Drug News
藥 物 情 報

Issue Number 66

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in April 2015 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

EU/Canada: Review confirms small increased cardiovascular risk with ibuprofen at high doses at or above 2,400 mg daily

On 13 April 2015, the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) had completed a review confirming a small increase in the risk of cardiovascular problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (at or above 2,400 mg per day). The review clarifies that the risk with high-dose ibuprofen is similar to the risk seen with some other non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors and diclofenac.

No increase in cardiovascular risk is seen with ibuprofen at doses up to 1,200 mg per day, which is the highest dose generally used for over-the-counter (OTC) preparations taken by mouth in the European Union (EU).

The PRAC concluded that the benefits of ibuprofen outweigh the risks but recommended updating advice on the use of high-dose ibuprofen to minimise the cardiovascular risk. High doses of ibuprofen (2,400 mg per day or higher) should be avoided in patients with serious underlying heart or circulatory conditions, such as heart failure, heart disease and circulatory problems or in those who have previously had a heart attack or stroke.

In addition, doctors should carefully assess a patient's risk factors for heart or circulatory conditions, before initiating long-term treatment with ibuprofen, particularly if high doses are required. Risk factors for these conditions include smoking, high blood pressure, diabetes and high blood cholesterol.

The PRAC also reviewed data on the interaction between ibuprofen and low-dose aspirin when the latter is taken to reduce the risk of heart attacks and strokes. The PRAC noted that ibuprofen has been shown in laboratory studies to reduce the anti-clotting effects of aspirin. However it remains uncertain whether long-term use of ibuprofen in clinical practice reduces the benefits of low-dose aspirin in preventing heart attacks and strokes. Occasional use of ibuprofen should not affect the benefits of low-dose aspirin.

The PRAC recommended that updated advice on the cardiovascular risk of high-dose ibuprofen be included in the product information of ibuprofen medicines, along with information on the available evidence on the interaction between ibuprofen and aspirin. The recommendations for ibuprofen also apply to dexibuprofen, a medicine similar to ibuprofen. A high dose of dexibuprofen is a dose at or above 1,200 mg per day. On 22 May 2015, the EMA announced that the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) had agreed the PRAC recommendations by consensus, and changes to the product information for ibuprofen- and dexibuprofen-containing medicines will be implemented by the Member States where the medicines are authorised, according to an agreed timetable.

In addition, on 23 April 2015, Health Canada also announced that the safety information regarding the risk of serious cardiovascular side effects (e.g., heart attack and stroke) when prescription oral ibuprofen products are used at high doses (at 2400 mg/day) would be updated. This risk increases with dose and duration of use.

The new information is in light of a Health Canada safety review found that oral ibuprofen taken at high doses (at or above 2400 mg per day) increases the risk of heart attack and stroke. The increased risk with high doses of ibuprofen is similar to the risk seen with some other NSAIDs, including COX -2 inhibitors (e.g. celecoxib) and diclofenac. Health Canada recently communicated new prescribing recommendations regarding the cardiovascular safety of diclofenac.

Health Canada's review concluded that the benefits of prescription oral ibuprofen products continue to outweigh the risks as an effective pain and inflammation treatment, but that additional measures are needed for these products to further reduce the cardiovascular risk.

Prescription oral ibuprofen products have a maximum recommended daily dose of 2400 mg, and are authorized to relieve the pain and inflammation of rheumatoid arthritis and osteoarthritis.

Health Canada will be working with the Canadian manufacturers of prescription oral ibuprofen products, to strengthen the existing cardiovascular safety warnings in the prescribing information (product monographs), including recommending that doses of 2400 mg per day should not be used in patients with a history of heart disease and stroke, or who have risk factors for cardiovascular disease. Risk factors include -- but are not limited to -- smoking, diabetes, high blood pressure, high blood cholesterol and strong family history of cardiovascular disease.

Healthcare professionals are advised of the following:

- Consider the cardiovascular risks when prescribing ibuprofen for all patients. These risks increase with dose and duration of therapy.
- Not to prescribe ibuprofen doses of 2400 mg per day in patients with ischemic heart disease, cerebrovascular disease, congestive heart failure or with risk factors for cardiovascular disease.
- Consider other management strategies that do not include NSAIDs first (particularly COX-2 inhibitors, ibuprofen or diclofenac NSAIDs) for patients with a high risk of a cardiovascular event.

