Drug News
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Issue Number 169

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in November 2023 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

The United Kingdom: Nirmatrelvir and ritonavir (Paxlovid): be alert to the risk of drug interactions with ritonavir

On 23 November 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that there is a risk of harmful drug interactions with the ritonavir component of the COVID-19 treatment Paxlovid due to its inhibition of the enzyme CYP3A, which metabolises many commonly used drugs.

Nirmatrelvir and ritonavir (Paxlovid 150mg/100mg film-coated tablets) is an anti-viral treatment that is indicated for the treatment of COVID-19. The ritonavir component of Paxlovid is not active against SARS-CoV-2 but inhibits the CYP3A-mediated metabolism of nirmatrelvir (the active antiviral), thereby increasing plasma concentrations of nirmatrelvir. It is this CYP3A inhibitory activity of ritonavir that poses a risk of harmful drug interactions with Paxlovid.

Harmful interactions can occur with many medicines. Section 4.3 of the Summary of Product Characteristics (SmPC) lists all the drugs with which Paxlovid is contraindicated and must not be co-administered, including commonly used medicines such as analgesics, antibiotics and antihistamines, and more specialized treatments such as antianginal drugs, anticancer drugs and anticonvulsants. Use of Paxlovid with these medicines may lead to serious or life-threatening side effects. Section 4.5 of the SmPC lists medicines which may lead to potentially significant interactions with Paxlovid, and where Paxlovid should be considered only if the benefits outweigh the risks. Healthcare professionals must review these sections of the SmPC in detail before prescribing Paxlovid.

The risks of potential drug interactions when taking Paxlovid, and what actions to take if an adverse event occurs, should be explained to patients by the prescriber. Paxlovid is also contraindicated in patients with hypersensitivities to nirmatrelvir, ritonavir or any of the listed excipients, and in patients with severe renal and/or hepatic impairment. Patients should be reminded to read the Patient Information Leaflet (PIL) and speak to a healthcare professional if they have questions.

Advice for healthcare professionals:

- There is a risk of potentially serious drug interactions with the ritonavir component of Paxlovid leading to increased toxicity from, or reduced effectiveness of concomitant medications.
- Ritonavir is a potent CYP3A4 inhibitor that acts to boost the plasma levels of the nirmatrelvir component of Paxlovid by preventing its degradation; as many commonly used drugs are metabolised by CYP3A4, the risk of harmful drug interactions with Paxlovid is significant.
- Drug interactions may also reduce the effectiveness of Paxlovid, in the treatment of COVID-19.
- Obtain a thorough history of patients' current medications, including over-the-counter medications, herbal remedies and illicit or recreational drug use.
- Refer to the Paxlovid SmPC before prescribing Paxlovid to check for contraindications and potential interactions.
- Remind patients to read the PIL and to be vigilant for any adverse reactions, seeking medical advice when required.

In Hong Kong, Paxlovid Tablets (HK-67360) and Paxlovid Tablets (HK-67683) are pharmaceutical products registered by Pfizer Corporation Hong

Kong Limited. Both products are prescription-only medicines. As of the end of November 2023, with regard to nirmatrelvir and ritonavir/Paxlovid, the Department of Health (DH) had received 96 cases of adverse drug reaction, of which one case was reported as drug interaction. The current product insert of the above locally registered Paxlovid products include safety information on drug interactions (including a listing of established and other potentially significant drug interactions). The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

Australia: Safety advisory: Fluoxetine: Presence of low levels of N-nitrosofluoxetine

On 27 November 2023, the Therapeutic Goods Administration (TGA) announced that it is investigating the presence of low levels of the nitrosamine impurity known as N-nitrosofluoxetine in medicines containing fluoxetine.

TGA determines acceptable intake (AI) limits for nitrosamines in medicines to ensure that these impurities do not pose a safety concern for patients. TGA has set an AI limit for N-nitrosofluoxetine over a lifetime exposure (i.e. long-term exposure). Some Australian sponsors of fluoxetine products have reported that their products currently contain levels of N-nitrosofluoxetine that are higher than this limit. TGA has determined that there are no health concerns associated with the short-term use of these medicines. Nitrosamine impurities also affect fluoxetine products supplied overseas, and TGA's approach is similar to other regulators such as the European Medicines Agency.

Alphapharm Pty Ltd, the sponsor that supplies Zactin Tabs (fluoxetine 20 mg dispersible tablets), has provided information to TGA that this product contains levels of N-nitrosofluoxetine above the temporary higher limit. As a precautionary measure, Alphapharm has paused distribution of the product and recalled stock from wholesalers while this issue is investigated. Fluoxetine capsule products remain available.

N-nitrosofluoxetine is a type of nitrosamine that is present as an impurity. 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 N-nitrosofluoxetine being detected in fluoxetine 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.

In Hong Kong, Zactin Tabs is not a registered pharmaceutical product. There are 22 registered pharmaceutical products containing fluoxetine in Hong Kong. All products are prescription-only medicines. As of the end of November 2023, the Department of Health (DH) had received 22 cases of adverse drug reaction related to fluoxetine. None of them is concluded to be related to the presence of N-nitrosofluoxetine. The DH will remain vigilant on the development of the issue and any safety update of the drug issued by overseas drug regulatory authorities for consideration of any action deemed necessary.

