Drug News
藥 物 情 報

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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: Pradaxa (dabigatran etexilate mesylate) - safety review of post-market reports of serious bleeding events

Further to the alert issued by the European Medicines Agency (EMA) on the risk of bleeding with the use of Pradaxa (dabigatran) as reported in Issue No. 31 of Drug News, the Food and Drug Administration (FDA) of the US released information about the risk of serious bleeding associated with use of Pradaxa and warfarin on 2 November 2012. Using insurance claims and administrative data from FDA's Mini-Sentinel pilot of the Sentinel Initiative, an assessment was performed. The results indicated that bleeding rates associated with new use of Pradaxa did not appear to be higher than the rates associated with new use of warfarin, which was consistent with observations from the large clinical trial used to approve Pradaxa. FDA therefore did not change its recommendations that Pradaxa provided an important health benefit when used as directed. Healthcare professionals who prescribe Pradaxa should carefully follow the dosing recommendations in the approved drug label, especially for patients with renal impairment to reduce the risk of bleeding.

In Hong Kong, Pradaxa (dabigatran) is an anticoagulant registered as 75mg capsules (HK-57316), 110mg capsules (HK-57315) and 150mg capsules (HK-60516) by Boehringer Ingelheim (HK) Ltd. and is a prescription medicine. The risk of bleeding with the use of Pradaxa 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. The Registration Committee decided that the warning on the sales pack or package insert of dabigatran-containing products should be strengthened to include its contraindicated use in patients with lesion or condition at significant risk of major bleeding, such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

Canada: Zocor® (simvastatin) - new safety recommendations on dosage associated with the increased risk of myopathy/ rhabdomyolysis

Subsequent to the news on Zocor® (simvastatin) as reported by US FDA and other regulatory agencies in Issues No. 20, 26 and 28 of Drug News, Health Canada endorsed important safety information on Zocor® regarding the new dosage recommendations associated with the increased risk of myopathy/ rhabdomyolysis on 7 November 2012. The regular use of the 80 mg dose of simvastatin had been associated with an increased risk of myopathy/ rhabdomyolysis, particularly during the first year of treatment. Health Canada advised that the recommended simvastatin dosage should range from 5 to 40 mg/day, and the 80 mg dose should only be restricted to patients who had been taking this dose with no evidence of muscle toxicity or cardiovascular complications. An increased risk of myopathy/rhabdomyolysis within the recommended dose range for Zocor® could also be seen with concomitant administration of certain drugs and food such as verapamil, diltiazem, fibrates, gemfibrozil, fenofibrate, amiodarone, amlodipine,

fusidic acid and grapefruit juice.

In Hong Kong, there are 120 simvastatin-containing products registered and all are prescription medicines indicated for the treatment of hypercholesterolemia. Letters to healthcare professionals were issued on 9 June 2011 and 29 February 2012. The matter had been discussed in the meetings of the Registration Committee of the Pharmacy and Poisons Board. The Committee decided that the sales pack or package insert of simvastatin-containing products should be updated to include the appropriate safety information, examples of wordings to be used are:

- "cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≧1g/day) of niacin. The dose of simvastatin should not exceed 20mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≧1g/day"; and
- "cases of myopathy, including rhabdomyolysis, have been reported with simvastatin co-administered with colchicine. Caution should be exercised when prescribing simvastatin with colchicine".

US: Risks of thrombosis and haemolysis potentially related to administration of injectable human immune globulin products

On 14 November 2012, FDA reported the potential risks of thrombosis and haemolysis associated with the intravenous, subcutaneous or intramuscular administration of human immune globulin products and made related recommendations. Thrombosis had previously been identified as a potential risk following the administration of human immune globulin. FDA continued to investigate whether or not specific characteristics of immune globulin products such as excipients, concentration, or trace procoagulant activity account for an increased risk of thrombosis. In an effort to determine the factors that were associated with the development of thrombosis, FDA scientists and manufacturers had examined different batches of immune globulin products. Using research assays, FDA and manufacturers found elevated levels of factor XIa, which was an activated clotting factor in certain lots of immune globulin products produced by different manufacturers. Such higher levels of factor XIa were associated with a higher incidence of arterial and venous clot formation in patients receiving the product. Acute intravascular haemolysis or delayed haemolytic anemia could occur after immune globulin therapy. At least in some cases, this happened because immune globulins contain blood group antibodies that could act as haemolysins by coating red blood cells, causing a positive direct antibody test result and haemolysis. Isolated cases of haemolysis-related renal dysfunction/failure or disseminated intravascular coagulation had also been reported following treatment with immune globulins.

