# Drug News
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**Issue Number 161**

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

**Singapore: TOPAMAX (topiramate) TABLETS 25mg, 50mg and 100mg: Risk of neurodevelopmental disorders (autism spectrum disorder and intellectual disability) in children following in utero exposure and reminder on use of topiramate during pregnancy**

On 3 March 2023, the Health Sciences Authority (HSA) announced that a Dear Healthcare Professional Letter has been issued by Johnson & Johnson International (Singapore) Pte Ltd to inform healthcare professionals of new safety updates regarding an increased risk of neurodevelopmental disorders (autism spectrum disorder and intellectual disability) in children exposed to topiramate in utero, as well as to remind about the existing risks of congenital abnormalities related to the use of topiramate during pregnancy. Revisions to the Singapore package inserts for TOPAMAX are being made, including the recommendation of highly effective contraception in women of childbearing potential before treatment initiation and informing patients of the risk related to the use of topiramate during pregnancy.

In Hong Kong, there are 32 registered pharmaceutical products containing topiramate. All products are prescription-only medicines. As of the end of March 2023, the Department of Health (DH) had received 4 cases of adverse drug reaction related to topiramate, but these cases were not related to neurodevelopmental disorders in children exposed to topiramate in utero.

Currently, the package insert and/or sales pack label of locally registered topiramate-containing products should include safety information on the increased risk of cleft lip and/or cleft palate (oral clefts) in infants exposed to topiramate in utero.

Related news on the initiation of safety review of topiramate and the risk of neurodevelopmental disorders in children with in utero exposure 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. 153, with the latest update reported in Drug News Issue No. 155. As the reviews are ongoing, the DH will remain vigilant on the conclusion of the reviews and any safety updates of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

**The United Kingdom: Pholcodine-containing cough and cold medicines: withdrawal from UK market as a precautionary measure**

On 14 March 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced advice for healthcare professionals regarding the withdrawal of pholcodine-containing medicines from the market.

Pholcodine is an opioid medicine approved in adults and children older than 6 years of age to treat non-productive (dry) cough and, in combination with other active substances, for the treatment of symptoms of cold and influenza. Previous reviews have examined the link between prior use of pholcodine and an increased risk of anaphylaxis during general anaesthesia involving neuromuscular blocking agents (NMBAs). The potential for cross-reactivity between pholcodine and NMBAs was added to the product information for pholcodine-containing medicines in January 2022.

The MHRA review considered the cumulative safety information, including the results from the recently completed ALPHO study, which showed that use of pholcodine during the 12 months preceding anaesthesia was significantly associated

with an increased risk of perianaesthetic anaphylaxis to NMBAs (adjusted odds ratio = 4.2; 95% CI 2.5 to 6.9). Data on the risk related to the use of pholcodine beyond the period of 12 months was not available from this study, although data from an earlier study in Norway suggest that the very small increased risk may persist for up to 3 years.

The Commission on Human Medicines (CHM) advised that there is sufficient overall evidence for an association with pholcodine, although the absolute risk of anaphylaxis remains very small in patients who have taken pholcodine. Anaphylaxis following use of NMBAs is roughly estimated as having an overall incidence of fewer than 1 case per 10,000 procedures. Given the advice of the CHM, and the lack of identifiable effective measures to minimise the increased risk of anaphylactic reactions to NMBAs, pholcodine-containing products are being withdrawn from the market as a precaution.

Pholcodine-containing products have only been available in the United Kingdom for purchase in a pharmacy. Pharmacists should provide advice to those who have any concerns about their medicine or would like to seek advice on alternative medicines or management of their symptoms.

The MHRA scientific review took place alongside a review conducted by the European Medicines Agency (EMA), which also concluded that the benefits did not outweigh the risks.

Advice for healthcare professionals:

- Pholcodine-containing cough and cold medicines are being withdrawn from the United Kingdom market as a precaution following a review which found that their benefits do not outweigh the increased risk of the very rare event of anaphylaxis to NMBAs used in general anaesthesia.
- Ask patients scheduled to undergo general anaesthesia involving NMBAs whether they have used pholcodine-containing medicines, particularly in the past 12 months, and maintain awareness about the potential for perianaesthetic anaphylaxis related to NMBAs.
- Do not dispense or sell pholcodine-containing medicines. Consider recommending appropriate treatment alternatives for patients who present with a new dry cough or who are currently taking pholcodine.
- Pharmacies should follow the MHRA Class 2 Medicines Recall Notice to quarantine stock of pholcodine-containing medicines and return it to the manufacturer.

