Drug News
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Issue Number 95

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in September 2017 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: FDA recommends separating dosing of potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) from all other oral drugs

On 6 September 2017, the United States (US) Food and Drug Administration (FDA) recommended that patients avoid taking the potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) at the same time as any other medicines taken by mouth. A study found that sodium polystyrene sulfonate binds to many commonly prescribed oral medicines, decreasing the absorption and therefore effectiveness of those oral medicines. To reduce this likelihood, FDA recommends separating the dosing of sodium polystyrene sulfonate from other orally administered medicines by at least 3 hours. FDA is updating the sodium polystyrene sulfonate drug labels to include information about this dosing separation.

Sodium polystyrene sulfonate is used to treat hyperkalemia, a serious condition in which the amount of potassium in the blood is too high. It works by binding with potassium in the intestines so it can be removed from the body. Potassium is a mineral that helps the body function properly. Too much potassium in the blood can cause problems with heart rhythm, which in rare cases can be fatal. Sodium polystyrene sulfonate is available as the brand name Kayexalate, as generic brands, and also as non-branded generics in US.

Patients should take orally administered prescription and over-the-counter (OTC) medicines at least 3 hours before or 3 hours after sodium polystyrene sulfonate. Patients should not stop taking their potassium-lowering medicines without talking to their healthcare professional first. If patients have questions or concerns, including about how to take sodium polystyrene sulfonate with other medicines, they should talk to a pharmacist or other healthcare professional.

When prescribing sodium polystyrene sulfonate, healthcare professionals should advise patients to separate dosing from other orally administered medicines by at least 3 hours. That time should be increased to 6 hours for patients with gastroparesis or other conditions resulting in delayed emptying of food from the stomach into the small intestine.

A study was conducted in the laboratory, called an *in vitro* study, to evaluate the binding potential for six orally administered medicines commonly taken together with sodium polystyrene sulfonate. These medicines were the blood pressure medicines amlodipine and metoprolol, the antibiotic amoxicillin, the water pill furosemide, the seizure medicine phenytoin, and the blood-thinner warfarin. The study found significant binding to sodium polystyrene sulfonate occurred with all of these medicines.

Based on the findings, FDA has concluded that sodium polystyrene sulfonate would also be likely to bind to many other oral medicines, and separating its dosing from other oral medications by 3 hours (6 hours if the patient has gastroparesis) would reduce the risk of binding. The recommended spacing interval is based on the expected amount of time it would take for either sodium polystyrene sulfonate or the other drugs to pass through the stomach. As a result, US FDA has determined that additional drug interaction studies

are no longer needed and will be releasing the manufacturer of Kayexalate, Concordia Pharmaceuticals, Inc., from its requirement to conduct further studies. FDA is also adding the new information about separating the time of administration of orally administered medicines and sodium polystyrene products to the sodium polystyrene sulfonate drug labels.

In Hong Kong, there are 3 registered pharmaceutical products containing sodium polystyrene sulfonate, namely Resonium A Powder (HK-42418), PMS-Sodium Polystyrene Sulfonate Powder (HK-44860) and Resinsodio Powder for Oral Suspension 99.75g/100g (HK-64694). As on 23 October 2017, the Department of Health (DH) has not received any adverse drug reaction (ADR) case related to sodium polystyrene sulfonate.

Related news of US FDA requiring the Kayexalate manufacturer to conduct studies to investigate Kayexalate's potential to bind to other medications administered by mouth has been released by US FDA, and was reported in the Drug News Issue No. 72. DH issued a letter to inform local healthcare professionals to draw their attention on the warnings on 23 October 2015. In view of the US FDA's recent recommendations on the separate dosing, DH further issued a letter to inform local healthcare professionals to draw their attention on the risk on 7 September 2017. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee).

US: New recommendations to increase the dose of GamaSTAN S/D (Immune Globulin [Human]) when used for prophylaxis for hepatitis A

On 6 September 2017, US FDA announced important new prescribing recommendations for GamaSTAN S/D when used for prophylaxis for Hepatitis A. GamaSTAN S/D, manufactured by Grifols Therapeutics Incorporated, is an intramuscularly administered Immune Globulin preparation used for prevention of several viral diseases. This notification reflects a change only in dosing for prevention of Hepatitis A virus (HAV) disease.

