Drug News
藥 物 情 報

Issue Number 80

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in June 2016 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

China: CFDA's consumer warning related to botulinum toxin A for injection

On 2 June 2016, the China Food and Drug Administration (CFDA) announced that according to promulgation of the National Health and Family Planning Commission (NHFPC) of the People's Republic of China, patients has been continuously acutely admitted to some hospitals in provinces including Beijing, Shanghai, Zhejiang and Guangdong after injection of unknown substances in non-medical institutions recently. They all suffer from symptoms of neurotoxicity. These patients received injection of "botulinum toxin" in non-healthcare settings for cosmetic purposes such as slimming faces and legs before hospitalization. In order to protect the interest of consumers and guide them to buy registered products and receive services from registered institutions, CFDA reminds consumers the following.

Inappropriate use of botulinum toxin A for injection can cause muscle weakness and numbness, in severe cases may lead to problems such as respiratory failure and heart failure which may result in death. CFDA implements various measures and control to regulate manufacture, import, wholesale and retail sale of botulinum toxin A products. Consumers are advised to receive injection for cosmetic purposes in registered medical institutions or registered medical cosmetic institutions.

There are two botulinum toxin A for injections approved by CFDA for marketing. One is manufactured by Lanzhou Institute of Biological Products Co., Ltd. in China, named as 衡力 in Chinese. Another is imported product named as BOTOX manufactured by Allergan Pharmaceuticals Ireland. For more details please refer to CFDA's website.

In Hong Kong, there are eight registered pharmaceutical products containing botulinum toxin for injection use, including six products containing botulinum toxin A and two products containing botulinum toxin. All these products are prescription only medicines. Among the products, two products namely Botox for Inj 100 Units (HK-41906) and 200 Units (HK-60427) are manufactured by Allergan Pharmaceuticals Ireland , and two products namely BTXA for Inj 50 Units (HK-51582) and 100 Units (HK-49886) are manufactured by Langzhou Inst. of Bio. Products. The labels on the outer packing of the local products are different from that of the Mainland. The Hong Kong registration number for a registered pharmaceutical product should be labelled on the sales pack in the form of "HK-XXXXX". The Department of Health (DH) has recently received ten cases of suspected botulism

after receiving botulinum toxin injections. Eight cases received injections in the Mainland and two cases received injections in Hong Kong. Press release was made on 27 May, 29 May, 30 May, 2 June, 3 June, 10 June, 22 June, 29 June, 20 July, 21 July and 5 August 2016. DH will continue to remain vigilant on the development of the incident.

US: FDA warned about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse

On 7 June 2016, the United States (US) Food and Drug Administration (FDA) warned that taking higher than recommended doses of the common over-the-counter (OTC) and prescription diarrhea medicine loperamide (Imodium), including through abuse or misuse of the product, can cause serious heart problems that can lead to death. The risk of these serious heart problems, including abnormal heart rhythms, may also be increased when high doses of loperamide are taken with several kinds of medicines that interact with loperamide.

In the 39 years from when loperamide was first approved in the US in 1976 through 2015, FDA received reports of 48 cases of serious heart problems associated with use of loperamide. This number includes only reports submitted to FDA, so there are likely additional cases about which FDA is unaware. Thirty-one of these cases resulted in hospitalizations, and 10 patients died. More than half of the 48 cases were reported after 2010. The serious heart problems occurred mostly in patients who were taking doses that were much higher than recommended. In other cases, patients were taking the recommended dose of loperamide, but they were also taking interacting medicines, causing an increase in loperamide levels. Additional cases of serious heart problems associated with the use of loperamide were reported in the medical literature. Cases reported to FDA and in the medical literature indicate that individuals are taking significantly high doses of loperamide in situations of both misuse and abuse, often attempting to achieve euphoria or self-treat opioid withdrawal. They are also combining loperamide with interacting drugs in attempts to increase these effects. FDA continues to evaluate this safety issue and will determine if additional FDA actions are needed.

Healthcare professionals should be aware that use of higher than recommended doses of loperamide can result in serious cardiac adverse events. Consider loperamide as a possible cause of unexplained cardiac events including QT interval prolongation, Torsades de Pointes or other ventricular arrhythmias, syncope, and cardiac arrest. In cases of abuse, individuals often use other drugs together with loperamide in attempts to increase its absorption and penetration across the blood-brain barrier, inhibit loperamide metabolism, and enhance its euphoric effects. If loperamide toxicity is suspected, promptly discontinue the drug and start necessary therapy. If loperamide ingestion is suspected, measure blood levels, which may require specific testing. For some cases of Torsades de Pointes in which drug treatment is ineffective, electrical pacing or cardioversion may be required.