In Hong Kong, there are 28 registered pharmaceutical products containing pholcodine. All products are pharmacy only medicines. As of the end of March 2023, the Department of Health (DH) had received one case of adverse drug reaction related to pholcodine, but this case was not related to anaphylaxis. Related news was previously issued by EMA and Australia Therapeutic Goods Administration, and was reported in the Drug News since Issue No. 17, with the latest update reported in Drug News Issue No.160. The DH issued letters to inform local healthcare professionals to draw their attention on 1 March 2023. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

**Australia: Check for pholcodine use before general anaesthesia**

On 17 March 2023, the therapeutic Goods Administration (TGA) announced that health professionals are reminded to check whether patients scheduled to undergo general anaesthesia with neuromuscular blocking agents (NMBAs) have used products containing pholcodine in the previous 12 months. This is due to a suspected link to an increased risk of potentially life-threatening anaphylactic reactions.

Pholcodine has been used in adults and children to treat non-productive cough and is most commonly used in non-prescription cough syrups and lozenge products. It has also been used in combination with other active substances in products that treat the symptoms of cold and flu.

TGA has recently made a decision to cancel the registration of pholcodine-containing medicines in Australia. All stock of pholcodine-containing products remaining on pharmacy shelves has also been recalled. The TGA decision followed a review by the European Medicines Agency recommending the withdrawal of marketing authorisations for these products in Europe. Health professionals are encouraged to discuss this safety issue with patients and to advise them to stop taking any pholcodine-containing medicines that they have. Recommend appropriate alternatives to treat cough and other cold and flu symptoms.

If a patient is scheduled to undergo general anaesthesia with NMBAs, check whether they have used pholcodine in the previous 12 months. Be aware of the risk of anaphylactic reactions in these patients. It is important to reassure patients this risk only applies to general anaesthesia containing NMBAs and not to local anaesthetics.

In Hong Kong, there are 28 registered pharmaceutical products containing pholcodine. All products are pharmacy only medicines. As of the end of March 2023, the Department of Health (DH) had received one case of adverse drug reaction related to pholcodine, but this case was not related to anaphylaxis. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 17, with the latest update reported in Drug News Issue No.160. The DH issued letters to inform local healthcare professionals to draw their attention on 1 March 2023. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

**Singapore: Epilim (valproate): Risk of neurodevelopmental disorders including autism spectrum disorders in children after paternal exposure**

On 20 March 2023, the Health Sciences Authority (HSA) announced that a Dear Healthcare Professional Letter has been issued by Sanofi-Aventis Singapore Pte. Ltd. to inform healthcare professionals of new safety information regarding a higher risk of neurodevelopmental disorders (NDDs), including autism spectrum disorders, in children after paternal exposure to valproate as compared to lamotrigine or levetiracetam.

This finding was from a retrospective observational study on electronic medical records in 3 European Nordic countries where there was an increased risk of NDDs in children (0 to 11 years old) born to men treated with valproate at the time of conception compared to those treated with lamotrigine or levetiracetam.

The Singapore package insert for Epilim (valproate) is being revised. There are also revised and new educational materials for healthcare professionals and patients. Healthcare professionals are advised to inform male patients of this potential risk and consider alternative therapeutic options with the patients. In men initiating or remaining on valproate treatment, it is recommended for healthcare professionals to discuss with the patient, at least annually, the need for effective contraception, and to ensure that the male patient has acknowledged the risk and precautions associated with valproate use.

In Hong Kong, there are 10 registered pharmaceutical products containing valproate. All products are prescription-only medicines. As of the end of March 2023, the Department of Health (DH) had received 14 cases of adverse drug reaction related to valproate, but these cases were not related to the risk of NDDs in children after paternal exposure to valproate. In light of the above HSA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 22 March 2023. The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

**Canada: Summary safety review: Cloxacillin: Assessing the potential risk of acute kidney injury**

On 22 March 2023, Health Canada announced that it reviewed the potential risk of acute kidney injury (AKI) with the use of cloxacillin. This safety review was triggered by case reports of AKI received through Health Canada's Canada Vigilance Program.