For thrombosis, FDA recommended that:

- care should be taken when immune globulin products were given to individuals with higher risk of thrombosis;
- patients with higher risk of thrombosis include those with acquired or hereditary hypercoagulable states, prolonged immobilization, in-dwelling vascular catheters, advanced age, estrogen use, a history of venous or arterial thrombosis, cardiovascular risk factors, and hyperviscosity;
- patients at risk for thrombosis should receive immune globulin products at the slowest infusion rate practicable, and these individuals should be monitored for thrombotic complications; and
- consideration should also be given to measurement of baseline blood viscosity in individuals at risk for hyperviscosity.

For haemolysis, FDA recommended that:

- heightened awareness of the potential for haemolysis was recommended in individuals receiving immune globulin products, particularly those who were determined with higher risk;
- patients with higher risk for haemolysis following treatment with immune globulins include those with non-O blood group types, those who had underlying associated inflammatory conditions, and those receiving high cumulative doses of immune globulins over the course of several days;

- patients receiving immune globulin products should be monitored for haemolysis, particularly those with higher risk; and
- clinical symptoms and signs of haemolysis included fever, chills and dark urine. If these occurred, relevant laboratory testings should be obtained.

In Hong Kong, there are 29 immunoglobulin-containing products registered and all are prescription medicines. They are indicated in disorders such as primary and secondary antibody deficiencies and passive immunisation. In view of FDA's recommendations, a letter to healthcare professionals was issued on 14 November 2012. The matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

EU: New safety recommendations to minimise the risk of gas embolism during spray application of fibrin sealants Evicel and Quixil

On 16 November 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) had recommended a number of risk-minimisation measures for the fibrin sealants Evicel and Quixil to minimise the risk of gas embolism when they were applied as spray during surgery. The review was initiated by reports received on gas embolism occurring in association with the use of spray devices that used a pressure regulator for administration. These events were related to the use of the spray device at higher-than-recommended pressures and/or in closer-than-recommended proximity to the tissue surface. CHMP concluded that the benefits of these medicines given by spray applications continued to outweigh their risks. However, the existing instructions for healthcare professionals were not sufficient, and therefore new recommendations were made:

- Evicel and Quixil should be sprayed using CO_2 (gas with greater solubility in blood) only, instead of pressurised air, to reduce the risk of embolism;
- the product information of these medicines should be updated with clear and consistent advice for healthcare professionals regarding recommended pressure and distance to use during spraying application;
- these medicines should not be sprayed in endoscopic surgery; when used in laparoscopic (abdominal) surgery, care should be taken to ensure that the minimum safe distance from tissue was observed; and
- the marketing authorisation-holder for Evicel and Quixil should ensure that these products were used with pressure regulators that did not exceed the maximum pressure required to deliver the fibrin sealant, and that they contained labels stating the recommended pressure and distance.

In Hong Kong, Evicel Solutions for Sealant 1ml (HK-61387), 2ml (HK-61386) and 5ml (HK-61369) are registered by Johnson & Johnson (HK) Ltd. They are prescription medicines indicated as supportive treatment for improvement of haemostasis in surgery where standard surgical techniques are insufficient. In view of EMA's recommendations, a letter to healthcare professionals was issued on 19 November 2012, and the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board. "Quixil" is not a registered pharmaceutical product in Hong Kong.

Singapore: Recommended storage conditions at 2 to 8° C for Neupro® (rotigotine) transdermal patch

On 19 November 2012, UCB reminded healthcare professionals in Singapore that Neupro® (rotigotine) transdermal patch was a cold-chain product which should be stored in a refrigerator (at 2 to 8°C) at the pharmacy and by patients to ensure stability of the product. If the product was stored outside the refrigerator, a crystalline form of the active ingredient (rotigotine), which was visible as a snowflake-like pattern in the matrix of the transdermal patch, may appear. Theoretically, the clinical efficacy of the product may be reduced although in most instances this snowflake-like pattern had no effect on product performance.

