Drug News
藥 物 情 報

Issue Number 68

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

Canada: Recall: Apo-Risperidone Tablet 4mg

On 4 June 2015, Apotex Inc was recalling one lot of Apo-Risperidone (lot no.: KM3974) to the wholesaler/distributor level due to out of specification result for an unidentified impurity.

Health Canada classified the hazard level of the recall as Type III, i.e. a situation in which the use of, or exposure to, a product is not likely to cause any adverse health consequences.

In Hong Kong, Apo-Risperidone Tab 4mg (HK-56335) is a pharmaceutical product registered by Hind Wing Co Ltd (Hind Wing), and is a prescription only medicine. As confirmed with Hind Wing, the affected batch KM3974 had been imported into Hong Kong and was distributed to private doctors. As on 24 July 2015, the DH has not received any adverse drug reaction report related to the product. In line with the Health Canada announcement to recall the product batch to the wholesaler/distributor level, Hind Wing has quarantined the remaining stock of the said batch for disposal.

Australia / Taiwan: Non-steroidal anti-inflammatory drugs (diclofenac, flurbiprofen, ibuprofen, ketoprofen, mefenamic acid and naproxen): proposed additional advisory statement for medicines

On 11 June 2015, the TGA has summarised the following issues in response to the consultation on non-steroidal anti-inflammatory drugs (NSAIDs) for oral use (diclofenac, flurbiprofen, ibuprofen, ketoprofen, mefenamic acid and naproxen).

- The TGA endorses the proposal that the label warning about liver damage should also be required for the other OTC NSAIDs, i.e. not just in the PI for diclofenac, but also in the PI documents for the innovator products containing ibuprofen ("Brufen"), naproxen ("Naprosyn"), ketoprofen ("Orudis") and mefenamic acid ("Ponstan").
- The TGA does not agree that paediatric-specific products should be exempted from the requirements on cardiovascular warnings.

The TGA comes to the following final proposal:

The labels of oral medicines containing diclofenac, flurbiprofen, ibuprofen, ketoprofen, mefenamic acid or naproxen will require an additional advisory statement to the effect that excessive or prolonged use can increase the risk of heart attack, stroke or liver damage. To minimise the total number of required statements for these medicine labels in the Required Advisory Statements for Medicine Labels (RASML), the TGA proposes that the new statement will be included in the RASML as an extension to the currently required statement 'Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful'; as follows.

- *Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.*

On 26 June 2015, the Food and Drug Administration of Taiwan (TFDA) made an

announcement on unification of contraindications and related matters regarding oral medicines containing flurbiprofen.

The TFDA, by bringing together relevant information and clinically relevant literature reports, recommended that:

Contraindications:

- Patients with recurrent peptic ulcers or peptic ulcers leading to bleeding, perforation.
- Severe liver failure.
- Severe kidney failure.
- Perioperative pain in coronary artery bypass graft (CABG) surgery patients.
- Those who are allergic to the drug.
- Patients with the following symptoms of allergy to aspirin or other NSAIDs: shortness of breath, urticaria, allergic rhinitis, angioedema.

Warnings:

- Women in the third trimester of pregnancy: use of the NSAID class of drugs may cause early closure of ductus arteriosus, they should be used cautiously.

In Hong Kong, there are 362 registered oral pharmaceutical products containing the NSAIDs mentioned in the TGA's announcement, including 141 products containing diclofenac, 2 products containing flurbiprofen, 87 products containing ibuprofen, 5 products containing ketoprofen or dexketoprofen, 102 products containing mefenamic acid, and 25 products containing naproxen. Most of them are prescripton only medicines. There are 2 registered products containing flurbiprofen namely Strepfen Honey & Lemon Lozenge 8.75mg (HK-61431) (manufactured in the United Kingdom) and Strepfen Honey & Lemon Lozenge 8.75mg (HK-63536) (manufactured in Thailand). The two products are registered by Reckitt Benckiser Hong Kong Ltd, and are prescription only medicines.

