



# Drug News

## 藥物情報

### Issue Number 81

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

### **EU: EMA to review modified-release paracetamol**

On 8 July 2016, the European Medicines Agency (EMA) is to review the benefits and risks of paracetamol modified- and prolonged-release tablets, which are available in several European Union (EU) Member States and are designed to release paracetamol over a prolonged period of time. They are different from the usual immediate-release tablets of paracetamol (which release their active substance more quickly and are not included in this review).

The standard procedures for assessing and managing overdose and poisoning with paracetamol are designed for the immediate-release products. In recent years there have been a number of cases of overdose with certain modified-release paracetamol tablets which indicate that the standard procedures may not be entirely suited to treat overdoses with the latter products.

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) will evaluate available evidence to determine the risk of overdose with modified- and prolonged-release paracetamol, and whether any additional measures need to be taken. In the meantime, patients who have any concerns about their medication should discuss them with their healthcare professional.

In Hong Kong, there are seven registered pharmaceutical products containing modified-release or prolonged-release paracetamol, namely Clariflu Sustained Release Tab (HK-47205), Panadol Long Lasting Tab 665 mg (HK-51314), Panadol Extend Tab 665mg (HK-51316), Panadol Extend Tab 665mg (Ireland) (HK-52683), Panadol Joint Extended Release Caplet 665mg (HK-59436), Xykaa Extend Prolonged Release Tablet 650mg (HK-61400) and Ensid –ER Extended Release Tablet 650mg (HK-62272). All these products are over-the-counter medicines, except HK-47205 which is a pharmacy-only-medicine. As on 28 September 2016, the Department of Health (DH) has received one adverse drug reaction (ADR) case related to modified-release or prolonged-release paracetamol products. In view of the above EMA announcement, DH will remain vigilance on the future review results by EMA.

### **UK: Warfarin: reports of calciphylaxis**

On 18 July 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) advised that there have been reports of calciphylaxis associated with the use of warfarin.

Warfarin is an oral anticoagulant. It is a vitamin K antagonist that acts by inhibiting the formation of active clotting factors II, VII, IX, and X.

Calciphylaxis is a very rare but serious condition that causes vascular calcification and cutaneous necrosis. The mortality rate is high. It is also known as calcific uremic arteriolopathy. The condition is most commonly observed in patients with end-stage renal disease on dialysis, or in those with known risk factors such as: protein C or S deficiency; hyperphosphataemia; hypercalcaemia; or hypoalbuminaemia.

Cases of calciphylaxis have been reported in patients taking warfarin. Pre-existing renal disease was commonly reported in cases, but some reports noted normal renal function. An EU-wide review of relevant evidence recently concluded that there is a reasonable possibility that on rare occasions warfarin use might lead to calciphylaxis. The product information for warfarin will be updated in the United Kingdom (UK) with the above advice. The patient information leaflet in the UK will also be updated to warn patients of the risk of calciphylaxis, with advice to consult their doctor if they develop a painful skin rash.

Calciphylaxis is poorly understood and the exact pathogenesis is unknown. Calciphylaxis and warfarin-induced skin necrosis can present with similar clinical findings, but can be differentiated by histopathology. The mechanism could be mediated through the matrix Gla protein, which is a vitamin-K-dependent protein involved in the inhibition of calcification. Warfarin inhibits Gla protein and may therefore promote vascular calcification in susceptible individuals.

The MHRA advised healthcare professionals that if calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.

In Hong Kong, there are 18 registered pharmaceutical products containing warfarin which

are all prescription only medicines. As on 28 September 2016, DH has received six ADR cases in connection with warfarin, but none of them was related to calciphylaxis. In view of the above MHRA announcement, DH issued a letter to inform local healthcare professionals to draw their attention to the risk of calciphylaxis on 19 July 2016, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board (the Registration Committee).

