Drug News
藥 物 情 報

Issue No. 31 : May 2012

This is a monthly digest of local and overseas drug safety news and information released by the Drug Office of the Department of Health in the month as stated above. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).

Safety Update

US, Canada: Label update of Revlimid® (lenalidomide) on the associated increased risk of second primary malignancies

As reported in Issue No. 18 of Drug News in April 2011, the Food and Drug Administration (FDA) of US alerted heathcare professionals about the risk of maligancies related to the use of Revlimid (lenalidomide). On 7 May 2012, FDA made further public announcement of an increased risk of second primary malignancies (SPM) in patients with newly diagnosed multiple myeloma who received Revlimid. Subsequently the Warnings and Precautions section of the Revlimid drug label and the patient Medication Guide had been updated accordingly. Healthcare professionals were advised to consider the potential benefit and the risk of SPM when deciding to treat patients with Revlimid.

On 1 May 2012, Health Canada also informed healthcare professionals regarding the update of the Revlimid® Product Monograph on the risk of SPM and advised them to assess the risk of occurrence of SPM before initiating and during treatment with Revlimid®.

In Hong Kong, four lenalidomide-containing pharmaceutical products are registered as Revlimid Cap 5mg, 10mg, 15mg and 25mg. They are registered by Celgene Ltd. and are prescription medicines. Revlimid is used in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy. Related safety announcement released by US had been reported in Issue No. 18 of Drug News and a letter to healthcare professionals was issued on 9 April 2011. The matter had been discussed in the meeting of the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certificate of Clinical Trial/ Medicine Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board on 28 Feburary 2012. The Committee decided that the package insert of products containing lenalidomide should include the safety information regarding the risks of new malignancies.

Canada: Label update of Cipralex (escitalopram) on its dose-related heart risk

On 7 May 2012, Health Canada informed Canadians regarding a labelling update for Cipralex (escitalopram). Data from clinical trial revealed that Cipralex could cause a dose-related risk of QT interval prolongation, which could lead to abnormal heart rhythms and could be life threatening. The label had been revised to include the warning on:

- Cipralex should not be used in patients with congenital long QT syndrome, or in patients with QT interval prolongation.
- The use of Cipralex was discouraged in patients who were also taking drugs that prolong QT interval or that decrease electrolyte levels in the body.
- The maximum daily recommended dose for most patients was still 20mg but was decreased to 10mg for patients who were 65 years of age or older, had liver problems, or were taking the heartburn drugs which could increase the blood level of Cipralex.

In Hong Kong, there are 17 registered pharmaceutical products containing the antidepressant escitalopram and are prescription medicines. A letter to healthcare professionals was issued on 8 May 2012, and the matter will be discussed in the meeting of Registration Committee

of the Pharmacy and Poisons Board.

China: Label update on the contraindication and warning for orlistat

On 7 May 2012, the State Food and Drug Administration (SFDA) of China announced the changes of the label of over-the-counter orlistat-containing products. The updated label included a new contraindication (on pregnancy) and the maximum dosing frequency (three times a day). In addition, since the use of orlistat might be associated with the risk of urinary crystallization, it was recommended to monitor the renal function for patients at risk of renal impairment and use with caution among those with a history of hyperoxaluria or calcium oxalate nephrolithiasis. Pharmaceutical manufacturers were instructed to include the updated warnings on the product information.

In Hong Kong, there are five registered pharmaceutical products containing orlistat. Four of them are prescription medicines and the remaining one is a Part I poison, which must be sold at registered pharmacy by a registered pharmacist under his supervision. They are indicated for the treatment of obesity. In response, a letter to healthcare professionals was issued on 8 May 2012, and the matter will be discussed in the meeting of Registration Committee of the Pharmacy and Poisons Board.

China: Label update on the contraindications of amantadine hydrochloride for infants under 1 year old

On 7 May 2012, SFDA announced the changes of the label of over-the-counter amantadine hydrochloride-containing products. In order to ensure the safe use for the paediatric patients, the product information was revised to include that its use was now contraindicated for infants under 1 year old. In addition, capsules containing amantadine hydrochloride which could be used in children and adult were now not recommended for children under 5 years old. SFDA instructed the pharmaceutical manufacturers to update the warnings on the relevant product inserts. They were also reminded to report any adverse drug reactions associated with the drug.

In Hong Kong, four amantadine-containing pharmaceutical products are registered which are indicated for patients over 10 years old. Amantadine is an anti-viral drug and is a prescription medicine. In view of SFDA's recommendations, the matter will be discussed in the meeting of Registration Committee of the Pharmacy and Poisons Board.