Health Canada reviewed the available information from searches of Canadian and international reports in the Canada Vigilance database and the scientific literature.

Health Canada reviewed 20 cases (9 Canadian and 11 international) of AKI in patients taking cloxacillin from the Canada Vigilance database. Of the 20 cases, 16 (7 Canadian) were found to be possibly linked to the use of cloxacillin, 3 (1 Canadian) were unlikely to be linked, and 1 (Canadian) could not be assessed due to insufficient clinical information. Three deaths (1 Canadian) were reported among the 16 cases that were assessed as having a possible link to the use of cloxacillin. The role of cloxacillin in these events could not be determined, as other medications and life-threatening medical conditions, including severe infections, could have contributed. In the 16 cases found to be possibly linked to use of cloxacillin, all patients had risk factors or were on other medications which were

known to cause AKI.

Health Canada's review of the scientific literature found a wide range of incidence rates of AKI in patients using cloxacillin. Overall, evidence of a link between cloxacillin and AKI in the scientific literature was inconclusive due to study limitations and contributing risk factors in patients.

Health Canada's review of the available information did not establish a link between the use of cloxacillin and the risk of AKI. Health Canada will work with the manufacturers to update the Canadian product monograph for cloxacillin-containing products to note that cases have been reported and to increase awareness of this potential risk.

In Hong Kong, there are 22 registered pharmaceutical products containing cloxacillin. All products are prescription-only medicines. As of the end of March 2023, the Department of Health (DH) had not received any case of adverse drug reaction related to cloxacillin. The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

**The United Kingdom: Terlipressin: new recommendations to reduce risks of respiratory failure and septic shock in patients with type 1 hepatorenal syndrome**

On 23 March 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced new recommendations following a recent clinical trial which found that in patients with type 1 hepatorenal syndrome terlipressin may cause serious or fatal respiratory failure at a frequency higher than previously known, and that terlipressin increases the risk of sepsis and septic shock.

A recent European review into the benefits and risks of terlipressin treatment, which was triggered by the CONFIRM trial findings, concluded that new measures were required to reduce the risk of respiratory failure and sepsis when terlipressin is used in patients with type 1 hepatorenal syndrome. The Pharmacovigilance Expert Advisory Group of the UK's Commission on Human Medicines agreed with the recommendations, while also highlighting the benefits of terlipressin treatment when an appropriate assessment of the benefits and risks has been made.

Changes will therefore be made to the product information for terlipressin medicines authorised for type 1 hepatorenal syndrome to note the new risk minimisation measures and information on risks. A letter has also been sent to UK healthcare professionals.

The review confirmed that terlipressin remains a highly effective treatment for type 1 hepatorenal syndrome but identified some risk factors that should be considered by prescribers when treatment decisions are made.

The review identified patients with severe renal impairment (in this review, defined as patients with baseline serum creatinine above 5 mg/dl) as being at reduced likelihood of response to terlipressin as well as at increased risk of death. A post-hoc subgroup analysis of the CONFIRM trial identified patients with severe renal impairment (in this review, defined as patients with baseline serum creatinine above 5 mg/dl) and severe reduction in liver function (in particular patients with ACLF grade 3 or a MELD score $\geq 39$) as having a reduced likelihood of response to terlipressin as well as an increased risk of developing respiratory failure and fluid-overload-related serious adverse events and of death.

An assessment of benefits and risks for the individual patient should be made when deciding on appropriate treatment in patients with these risk factors.

It was acknowledged that the doses of albumin given in the CONFIRM trial were higher than would usually be advised in European guidelines and this may have contributed to fluid overload and the respiratory events seen. The dose of albumin should therefore be considered if signs of respiratory failure or fluid overload arise.

Continuous infusion has been added to the product information as an alternative method of administration to bolus injection.

Continuous infusion has been recommended within the European Association for the Study of the Liver (EASL) guidelines for some time and a small amount of literature suggests that this method is associated with a better safety profile and has a more stable lowering effect on portal pressure than bolus administration by avoiding high peak plasma concentrations of terlipressin. While the literature is insufficient to suggest that continuous infusion

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would lower the rate of respiratory events specifically, the evidence is sufficient to recommend this as an alternative method of administration.

