Drug News
藥 物 情 報

Issue Number 150

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in April 2022 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: mRNA COVID-19 vaccines: PRAC finds no link with autoimmune hepatitis

On 8 April 2022, European Medicines Agency (EMA) announced that its Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that available evidence does not support a causal link between COVID-19 vaccines Comirnaty and Spikevax and very rare cases of autoimmune hepatitis (AIH).

AIH is a serious chronic inflammatory condition in which the immune system attacks and damages the liver. Signs and symptoms of autoimmune hepatitis vary from person to person and may include yellowing of the skin (jaundice), build-up of fluid in the legs (oedema) or belly (ascites) and gastrointestinal symptoms.

The committee's assessment is based on data from medical literature, cases of AIH spontaneously reported in the EudraVigilance database and further data and analyses provided by the marketing authorisation holders.

The PRAC concluded that the available evidence does not currently warrant an update to the product information of the vaccines.

EMA will continue to closely monitor any new reports of the condition and take appropriate measures if necessary.

In Hong Kong, the above products are not registered pharmaceutical products under the Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). The Department of Health will remain vigilant on any safety update of the product issued by other overseas drug regulatory authorities.

Taiwan: Safety information for medicines containing anagrelide hydrochloride

On 19 April 2022, Taiwan Food and Drug Administration (TFDA) announced that European Medicines Agency (EMA) has issued a direct healthcare professional communication (DHPC) to remind healthcare professionals that abrupt treatment discontinuation of Xagrid (anagrelide hydrochloride) may increase the risk of thrombotic complications, including cerebral infarction, and the product information of anagrelide hydrochloride will be updated to include the relevant risk information and recommendations on use related to thrombotic risk and cerebral infarction. (Related EMA website: https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-xagrid-anagrelide-hydrochloride-risk-thrombosis_en.pdf)

After investigation, there are 5 drugs containing anagrelide hydrochloride licensed in Taiwan, the Chinese package inserts of these licensed drugs do not include relevant information related to abrupt anagrelide discontinuation may increase the risk of thrombotic complications, including cerebral infarction. The TFDA is evaluating if further risk control measures will be imposed on drugs containing anagrelide hydrochloride.

Please refer to the following website in TFDA for details:
http://www.fda.gov.tw/TC/siteList.aspx?sid=1571

In Hong Kong, there is one registered pharmaceutical product containing anagrelide, namely Agrylin Cap 0.5mg (HK-51737). The

product is registered by Takeda Pharmaceuticals (Hong Kong) Limited. It is a prescription-only medicine. As of the end of April 2022, the Department of Health (DH) had not received any case of adverse drug reaction related to anagrelide.

In light of the above TFDA's announcement and the relevant information issued by the EMA, the DH issued letters to inform local healthcare professionals to draw their attention on 19 April 2022. The DH will remain vigilant on any safety updates issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

The United Kingdom: Pregabalin (Lyrica): Findings of safety study on risks during pregnancy

On 19 April 2022, Medicines and Healthcare products Regulatory Agency (MHRA) announced that a new study has suggested pregabalin may slightly increase the risk of major congenital malformations if used in pregnancy. Patients should continue to use effective contraception during treatment and avoid use in pregnancy unless clearly necessary.

New review of study of pregabalin in pregnancy
Fuller data is now available from a Nordic observational study of more than 2,700 pregnancies exposed to pregabalin in the first trimester.

The MHRA has carefully reviewed the results of the study alongside a recent European review of the same findings. The review concluded that pregabalin use during the first trimester of pregnancy may cause a slightly increased risk of major congenital malformations in the unborn child.

The MHRA has considered the recommendations of the European review, together with the other limited safety data available regarding pregabalin safety in pregnancy, and agreed that the product information should be updated to include information from this study. The Summary of Product Characteristics and Patient Information Leaflet have now been updated.

The product information continues to advise that effective contraception should be used during treatment and that use in pregnancy avoided unless clearly necessary. Healthcare professionals are advised to consider our guidance on contraceptive methods, and take into account the patient's personal circumstances when advising on contraception.