The increase in dosage is based on recently observed decreasing concentrations of antibodies to HAV in GamaSTAN S/D, attributed to the decreasing prevalence of previous HAV infection among plasma donors. This change in the dosage recommendations for HAV prophylaxis is a precautionary measure, to ensure continued effectiveness of GamaSTAN S/D.

New Dosing Recommendations

GamaSTAN S/D prescribing information has been updated with the following changes to the dosing instructions for the HAV prophylaxis indication:

• GamaSTAN® S/D for household and institutional hepatitis A case contacts.

Prior Dose	New Dose
0.02 mL/kg	0.1 mL/kg

• The following doses of GamaSTAN® S/D are recommended for persons who plan to travel in areas where hepatitis A is common.

Length of Stay	Prior Dose	New Dose
Up to 1 month	----------	0.1 mL/kg
Up to 2 months	----------	0.2 mL/kg
More than 2 months	----------	repeat dose of 0.2 mL/kg every 2 months
Less than 3 months	0.02 mL/kg	----------
3 months or longer	0.06 mL/kg (repeat every 4-6 months)	----------

VAQTA, HAVRIX and TWINRIX vaccines are approved in US for prevention of disease caused by HAV. VAQTA and HAVRIX are indicated for persons 12 months of age or older. TWINRIX is licensed for persons 18 years of age or older. The Hepatitis A vaccines are highly effective and are licensed to be administered at least two weeks prior to the anticipated exposure to HAV.

In Hong Kong, Gamastan S/D Inj 16.5% (HK-56470) manufactured by Grifols Therapeutics Inc. is a pharmaceutical product registered by Luen Cheong Hong Ltd (LCH), and is a prescription-only medicine. LCH confirmed that LCH has not imported and distributed the product since 2010. The matter will be discussed by the Registration

Committee.

EU: EMA concludes review of human factor VIII medicines authorised in EU - no clear and consistent evidence of difference in risk of inhibitor development between classes

On 15 September 2017, the European Medicines Agency (EMA) of the European Union (EU) has concluded that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between the two classes of factor VIII medicines: those derived from plasma and those made by recombinant DNA technology.

EMA's review was started following publication of the SIPPET (Survey of Inhibitors in Plasma-Product Exposed Toddlers) study, which concluded that recombinant factor VIII medicines had a higher incidence of inhibitor development than plasma-derived medicines. The review also covered other relevant interventional clinical trials and observational studies. When all these data were examined, they did not provide clear evidence of a difference in risk of inhibitor development between the two classes of medicines.

Factor VIII is needed for blood to clot normally and is lacking in patients with haemophilia A. Factor VIII medicines replace the missing factor VIII and help control and prevent bleeding. However the body may develop inhibitors as a reaction to these medicines, particularly when patients first start treatment. The inhibitors reduce the medicines' effect, so bleeding is no longer controlled.

Due to the different characteristics of individual products within the two classes, EMA concluded that the risk of inhibitor development should be evaluated individually for each medicine, regardless of class. The risk for each product will continue to be assessed as more evidence becomes available.

To reflect current knowledge, the prescribing information of factor VIII medicines will be updated to include, as appropriate, inhibitor development as a very common side effect in previously untreated patients, and as an uncommon side effect in previously treated patients. The warning on inhibitor development will be amended to state that low levels of inhibitors pose less risk of severe bleeding than high levels.

Healthcare professionals are advised of the followings:

• Current evidence does not support a conclusion of a difference in risk of inhibitor development between recombinant and plasma-derived factor VIII medicines and does not warrant any change in clinical practice.

• EMA's review of factor VIII medicines followed publication of the SIPPET study, a randomised clinical trial in which previously untreated patients with severe haemophilia A were treated with either blood-derived or recombinant factor VIII and development of inhibitors was assessed. The SIPPET investigators concluded that 'patients treated with plasma-derived factor VIII containing von Willebrand factor had a lower incidence of inhibitors than those treated with recombinant factor VIII.' This study and additional clinical trial and observational study data were examined in the review.

• The review concluded that the data did not show any statistically or clinically meaningful difference in inhibitor risk between factor VIII classes. The SIPPET study was designed to assess class effects and included a small number of factor VIII medicines, and the review considered that the results cannot be extrapolated to individual medicines, especially since many were not included in the study.

