# Drug News
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**Issue Number 172**

***This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in February 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: Paxlovid: Reminder of serious adverse reactions when taken together with certain immunosuppressants**

On 9 February 2024, the European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) is reminding healthcare professionals of the risk of serious and potentially fatal adverse reactions with Paxlovid (nirmatrelvir, ritonavir) when used in combination with certain immunosuppressants that have a narrow safe dosage range (where small changes in the dose can lead to serious adverse reactions), due to drug-drug interactions reducing the body's ability to eliminate these medicines.

Paxlovid is a medicine used for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of the disease becoming severe. The immunosuppressants concerned are called calcineurin inhibitors (tacrolimus, ciclosporin) and mTOR inhibitors (everolimus, sirolimus), which reduce the activity of the immune system. They are used for treating certain autoimmune disorders or for preventing the body from rejecting transplanted organs.

Paxlovid should only be given with tacrolimus, ciclosporin, everolimus or sirolimus if close and regular monitoring of their blood levels is possible, to reduce the risk of drug-drug interactions causing serious reactions. Healthcare professionals need to consult with a multidisciplinary group of specialists to manage the complexity of taking these medicines together.

Paxlovid must not be given in combination with medicines for which elimination from the body is highly reliant on a set of liver enzymes (proteins), known as CYP3A, and that also have a narrow safe dosage range. This includes the immunosuppressant called voclosporin. Before starting the treatment with Paxlovid, healthcare professionals should carefully weigh the potential benefits of Paxlovid treatment against the risks of serious adverse reactions in case of administration together with immunosuppressants.

The PRAC reviewed all available evidence, including reports of serious adverse reactions, some of which were fatal, resulting from drug-drug interactions between Paxlovid and these immunosuppressants. In several cases, blood levels of these immunosuppressants increased rapidly to toxic levels resulting in life-threatening conditions. Therefore, the PRAC agreed on a direct healthcare professional communication (DHPC) to remind healthcare professionals of the risk of these interactions, which is known and already described in the product information for this medicine. The DHPC for Paxlovid will be forwarded to the Committee for Medicinal Products for Human Use (CHMP). When adopted, the DHPC will be disseminated to healthcare professionals by the marketing authorisation holder, according to an agreed communication plan, and published on the direct healthcare professional communications page and in national registers in European Union Member States.

In Hong Kong, 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 February 2024, with regard to nirmatrelvir and ritonavir/Paxlovid, the Department of Health (DH) had received 97 cases of adverse drug reaction, of which one case was reported as drug interaction (between Paxlovid and a drug which is not an immunosuppressant).

Related news on the risk of drug interactions associated with the use of Paxlovid due to its inhibition of the enzyme CYP3A was previously issued by the United Kingdom Medicines and Healthcare products Regulatory Agency, and was reported in the Drug News Issue No. 169.

The current product insert of the above locally registered Paxlovid products include safety information on drug interactions (including those with the immunosuppressants: tacrolimus, ciclosporin, everolimus, sirolimus and voclosporin). The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

**The United Kingdom: Pseudoephedrine: very rare risk of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)**

On 20 February 2024, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that there have been very rare reports of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) with pseudoephedrine.

A review of the available evidence, including the assessment of cumulative reporting of adverse drug reaction reports, was considered by the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines (CHM). The PEAG recommended updates to the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) to further describe the risk of PRES and RCVS and the potential risk factors for these conditions, and advised the MHRA to remind healthcare professionals and patients of these risks.

PRES, also known as reversible posterior leukoencephalopathy syndrome (RPLS), is a rare condition in which parts of the brain are affected by swelling, usually as a result of an underlying cause such as severely elevated blood pressure, kidney failure, severe infections, certain medications, some autoimmune diseases and pre-eclampsia. The diagnosis is usually made by imaging of the brain, which may enable areas of swelling to be identified. PRES usually has an acute onset characterised by headaches and seizures; many people also experience visual changes, confusion and drowsiness, weakness of the arm and/or leg on one side of the body (hemiplegia), difficulty speaking, or more rarely other neurological symptoms.

RCVS, also known as Call-Fleming syndrome, is a rare condition characterised by thunderclap headaches which are sudden, intense headaches that can reoccur over a few days to weeks and are often associated with nausea and sensitivity to light. RCVS can also be associated with acute neurological symptoms such as seizure and stroke. Symptoms are thought to arise from transient constriction in the blood vessels of the brain. In some cases, RCVS may be associated with childbirth, vasoactive or illicit drug use, head trauma, autoimmune or blood disorders, or complications of pregnancy. RCVS is usually diagnosed by brain imaging with angiography, to identify constrictions in cerebral blood vessels.

For both conditions, patients typically fully recover within 3 months with early recognition and treatment.

To date, the MHRA has received 4 Yellow Card reports of suspected PRES or RCVS with pseudoephedrine. This is in the context of widespread usage with over 4 million packets sold in the United Kingdom in 2022 alone.

