Drug News
藥 物 情 報

Issue Number 102

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in April 2018 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

US: Recall of E-Z-Paste Barium Sulfate Esophageal Cream (60% w/w), 454g tube

On 4 April 2018, the United States (US) Food and Drug Administration (FDA) announced that Bracco Diagnostics Inc. is recalling one lot (lot number: 00538529) of E-Z-Paste Barium Sulfate Esophageal Cream (60% w/w), 454g tube, manufactured by E-Z-EM Canada Inc. for E-Z-EM Inc. a subsidiary of Bracco Diagnostics Inc., Monroe Twp., NJ 0883. The reason for recall is out-of-specification result for a preservative assay - methylparaben - during stability testing of one lot.

In Hong Kong, E-Z-Paste 60% W/W (Barium Sulfate Esophageal Cream) (HK-19221) is a pharmaceutical product registered by A R Burkill & Sons (HK) Ltd. According to the company, a total of 108 tubes of the affected batch were imported in 2016 and 2017 and were all supplied to the Hospital Authority. The Department of Health (DH) endorsed A R Burkill & Sons (HK) Ltd to recall the affected batch from the market. The company was also instructed to seek investigation report from the manufacturer in Canada. The product, containing barium sulphate, is a medicine used for single contrast radiography of the esophagus. DH will closely monitor the recall. As on 7 May 2018, DH has not received any adverse reaction reports in connection with the affected batch of product.

EU: EMA reviewing risk of dosing errors with methotrexate. Review prompted by continued reports of overdose

On 13 April 2018, the European Medicines Agency (EMA) of the European Union (EU) announced that EMA has started a review of the risk of dosing errors with methotrexate medicines.

When used for inflammatory diseases, such as arthritis and psoriasis, methotrexate is taken once a week whereas for some types of cancer, the dose is higher and the medicine is used more frequently. Mistakes have led to some patients incorrectly receiving a dose every day instead of every week. As a result, patients have received too much of the medicine, with serious consequences in some cases.

The risk of dosing errors with methotrexate has been recognised for many years and several measures are already in place in some EU countries to reduce this risk, including the use of visual reminders on the medicine packs. However, a recent assessment found that serious adverse events related to overdose, including fatalities, are still occurring. The Spanish medicines regulator, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), therefore asked EMA to further investigate the reasons why dosing errors continue to occur in order to identify measures to prevent them.

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) will examine the available evidence and recommend whether further measures are needed to minimise the risk of dosing errors. PRAC will also take into account the work of bodies specialising in patient safety.

In Hong Kong, there are 17 registered pharmaceutical products containing methotrexate (including 7 products in oral form and 10 parenteral products). All these products are prescription-only medicines.

As on 7 May 2018, DH has received 11 cases of adverse drug reaction (ADR) with methotrexate, but they were not reported to be related to the overdosing mentioned in the above EMA announcement.

In view of EMA's PRAC announcement, DH will keep vigilant on any further update from EMA and other health authorities.

EU: PRAC to further consider unmet medical needs for hydroxyethyl-starch (HES) solutions for infusion

On 13 April 2018, EMA announced that, following the PRAC recommendation in January 2018 to suspend the marketing authorisations for HES solutions for infusion across EU, the European Commission (EC) has requested PRAC further consider any possible unmet medical need that could result from the suspension, as well as the feasibility and likely effectiveness of additional risk minimisation measures.

PRAC is looking at these specific aspects and will discuss its recommendation at its May meeting. PRAC's revised recommendation will then be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position.

In Hong Kong, there are 6 registered pharmaceutical products containing hydroxyethyl starch, namely Voluven Infusion 6% (HK-50474) and Volulyte 6% Solution for Infusion (HK-58087) registered by Fresenius Kabi Hong Kong Limited, Tetraspan 6% Solution for Infusion (HK-56978) and Tetraspan 10% Solution for Infusion (HK-56979) registered by B. Braun Medical (HK) Ltd, and Hestar-200 Inj. 10% (HK-57095) and Hestar-200 Inj. 6% (HK-57096) registered by Unico & Co. All products are prescription-only medicines.

Related news on increased risks of death and kidney injury in critically ill patients was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 44, 48, 50 and 99. DH issued letters to inform local healthcare professionals to draw their attention on the above risks on 17 June 2013 and 15 January 2018.

The Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the matter in the meeting on 5 December 2013, and decided that DH will remain vigilant on the final version of the warnings by EU health authority and the final legally binding decision by EC for further consideration. CMDh endorsed the recommendation of PRAC and concluded that HES solutions must no longer be used in treating patients with sepsis or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality. Subsequently, EC endorsed it on 19 December 2013 for the adoption of a final legally binding decision valid throughout EU.