Since the cardiovascular risk of NSAID was announced, letter to healthcare professionals to draw their attention to the alerts was issued on 30 September 2011 and the relevant matterwas 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 Committee concluded that NSAIDs-containing products, other than external preparations and aspirin, should include new safety warnings regarding the cardiovascular risk. However, hepatotoxicity of NSAIDs has not been reported. As on 24 July 2015, the DH has received five adverse drug reaction (ADR) reports on diclofenac and one ADR report on mefenamic acid, and none of them is related to hepatotoxicity. No ADR reports on the other abovementioned NSAIDs have been received. In view of the latest TGA's announcement on hepatotoxicity of NSAIDs, a letter to healthcare professionals was issued on 12 June 2015 to draw their attention to the warning, and the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board .

Singapore: Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) associated with ziprasidone

It was noted from Health Sciences Authority (HSA) website on 29 May 2015 that HSA would like to inform healthcare professionals about overseas cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) that have been reported with the use of ziprasidone.

Ziprasidone (Zeldox, Pfizer Private Limited) is an antipsychotic drug that has been registered in Singapore since 2002. It is indicated for the treatment of schizophrenia, related psychoses, prevention of relapse and for maintenance of clinical improvement during continuation therapy. It is also indicated for the treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

DRESS is a serious adverse drug-induced reaction that is potentially life-threatening. It has a delayed onset, usually appearing two to six weeks after initiation of the causative drug. Manifestations of DRESS may include cutaneous reactions such as rash or exfoliative dermatitis, fever, lymphadenopathy, eosinophilia and other systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, pericarditis and

pancreatitis. The estimated incidence of this syndrome ranges from 1 in 1,000 to 1 in 10,000 drug exposures, with a mortality rate of up to 10%. The pathogenesis of DRESS is unclear and there is no specific treatment for DRESS. Early recognition of the syndrome, prompt discontinuation of the offending agent and supportive care are important in the management of DRESS. Treatment with corticosteroids may also be considered in cases with extensive organ involvement.

In December 2014, the US Food and Drug Administration (FDA) issued a drug safety communication informing that ziprasidone was associated with DRESS. This safety communication followed the review of six worldwide cases of DRESS associated with the use of ziprasidone that were reported to the FDA Adverse Event Reporting System (FAERS). In all six cases, the signs and symptoms of DRESS appeared between 11 and 30 days after ziprasidone treatment was initiated. Of these, a recurrence of symptoms following the discontinuation and re-initiation of ziprasidone was reported for three cases, where a faster time to onset of the symptoms was observed following the re-initiation. Three cases were reported to have concomitant therapy with drugs associated with the occurrence of DRESS. While none of the cases reported death, serious outcomes including hospitalisation had been reported.

In view of the consistency of the case characteristics to the signs and symptoms of DRESS, the temporal relationship between ziprasidone initiation and the onset of symptoms, and the reported cases of positive re-challenge, FDA's assessment concluded that an association between ziprasidone use and the occurrence of DRESS was supported. Based on the available evidence, the FDA had requested for the package inserts (PI) of ziprasidone-containing products to be updated to include warnings on the risk of DRESS.

HSA has not received any adverse drug reaction reports of DRESS associated with ziprasidone use. The local PI for Zeldox has been strengthened to include warnings on the risk of DRESS.

In Hong Kong, there are five registered pharmaceutical products containing ziprasidone, namely Zeldox for Inj 20mg/ml (with solvent) (HK -51214) and Zeldox Cap 20mg (HK-48922), 40mg (HK-48923), 60mg (HK-48924) and 80mg (HK-48925). All of them are prescription only medicines registered by Pfizer Corporation Hong Kong Limited. Related news has been released by the FDA, and was reported on the Drug News Issue No. 62. A letter to healthcare professionals was issued on 12 December 2014 to draw their attention to the new warning. As on 24 July 2015, the DH has not received any adverse drug reaction report on ziprasidone. The matter was discussed in the meeting of the Registration Committee in February 2015. The Committee decided that the package insert of the products should be updated to include the new safety information:

Under "Warnings and Precautions":

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with ziprasidone exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. DRESS is sometimes fatal. Discontinue ziprasidone if DRESS is suspected.