### **UK: Citalopram: suspected drug interaction with cocaine; prescribers should consider enquiring about illicit drug use**

On 18 July 2016, MHRA received a Coroner's report that raised concerns about a suspected drug interaction between citalopram and cocaine after the death of a man due to subarachnoid haemorrhage.

The case was discussed by the UK Commission on Human Medicine's Pharmacovigilance Expert Advisory Group. There are plausible mechanisms for an interaction between cocaine and citalopram that could lead to subarachnoid haemorrhage, including hypertension related to cocaine and an additive increased bleeding risk in combination with citalopram.

Guidance from the General Medical Council states that, together with the patient, healthcare professionals should make an assessment of the patient's condition before deciding to prescribe a medicine. The professional must have, or take, an adequate history, which considers recent use of other medicines—including non-prescription medicines, herbal medicines, illegal drugs, and medicines purchased online.

In particular, when prescribing selective serotonin reuptake inhibitors (SSRIs), prescribers are

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reminded to enquire about cocaine use when considering drug–drug interactions and the need to avoid concurrent use of multiple serotonergic drugs.

In light of this Coroner's case, MHRA reminds prescribers to note the potential increased risk of bleeding when citalopram is prescribed to patients who are taking cocaine. More generally, the possibility of illicit drug use and interactions should be considered when prescribing any medicines that have the potential to interact adversely. Possible interactions with illicit drugs should also be considered in patients who present with suspected adverse reactions to a medicine.

In Hong Kong, there are 48 registered pharmaceutical products containing citalopram which are all prescription only medicines. As on 28 September 2016, DH has not received any ADR report related to citalopram. DH will continue to remain vigilant on drug safety update related to citalopram by other overseas drug regulatory authorities for consideration of any action deemed necessary.

### **EU: CHMP confirms recommendations for use of Zydelig**

On 22 July 2016, the EMA's Committee for Medicinal Products for Human Use (CHMP) has confirmed that the benefits of Zydelig (idelalisib) in the treatment of the blood cancers chronic lymphocytic leukaemia (CLL) and follicular lymphoma outweigh the risk of side effects. However, following a review it has updated recommendations to minimise the risk of serious infections in patients treated with the medicine.

All patients treated with Zydelig should be given preventive medication against the lung infection *Pneumocystis jirovecii* pneumonia during treatment

and this should be continued for up to 6 months after treatment with Zydelig has stopped. Patients receiving Zydelig should also be monitored for signs of infection and have regular blood tests to measure the level of white blood cells. Low white cell counts can indicate an increased risk of infection and treatment may need to be interrupted. Zydelig should also not be started in patients with any generalised infection.

In addition, following an interim precautionary recommendation not to start Zydelig treatment in previously untreated patients with CLL that has certain genetic mutations, CHMP now concludes that treatment with Zydelig can again be started in these patients provided alternative treatments are not suitable and provided that the measures to prevent infection are followed.

In Hong Kong, there are two registered pharmaceutical products containing idelalisib, namely Zydelig Tablets 100mg (HK-64093) and 150mg (HK-64094). Both products are prescription only medicines, and are registered by Gilead Sciences Hong Kong Limited (Gilead). Similar news on the serious adverse effects including deaths related to idelalisib had been announced by EMA, UK MHRA, Australia Therapeutic Goods Administration (TGA), Health Canada and Singapore Health Sciences Authority (HSA), and was reported in the Drug News Issue No.77. DH issued a letter to inform local healthcare professionals to draw their attention on 14 March 2016. As on 28 September 2016, DH has received one ADR case related to idelalisib. Besides, Gilead has informed DH that the company will submit application to include the above new safety information in the product label or package insert. DH will continue to remain vigilant on the reviews and safety updates related to idelalisib by other overseas drug regulatory authorities

## **US: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects**

On 26 July 2016, the United States (US) Food and Drug Administration (FDA) approved changes to the labels of fluoroquinolone antibacterial drugs for systemic use (i.e., taken by mouth or by injection). These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. As a result, FDA revised the *Boxed Warning*, FDA's strongest warning, to address these serious safety issues. FDA also added a new warning and updated other parts of the drug label, including the patient Medication Guide.