Advice for healthcare professionals:

- an observational study of more than 2,700 pregnancies exposed to pregabalin has shown use in the first trimester to be associated with a slightly increased risk of major congenital malformations compared with exposure to no antiepileptic drugs or to lamotrigine or to duloxetine
- continue to provide counselling to patients using pregabalin on:
  - the potential risks to an unborn baby
  - the need to use effective contraception during treatment
- continue to avoid use of pregabalin during pregnancy unless clearly necessary and only if the benefit to the patient clearly outweighs the potential risk to the fetus – ensure the patient has a full understanding of the benefits, risks, and alternatives, and is part of the decision-making process
- advise patients planning a pregnancy or who become pregnant during treatment to make an appointment to discuss their health condition and any medicines they are taking
- in cases where the benefit outweighs the risk, and it is clearly necessary that pregabalin should be used during pregnancy, it is recommended to:
  - use the lowest effective dose
  - report any suspected adverse drug reactions, including for the baby

In Hong Kong, there are 52 registered pharmaceutical products containing pregabalin. All products are prescription-only medicines. As of the end of April 2022, the Department of Health (DH) had received 16 cases of adverse drug reaction related to pregabalin, but these cases are not related to congenital malformations. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 20 April 2022 and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Updates to the pregnancy and breastfeeding information for Spikevax COVID-19 vaccine and Comirnaty COVID-19 Vaccine

On 19 April 2022, Medicines and Healthcare

products Regulatory Agency (MHRA) announced that they have made changes to the product information for the Spikevax (Moderna) COVID-19 Vaccine and the Comirnaty (Pfizer/BioNTech) COVID-19 Vaccine to reflect the large amount of real-world data on pregnancy and breastfeeding that has now been collected. The available data are reassuring on safety and that the vaccines can be used during pregnancy and breastfeeding.

A large amount of information from pregnant women vaccinated with Spikevax and Comirnaty during the second and third trimester has not shown negative effects on the pregnancy or the newborn baby.

Published studies from the USA and Norway have compared miscarriage rates for vaccinated and unvaccinated women who were pregnant over the same time periods. The studies included data from a large number of women (more than 15,000) who received Spikevax or Comirnaty COVID-19 vaccines. Both studies found that the occurrence of miscarriage was equally likely amongst unvaccinated women as amongst women at the same stage of pregnancy who were vaccinated in the previous 3 to 5 weeks. These studies provide strong evidence for no increased risk of miscarriage in association with the mRNA vaccines in current use.

The numbers of Yellow Card reports for pregnant women are low in relation to the number of pregnant women who have received COVID-19 vaccines to date. There is no pattern from the reports to suggest that any of the COVID-19 vaccines used in the UK, or any reactions to these vaccines, increase the risk of miscarriage, stillbirths, congenital anomalies or birth complications.

There is no current evidence that COVID-19 vaccination while breastfeeding causes any harm to breastfed children or affects the ability to breastfeed. Spikevax and Comirnaty can be given during breastfeeding.

In Hong Kong, the above products are not registered pharmaceutical products under the Pharmacy and Poisons Ordinance (Cap. 138). The COVID-19 vaccine by Fosun Pharma/BioNTech (i.e. Comirnaty) is authorised for emergency use in Hong Kong in accordance with the Prevention and Control of Disease (Use of Vaccines) Regulation (Cap. 599K). The DH will remain vigilant on any safety update of the product issued by other overseas drug regulatory authorities.

Related news on the safety data associated with the use of mRNA vaccines during pregnancy was previously issued by the European Medicines Agency (EMA) and was reported in Drug News Issue No. 147.

Australia: Clozapine and gastrointestinal hypomotility with severe complications

On 22 April 2022, Therapeutic Goods Administration (TGA) announced that the potentially fatal risk of gastrointestinal hypomotility in patients taking clozapine has been highlighted with a new boxed warning in the Product Information (PI) for this medicine. Health professionals should assess for constipation before and during treatment with clozapine, and manage suspected constipation promptly to prevent severe complications.

The severe gastrointestinal effects of intestinal obstruction, severe constipation and gastrointestinal hypomotility are among the most serious adverse reactions experienced with clozapine. In post-marketing experience, severe complications of gastrointestinal hypomotility (such as intestinal obstruction, faecal impaction, megacolon, paralytic ileus and intestinal ischaemia or infarction) have resulted in hospitalisation, surgery and death.