US: The small risk of cardiovascular death with Zithromax (azithromycin)

On 17 May 2012, FDA announced that a review of the study published in the New England Journal of Medicine about the risks of cardiovascular death with treatment of different antibiotics was in progress. The study revealed a small increase in cardiovascular deaths, and in the risk of death from any cause, in persons treated with a 5-day course of Zithromax (azithromycin) compared to persons treated with amoxicillin, ciprofloxacin, or no drug. FDA advised healthcare professionals to be aware of this risk and heart arrhythmias when prescribing or administering azithromycin. Patients taking azithromycin were advised not to stop the treatment without consulting their healthcare professionals.

In Hong Kong, there are around 61 azithromycin-containing pharmaceutical products registered and are prescription medicines. In response, a letter to healthcare professionals was issued on 18 May 2012. The Department of Health (DH) will keep vigilance against any updated issues released by FDA and other regulatory authorities.

China: Overdose of injectable amoxicillin sodium may increase the risk of renal impairment

On 17 May 2012, SFDA alerted healthcare professionals and the trades on the increased risk of renal impairment associated with the overdose of injectable amoxicillin sodium. Among the serious case reports of renal damage associated with injectable amoxicillin sodium kept in the database of the National Centre for Adverse Drugs Reactions Monitoring of China, 90% was related to amoxicillin overdose. The main presenting clinical features included hematuria, acute renal failure, renal impairment and interstitial nephritis. Healthcare professionals were advised to follow the dosing recommendations as stated in the product inserts and make appropriate dose adjustment when treating elderly or paediatric patients, as well as patients with renal impairment. They were also advised to closely monitor the renal function during

treatment. The pharmaceutical manufacturers were advised to revise the product inserts accordingly and conduct effective risk management measures to ensure the safe use of the medicine.

In Hong Kong, there are 19 injectable amoxicillin-containing pharmaceutical products registered. Amoxicillin is an antibacterial drug and is a prescription medicine. Drug Office had not received any relevant adverse event report in connection with the use of amoxicillin, and would keep vigilant against any updated news related to the issue.

UK: Oral tacrolimus products should be prescribed and dispensed by brand name to avoid the risk of medication errors

On 24 May 2012, the Medicines and Healthcare Products Regulatory Agency (MHRA) advised healthcare professionals to prescribe and dispense oral tacrolimus products by brand name in order to minimise the associated risk of toxicity and graft rejection with inadvertent switching between products. The advice was made after a safety review of oral tacrolimus products by the Commission on Human Medicines. Tacrolimus is a drug with a narrow therapeutic index, and a minor change in blood levels could cause transplant rejection or adverse reactions. The Commission considered the risk of medication errors between different oral pharmacetuical forms might increase with a growing numbers of approved tacrolimus products in the market, and the advice could ensure maintenance of therapeutic response once a patient was stabilised on a particular brand. On the other hand, the Commission emphasized that patients could change to a different tacrolimus pharmaceutical form or brand if the prescriber considered it appropriate and careful therapeutic monitoring of the changes by an appropriate specialist was in place.

In Hong Kong, tacrolimus in oral dosage form is registered under three brand names of Prograf Cap, Advagraf Prolonged-release Hard Cap and Tacrolimus Sandoz Cap, and all with the strengths of 0.5mg, 1mg and 5mg. Tacrolimus is an immunosuppressant indicated for the prophylaxis of transplant rejection and is a prescription medicine. In light of MHRA's advice, a letter to healthcare professionals was issued on 25 May 2012. DH would keep vigilant against any updated news related to the medicine.

EU: Positive benefit-risk balance of Pradaxa (dabigatran etexilate) remained and revision of product information for clearer guidance was recommended

Further to the review of risk of Pradaxa by Therapeutic Goods of Administration of Australia and Health Canada as reported in the previous issues of Drug News, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) also assessed the risk of bleeding related to Pradaxa and concluded that the benefits of Pradaxa continued to outweigh the potential risks but more prescribing recommendations should be included in the product label to enhance its safe use. The label would include the details on the specific situations where Pradaxa must not be used, the types of lesions or conditions and the concomitant medications which were associated with a significant risk of major bleeding. It would also include details on the ways of renal assessment and managing patients and reversing the anticoagulant effect of Pradaxa if bleeding occurred.