In Hong Kong, rotigotine is registered as Neupro Transdermal Patch 8mg/24h (HK-55444), 6mg/24h (HK-55445), 4mg/24h (HK-55446) and 2mg/24h (HK-55447). They are registered by UCB Pharma (HK), and are prescription medicines indicated for

the treatment of Parkinson's disease. The instruction of storing the products in a refrigerator (2°C to 8°C) has already been included in the approved product insert in Hong Kong.

The Mainland: SFDA warned Statins may cause blood glucose abnormalities and interact with HIV protease inhibitors

Subsequent to the reports by US FDA and other regulatory agencies as published in Issues No. 28 and 29 of Drug News, the State Food and Drug Administration (SFDA) of the Mainland alerted healthcare professionals and the public on the risk of blood glucose abnormalities and the interactions between statins and the human immunodeficiency (HIV) protease inhibitors on 20 November 2012. SFDA stated that studies had found statins could cause blood glucose abnormalities, manifested as elevated fasting glucose levels, glycated haemoglobin levels, new-onset diabetes, and blood sugar level of the diabetes may be deteriorating. When statins were taken concurrently with HIV protease inhibitors, it might cause increased blood concentration of statins, thus increased the risk of serious adverse reactions, including rhabdomyolysis. SFDA recommended that healthcare professionals should review the patient's past medical history before commencing treatment with statins and should monitor the patient's blood sugar level closely. Patients experienced symptoms such as polyuria, polyphagia, fatigue, suspected diabetes or blood sugar disorder-related symptoms should consult a physician immediately.

In Hong Kong, there are 248 and 16 registered pharmaceutical products which belong to the classes of statins and HIV protease inhibitors respectively. All are prescription medicines. Statins are indicated for hypercholesterolemia, whereas HIV protease inhibitors have antiviral activity and are used in the treatment of HIV infection. Letters to healthcare professionals were issued on 29 February and 2 March 2012. The matter had been discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board. The Committee decided that the sales pack or package insert of following pharmaceutical products should be updated to include the appropriate safety information, examples of wordings to be used are:

- statins-containing products: "increases in HbAlc and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors";
- atorvastatin-containing products: "co-administration of strong CYP3A4 inhibitors (e.g HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided, lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended. In patients taking telaprevir concomitant use of atorvastatin should be avoided. The dose of atorvastatin should not exceed 40 mg daily when taking with boceprevir and close clinical monitoring is recommended";
- simvastatin-containing products: "simvastatin is contraindicated with strong CYP3A4 inhibitors (e.g. HIV protease inhibitors), gemfibrozil, ciclosporin and danazol";
- lovastatin-containing products: "lovastatin is contraindicated with strong CYP3A4 inhibitors (e.g. HlV protease inhibitors)";
- rosuvastatin-containing products: "the concomitant use with protease inhibitors is not recommended"; and
- products containing HIV protease inhibitors: "co-administration of atorvastatin should be avoided. In cases where co-administration of atorvastatin cannot be avoided, lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended. Concomitant use of lovastatin or simvastatin is contraindicated. Rosuvastatin is not recommended to use with protease inhibitors".

Singapore: Wellbutrin SR tablet 150mg (Bupropion) – possible increased risk of some congenital cardiovascular malformations

Health Sciences Authority (HSA) of Singapore announced that on 30 November 2012, GlaxoSmithKline informed healthcare professionals of the possible increased risk of congenital cardiovascular malformations associated with bupropion. Results from an epidemiology study

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investigating this risk following bupropion exposure during the first trimester of pregnancy as well as findings from other studies suggest a potential increased risk of some congenital cardiovascular malformations such as ventricular septal and left outflow tract heart defects. The pregnancy and pre-clinical safety data sections of the product inserts for all bupropion containing products in Singapore would be updated accordingly. Healthcare professionals were encouraged to consider this new information and to weigh the option of alternative treatments in women who were pregnant or were planning to become pregnant.