In Hong Kong, there are 84 registered pharmaceutical products (excluding external preparations) containing ibuprofen, and are pharmacy only medicines. There are no registered pharmaceutical products containing dexibuprofen. Safety alerts regarding the cardiovascular risks associated with NSAIDs have been released by various overseas health authorities, and were reported in the Drug News Issues No. 24, 36, 43, 53, 54 and 60. Letter to healthcare professionals to draw their attention to the issue was issued on 30 September 2011. The matter related to cardiovascular risk of NSAID was discussed in the meeting of the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board in February 2013. The Registration Committee concluded that NSAIDs-containing products, other than external preparations and aspirin, should include new safety warnings regarding the cardiovascular risk. So far, the Department of Health (DH) has not received any adverse drug reaction reports on ibuprofen. In view of the latest EMA's and Health Canada's announcements which clarify the cardiovascular risk related to ibuprofen taken at high doses and the interaction between ibuprofen at any dose and aspirin, the matter will be further discussed in the meeting of the Registration Committee.

Macau: Recall of 育胃源錠 (E-WEGEN Tablet)

On 18 April 2015, the Health Bureau of Macau (HBM) announced that, as indicated in the announcement of Taiwan health authority on the same day, the Taiwan health authority had conducted a second round inspection on magnesium carbonate and calcium carbonate active pharmaceutical ingredients used by Taiwan pharmaceutical companies. It was found that there were 19 pharmaceutical companies of 23 products did not comply with the requirements, mainly due to the use of food grade active pharmaceutical ingredients in the products. As the active pharmaceutical ingredients are not pharmaceutical grade, the authority instructed the manufacturers to recall the related products. The HBM announced that among the affected products, the stomach medicine "育胃源錠 (E-WEGEN Tablet)" manufactured by Ming Ta Chemistry Pharmacy Co. Ltd. had been approved to import to Macau, and

therefore the HBM requested the related importers/ exporters, wholesalers and drug stores in Macau to recall the above product.

In Hong Kong, the above product "育胃源錠 (E-WEGEN Tablet)" is not a registered pharmaceutical product and there is no registered pharmaceutical product manufactured by Ming Ta Chemistry Pharmacy Co. Ltd. The DH has contacted the Taiwan health authority to follow up on the incident related to the use of industrial grade or food grade magnesium carbonate and calcium carbonate active pharmaceutical ingredients. So far, among the 46 products which needed to be taken off the shelf as indicated in the announcement of Taiwan health authority on 10 April and 16 April, only one product matches the product name and manufacturer of a registered pharmaceutical product in Hong Kong, namely "益胃片 (Well Tablets)" (registration number HK-02886). The product is registered by Kai Yuen Pharmaceutical Co (Kai Yuen). In response to the event, the DH has contacted Kai Yuen, and was informed that the company has not imported Well Tablets since 2011, and there is no stock of the product in the market. The DH remains vigilant against the event, and will conduct timely follow-up actions.

Singapore: HSA alerts public to five illegal sexual enhancement products sold online found to contain potent chemical ingredients

On 21 April 2015, the Health Sciences Authority (HSA) alerted members of the public not to purchase or use five illegal sexual enhancement products sold online as these can cause serious adverse reactions. These illegal products were tested at HSA's pharmaceutical laboratory and found to contain potent chemical ingredients, including the prescription medicine, sildenafil, which is used in the treatment of male impotence. They were detected through HSA's ongoing surveillance of Internet sales activities. HSA's investigations show that some consumers in Singapore may have bought the products online. The five products are:

- STARKRx PERFORMANCE ENHANCER, Stark-Rx and MAXIMUM STRENGTH SEXUAL ENHANCER: contain sildenafil;
- FORTA PLUS for Men: contains nortadalafil; and
- STUD 100® Male Genital Desensitizer Spray: contains lignocaine

Three products, 'STARKRx PERFORMANCE ENHANCER', 'MAXIMUM STRENGTH SEXUAL ENHANCER' and 'FORTA PLUS for Men', claimed to contain only natural herbal ingredients. However, they were tested to contain either sildenafil or nortadalafil. Nortadalafil is a chemically-related compound of tadalafil. Sildenafil and tadalafil are prescription medicines used to treat male erectile dysfunction and can potentially cause serious adverse effects such as decreased or loss of vision and hearing, strokes, heart attacks and priapism (painful and exceedingly long erections). If priapism is not treated immediately, it may lead to permanent impotence. Sildenafil and tadalafil are also not suitable for patients with medical conditions such as certain heart-related problems or who are on heart medications such as nitrates. Deaths of patients found to be using sildenafil while on nitrates have been reported overseas.