Patients who are taking fluoxetine-containing products should not stop taking the medicines unless advised by their prescribers.

Australia: Safety advisory: Duloxetine: Presence of low levels of N-nitroso-duloxetine

On 27 November 2023, the Therapeutic Goods Administration (TGA) announced that it is investigating the presence of low levels of the nitrosamine impurity known as N-nitroso-duloxetine (NDLX) in medicines containing duloxetine.

TGA determines acceptable intake (AI) limits for nitrosamines in medicines to ensure that these impurities do not pose a safety concern for patients. TGA has set an AI limit for NDLX over a lifetime exposure (i.e. long-term exposure). Some Australian sponsors of duloxetine products have reported that their products currently contain levels of NDLX that are higher than this limit. TGA has determined that there are no health concerns associated with the short-term use of these medicines. Nitrosamine impurities also affect duloxetine products supplied overseas, and TGA's approach is similar to other regulators such as the European Medicines Agency.

Duloxetine medicines remain available and consumers are advised to continue to take their

medicine as prescribed.

NDLX is a type of nitrosamine that is present as an impurity. 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 NDLX being detected in duloxetine 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.

In Hong Kong, there are 14 registered pharmaceutical products containing duloxetine. All products are prescription-only medicines. As of the end of November 2023, the Department of Health (DH) had received 2 cases of adverse drug reaction related to duloxetine. None of them is concluded to be related to the presence of N-nitroso-duloxetine (NDLX). The DH will remain vigilant on the development of the issue and any safety update of the drug issued by overseas drug regulatory authorities for consideration of any action deemed necessary.

Patients who are taking duloxetine-containing products should not stop taking the medicines unless advised by their prescribers.

The United States: FDA investigating serious risk of T-cell malignancy following BCMA-directed or CD19-directed autologous chimeric antigen receptor (CAR) T cell immunotherapies

On 28 November 2023, the US Food and Drug Administration (FDA) announced that it has received 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.

FDA has determined that the risk of T-cell malignancies is applicable to all currently approved BCMA-directed and CD19-directed genetically modified autologous CAR T cell immunotherapies. T-cell malignancies have occurred in patients treated with several products in the class. 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)

Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, FDA is investigating the identified risk of T cell malignancy with serious outcomes, including hospitalization and death, and is evaluating the need for regulatory action.

As with all gene therapy products with integrating vectors (lentiviral or retroviral vectors), the potential risk of developing secondary malignancies is labeled as a class warning in the United States prescribing information for approved BCMA-directed and CD19-directed genetically modified autologous T cell immunotherapies. The initial approvals of these products included postmarketing requirements under Section 505(o) of the Federal Food, Drug, and Cosmetic Act to conduct 15-year long term follow-up observational safety studies to assess the long-term safety and the risk of secondary malignancies occurring after treatment.

Patients and clinical trial participants receiving treatment with these products should be monitored life-long for new 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 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 November 2023, 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 current product insert of the locally registered Kymriah product includes safety information on secondary malignancies – Patients treated with Kymriah may develop secondary malignancies or recurrence of

their cancer. They should be monitored life-long for secondary malignancies. The other products mentioned in the above FDA's announcement are not registered pharmaceutical products in Hong Kong.

As the FDA's investigation is ongoing, the DH will remain vigilant on the result of the investigation and safety update of the drugs issued by FDA and other overseas drug regulatory authorities for consideration of any action deemed necessary.

The United States: FDA warns of rare but serious drug reaction to the antiseizure medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan)

On 28 November 2023, the US Food and Drug Administration (FDA) announced that the antiseizure medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan) can cause a rare but serious reaction that can be life-threatening if not diagnosed and treated quickly. This reaction is called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). It may start as a rash but can quickly progress, resulting in injury to internal organs, the need for hospitalization, and even death.

This hypersensitivity reaction to these medicines is serious but rare. DRESS can include fever, rash, swollen lymph nodes, or injury to organs including the liver, kidneys, lungs, heart, or pancreas.

FDA is requiring manufacturers of these medicines to add new warnings about DRESS to the prescribing information and the medication guide for patients and caregivers. For levetiracetam, this involves adding a new warning in the Warnings and Precautions section of the prescribing information, which describes the most serious and significant potential safety issues. Currently the symptoms associated with this condition are described less prominently. For clobazam, FDA is requiring a new warning specifically about DRESS to be added to the prescribing information. Symptoms related to this risk are already described more generally in other sections of the clobazam prescribing information.

The warnings for both levetiracetam and clobazam medicines will include information that early symptoms of DRESS such as fever or swollen lymph nodes can be present even when a rash cannot be seen. This is different from other serious skin-related reactions that can happen with these medicines and where a rash is present early on, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). FDA is also requiring information on this risk to be added to the medication guides to help inform patients and caregivers about this risk.