FDA reminded healthcare professionals to advise patients taking loperamide to follow the dosing recommendations on the label because taking higher than recommended doses, either intentionally or unintentionally, may lead to abnormal heart rhythms and serious cardiac events leading to death. Also advise patients that drug interactions with commonly used medicines also increase the risk of serious cardiac adverse events. Healthcare professionals should refer patients with opioid use disorders for treatment.

Patients and consumers who have diarrhea lasting

more than 2 days should stop taking loperamide and contact their health care professional. Seek medical attention immediately if they experience any of the following: fainting, rapid heartbeat or irregular heart rhythm, or unresponsiveness.

In Hong Kong, there are 68 registered pharmaceutical products containing loperamide. As on 2 September 2016, DH has not received any adverse drug reaction (ADR) case related to loperamide. In view of the above FDA announcement, DH issued a letter to inform local healthcare professionals to draw their attention to the warning on 8 June 2016. As FDA is evaluating this safety issue to determine if additional actions are needed, DH will remain vigilant on the conclusion of the evaluation and any safety updates by other overseas drug regulatory authorities for consideration of any action deemed necessary.

US: Canagliflozin (Invokana, Invokamet) and Dapagliflozin (Farxiga, Xigduo XR): Strengthened kidney warnings

On 14 June 2016, the US FDA has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet in US) and dapagliflozin (Farxiga, Xigduo XR in US). Based on recent reports, FDA has revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk.

Canagliflozin and dapagliflozin are prescription medicines used with diet and exercise to help lower blood sugar in adults with type 2 diabetes. They belong to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors. Canagliflozin and dapagliflozin lower blood sugar by causing the kidneys to remove sugar from the body through the urine.

From March 2013, when canagliflozin was approved in the US, to October 2015, FDA received reports of 101 confirmable cases of acute kidney injury, some requiring hospitalization and dialysis, with canagliflozin or dapagliflozin use. This number includes only reports submitted to FDA, so there are likely additional cases about which FDA is unaware.

FDA advised health care professionals to consider factors that may predispose patients to acute kidney injury prior to starting them on canagliflozin or dapagliflozin. These include decreased blood volume; chronic kidney insufficiency; congestive heart failure; and taking other medications such as diuretics, blood pressure medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs). Assess kidney function prior to starting canagliflozin or dapagliflozin and monitor periodically thereafter. If acute kidney injury occurs, promptly discontinue the drug and treat the kidney impairment.

Patients should seek medical attention immediately if they experience signs and symptoms of acute kidney injury. This is a serious condition in which the kidneys suddenly stop working, causing dangerous levels of wastes to build up in the body. Signs and symptoms of acute kidney injury may include decreased urine or swelling in the legs or feet. Patients should not stop taking their medicine without first talking to their health care professionals. Doing so can lead to uncontrolled blood sugar levels that can be harmful.

In Hong Kong, there are two pharmaceutical products containing canagliflozin, namely Invokana Tablets 100mg (HK-63499) and 300mg (HK-63500) which are registered by Johnson & Johnson (HK) Ltd; and two pharmaceutical products containing dapagliflozin, namely Forxiga

Tablets 5mg (HK-63301) and 10mg (HK-63302) which are registered by AstraZeneca Hong Kong Ltd. All products are prescription only medicines. As on 2 September 2016, DH has received one case of ADR in connection with canagliflozin and another case of ADR in connection with dapagliflozin, but both were not related to acute kidney injury. In view of the above FDA announcement, DH issued a letter to inform local healthcare professionals to draw their attention to the warnings on 15 June 2016. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

UK: Topical miconazole, including oral gel: reminder of potential for serious interactions with warfarin

On 15 June 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) advised that in view of reports of serious bleeding events in patients taking miconazole and warfarin, MHRA is considering further measures to minimise the risk of potentially serious interactions between miconazole and warfarin.

Healthcare professionals are reminded that miconazole, including the topical gel formulation, can enhance the anticoagulant effect of warfarin—if miconazole and warfarin are used concurrently, the anticoagulant effect should be carefully monitored and, if necessary, the dose of warfarin reduced. Patients should be advised to tell their doctor or pharmacist if they are receiving warfarin before using products that contain miconazole (including those available without prescription), and to seek medical advice if they notice signs of over-anticoagulation during treatment, such as sudden unexplained bruising, nosebleeds or blood in the urine.

Miconazole (Daktarin, Daktacort in UK) is an antifungal indicated for prevention and treatment of various infections of the mouth, throat, skin, nails, or genitals. It is usually applied topically as a cream, ointment, powder, or oral gel. Some products are available without a prescription.