'STUD 100® Male Genital Desensitizer Spray' was found to contain high concentrations of lignocaine exceeding its permissible level in external preparations. Lignocaine is a medicine used to decrease or eliminate the feeling of pain. The inappropriate use of products with high concentrations of lignocaine can cause dizziness and low blood pressure.

Although HSA has yet to receive any adverse reaction reports associated with these products, this does not mean that these products will not cause any harm. Persons taking these products may not link the adverse effects they experienced with the product or share with their doctors that they are taking such a product. Consumers should be aware that illegal health products are generally produced under poor manufacturing conditions with no quality control, and the contents of the product can vary from batch to batch, which can pose serious health hazards.

In Hong Kong, STARKRx PERFORMANCE ENHANCER, Stark-Rx, MAXIMUM STRENGTH SEXUAL ENHANCER and FORTA PLUS for Men are not registered pharmaceutical products, while Stud 100 Spray (HK-03640) is a pharmaceutical product registered by Dicken Trading Company (Dicken), and is a pharmacy

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only medicine. So far, the DH has not received any adverse drug reaction reports related to Stud 100 Spray. In view of the HSA's announcement, the DH made an enquiry to HSA for more details of the incident related to the concerned product and drew samples of the product from Dicken to test for compliance against its registered specifications. HSA replied that the affected product was labelled to be manufactured in the United Kingdom and no other detail of the manufacturer was found on the product label. Based on the available information, it cannot be ascertained whether the product in the news is the same as the product registered by Dicken in Hong Kong. Meanwhile, the test results of the samples from Dicken show that the product complies with its registered specifications.

US: FDA Sentinel study finds no association between venous thromboembolism and Gardasil vaccination

On 23 April 2015, the US Food and Drug Administration (FDA) announced that the Sentinel study finds no association between venous thromboembolism and Gardasil vaccination.

The FDA presented a comprehensive postlicensure safety evaluation of Gardasil (Merck Inc. & Co.) to FDA's Pediatric Advisory Committee (PAC). In this review, FDA presented safety data from the Vaccine Adverse Event Reporting System (VAERS) and the Centers for Disease Control and Prevention's Vaccine Safety Datalink (VSD) suggesting that more venous thromboembolism (VTE) cases were being observed than expected after vaccination with Gardasil. Venous thromboembolism is a condition where blood clots form in the deep veins of the body, especially the lungs and extremities. Because both the VAERS and VSD data were inconclusive, FDA conducted a follow up study in the Sentinel system. This FDA update provides a summary of the final analysis, which did not find any evidence of an association between venous thromboembolism and Gardasil vaccination.

The Sentinel study evaluated the risk of venous thromboembolism in more than 650,000 females aged 9 through 26 years of age, totaling more than 1.4 million doses of Gardasil evaluated. The study identified only 30 medical record confirmed cases of venous thromboembolism in the 8–9 week observation period after each dose administered in the 3-dose series. The VTE cases were identified from 5 Sentinel data partners during the time period of 2006–2013. The study evaluated the risk of VTE 1–28 days after Gardasil vaccination compared to a period approximately one to two months after vaccination. The study did not identify any evidence of an increased risk of VTE in the 1–28 days after any of the 3 doses of Gardasil vaccination. The study also scanned the entire 8–9 week observation period and did not find any unusual VTE clusters appearing after Gardasil vaccination, further strengthening the conclusion that there is no increased risk of VTE.

The Sentinel study is the largest study of VTE after Gardasil in the United States to date and builds upon other published studies, including those from Denmark and Sweden that also found no evidence of an increased risk for venous thromboembolism after Gardasil vaccination. FDA is not requesting any changes to Gardasil labeling as a result of this new safety information.

In Hong Kong, Gardasil Vaccine Inj (Vial) (HK-54934) and Gardasil Vaccine Inj (Pre-filled syringe) (HK-54935) are prescription only medicines registered by Merck Sharp & Dohme (Asia) Ltd. So far, the DH has not received any adverse drug reaction reports on venous thromboembolism related to Gardasil. The DH remains vigilant on any safety updates of Gardasil by other overseas regulatory authorities.