In Hong Kong, Pradaxa (dabigatran) is an anticoagulant registered as 75mg, 110mg and 150mg capsules by Boehringer Ingelheim (HK) Ltd. and is a prescription medicine. Safety issues concerning Pradaxa released by different countries had been reported in Issues No. 24, 25 and 29 of Drug News and the issue related to renal function assessment had been discussed at the meeting of the Registration Committee of the Pharmacy and Poisons Board on 26 April 2012. Thus, the safety information on the need for renal function assessment and its contraindicated use in patients with severe renal impairment had been included into the product label and/ or insert. In view of the updated recommendation of the EMA, the matter will be further discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

EU: Batches of MabThera (rituximab) produced at the Vacaville manufacturing site do not pose risk to public health

In December 2011, Roche informed EMA that *Leptospira licerasiae* bacteria was detected in some bioreactors for manufacturing rituximab during its

early (pre-harvest) stages of production at the manufacturing site in Vacaville, US. The laboratories, warehouses, manufacturing and utility facilities and quality management systems at the site were then inspected by the Danish Health and Medicines Authority at the request of the CHMP. It was found that the contaminant was not detected at later stages of manufacturing of the active substance or the finished product. On 25 May 2012, CHMP released the result of the investigation and revealed the most likely source of contamination was through personnel acting as external carriers and/or through the media preparation process itself. The findings did not suggest any clinically relevant risk for patients treated with MabThera. Therefore, the benefit-risk balance of MabThera made from the active substance produced at the Vacaville site was concluded to remain positive.

In Hong Kong, MabThera injection 500mg/50ml, 100mg/10ml, MabThera concentrate for solution for infusion 500mg/50ml and 100mg/10ml are registered by Roche Hong Kong Ltd. and are prescription medicines indicated for non-Hodgkin's lymphoma. DH would keep vigilant against any updated news of the medicine.

UK: Risks of increased heart rate and blood pressure are associated with the use of atomoxetine

On 25 May 2012, MHRA issued a report to review the effects of atomoxetine (brand name Strattera) on heart rate and blood pressure. Based on the available data from clinical trials, approximately 10% of patients developed large and sustained increases in heart rate and blood pressure, which might have clinical implications in some patient groups. Healthcare professionals were advised to closely monitor blood pressure and heart rate in patients treated with atomoxetine and not to use atomoxetine in patients with severe cardiovascular or cerebrovascular conditions such as severe hypertension, heart failure, inherited heart conditions or disease, heart attack or stroke, cardiomyopathy or cerebral aneurysm. Nevertheless, MHRA considered the benefits of atomoxetine continued to outweigh the risks in patients without pre-existing cardiovascular conditions.

In Hong Kong, Strattera Cap 10mg, 18mg, 25mg, 40mg and 60mg are registered by Eli Lilly Asia, Inc. and are prescription medicines indicated for the treatment of attention-deficit and hyperactivity disorder (ADHD) in children and adults. Similar safety alerts on the cardiovascular events with the use of Strattera (atomoxetine) had been released by various regulatory authorities in October and November 2011 which were reported in Issue No. 25 of Drug News. In response, a letter to healthcare professionals was issued on 25 October 2011. The matter had been discussed at the meeting of the Registration Committee of the Pharmacy and Poisons Board on 28 February 2012. The Committee decided that the sales pack label and/or package insert of products containing atomoxetine should include the safety information in relation to the risk of increased blood pressure and heart rate with atomoxetine.

Canada: Label update of Xgeva® (denosumab) on the associated risk of severe symptomatic hypocalcemia

On 28 May 2012, Health Canada informed healthcare professionals regarding the update of the Xgeva® (denosumab) Product Monograph to include the risk of severe symyptomatic hypocalcemia. Data from post-marketing cases and clinical trials revealed severe hypocalcemia following Xgeva® treatment occurred at a rate of 1 - 2% and 3.1% respectively. Signs and symptoms of hypocalcemia may include altered mental status, tetany, seizures and QT prolongation. Healthcare professionals were advised to monitor the serum calcium levels in treated patients and corrected before and during treatment with Xgeva® if necessary with calcium and vitamin D supplements. They were also advised to be cautious when treating patients at risk of developing hypocalcemia (e.g. patients with severe renal impairment or on dialysis) and reassess the treatment benefit in those patients who developed severe symptomatic hypocalcemia.

In Hong Kong, Xgeva (denosumab) is registered by GlaxoSmithKline Ltd. and is a prescription medicine. Xgeva is indicated for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours. In view of the Health Canada's recommendation, a letter to healthcare professionals was issued on 1 June 2012, and the matter will be discussed in the meeting of Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Total recall of Noderin Tablets 200mg (HK-56889)

On 3 May 2012, DH instructed a licensed drug wholesaler, Synmosa Biopharma (Hong Kong) Co Ltd (Synmosa), to recall from customers all batches of Noderin Tablets 200mg (Noderin) due to quality defect. Noderin contains carbamazepine and is indicated for epilepsy and trigeminal neuralgia. It is a prescription medicine which can only be sold with doctor's prescription and under the supervision of a pharmacist at registered pharmacies.

DH was notified by Synmosa that the Taiwan manufacturer found one batch of the product failed the dissolution test. As the quality defect might affect the efficacy of the product, total recall from consumers was warranted.