Warfarin is an oral anticoagulant that has been widely used since the 1950s for prophylaxis of thromboembolic events. Daily dose depends on individual requirements, and patients receiving long-term therapy require regular coagulation tests.

The potential for drug interactions between miconazole and warfarin is well established. The mechanism is understood to be inhibition by miconazole of one of the main cytochrome P450 isozymes involved in warfarin metabolism (CYP2C9), resulting in reduced warfarin clearance and an enhanced anticoagulant effect.

In the UK, prescribing information for products that contain miconazole warns that because miconazole inhibits CYP2C9, caution should be exercised for patients on oral anticoagulants such as warfarin, and the anticoagulant effect monitored (warfarin dose reduction may be needed). Patient Information Leaflets for miconazole products advise users to tell their doctor or pharmacist if they are taking warfarin.

Up to 13 April 2016, MHRA has received 146 Yellow Cards that report possible drug interactions between miconazole and warfarin. Most reports (128, 88%) concerned the oral gel form of miconazole. The most frequently reported events were: increased international normalised ratio (INR, 111 reports); contusion (21); haematuria (17); and epistaxis (8). Approximately half of the 146 cases reported an INR increase above 10—ie, the patient was at significantly increased risk of bleeding events (noting that the target INR range for a patient on long-term warfarin therapy is

usually between 2 and 3). In 3 cases, a fatal outcome was reported as a result of a haemorrhagic event.

The MHRA is currently reviewing available data for this interaction to determine whether further measures are required to minimise the risks to patients. This review follows a coroner's report of a death, which may have been partly due to the coadministration of miconazole oral gel and warfarin. Further advice will be communicated as appropriate when the review is complete.

In Hong Kong, there are 93 registered pharmaceutical products containing miconazole, and 18 registered pharmaceutical products containing warfarin. As on 2 September 2016, DH has not received any ADR case resulting from coadministration of topical miconazole and warfarin. In view of the above MHRA announcement, DH issued a letter to inform local healthcare professionals to draw their attention to the risk on 16 June 2016. As MHRA is currently reviewing available data for this interaction to determine whether further measures are required, DH will remain vigilant on the conclusion of the evaluation and safety updates by other overseas drug regulatory authorities for consideration of any action deemed necessary.

Singapore: Risk of premature epiphyseal fusion with Erivedge® (vismodegib)

On 22 June 2016, Singapore Health Sciences Authority (HSA) announced that Roche would like to inform healthcare professionals of the risk of premature epiphyseal fusion associated with the use of Erivedge® (vismodegib).

Three cases of premature epiphyseal fusion in paediatric medulloblastoma patients have been reported with Erivedge® treatment, two of which were within the setting of a clinical trial and one case was from off-label use. In 2 of 3 cases, the fusion of the growth plate appeared to progress even after treatment discontinuation. These findings confirm the risk that was identified based on observation of irreversible closure of the femoral epiphyseal growth plate in vismodegib treated rats.

Roche advised healthcare professionals to take into consideration the above safety information when prescribing Erivedge®, and to use Erivedge® in accordance to its approved indication.

In Hong Kong, Erivedge Capsules 150mg (HK-63786) is a pharmaceutical product registered by Roche Hong Kong Limited (Roche HK), and is a prescription only medicine. On 10 June 2016, Roche HK notified the DH that the company has issued a "Dear Healthcare Professional Letter" on the above risk, and related information was posted on the Drug Office website on the same day. As on 2 September 2016, DH has not received any ADR case related to the product. Roche HK is going to submit application to update the package insert of the product to include the relevant information. DH will remain vigilant on any safety update on the product by overseas drug regulatory authorities.

Drug Recall

DH endorsed recall of Candinox Vaginal Tablet 100mg (HK-41076)

On 15 June 2016, DH endorsed a licensed drug wholesaler, Deltapharm Ltd, to recall all batches of Candinox Vaginal Tablet 100mg (HK-41076) from shelves due to a quality issue.

During the DH's market surveillance, samples of the above pharmaceutical product were collected for analysis. Testing results from the Government Laboratory showed that all samples failed the disintegration test, which might affect the efficacy of the product. Deltapharm hence recalled the product from the market.

Deltapharm was instructed to report the root cause upon investigation by the manufacturer in Thailand. DH's investigation was continuing.

The above pharmaceutical product contains a Part 1 poison, clotrimazole, and is used for the treatment of vulvovaginal candidiasis. It can only be supplied at a pharmacy under the supervision of a registered pharmacist.

According to Deltapharm, the product has been supplied to local private doctors and pharmacies, and exported to Macau.