The new boxed text and other changes to the PI expand on existing warnings about severe gastrointestinal adverse reactions associated with clozapine, which are primarily due to its potent anticholinergic effects.

The boxed warning states:
Clozapine-induced gastrointestinal hypomotility
Severe gastrointestinal adverse reactions have occurred with the use of clozapine resulting in potential outcomes of hospitalisation, surgery and death (see Section 4.4 Special warnings and precautions for use, and Section 4.8 Adverse effects (undesirable effects)). Prior to initiating and during treatment with clozapine, screen for constipation and, if necessary, manage as per current clinical guidelines.

The changes to the PI note that:

- the subjective symptoms of constipation may not accurately reflect the degree of

gastrointestinal hypomotility. Therefore, health professionals should carefully monitor any changes in the frequency or character of a patient's bowel movements, as well as signs and symptoms of complications of hypomotility, such as:
  - nausea and/or vomiting
  - abdominal distension and/or pain
  - lack of urge and/or inability to defecate
  - constipation
- patients with evidence of constipation or gastrointestinal hypomotility should be managed promptly to prevent severe complications
- clozapine should be used with caution and under careful supervision in patients with a current diagnosis or prior history of constipation
- concomitant use of clozapine with anticholinergic medicines should be avoided where possible because of the increased risk of severe gastrointestinal side effects or anticholinergic toxicity.

The PI updates are based on evidence published in the literature and from post-market adverse event data in Australia and internationally. To 1 March 2022, there were 1,523 reports of gastrointestinal disorder for clozapine in the TGA's Database of Adverse Event Notifications (DAEN), which included 260 reports of constipation, 146 of intestinal obstruction, 93 of abdominal pain and 41 of small intestinal obstruction. Of the 1,023 clozapine reports with a fatal outcome, 103 were due to gastrointestinal disorders.

The adverse reactions listed in the post-marketing experience category in the PI for clozapine are sourced from spontaneous reports and literature, and therefore their frequency is unknown. Megacolon, intestinal infarction/ischaemia, intestinal necrosis, intestinal ulceration and intestinal perforation are listed as potentially fatal adverse gastrointestinal reactions in this category; diarrhoea, abdominal discomfort, heartburn, dyspepsia and colitis are also listed as gastrointestinal adverse reactions, but not as potentially fatal.

In Hong Kong, there are 9 registered pharmaceutical products containing clozapine. All products are prescription-only medicines. As of the end of April 2022, the Department of Health (DH) had received 3 cases of adverse drug reaction related to clozapine, but these cases are not related to gastrointestinal hypomotility. Related news was previously issued by various overseas drug regulatory authorities and was reported in Drug News Issue No. 70. In December 2016, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the sales pack labels and/or package inserts of clozapine-containing products should include the relevant safety warning. DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

Drug Recall

Recall of Apo-Acyclovir Tablets 200mg and 800mg

On 28 April 2022, the Department of Health (DH) endorsed a licensed drug wholesaler, Hind Wing Co Ltd (Hind Wing), to recall a total of four batches of the following two products from the market as a precautionary measure due to the presence of an impurity in the products.

Name of product	Hong Kong registration number	Batch number
Apo-Acyclovir Tablets 200mg	HK-43427	RH9368 RH9370
Apo-Acyclovir Tablets 800mg	HK-58228	RP8516 RP8517

The DH received notification from Hind Wing on 28 April 2022 that the overseas manufacturer of the products is initiating a voluntary recall of the above batches due to the presence of a higher than accepted level of an impurity, N-nitrosodimethylamine (NDMA) in the affected batches. NDMA is classified as a probable human carcinogen based on results from laboratory tests. As a precautionary measure, Hind Wing is voluntarily recalling the affected products from the market.

The above products are prescription medicines used for the treatment of herpes simplex. According to Hind Wing, the products have been imported into Hong Kong and supplied to local doctors, pharmacies and DH clinics.

As of the end of April 2022, the DH had not received any adverse reaction reports in connection with the products. A press release was posted on the Drug Office website on 28 April 2022 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.

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,
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.