of the risks of neuropsychiatric effects with montelukast, new boxed warnings will be introduced to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) to make these risks more prominent to the reader. These warnings have been updated with the current evidence on the risk. Healthcare professionals and patients should familiarise themselves with this information.

To increase awareness of the risks of neuropsychiatric effects with montelukast, new boxed warnings will be introduced to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) to make these risks more prominent to the reader. These warnings have been updated with the current evidence on the risk. Healthcare professionals and patients should familiarise themselves with this information.

A range of neuropsychiatric reactions have been reported in association with montelukast. Among these are:
- sleep disturbances, depression and agitation including aggressive behaviour (may affect up to 1 in 100 people taking montelukast)
- disturbances of attention or memory (up to 1 in 1,000 people)
- very rarely, hallucinations and suicidal thinking and behaviour (up to 1 in 10,000 people)

Since first authorised in the United Kingdom (UK) in 1998, there have been approximately 44 million prescriptions of montelukast issued. During this time, MHRA has received 1,223 reports of suspected neuropsychiatric adverse reactions. Information on neuropsychiatric reactions with montelukast was first introduced in the SmPC in 2008 and a detailed warning was added in 2019.

Of these, the most frequently reported suspected neuropsychiatric reactions associated with montelukast for all age groups were sleep disorders, hallucinations, anxiety and depression, as well as changes in behaviour and mood. The most frequently reported reactions in younger children (up to and including 12 years old) were aggression, nightmares and anxiety while in older children (13 years old up to and including 17 years old) the

Safety Update

most commonly reported were anxiety, suicidal ideation and depression.

Advice for healthcare professionals:

- the warnings in the Patient Information Leaflet and Summary of Product Characteristics for all montelukast products in the UK have been strengthened and highlighted with a black box for greater emphasis
- be alert for neuropsychiatric reactions in patients taking montelukast; events have been reported in adults, adolescents, and children
- discontinue montelukast if patients experience new or worsening symptoms of neuropsychiatric reactions
- advise patients and their caregivers to carefully read the list of neuropsychiatric reactions in the Patient Information Leaflet and to seek medical advice immediately should they occur

In Hong Kong, there are 58 registered pharmaceutical products containing montelukast. All products are prescription-only medicines. As of the end of April 2024, with regard to montelukast, the Department of Health (DH) had received 7 cases of adverse drug reaction, of which 5 cases were reported as neuropsychiatric reactions.

Related news on the risk of neuropsychiatric reactions associated with the use of montelukast was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issue No. 119 and 125. The DH issued letters to remind local healthcare professionals to draw their attention on 20 September 2019 and 5 March 2020. In April 2021, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the sales pack label and/or package insert of montelukast-containing products should include the relevant safety information. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

Drug Recall

Batch Recall of PMS-Duloxetine Delayed-Release Capsules 60mg

On 22 April 2024, the Department of Health (DH) endorsed a licensed drug wholesaler, namely Trenton-Boma Limited (Trenton-Boma), to recall one batch (batch number: 640627) of PMS-Duloxetine Delayed-Release Capsules 60mg (HK-65447) from the market due to the presence of an impurity in the product.

The DH received notification from Trenton-Boma that the overseas manufacturer of the product is recalling the above batch due to the affected batch exceeded the interim acceptable limit for N-nitroso-duloxetine (NDLX). Some nitrosamine impurities are classified as probable or possible human carcinogen based on results from laboratory tests. As a precautionary measure, Trenton-Boma is voluntarily recalling the above batch from the market.

The above product, containing duloxetine, is a prescription medicine used for the treatment of depression. According to Trenton-Boma, the product has been imported into Hong Kong and supplied to the private doctors, veterinary surgeon and pharmacies.

As of the end of April 2024, the DH had not received any adverse reaction reports in connection with the above batch of product. A notice was posted in the Drug Office website on 22 April 2024 to alert the public of the product recall. The DH will closely monitor the recall.

Drug Incident

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

On 16 April 2024, the Department of Health (DH) appealed to the public not to buy or consume a slimming product, namely Honey Q Level Up, as it was found to contain undeclared controlled and banned drug ingredients.

During the DH's market surveillance, samples of the above product were purchased via an online sales platform for analysis. Test results from the Government Laboratory revealed that the samples contained sibutramine, benzyl sibutramine and fluoxetine, which are Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap. 138) (the Ordinance). The DH's investigation is continuing.

Drug Incident

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. Benzyl sibutramine is a substance structurally similar to sibutramine. Fluoxetine is used for treatment of mood disorders and may cause hallucination and insomnia.

A press release was posted in the Drug Office website on 16 April 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/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: Clinical Trials and Pharmacovigilance Unit,
Drug Office, Department of Health,
Suite 2002-05, 20/F, AIA Kowloon Tower, Landmark East,
100 How Ming Street,
Kwun Tong, Kowloon

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.