According to Synmosa, the product had been supplied to pharmacies and private doctors. DH had alerted professional healthcare bodies about the matter and been closely monitored the recall. DH had not received any adverse event report in connection with the product concerned. A press statement was released on the same day to alert the public of the recall.

Selling any drug not of the nature, substance or quality demanded by the purchaser is an offence under Section 52(1) of the Public Health and Municipal Services Ordinance (Cap 132). The maximum penalty involved is $10,000 and three months' imprisonment.

Total recall of unregistered pharmaceutical product Maximum Strength Fungicure Liquid 25% (HK-58917)

On 11 May 2012, DH instructed Warwick Trading Co (Warwick), a licensed wholesaler, to recall from shelves all batches of Maximum Strength Fungicure Liquid 25% (Fungicure) as the product might bear an unapproved package insert that would make it an unregistered pharmaceutical product. Fungicure is an over-the-counter medicine containing undecenoic acid for anti-fungal treatment.

The matter came to light upon DH's investigation into a public enquiry that the Chinese package insert of Fungicure carried the indication "onychomycosis", which was not found in the English version and was not an approved indication. Investigation revealed that all of the product concerned at Warwick's warehouse was found to contain an unregistered version of the package insert and label.

Warwick had imported 4,757 boxes of Fungicure, among which 4,109 boxes had been sold to local pharmacies and exported to Macau. DH had alerted the Macau authority and local professional healthcare bodies about the matter and been closely monitored the recall. DH had not received any adverse event report in connection with the product concerned. A press statement was released on the same day to alert the public of the recall.

The sale or possession of unregistered pharmaceutical product is an offence under the Pharmacy and Poisons Ordinance (Cap 138). The maximum penalty is a fine of $100,000 and two years' imprisonment.

Drug Incident

Persons arrested for selling and possession of unregistered pharmaceutical products and illegal sale of Part I Poison

On 21 May and 25 May 2012, joint operations were conducted by DH and the Police resulting in the arrests of a 22-year-old woman for suspected illegal sale and possession of unlabelled slimming products, and a 27-year-old man for suspected illegal sale of Ventolin Inhaler, a registered pharmaceutical product containing Part I poison for asthma control. DH issued press statements on the days of operations.

For the former case, it was discovered through DH's surveillance programme that three unlabelled slimming products were found to be sold on the Internet auction website. Laboratory test findings revealed that the products contained Western medicines including fluoxetine, bisacodyl and the banned drug ingredient sibutramine. Sibutramine was used as an appetite suppressant. In November 2010, products containing sibutramine were banned because of increased cardiovascular risk and they are no longer allowed for sale in Hong Kong. Fluoxetine is used for depression and may cause

postural hypotension and alopecia. It must be sold with prescriptions at registered pharmacies under the supervision of pharmacists. Bisacodyl is a laxative that may cause abdominal pain and is an over-the-counter medicine.

Weight control should only be achieved through a good diet and appropriate exercise. People ought to consult healthcare providers for professional advice if they have questions and definitely before using any medication for weight control.

For the latter case, it was also discovered through DH's surveillance programme that Ventolin Inhaler was sold on the Internet. Laboratory test findings revealed that the product contained the ingredient salbutamol, a Part I poison, which must be sold at registered pharmacies under the supervision of pharmacists. Salbutamol is a western medicine and is used as bronchodilator for control of asthma. The side effects include fine tremor, palpitation and arrhythmias.

Asthma is caused by inflammation of the airways and may result in cough, wheezing and breathlessness. Severe asthma attack may require hospital treatment and can sometimes be life-threatening. Patient should seek medical advice from healthcare professional on the management of asthma. Self-treatment with bronchodilator may result in poor control of asthma and serious consequences.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance (Cap 138) before it can be sold in Hong Kong. Part I poisons such as salbutamol must not be sold on Internet. They must be sold at registered pharmacy by a registered pharmacist or under his or her supervision. In addition, products containing fluoxetine can only be sold with a doctor's prescription. Possession or sale of unregistered pharmaceutical product and illegal sale of Part I poison are offences under the Ordinance with each of them liable to the maximum penalties of a $100,000 fine and two year's imprisonment.

DH appealed to members of the public not to sell or use products of unknown or doubtful composition from the market or the Internet as unregistered pharmaceutical products have not been evaluated by the Pharmacy and Poisons Board, their product safety, quality and efficacy may not be guaranteed. They were advised to stop using the products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. They should destroy, dispose or submit them to the Department's Drug Office during office hours.

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 2147 0457 & 2123 1996

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920

Fax: 2147 0457

E-mail: adr@dh.gov.hk

Link: http://www.drugoffice.gov.hk/adr.html

Post: ***Pharmacovigilance Unit,***
Drug Office, Department of Health,
3/F, Public Health Laboratory Centre,
382 Nam Cheong Street, Kowloon

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.