• The prescribing information for factor VIII products will be updated as appropriate to add inhibitor development as a very common side effect in previously untreated patients and as uncommon in previously treated patients. The warning on inhibitor development will be amended to state that low titres of inhibitors pose less risk of insufficient response than high titres.

In Hong Kong, there are 20 registered pharmaceutical products containing human coagulation factor VIII and 5 registered pharmaceutical products containing octocog alfa (a recombinant factor VIII product). All of them are prescription-only medicines. Related news was previously issued by EMA, was reported in the Drug News Issue No. 50, 61, 79 and 91. DH issued a letter to inform local healthcare professionals to draw their attention on 4 September 2017. As on 23 October 2017, DH has not received any ADR case related to human coagulation factor VIII and

octocog alfa. In view of the above EMA announcement, the matter will be discussed by the Registration Committee.

US: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

On 20 September 2017, US FDA advised that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS) based on its additional review. The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by healthcare professionals can reduce these risks. This provides updated information to the FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning issued on 31 August 2016.

Buprenorphine and methadone help people reduce or stop their abuse of opioids, including prescription pain medications and heroin. Methadone and buprenorphine have been shown to be effective in reducing the negative health effects and deaths associated with opioid addiction and dependency. These medications are often used in combination with counseling and behavioral therapies, and patients can be treated with them indefinitely. Buprenorphine and methadone work by acting on the same parts of the brain as the opioid that the patient is addicted to. The patient taking the medication as directed generally does not feel high, and withdrawal does not occur. Buprenorphine and methadone also help reduce cravings. Medicines containing buprenorphine or methadone as the active ingredient are FDA-approved to treat opioid addiction and dependency. These medicines are called medication-assisted treatment (MAT).

Many patients with opioid dependence may also use benzodiazepines or other CNS depressants, either under a healthcare professional's direction or illicitly. Although there are serious risks with combining these medicines, excluding patients from MAT or discharging patients from treatment because of use of benzodiazepines or CNS depressants is not likely to stop them from using these drugs together. Instead, the combined use may continue outside the treatment setting, which could result in more severe outcomes.

Healthcare professionals should take several actions and precautions and develop a treatment plan when buprenorphine or methadone is used in combination with benzodiazepines or other CNS depressants. These include:
- Educating patients about the serious risks of combined use, including overdose and death, that can occur with CNS depressants even when used as prescribed, as well as when used illicitly.
- Developing strategies to manage the use of prescribed or illicit benzodiazepines or other CNS depressants when starting MAT.
- Tapering the benzodiazepine or CNS depressant to discontinuation if possible.
- Verifying the diagnosis if a patient is receiving prescribed benzodiazepines or other CNS depressants for anxiety or insomnia, and considering other treatment options for these conditions.
- Recognizing that patients may require MAT medications indefinitely and their use should continue for as long as patients are benefiting and their use contributes to the intended treatment goals.
- Coordinating care to ensure other prescribers are aware of the patient's buprenorphine or methadone treatment.
- Monitoring for illicit drug use, including urine or blood screening.

FDA's review of a published study and other drug use data showed that buprenorphine and benzodiazepines frequently have been prescribed for the same patient, often by the same prescriber, and these drugs are usually dispensed by the same pharmacy. An epidemiological study from Sweden found that receiving MAT with benzodiazepines or other CNS depressants such as drugs to treat insomnia appears to increase the risk of death. Based on this information, for the methadone products, information about the interaction with benzodiazepines and other CNS depressants will be added to an existing *Boxed Warning* about the risks of slowed or difficult breathing and death.

Safety Update

Expanded guidance will be added to the *Warnings and Precautions* section on how to manage patients in methadone treatment in Opioid Treatment Programs (OTPs) who are also taking CNS depressants. For the buprenorphine products, an existing statement in the *Warnings and Precautions* section will be expanded and revised to provide more detailed guidance on managing patients in buprenorphine treatment who are also taking CNS depressants.