Advice for healthcare professionals:

- PRES and RCVS present with the following symptoms: sudden severe headache or thunderclap headache, sudden onset of nausea and vomiting, confusion, seizures and/or visual disturbances.
- PRES and RCVS are recognised very rare side effects with pseudoephedrine-containing medicines, which are used for the symptomatic treatment of nasal and sinus congestion with colds, flu and allergies.
- Pseudoephedrine is for short term use only and should not be used for prolonged or extended use.
- Use of the product is contraindicated in patients with severe hypertension or uncontrolled hypertension, or severe renal disease.

In Hong Kong, there are 100 registered pharmaceutical products containing pseudoephedrine. All products are pharmacy only medicines. As of the end of February 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.

# Safety Update

Related news was previously issued by European Medicines Agency and MHRA, and reported in the Drug News since Issue No. 160, with the latest update reported in Drug News Issue No. 171. 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.

**Canada: Summary Safety Review: Colistin (colistimethate sodium): Assessing the potential risk of pseudo-Bartter syndrome**

On 29 February 2024, Health Canada announced that it reviewed the potential risk of pseudo-Bartter syndrome with the use of colistin (colistimethate sodium). The safety review was triggered by published cases of pseudo-Bartter syndrome with the use of colistin (colistimethate sodium) in the scientific literature.

Pseudo-Bartter syndrome is an acquired condition (not passed on from a parent) primarily presenting as metabolic alkalosis (an acid-base disorder), hypokalemia (low blood potassium) and other electrolyte abnormalities. Colistin (colistimethate sodium) is a prescription antibiotic drug authorized for sale in Canada to treat acute or chronic infections.

Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases, and scientific literature. At the time of the review, Health Canada had not received any Canadian reports of pseudo-Bartter syndrome related to the use of colistin (colistimethate sodium). Health Canada reviewed 7 international cases of pseudo-Bartter syndrome in patients who were administered colistin (colistimethate sodium). All 7 cases were identified in the published literature. Of the 7 cases reviewed, 6 were found to be probably linked to the use of colistin (colistimethate sodium), and 1 was found to be possibly linked. In all 7 cases, hypokalemia, metabolic alkalosis, and loss of potassium in the urine were reported. Some cases also involved hypomagnesemia (low blood magnesium) and hypocalcemia (low blood calcium). In all 7 cases, electrolyte abnormalities resolved or significantly improved following the discontinuation of colistin (colistimethate sodium).

Health Canada's review of the available information found a link between the use of colistin (colistimethate sodium) and the risk of pseudo-Bartter syndrome. Health Canada is working with the manufacturers to update the Canadian product monograph for colistin (colistimethate sodium)-containing products with a warning about reported cases of pseudo-Bartter syndrome.

In Hong Kong, there are 3 registered pharmaceutical products containing colistin (colistimethate sodium) for human use. All products are prescription-only medicines. As of the end of February 2024, the Department of Health (DH) had not received any case of adverse drug reaction related to colistin (colistimethate sodium). In light of the above Health Canada's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 1 March 2024, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

# Drug Recall

**Batch recall of Apo-Mometasone Aqueous Nasal Spray 50mcg/metered spray**

On 16 February 2024, the Department of Health (DH) endorsed a licensed drug wholesaler, Hind Wing Co Ltd (Hind Wing), to recall a batch (batch number: TX5343) of Apo-Mometasone Aqueous Nasal Spray 50mcg/metered spray (HK-62898) from the market as a precautionary measure due to potential quality issue.

The DH received notification from Hind Wing today that the overseas manufacturer of the product is initiating a voluntary recall of the above batch due to potential presence of Burkholderia cepacia complex. As a precautionary measure, Hind Wing is voluntarily recalling the affected batch from the market.

The above product, containing mometasone furoate, is a prescription medicine indicated for the prophylaxis and treatment of allergic rhinitis. According to Hind Wing, the above batch of product has been imported into Hong Kong and supplied to the Hospital Authority, private hospitals, private doctors and pharmacies.

As of the end of February 2024, the DH had not

# Drug Recall

received any adverse reaction reports in connection with the affected batch of product. A notice was posted in the Drug Office website on 16 February 2024 to alert the public of the product recall. The DH will closely monitor the recall.

# Drug Incident

**Woman arrested for suspected illegal sale and possession of slimming products with undeclared controlled and banned drug ingredient**

On 6 February 2024, the Department of Health (DH) conducted an operation against the sale of two slimming products, namely HOTCHA Botanical Beverage Mix chocolate with Morosil and HOTCHA Botanical Beverage Mix Hazelnut Coffee with Morosil, which were found to contain an undeclared controlled and banned drug ingredient. During the operation, a 40-year-old woman was arrested by the Police for suspected illegal sale and possession of unregistered pharmaceutical products and Part 1 poisons.

Acting upon a public complaint, the DH obtained samples of the above products via an online platform for analysis. Test results from the Government Laboratory revealed that the samples contained sibutramine, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138) (the Ordinance). The DH conducted an operation today and a 40-year-old woman selling the products concerned was arrested. The 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 6 February 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.***