In Hong Kong, five pharmaceutical products containing bupropion including Wellbutrin SR sustained-release tab 150 mg (HK-52125) are registered. They are prescription medicines and are indicated for the treatment of major depressive disorder or treatment of smoking cessation. In view of HSA's announcement, a letter to healthcare professionals was issued, and the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Drug Incident

Warning on slimming products with banned and undeclared drug ingredients

In November 2012, DH appealed to members of the public not to buy or consume two slimming products called "Ku Xiu Ba Xiang Jian Fei Wan"「酷秀靶向減肥丸」and "Aulura Energy Balance Dietary Supplement"「奧露娜能量平衡素」as they were found to contain banned and undeclared western ingredients that are dangerous to health.

DH was notified by the Hospital Authority (HA) about the patients feeling unwell after consumption of the products. Investigation showed that both products were purchased from the Internet. The details of these two cases are listed as follows.

Patients	Products consumed	Symptoms developed	Drug ingredients detected in laboratory test
18-year-old woman	Ku Xiu Ba Xiang Jian Fei Wan 「酷秀靶向減肥丸」	psychiatric symptom of persecutory delusion	Sibutramine, Phenolphthalein
19-year-old woman	Aulura Energy Balance Dietary Supplement 「奧露娜能量平衡素」	psychiatric symptom of tactile hallucination	Sibutramine, Phenolphthalein

Sibutramine is a Part I poison and was once a western medicine used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned in Hong Kong because of the increased cardiovascular risk. Phenolphthalein was once used for treating constipation but has been banned for its possible cancer-causing effect.

Weight control should be achieved through balanced diet and appropriate exercise. People should consult healthcare professionals before using any medication for weight control.

Press statements related to the cases were issued on 7 November and 27 November 2012 respectively.

Persons arrested for illegal medical practice and illegal possession of unregistered pharmaceutical products in beauty centre

On 6 November 2012, a joint operation was conducted by DH and the Police against a beauty centre resulting in the arrest two persons for suspected illegal possession of unregistered pharmaceutical products and one of them was also suspected of illegal medical practice.

Acting on a public complaint, the enforcement team found that during the operation, a 58-year-old man, who was not a registered medical practitioner, presented himself as a doctor to his client in the beauty centre. Investigations also found that the man offered botulinum toxin injection to a client at the centre. The product

was suspected to be unregistered. He was arrested for suspected illegal practice of medicine. A subsequent search of the premises also revealed the illegal possession of Part I poisons and antibiotics. The man and a 54 -year-old woman were arrested for illegal possession of Part I poisons and antibiotics as well as unregistered pharmaceutical products.

Botulinum toxin for injection is a prescription medicine with one of the indications for the treatment of facial spasms.

Members of the public were reminded that invasive beauty procedures such as injections of chemical substances or pharmaceutical products may carry risks such as bleeding, infection, scarring and nerve injury. These procedures require a client's informed choice and potential users were advised to discuss with their doctors about the benefits and risks of such procedures and the full details of the procedure before making a decision.

Woman arrested for illegal sale of unregistered pharmaceutical product on the Internet

On 28 November 2012, a joint operation was conducted by DH and the Police resulting in the arrest of a 47-year-old woman for suspected illegal sale of an unregistered pharmaceutical product which claimed to contain glucosamine.

Through DH's surveillance programme, the product "Kirkland Signature Glucosamine and Chondroitin" was offered for sale in an Internet auction website. The product is a pharmaceutical product which is not registered with the Pharmacy and Poisons Board. The product label indicates it contains glucosamine.

A press statement related to the case was issued on the same day.

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. Products containing sibutramine and phenolphthalein are banned and are not accepted for registration as pharmaceutical products in Hong Kong. Part I poisons such as botulinum toxin must be sold at registered pharmacy by a registered pharmacist or under his or her supervision. In addition, products containing botulinum toxin can only be sold with a doctor's prescription. Possession or sale of unregistered pharmaceutical product and possession or sale of Part I poison are offences under the Ordinance. The maximum penalty is a $100,000 fine and two years' imprisonment for each offence. Illegal possession of antibiotics is an offence under the Antibiotics Ordinance (Cap 137). The maximum penalty is a $30,000 fine and 12 months' imprisonment. Furthermore, illegal practice of medicine is an offence under the Medical Registration Ordinance (Cap 161). The maximum penalty is a $100,000 fine and three years' imprisonment.

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, or consume products from unknown sources such as the Internet. 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, disposed or submitted to the Department's Drug Office during office hours.

Useful Contact

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Adverse Drug Reaction (ADR) Reporting:

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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.