Fluoroquinolones are antibiotic medicines that work by killing or stopping the growth of bacteria that can cause illness. They are FDA-approved to prevent or treat certain serious bacterial infections. FDA-approved fluoroquinolones include levofloxacin (Levaquin), ciprofloxacin (Cipro), ciprofloxacin extended-release tablets, moxifloxacin (Avelox), ofloxacin and gemifloxacin (Factive).

FDA has determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients. For some serious bacterial infections the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.

The labels of fluoroquinolone medicines already have a *Boxed Warning* for tendinitis, tendon

rupture, and worsening of myasthenia gravis in US. The labels in US also include warnings about the risks of peripheral neuropathy and central nervous system effects. Other serious risks associated with fluoroquinolones are described in the labels in US, such as cardiac, dermatologic, and hypersensitivity reactions. After FDA's 2013 review that led to the additional warning that peripheral neuropathy may be irreversible, FDA evaluated post-marketing reports of apparently healthy patients who experienced disabling and potentially permanent side effects involving two or more body systems after being treated with a systemic fluoroquinolone. FDA evaluated only reports submitted to them, so there are likely additional cases of which FDA is unaware. The side effects occurred within hours to weeks after starting the fluoroquinolone, and at the time they received the reports, the side effects had continued for an average of 14 months, to as long as 9 years after stopping the medicines. Several cases reported that some side effects stopped or improved after discontinuation of the medicine; others reported the side effects worsened or continued.

In addition to updating information in the *Boxed Warning*, FDA is also including information about these safety issues in the *Warnings and Precautions* section of the label in US. The *Indications and Usage* section contains new limitation-of-use statements to reserve fluoroquinolones for patients who do not have other available treatment options for ABS, ABECB, and uncomplicated UTIs. The patient Medication Guide in US that is required to be given to the patient with each fluoroquinolone prescription describes the safety issues associated with these medicines. FDA is continuing to assess safety issues with fluoroquinolones as part of FDA's usual ongoing review of drugs and will update the public if additional actions are needed.

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Patients are advised to contact their health care professional immediately if they experience any serious side effects while taking fluoroquinolone medicine. Some signs and symptoms of serious side effects include unusual joint or tendon pain, muscle weakness, a “pins and needles” tingling or pricking sensation, numbness in the arms or legs, confusion, and hallucinations.

Health care professionals should not prescribe systemic fluoroquinolones to patients who have other treatment options for ABS, ABECB, and uncomplicated UTI because the risks outweigh the benefits in these patients. Stop fluoroquinolone treatment immediately if a patient reports serious side effects, and switch to a non-fluoroquinolone antibacterial drug to complete the patient’s treatment course.

In Hong Kong, there are 249 registered pharmaceutical products which are fluoroquinolone

antibacterial drugs, including ciprofloxacin (106 products), levofloxacin (66), ofloxacin (53), moxifloxacin (9), norfloxacin (11), lomefloxacin (2), prulifloxacin (1) and sparfloxacin (1). All these products are prescription only medicines. Related news was previously issued by US FDA, and was reported in the Drug News Issue No. 79. DH issued a letter to inform local healthcare professionals of restricting fluoroquinolone antibiotic use for certain uncomplicated infections on 13 May 2016. As on 28 September 2016, DH has received one ADR case in connection with levofloxacin, but it was not related to the serious side effects mentioned in the above announcement. No ADR report has been received for the other fluoroquinolone drugs. The matter has been discussed by the Registration Committee in September 2016. The Registration Committee decided to keep vigilant on any update from other health authorities on this issue.