In Hong Kong, there are 8 registered pharmaceutical products containing buprenorphine, and 6 registered pharmaceutical products containing methadone. All products are prescription-only medicines. As on 23 October 2017, DH has not received any ADR case related to buprenorphine and methadone. News related to opioid pain or cough medicines combined with benzodiazepines was previously issued by US FDA, was reported in the Drug News Issue No. 82. DH issued a letter to inform local healthcare professionals on 1 September 2016. In view of the US FDA's updated safety information on the combined use of opioid addiction medicines (buprenorphine and methadone) with benzodiazepines or other CNS depressants, DH further issued a letter to inform local healthcare professionals on 21 September 2017. The matter will be discussed by the Registration Committee.

Drug Recall

DH endorsed batch recall of Hydrocortisone Sodium Succinate for Injection 100mg (HK-57120)

On 29 September 2017, DH endorsed a licensed drug wholesaler, Universal Division O/B LF Asia (Hong Kong) Limited (LF Asia), to recall a batch (batch number: 304404) of Hydrocortisone Sodium Succinate for Injection 100mg (HK-57120) from the market for a potential quality issue.

DH received notification from LF Asia that the product was recalled due to a defect of the glass vials for precautionary measure. The defect can lead to non-integrity of the container and cannot be visually detected.

The above product, containing hydrocortisone, is a prescription-only medicine used for any condition in which rapid and intense corticosteroid effect is required. According to LF Asia, 446 boxes (each box containing 100 vials of 8ml) of the affected batch have been supplied to Hospital Authority's hospitals.

As on 23 October 2017, DH has not received any ADR case in connection with the product. A notice was posted on the Drug Office website on 29 September 2017 to alert the public of the product recall.

Drug Incident

Man arrested for suspected illegal sale of nicotine-containing liquids for electronic cigarettes

On 7 September 2017, a joint operation was conducted between DH and the Police in Sheung Shui resulting in the arrest of a man aged 23 for the suspected illegal sale of a product called "envii FITT tobacco starter kit", with four cartridges of nicotine-containing liquid intended for use with electronic nicotine delivery systems commonly known as electronic cigarettes.

Acting upon a public complaint, DH found that the above product was offered for sale on a mobile application. A sample of the product was then purchased for laboratory analysis. Testing results from Government Laboratory revealed that the cartridges of the sample contained nicotine, a Part 1 poison. The seller was arrested by the Police for suspected illegal sale and possession of a Part 1 poison and unregistered pharmaceutical product.

According to the Pharmacy and Poisons Ordinance (Cap 138), nicotine-containing electronic cigarettes are classified as pharmaceutical products requiring registration with the Pharmacy and Poisons Board

of Hong Kong before they can be sold in Hong Kong.

Smokers are advised to quit smoking for their own and other people's health. They are encouraged to make use of smoking cessation services through DH's Integrated Smoking Cessation Hotline (1833 183). Information on smoking cessation can also be obtained from DH's Tobacco Control Office website (www.tco.gov.hk).

A notice was released on the website of Drug Office on 7 September 2017 to alert the public of the drug incident.

Man arrested for suspected illegal sale of nicotine-containing liquids for electronic cigarettes

On 27 September 2017, a joint operation was conducted by DH and the Police in Mong Kok resulting in the arrest of a 25-year-old man for illegal sale of nicotine-containing liquids which are intended for use with electronic nicotine delivery systems, commonly known as electronic cigarettes.

Acting upon a public complaint, DH found that the nicotine-containing liquids were offered for sale on a social networking website. Samples of the products were purchased for laboratory analysis. Test results from Government Laboratory revealed that all samples contained the Part 1 poison nicotine. During the operation conducted on 27 September 2017, the seller was arrested by the Police for suspected illegal sale and possession of Part 1 poison and unregistered pharmaceutical products.

According to the Pharmacy and Poisons Ordinance (Cap 138), nicotine-containing electronic cigarettes are classified as pharmaceutical products requiring registration with the Pharmacy and Poisons Board of Hong Kong before they can be sold in Hong Kong.

Smokers are advised to quit smoking for their own and other people's health. They are encouraged to make use of smoking cessation services through DH's Integrated Smoking Cessation Hotline (1833 183). Information on smoking cessation can also be obtained from DH's Tobacco Control Office website (www.tco.gov.hk).

A notice was released on the website of Drug Office on 28 September 2017 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

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