Advice for healthcare professionals:

- Findings of the CONFIRM trial showed terlipressin to be effective at reversing type 1 hepatorenal syndrome, but also showed that patients who received terlipressin were more likely to die by day 90 (largely due to respiratory disorders) than those who received placebo
- There were also more serious respiratory events and cases of sepsis or septic shock in patients who received terlipressin than in those who received placebo
- Since both advanced renal impairment and advanced liver impairment were risk factors for poorer outcomes in patients with type 1 hepatorenal syndrome:
  - Avoid terlipressin in those with advanced renal dysfunction (baseline serum creatinine at or above 442 µmol/L (5.0 mg/dL)), unless the benefit is judged to outweigh the risks
  - Avoid terlipressin in those with severe liver disease (defined as Acute-on-Chronic Liver Failure (ACLF) grade 3, a Model for End-stage Liver Disease (MELD) score ≥ 39, or both), unless the benefit is judged to outweigh the risks
- Stabilise patients with new-onset breathing difficulties or worsening of existing respiratory disease before administering terlipressin and monitor closely during treatment
- Consider a reduction in albumin dose in patients with signs or symptoms of respiratory failure or fluid overload; discontinue terlipressin if symptoms are severe or do not resolve
- Monitor patients daily for signs and symptoms of infection
- Monitor blood pressure, heart rate, oxygen saturation, serum sodium and potassium levels, and fluid balance; terlipressin may induce myocardial ischaemia and pulmonary vascular congestion, especially in those with pre-existing cardiopulmonary disease
- Terlipressin can be administered as a continuous intravenous infusion as an alternative to bolus injection as infusion may be associated with lower rates of severe adverse events than bolus injection
- Patients with type 1 hepatorenal syndrome receiving terlipressin should be counselled on the benefits and risks, even if circumstance necessitates that counselling occurs after treatment with terlipressin is given
- This advice is not relevant to use of terlipressin for bleeding oesophageal varices

In Hong Kong, there are 4 registered pharmaceutical products containing terlipressin. All products are prescription-only medicines. As of the end of March 2023, the Department of Health (DH) had not received any case of adverse drug reaction related to terlipressin. Related news was previously issued by EMA, and was reported in the Drug News since Issue No. 147, with the latest update reported in Drug News Issue No.157. The DH issued letters to inform local healthcare professionals to draw their attention on 3 October 2022. As previously reported, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

# Drug Recall

**Recall 4 batches of Haloperidol-Neuraxpharm Decanoate Injection 50mg and 100mg**

On 24 March 2023, the Department of Health (DH) endorsed a licensed drug wholesaler, Hind Wing Co Ltd (Hind Wing), to recall three batches (batch number: 200176, 210247, 210656) of Haloperidol-Neuraxpharm Decanoate Injection 50mg (HK-65059) and one batch (batch number: 200178) of Haloperidol-Neuraxpharm Decanoate Injection 100mg (HK-65060) from the market as a precautionary measure due to potential quality issue.

The DH received notification from Hind Wing on 24 March 2023 that the overseas manufacturer identified a defective filter that was used in the manufacturing process of another product. The same filter was also used in the manufacturing of certain batches of the above-mentioned products. As a precautionary measure, Hind Wing is voluntarily recalling the affected products from the market.

The above product, containing haloperidol, is a prescription medicine used for the treatment of psychotic disorders such as schizophrenia. According to Hind Wing, the product has been

imported into Hong Kong and supplied to the Hospital Authority and private doctors.

As of the end of March 2023, the DH had not received any adverse drug reaction reports in connection with the products. A notice was posted in the Drug Office website on 24 March 2023 to alert the public of the product recall. The DH will closely monitor the recall .

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

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

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

**Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.**
**Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.**

# *Useful Contact*

## Drug Complaint:

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

## Adverse Drug Reaction (ADR) Reporting:

**Tel: 2319 2920**
**Fax: 2319 6319**
**E-mail: adr@dh.gov.hk**
**Link: http://www.drugoffice.gov.hk/adr.html**
***Post: Adverse Drug Reaction and Adverse Event Following Immunization Unit,***
***Drug Office, Department of Health,***
***Room 1856, 18/F, Wu Chung House,***
***213 Queen's Road East,***
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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.***