UK: Intrauterine contraception: uterine perforation - updated information on risk factors

On 26 June 2015, the UK Medicines and Healthcare products Regulatory Agency (MHRA) confirmed that intrauterine contraception includes levonorgestrel-releasing intrauterine systems (IUSs) and copper intrauterine devices (IUDs), are licensed for several gynaecological conditions, including:

- long-term contraception
- heavy menstrual bleeding
- protection from endometrial hyperplasia during oestrogen replacement therapy

Use of intrauterine contraception can rarely result

in uterine perforation. Perforation most often occurs during insertion, but might not be detected until some time later. The European Active Surveillance Study for Intrauterine Devices (EURAS-IUD) was an observational study which examined the risk of uterine perforation with intrauterine contraception. The study followed 43,078 women who used levonorgestrel-releasing IUSs and 18,370 women who used copper IUDs.

The results review that the risk of perforation was increased in the following instances:

- in women who were lactating (compared with women not lactating) at the time of insertion
- when the IUS or IUD was inserted up to 36 weeks (compared with more than 36 weeks) after giving birth

These risk factors were independent of the type of intrauterine contraception inserted.

The benefits of intrauterine contraception still strongly outweigh the rare risk of perforation for most women, including those who are lactating or have recently given birth. Therefore the MHRA has not put in place any new restrictions on use of intrauterine contraception based on the study findings. The summaries of product characteristics and patient information leaflets in the UK have been updated.

Healthcare professionals are advised of the following before inserting IUSs or IUDs:

- inform women that perforation occurs in less than 1 in 1,000 women and that the symptoms include:
  - severe pelvic pain after insertion (worse than period cramps)
  - pain or heavy bleeding after insertion which continues for more than a few weeks
  - sudden changes in periods
  - pain during sex
  - not being able to feel the threads, and
- explain to women how to check their threads and tell them to return for a check-up if they cannot feel them (especially if they also have significant pain). Partial perforation may have occurred even if the threads can still be seen; consider this if there is severe pain following insertion.

In Hong Kong, there is one registered pharmaceutical product which is an intrauterine device, namely Mirena Intrauterine system 52mg (HK-41251). It is a prescription only medicine registered by Bayer Healthcare Ltd. As on 24 July 2015, the DH has not received any adverse drug reaction report on the product. In view of the MHRA's announcement, a letter to healthcare professionals was issued on the same date, and the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board . The DH will remain vigilant on any safety updates of the drug.

Drug Incident

Woman arrested for suspected illegal sale of slimming product with undeclared controlled drug substances

On 10 June 2015, a 20-year-old woman was arrested in a joint operation by the DH and the Police for suspected illegal sale of a slimming product called Secrate SRIM&FERM, which is suspected to contain undeclared Part I poisons.

The DH was notified by the Hospital Authority that a female patient, who was found to have hypokalemia, had a history of consuming the above product purchased from a seller via the Internet. Test results from the Government Laboratory revealed that the product contained dipyrone, diclofenac, lignocaine and phenolphthalein. The patient has been discharged and is in a stable condition.

Dipyrone, diclofenac and lignocaine are Part I poisons. Dipyrone and diclofenac are non-steroidal anti-inflammatory drugs which are used to relieve pain and side-effects include gastrointestinal discomfort, nausea and peptic ulcers. Lignocaine is a local anaesthetic and

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may cause hypersensitivity reactions. Phenolphthalein was once used to treat constipation, but has been banned in Hong Kong for its cancer-causing effect.

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

Retail shop raided for suspected illegal sale and possession of unregistered pharmaceutical products

On 26 June 2015, three women aged 24 to 32 of retail shop in Tuen Mun were arrested in a joint operation by the DH and the Police for suspected sale and possession of Part I poisons, unregistered pharmaceutical products and antibiotics.

Following a public complaint, it was found that the above retail shop has been offering for sale various unregistered pharmaceutical products. During the operation, various pain killers, eye-drops and external preparations, all labelled in Japanese, were seized. Preliminary investigation indicated that the products contain ibuprofen, neostigmine, dexamethasone, fluocinolone and neomycin. Hong Kong pharmaceutical product registration numbers were not found on any of the products' label.