Drug Recall

Batch recall of Apo-Pregabalin 50mg Capsules (HK-62682) and Apo-Verap SR 240mg Tablets (HK-59212)

On 13 April 2015, the DH endorsed a licensed drug wholesaler, Hind Wing Co. Ltd (Hind Wing), to recall one batch (batch number: KW3889) of Apo-Pregabalin 50mg Capsules (HK-62682) and one batch (batch number: KL7884) of Apo-Verap SR 240mg Tablets (HK-59212) from shelf due to quality issue.

The DH received notification from Hind Wing that the Canadian manufacturer of the products had

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found an unidentified impurity out of specification in a batch of Apo-Pregabalin 50mg Capsules (batch number: KW3889) during a stability testing.

In addition, the Canadian manufacturer had also found a batch of Apo-Verap SR 240mg Tablets (batch number: KL7884) failed the dissolution test.

As on 13 April 2015, the DH has not received any adverse reports in connection with the products concerned. The DH has requested Hind Wing to liaise with the Canadian manufacturer to provide the detailed investigation report.

Apo-Pregabalin 50mg Capsules, containing pregabalin, is a prescription medicine used for the treatment of epilepsy and neuropathic pain. According to Hind Wing, 4 bottles of 100 capsules of the affected batch had been supplied to private doctors.

Apo-Verap SR 240mg Tablets, containing verapamil, is a prescription medicine used for the treatment of hypertension. According to Hind Wing, 96 bottles of 100 tablets of the affected batch had been supplied to private doctors.

The DH closely monitored the recall. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

Recall of three batches of Apo-Fluoxetine 20mg Capsules (HK-41383)

On 20 April 2015, the DH endorsed a licensed drug wholesaler, Hind Wing Co. Ltd (Hind Wing), to recall three batches (batch number: KT8932, KZ8595 and ME3862) of Apo-Fluoxetine 20mg Capsules (registration number: HK-41383) at retailer level due to potential safety issue.

Through the DH's surveillance system, it was noted that Health Canada, drug regulatory authority in Canada, announced a batch recall of Apo-Fluoxetine 20mg capsules because the active pharmaceutical ingredient used in the manufacturing of the affected batches may not meet the specification for the impurity (isobutyl vinyl ketone).

As on 20 April 2015, the DH has not received any adverse reports in connection with the concerned product. The DH has requested Hind Wing to liaise with the Canadian manufacturer to provide further information regarding the incident and a detailed investigation report.

Apo-Fluoxetine 20mg Capsules, containing fluoxetine, is a prescription medicine used for the treatment of major depressive disorder. According to Hind Wing, about 2727 bottles of 100 capsules of the affected batches have been supplied to private doctors and pharmacies since March 2014.

DH closely monitored the recall. A notice was released on the website of the Drug Office on the same day to alert the public of the recall.

"Healthcare professionals and pharmacies are advised to stop supplying the affected batches of the product to patients. Members of the public who are taking the product should consult their doctors for advice," a DH spokesperson advised.

Drug Incident

DH investigates retail shop raided for suspected illegal sale of unregistered pharmaceutical product

On 15 April 2015, a retail shop in Mong Kok was raided in a joint operation by the DH and the Police for suspected offering for sale and possession of an unregistered pharmaceutical product labelled to contain Part I poison.

Acting upon a complaint, it was found that the retail shop was offering for sale a dietary supplement called LIPO RED, which was labelled as containing yohimbine. Yohimbine is a Part I poison and products containing yohimbine should be sold in a pharmacy under the supervision of a registered pharmacist.

During the operation, a man aged 36 was arrested by the Police for suspected possession of Part I poison and unregistered pharmaceutical product.

Yohimbine has an antidiuretic effect and its side-effects include increase in heart rate and blood pressure, anxiety, manic reactions and bronchospasm.

Members of the public who have purchased the above product should stop consuming it immediately. They should consult healthcare professionals for advice if feeling unwell or in doubt after consumption.

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

On 20 April 2015, a retail shop in Cheung Chau was raided in a joint operation by the DH and the Police for suspected illegal sale and possession of unregistered pharmaceutical products.

During the DH's market surveillance, it was found that suspected unregistered pharmaceutical products were being offered for sale by the retail shop. Various products, including pain killers, cold and flu medicines, and cream, labelled in Japanese were seized in the operation. The products were labelled to contain ibuprofen, dihydrocodeine, fluocinolone and neomycin respectively.