## Drug Recall

### **DH endorsed recall of 4 batches of Sodium Chloride Injection 23.4% w/v 30ml vial (HK-63077)**

On 8 July 2016, DH endorsed the licensed drug wholesaler, Sino-Asia Pharmaceutical Supplies Ltd. (Sino-Asia), to recall four batches of Sodium Chloride Injection 23.4% w/v (Registration no.: HK-63077) (batch no.: 4D603, 4F660, 5A864, 5C921) from the market because of a potential quality issue.

DH received notifications from Sino-Asia that the product's Canada manufacturer is recalling the above batches of product as precautionary measure because 3 other batches of the product were found out-of-specification (OOS) result for the pH value. The 3 problematic batches have not been imported into Hong Kong.

The above product containing sodium chloride is an over-the-counter medicine used for management of deficiencies of sodium and chloride ions in salt-losing conditions.

According to Sino-Asia, a total of 5680 vials of the product have been supplied to Hospital Authority hospitals and one private doctor. Sino-Asia has already notified the hospitals and the doctor involved.

As on 28 September 2016, DH has not received any ADR report in connection with these batches of product. A notice was released on the website of the Drug Office on 8 July 2016 to alert the public of the recall.



# Drug Incident

## **Public urged not to buy or consume slimming product with undeclared and banned Western drug ingredient**

On 8 July 2016, DH appealed to members of the public not to buy or consume a slimming product called "Lose Weight Coffee" as it was found to contain an undeclared and banned drug ingredient that might be dangerous to health.

The appeal followed DH's receipt of notification from the Hospital Authority (HA) regarding a 43-year-old female patient who felt sick and was admitted to hospital after having consumed the above slimming product. DH commenced investigation immediately.

The patient was admitted to Tuen Mun Hospital on June 16 for psychotic symptoms. She described a history of consuming the above slimming product. Sibutramine metabolites were detected in her urine sample. She was in a stable condition and was discharged on June 18.

According to the HA, and as later confirmed by the Government Laboratory, a sample of the product provided by the patient was found to contain the Part 1 poison sibutramine. Preliminary investigations revealed that the patient's husband purchased the slimming product from a van parked in Sham Shui Po.

Sibutramine was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of increased cardiovascular risk.

Weight control should be achieved through a balanced diet and appropriate exercise. The public

should consult healthcare professionals before using any medication for weight control.

A notice was released on the website of the Drug Office on 8 July 2016 to alert the public of the drug incident.

## **DH issued warning on oral product containing banned and undeclared Western drug ingredients**

On 14 July 2016, DH urged the public not to buy or consume an oral product called TANGKE TEGONGYIHAOJIAONANG as it was found to contain two undeclared Western drug ingredients, including one banned locally. The product is neither a registered pharmaceutical product nor a registered proprietary Chinese medicine in Hong Kong.

Upon notification from the HA of a case affecting a man aged 58 who consumed the above product before admission, DH immediately commenced investigations.

The patient with underlying illnesses was admitted to Queen Elizabeth Hospital on July 5 for shortness of breath. He was later found to suffer from lactic acidosis and respiratory failure. His condition deteriorated and he died on July 7.

While substances including phenformin and glibenclamide metabolite were detected in the patient's urine specimen, a sample of the product's remnants was also found to contain phenformin and glibenclamide upon testing by the Government Laboratory.

Both phenformin and glibenclamide are

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hypoglycaemic agents. Drugs containing phenformin have been banned in Hong Kong since 1985 for potentially fatal lactic acidosis. Glibenclamide is used for treating diabetes and improper use may lead to a significant fall in blood sugar levels. It is a prescription drug which should only be used under medical supervision.

According to the patient's family, he had been taking the above product for at least three to four months, but the exact source of the product as well as his consumption pattern and dosage were unknown.

Patients with chronic diseases like diabetes should consult healthcare professionals for appropriate advice and holistic management. They should refrain from self-medication or using over-the-counter products without professional supervision as consequences can be very serious. Extra caution is warranted for taking drugs obtained outside Hong Kong and medical advice should be sought.

A notice was released on the website of the Drug Office on 14 July 2016 to alert the public of the drug incident.