Ibuprofen, neostigmine, dexamethasone and fluocinolone are Part I poisons. Side effects of ibuprofen include gastrointestinal bleeding while eye-drops with neostigmine may cause ocular pain and irritation as well as blurred vision. Inappropriate use of steroids like dexamethasone and fluocinolone may cause serious side-effects such as Cushing's Syndrome. Neomycin is an antibiotic and inappropriate use of antibiotics may lead to antibiotics resistance.

News in Brief

Warning in relation to 2,4-dinitrophenol (DNP) consumption

On 8 June 2015, the DH, upon notification from World Health Organisation (WHO), is alerting members of the public not to use the chemical 2,4-dinitrophenol (DNP) which is sold over the Internet as a slimming aid for dieters (including those who are suffering from eating disorders or body dysmorphia) and body builders.

This industrial chemical DNP has caused cases of severe illness and deaths in multiple countries in the last 2-3 years. WHO's notification is triggered by the report of a death in the United Kingdom following the use of a product containing DNP. As a result of this death and other evidence of the continuing sale of products containing DNP, on 29 April 2015 Interpol issued a global alert, in the form of an Orange Notice warning, to law enforcement agencies in 190 countries.

DNP can be used in the manufacture of munitions, as a herbicide, and in the manufacture of dyes, wood preservatives and photographic chemicals. In the 1930s it was discovered that DNP increases metabolic rate and induces weight loss, leading to its use as a slimming drug. The high incidence of severe adverse effects and deaths resulted in the prohibition of its medical use in the USA. DNP has also been banned as a weight-loss drug in the UK.

While DNP is not a licensed drug, it is still widely sold over the Internet under a variety of names. Websites often refer to the chemical as a ‘fat burner’, implying its suitability for human consumption, even if the same website also publishes a disclaimer about the dangers of ingesting this chemical. The fact that a product contains DNP will not always be mentioned on the website or product label. Some of the websites selling the products purport to be pharmaceutical companies or claim to make products to GMP standards. Since, however, there is no regulatory control of the manufacture of products containing DNP, or in the jurisdictions where it is sold, there is no guarantee whatsoever of the quality and purity of the chemical.

DNP is sold as a yellow powder or crystals, in

capsules, and as a cream. Typical quantities of DNP contained in capsules are 100 to 250 mg, and some websites sell the powder in bulk.

Some websites recommend the use of doses of 100 to 400 mg per day, usually building up to the higher dose over time. Websites might also suggest the concomitant use of thyroid hormone and/or anabolic steroids. The toxic dose is variable. The lowest published lethal dose is 4.3 mg/kg and other doses reported as being lethal range from 2.8 to 5g. Conversations around the most suitable dosing 'cycles' are noted in online discussion fora linked to bodybuilding. DNP is absorbed by ingestion, inhalation and through the skin. It acts by uncoupling oxidative phosphorylation and stimulating glycolysis.

The most common side effect associated with the use of DNP is a rash. Other adverse effects reported include peripheral neuritis particularly affecting the hands, gastroenteritis and anorexia, agranulocytosis and neutropaenia, cataracts, permanent deafness and yellow discolouration of the skin, sclera and urine.

Toxic effects include confusion, agitation, coma, convulsions, hyperthermia, tachycardia, sweating and tachypnoea and cardiovascular collapse. Hyperthermia may be severe and life-threatening, and body temperatures exceeding 40° C have been reported. Changes found at post-mortem include heart muscle damage and acute tubular necrosis.

There is no antidote for poisoning with DNP and management involves symptomatic and supportive care with particular attention to monitoring body temperature, cardiac rhythm, heart rate and oxygen saturation. A range of measures may be used to correct hyperthermia including external cooling measures, benzodiazepines and dantrolene.

In Hong Kong, there is no registered pharmaceutical product containing DNP. Members of the public are strongly advised not to buy or consume DNP containing products and products of unknown or doubtful composition, or consume products from unknown sources including through internet. 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 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,
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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.