In April 2018, the Registration Committee further reviewed and discussed the suspension of the marketing authorisations for HES solutions for infusion across EU, and decided to keep vigilant on any update on the issue from other regulatory authorities.

As on 7 May 2018, DH has not received any case of ADR related to hydroxyethyl starch. In light of the above EMA's announcement, DH will remain vigilant on any updates of recommendation of hydroxyethyl starch issued by EMA and other overseas regulatory authorities.

US: FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal)

On 25 April 2018, US FDA is warning that the medicine lamotrigine for seizures and bipolar disorder can cause a rare but very serious reaction that excessively activates the body's infection-fighting immune system. This can cause severe inflammation throughout the body and lead to hospitalization and death, especially if the reaction is not diagnosed and treated quickly. As a result, FDA is requiring a new warning about this risk be added to the prescribing information in the lamotrigine drug labels.

The immune system reaction, called hemophagocytic lymphohistiocytosis (HLH), causes an uncontrolled response by the immune

system. HLH typically presents as a persistent fever, usually greater than 101°F, and it can lead to severe problems with blood cells and organs throughout the body such as the liver, kidneys, and lungs.

Healthcare professionals should be aware that prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality. Diagnosis is often complicated because early signs and symptoms such as fever and rash are not specific. HLH may also be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms. Healthcare professionals should evaluate patients who develop fever or rash promptly, and discontinue lamotrigine if HLH or another serious immune-related adverse reaction is suspected and an alternative etiology for the signs and symptoms cannot be established. Healthcare professionals should also advise patients to seek immediate medical attention if they experience symptoms of HLH during lamotrigine treatment. A diagnosis of HLH can be established if a patient has at least five of the following eight signs or symptoms:

- fever and rash
- enlarged spleen
- cytopenias
- elevated levels of triglycerides or low blood levels of fibrinogen
- high levels of blood ferritin
- hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy
- decreased or absent Natural Killer Cell activity
- elevated blood levels of CD25 showing prolonged immune cell activation

Patients or their caregivers should contact their healthcare professionals right away if they experience any symptom of HLH while taking lamotrigine. HLH can occur within days to weeks after starting treatment. A physical examination and specific laboratory blood tests and other evaluations are used to diagnose HLH. Patients should not stop taking lamotrigine without talking to their healthcare professionals first as doing so can cause serious problems. Signs and symptoms of HLH include but are not limited to:

- fever
- enlarged liver; symptoms may include pain, tenderness, or unusual swelling over the liver area in the upper right belly
- swollen lymph nodes
- skin rashes
- yellow skin or eyes
- unusual bleeding
- nervous system problems, including seizures, trouble walking, difficulty seeing, or other visual disturbances

In the 24 years since lamotrigine's 1994 approval in US, FDA identified eight cases worldwide of confirmed or suspected HLH associated with the medicine in children and adults. This number includes 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 lamotrigine was the cause of HLH in these eight cases based on the timing of events and the order in which they occurred. The patients in these cases required hospitalization and received drug and other medical treatments, with one dying.

In Hong Kong, there are 22 registered pharmaceutical products containing lamotrigine, and are prescription-only medicines. As on 7 May 2018, DH has received one case of ADR related to lamotrigine, but it was not related to HLH. In light of the above FDA's announcement, DH issued a letter to inform local healthcare professionals to draw their attention on 26 April 2018 and the matter will be discussed by the Registration Committee.

Drug Incident

Woman arrested for suspected illegal sale of unregistered pharmaceutical product

At 23 April 2018 night, a 41-year-old woman was arrested in a joint operation by DH and the Police for suspected illegal sale of an unregistered pharmaceutical product.

Acting upon a public complaint, a patch labelled in Japanese as containing felbinac, a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138), was found being offered for sale via a social media network platform. A Hong Kong pharmaceutical product registration number was not found on the product label.

Felbinac is a non-steroidal anti-inflammatory drug used topically to relieve pain. It should be supplied at pharmacies under the supervision of a registered pharmacist. Inappropriate use of Felbinac may cause erythema and dermatitis. Pharmaceutical products should be used under the advice of healthcare professionals.

People who have purchased the above product should stop using it and consult healthcare professionals for advice if they are feeling unwell. A notice was posted on the Drug Office website on 24 April 2018 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 $30,000 fine and one year's imprisonment for each offence.

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: ***Pharmacovigilance Unit,***
Drug Office, Department of Health,
Rm 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wan Chai, 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.