FDA's cumulative review found serious cases of DRESS in children and adults worldwide (32 for levetiracetam and 10 for clobazam). Most patients in these cases required hospitalization and received medical treatments, and two patients treated with levetiracetam died. These numbers include only reports submitted to FDA and found in the medical literature, so there are likely additional cases about which FDA is unaware. FDA determined there was reasonable evidence that levetiracetam and clobazam were the cause of DRESS in these cases based on the timing of the onset of these events after receiving the medicines and the order in which they occurred. The majority of cases for which information about discontinuation was available reported that DRESS symptoms improved when the medicines were discontinued.

Healthcare professionals should be aware that prompt recognition and early treatment is important for improving DRESS outcomes and decreasing mortality. Diagnosis is often difficult because early signs and symptoms such as fever and swollen lymph nodes may be present without evidence of a rash. DRESS can develop 2 weeks to 8 weeks after starting the medicines, and symptoms and intensity can vary widely. DRESS can also be confused with other serious skin reactions such as SJS and TEN. Advise patients of the signs and symptoms of DRESS and to stop taking their medicine and seek immediate medical attention if DRESS is suspected during treatment with levetiracetam or clobazam.

In Hong Kong, there are registered pharmaceutical products containing levetiracetam (38 products) and clobazam (3 products). All products are prescription-only medicines. As of the end of November 2023, the Department of Health (DH) had received adverse drug reaction related to levetiracetam (7 cases) and clobazam (one case), but these cases were not related to DRESS.

Related news on the risk of DRESS associated with the use of clobazam was previously issued by Health Canada, and was reported in Drug News

Issue No. 134. The DH issued letters to inform local healthcare professionals to draw their attention on 10 December 2020. In December 2021, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided to keep vigilant on any update from other health authorities.

In light of the above FDA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 29 November 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: MHRA instructs health organisations to prepare now for new measures to reduce ongoing serious harms of valproate

On 28 November 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that healthcare organisations are being instructed now to put in place a plan to implement the first phase of new regulatory measures to reduce the known harms of valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the risk of impaired fertility in males.

From January 2024, valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or unless there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available.

All women who could become pregnant and girls who are currently taking valproate will be reviewed at their next annual specialist review, using a revised valproate Annual Risk Acknowledgement Form, which will include the need for a second opinion's signature if the patient is to continue with valproate.

A similar system will be introduced later in 2024 for male patients currently taking valproate. This follows advice from an independent expert group of the Commission on Human Medicines (CHM), with representation from across the healthcare system, that the measures should be introduced in a phased manner to ensure ongoing patient care is not disrupted.

These are important regulatory changes recommended by the CHM to increase scrutiny of valproate prescribing and ensure that valproate is only used when the benefits outweigh the risk.

The MHRA urges patients to attend any offered appointments to discuss their treatment plan and to talk to a healthcare professional if they are concerned. Clinicians should discuss the current warnings and upcoming measures relating to valproate with their patients and consider together how it affects the patient's individual circumstances.

These changes are being introduced following concerns that the existing regulatory requirements are not being consistently followed. In light of these concerns, the MHRA conducted a review of the available data and asked for advice from the independent CHM, which listened to the views of patients and healthcare professionals. The review also considered risks of valproate in males including the risk of male infertility.

The CHM recommended that their safety measures apply to people under the age of 55 because this is the age-group evidence suggests is most likely to be affected by the risks of valproate when taken during pregnancy and the possible risk of impaired fertility in males, which is thought to be reversible upon dose reduction or discontinuation. The possible risk of impaired fertility in males has been in the product information since 2011 and should be discussed between patient and doctor as part of the informed consent process.

As stated in the product information, there are some animal studies that show adverse effects of valproate on the testes of juvenile animals as well as transgenerational effects. It is unknown what this means for human patients as it's not always possible to be sure that an effect seen in animals will be the same in a person taking a medicine. Further work on this is being undertaken.

No one should stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may become worse without treatment, which can be harmful.

In Hong Kong, there are 10 registered pharmaceutical products containing valproate. All products are prescription-only medicines. As of the end of November 2023, the Department of Health (DH) had received 15 cases of adverse drug

reaction related to valproate, but these cases were not related to the risks in pregnancy or impaired fertility in males.

Related news on the risks in pregnancy and impaired fertility in males associated with the use of valproate was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 21, with the latest update reported in Drug News Issue No. 158. The DH issued letters to inform local healthcare professionals to draw their attention on 4 July 2011, 7 May 2013, 13 October 2014, 12 February 2018 and 13 December 2022.

The Registration Committee of the Pharmacy and Poisons Board discussed the matter related to the risks in pregnancy associated with the use of valproate in September 2011, December 2014, December 2018 and June 2019. Currently, the package insert or sales pack label of locally registered valproate-containing products should include safety information on the risk of malformations and impaired cognitive development in children exposed to valproate during pregnancy, and contraindications, e.g. in women of childbearing potential unless pregnancy preventive measures have been implemented, etc. The certificate holders of locally registered valproate-containing products are also required to implement risk minimisation measures, e.g. patient information leaflet should be provided, etc.

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

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.

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

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Adverse Drug Reaction (ADR) Reporting:

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Link: http://www.drugoffice.gov.hk/adr.html
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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.