According to the Pharmacy and Poisons Board of Hong Kong, these are not registered pharmaceutical products and Hong Kong registration numbers were not found on any of the product labels. Preliminary investigations have so far revealed that the products were sourced outside Hong Kong.

During the operation, a man aged 57 was arrested by the Police for suspected sale and possession of Part I poisons, unregistered pharmaceutical products and antibiotics.

"Use of unregistered pharmaceutical products may pose health threats to people as their safety, efficacy and quality are not guaranteed. Ibuprofen, dihydrocodeine and fluocinolone are Part I poisons. Inappropriate use of steroids like fluocinolone may cause serious side-effects, such as Cushing's Syndrome with symptoms including moon face and muscle atrophy while inappropriate use of pain killers like ibuprofen without medical supervision may lead to gastrointestinal bleeding, and products with dihydrocodeine may cause nausea and vomiting. Neomycin is an antibiotic and inappropriate use of antibiotics may lead to antibiotics resistance. Members of the public should not self-medicate without advice from healthcare professionals," a spokesman for the DH explained.

People who have purchased and used the above products should consult healthcare professionals for advice.

Public urged not to buy or use product with doubtful composition

On 22 April 2015, the DH urged the public not to buy or use a product, namely Snake Powder Capsules, as it was found to contain undeclared controlled drug ingredients.

The appeal resulted from the DH's investigation upon the receipt of notification of a case from the Hospital Authority (HA) on 21 April regarding a 58 -year-old male patient who had consumed the above product.

The patient attended the Accident and Emergency Department of Queen Elizabeth Hospital on 7 April for chest discomfort and bilateral ankle swelling and was admitted for treatment on the same day. He gave a history of consuming Snake Powder Capsules, which was purchased locally. Preliminary test results from the HA's laboratory revealed that the product may contain undeclared Part I poisons and antibiotics. The DH conducted investigation immediately.

A Chinese medicine centre in Mong Kok was subsequently raided in a joint operation by the DH and the Police. During the operation, a woman aged 50 and a man aged 29 were arrested for suspected illegal sale and possession of Part I poisons, an unregistered pharmaceutical product and antibiotics. Snake Powder Capsules were found and seized for analysis. The Government Laboratory on 22 April confirmed that the product contains dexamethasone, ibuprofen, chlorpheniramine, tetracycline and chloramphenicol.

Dexamethasone and ibuprofen are Part I poisons whereas tetracycline and chloramphenicol are antibiotics. Products containing dexamethasone, tetracycline and chloramphenicol are prescription medicines which should only be used under the advice of a medical doctor or supplied by pharmacies under the supervision of a registered pharmacist upon a doctor's prescription.

Dexamethasone is a steroid, and its side effects include moon face, high blood pressure, high blood sugar, muscle atrophy, adrenal insufficiency and even osteoporosis. Ibuprofen is a non-steroidal anti -inflammatory drug for the relief of pain and inflammation, and its side effects include gastrointestinal discomfort, nausea, peptic ulcers and renal impairment. Chlorpheniramine is an

antihistamine for the treatment of allergic reaction, and its side effects include blurred vision and drowsiness.

Tetracycline and chloramphenicol are antibiotics for the treatment of various infections. Tetracycline may cause nausea, vomiting, diarrhoea and dysphagia while chloramphenicol is associated with serous haematological side effects when given orally.

Members of the public who have purchased and consumed the above product should consult healthcare professionals for advice immediately.

Retail shop raided for suspected illegal possession of unregistered pharmaceutical products

On 24 April 2015, a retail shop in Mong Kok was raided by the DH for suspected illegal possession of Part I poisons and unregistered pharmaceutical products.

Acting upon intelligence, the DH found in the operation that various suspected unregistered pharmaceutical products, including eye drops and creams, were being offered for sale in the retail shop. The products were mainly labelled in Japanese. Preliminary information indicated that some eye drops were labelled as containing neostigmine, a Part I poison. Hong Kong registration numbers were not found on any of these product labels.

Eye drops containing neostigmine are prescription medicines and should only be used under the advice of a medical doctor or supplied at pharmacies under the supervision of a registered pharmacist upon doctor's prescription. Inappropriate use may cause ocular pain and irritation as well as blurred vision.

Members of the public who have bought the unregistered products with no registration number should stop using them immediately. They should consult healthcare professionals for advice if they are in doubt or feeling unwell after using the concerned products.

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 I poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part I 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,
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.