As on 2 September 2016, DH has not received any ADR case related to the above product. People who have used the above product should consult their healthcare professionals when in doubt or feeling unwell after use. A notice was released on the website of Drug Office on 15 June 2016 to alert the public of the recall.

DH endorsed recall of 10-capsule pack of Tycil Capsule 250mg (HK-55608)

On 29 June 2016, DH endorsed a licensed drug wholesaler, Eugenpharm International Ltd. ("Eugenpharm"), to recall all batches of 10-capsule pack of Tycil Capsule 250mg (HK-55608) from the market because this pack size is not registered with the Pharmacy and Poisons Board. This recall does not involve the registered 100-capsule pack.

During DH market surveillance, it was found that the above 10-capsule pack of Tycil Capsule 250mg was available at a local pharmacy. Since the supply of unregistered pharmaceutical product contravenes the Pharmacy and Poisons Regulations (Cap. 138A), Eugenpharm voluntary recalled the 10-capsule pack from the market. DH's investigation was continuing.

The above product, containing amoxicillin, is an antibiotic for the treatment of bacterial infections. According to Eugenpharm, the 10-capsule pack has only been supplied to local pharmacies.

As on 2 September 2016, DH has not received any ADR case in connection with the product concerned. A notice was released on the website of Drug Office on 29 June 2016 to alert the public of the recall.

DH raided shops for suspected illegal sale of slimming products with undeclared controlled drug ingredient

On 27 June 2016, DH raided two retail shops in Mong Kok and Yuen Long for suspected illegal sale of two slimming products called 4L SLIMNESS and 4L SLIMBURN PLUS, which are suspected to contain an undeclared Part 1 poison.

Acting upon intelligence, samples of the above products were previously purchased for analysis. The test results from the Government Laboratory revealed that the samples contained diclofenac, a Part 1 poison.

Diclofenac is a non-steroidal anti-inflammatory drug for pain relief and its side-effects include gastrointestinal discomfort, nausea and peptic ulcers. Products containing diclofenac are prescription drugs and should be supplied at pharmacies under the supervision of a registered pharmacist upon a doctor's prescription.

A notice was released on the website of Drug Office on 27 June 2016 to alert the public of the drug incident.

DH raided a retail shop for suspected illegal sale of nicotine-containing liquid for electronic cigarettes

On 29 June 2016, DH raided a retail shop in Mong Kok in a joint operation with the Police for suspected illegal sale of a nicotine-containing liquid called Liqua Original Smoke Juice Cuban Cigar Tobacco intended for use with electronic nicotine delivery systems, commonly known as electronic cigarettes.

A sample of the above product was purchased previously from the above shop by DH for laboratory analysis. Test results from the Government Laboratory revealed that the sample contained nicotine, a Part 1 poison.

A woman aged 34 was arrested by the Police for suspected illegal sale and possession of a Part 1 poison and unregistered pharmaceutical products in the operation.

Under the Pharmacy and Poisons Ordinance (Cap 138), nicotine-containing electronic cigarette products 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 and may call the DH's Integrated Smoking Cessation Hotline (1833 183). Information on smoking cessation can also be obtained from the DH's Tobacco Control Office website (www.tco.gov.hk).

A notice was released on the website of Drug Office on 29 June 2016 to alert the public of the drug incident.

DH raided retail shops for suspected illegal sale and possession of unregistered pharmaceutical products

On 29 June 2016, two retail shops in Sheung Shui were raided in a joint operation by DH and the Police for suspected illegal sale and possession of unregistered pharmaceutical products and Part 1 poisons.

Following a public complaint, DH found that the above retail shops have been offering for sale various unregistered pharmaceutical products. During the operation, various external preparations, eye drops and cold and cough medicines, mostly labelled in Japanese, were seized. Preliminary investigation indicated that the products contain dexamethasone, hydrocortisone, neostigmine, methylephedrine and dihydrocodeine. Hong Kong pharmaceutical product registration numbers were not found on any of the products' labels.

Two women aged 41 and 42 were arrested by the Police for suspected illegal sale and possession of unregistered pharmaceutical products and Part 1 poisons in the operation.

Dexamethasone, hydrocortisone, neostigmine, methylephedrine and dihydrocodeine are Part 1

poisons. Inappropriate or excessive application of dexamethasone and hydrocortisone could cause skin problems. Eye drops with neostigmine may cause ocular pain and irritation as well as blurred vision. Side effects of methylephedrine include tachycardia, anxiety, restlessness and insomnia while dihydrocodeine may cause nausea, vomiting and constipation.

A notice was released on the website of Drug Office on 29 June 2016 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.

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,
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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.