## **DH endorsed recall of slimming product with undeclared Western drug ingredients**

On 25 July 2016, DH endorsed a local distributor, Catil International Holdings Limited (Catil), to recall a slimming product called B-finn from the market as it was found to contain undeclared Western drug ingredients.

Acting on intelligence, DH purchased a sample of the above slimming product for analysis. Test results from the Government Laboratory revealed that the sample contained two undeclared substances, namely orlistat and 2-(Diphenylmethyl)

pyrrolidine (desoxy-D2PM). Investigations revealed that Catil is the local distributor for the product. Catil has agreed to recall the product from the market.

Orlistat is a Part 1 poison used for the treatment of obesity. Its side effects include faecal urgency, fatty stool, increased frequency of defecation, faecal incontinence, headache and abdominal pain. Severe liver injuries may also be induced. Products containing orlistat should only be sold at pharmacies under the supervision of a registered pharmacist. Desoxy-D2PM is a psychoactive substance and has been reported to cause hallucinations and severe agitation. It has no medicinal uses.

A notice was released on the website of the Drug Office on 25 July 2016 to alert the public of the drug incident.

## **Woman arrested for suspected illegal sale of slimming product with undeclared banned drug ingredient**

On 29 July 2016, a woman aged 19 was arrested in a joint operation by DH and the Police for suspected illegal sale of a slimming product called "Double S", which is suspected to contain an undeclared banned drug ingredient.

From DH's market surveillance, a sample of the above slimming product was purchased through the Internet for analysis. Test results from the Government Laboratory revealed that the sample contains sibutramine.

Sibutramine is a Part 1 poison once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned because of increased cardiovascular risk.

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

## News In Brief

### **New medicine labelling requirements to take effect from August 5, 2016**

On 25 July 2016, DH issued a press release to remind the pharmaceutical trade and the public that provisions under the Pharmacy and Poisons Ordinance (Cap 138) (PPO) in relation to the labelling of pharmaceutical products containing poisons will take effect on August 5, 2016 to alleviate unnecessary concerns of consumers that such products might be harmful and unsuitable for use or consumption.

According to section 27 of the PPO, no person shall sell any poison unless the container is labelled in accordance with the Pharmacy and Poisons Regulations (Cap 138A) (PPR). Under the PPR, the container of a poison-containing pharmaceutical product must be clearly printed with both English and Chinese text as specified in Schedule 5 in respect of the kind of poison contained. The text must not be modified in meaning by the addition of any other text or marks.

Depending on the sale restriction, the new labelling requirements are:

1. For medicine containing a poison included in Schedule 3 of the PPR, it must be labelled with the text "Prescription Drug 處方藥物"; and
2. For medicine containing a poison included in Part 1 of the Poisons List but not in Schedule 3 of the PPR, it must be labelled with the text "Drug under

Supervised Sales 監督售賣藥物".

The Drug Office of DH has issued letters to the pharmaceutical trade and relevant associations to remind them of the above requirements, and has updated the Guidelines on the Labelling of Pharmaceutical Products online.

The amended PPO, with exceptions on the labelling of pharmaceutical products containing poisons, has been in operation since February 2015 and 18 months have been reserved for the pharmaceutical trade to prepare for the above requirements before their commencement on August 5, 2016.

From 5 August 2016 onwards, DH will take enforcement actions for contravention of the above new labelling requirements. The maximum penalty is a fine of \$100,000 and two years' imprisonment upon conviction. DH urge the pharmaceutical trade to comply with the new requirements in response to recommendations of the former Review Committee on the Regulation of Pharmaceutical Products in Hong Kong which reinforce local regulatory framework.



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](mailto:pharmgeneral@dh.gov.hk)**

#### **Adverse Drug Reaction (ADR) Reporting:**

**Tel: 2319 2920**

**Fax: 2319 6319**

**E-mail: [adr@dh.gov.hk](mailto: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.***