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 in the previous month. 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: Risk of abnormal heart rhythms associated with Zofran (ondansetron)

15 September 2011 –The Food and Drug Administration (FDA) notified healthcare professionals of an ongoing safety review and labeling changes for the anti-nausea drug Zofran (ondansetron and ondansetron hydrochloride). Ondansetron might increase the risk of developing prolongation of the QT interval of the electrocardiogram, which could lead to an abnormal and potentially fatal heart rhythm, including Torsade de Pointes. Patients at particular risk for developing Torsade de Pointes included those with underlying heart conditions, such as congenital long QT syndrome, those who were predisposed to low levels of potassium and magnesium in the blood, and those taking other medications that led to QT prolongation. The labels were being revised accordingly to include a warning to avoid its use in patients with congenital long QT syndrome. Recommendations for ECG monitoring in patients with electrolyte abnormalities (e.g. hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or those taking other medications that could lead to QT prolongation, were also being included in the labels.

In Hong Kong, there are 21 ondansetron-containing registered pharmaceutical products and they are prescription medicines. They are used for management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and prevention and treatment of postoperative nausea and vomiting. The Department of Health (DH) issued letters to inform healthcare professionals on 16 September 2011. The matter would be discussed in the next meeting of the Registration Committee of the Pharmacy and Poisons Board.

EU: Updated recommendation on restricting use of Multaq (Dronedarone)

22 September 2011 – After reviewing the currently available data on the benefits and risks of Multaq, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended to restrict the use of Multaq to maintain heart rhythm in patients with paroxysmal or persistent atrial fibrillation for the maintenance of sinus rhythm after successful cardioversion. The Committee recommended of the following measures to reduce the risk of injuries to liver, lung and cardiovascular system:

- Treatment with Multaq should be restricted to patients with paroxysmal or persistent atrial fibrillation when sinus rhythm has been obtained. It is no longer indicated for use in patients when atrial fibrillation is still present.
- Treatment with Multaq should only be started and monitored by a specialist after other anti-arrhythmic medicines have been considered.
- Multaq must not be used in patients with permanent atrial fibrillation, heart failure or left ventricular systolic dysfunction (impairment of the left side of the heart).
- Doctors should consider discontinuation of treatment if atrial fibrillation reoccurs.
- Multaq must not be used in patients who have had previous liver or lung injury following treatment with amiodarone, another anti-arrhythmic medicine.
- Patients on Multaq should have their lung and liver function as well as their heart rhythm regularly monitored. Especially the liver

function should be closely monitored during the first few weeks of treatment.

In Hong Kong, Multaq is registered by Sanofi-Aventis Hong Kong Ltd. and is a prescription medicine for reducing the risk of cardiovascular hospitalization in patients with atrial firbrillation or atrial flutter. The risk of liver injury and cardiovascular events associated with the use of Multaq was previously reported by various overseas regulatory authorities . DH has issued letters to inform healthcare professionals in January and July this year and reported the matter in previous issues of Drug News. The package insert of Multaq has been updated to include the appropriate warnings of liver injury. As regard to CHMP's new recommendation, DH sent another letters on 23 September 2011 to update healthcare professionals. Additional labeling requirement related to the issue would be discussed at the next meeting of the Registration Committee of Pharmacy and Poisons Board. According to Sanofi-Aventis Hong Kong Ltd., the package insert would be revised to include the above updated safety information.

Canada: New recommendations for use of Plavix (Clopidogrel) with proton pump inhibitors

22 September 2011 – Health Canada informed health professionals and patients of the updated recommendations about the use of Plavix in combination with proton pump inhibitors (PPIs). In 2009, the labeling of Plavix was revised to discourage the use of PPI with Plavix because of their interaction in reducing the clinical effect of Plavix. New evidence had shown that while PPIs did interact with Plavix, not all reduced the effectiveness of Plavix to the same degree. The labelling for Plavix had been updated with new recommendations regarding the use of PPIs:

- PPIs known to strongly or moderately reduce Plavix effectiveness should be avoided. Omeprazole is one of these.
- If a PPI must be used in a patient taking Plavix, consider a PPI that does not interact as strongly. Pantoprazole is one of these.

In Hong Kong, there are about thirty pharmaceutical products containing clopidogrel including Plavix and all are prescription drugs. Plavix is registered by Sanofi-Aventis Hong Kong Limited used for prevention of atherothrombotic events in myocardial infarction (MI), ischaemic stroke, or established peripheral arterial disease; in non-ST segment elevation acute coronary syndrome, including patients undergoing stent placement following percutaneous coronary intervention in combination with aspirin; in ST segment elevation acute MI in combination with aspirin in patients eligible for thrombolytic therapy. Its package insert has already mentioned the drug interaction with PPIs. As regard to the new recommendations of Health Canada, DH would consider the issue in the next meeting of the Registration Committee of Pharmacy and Poisons Board.

US: Update on the increased risk of blood clots with drospirenone-containing birth control pills

26 September 2011 – FDA had reviewed six published epidemiologic studies that evaluated the risk of blood clots (venous thromboembolism, VTE) for women who used drospirenone-containing birth control pills. They were found to have conflicting findings. The Agency was continuing its review of a separate FDA-funded study that evaluated the risk of blood clots in users of several different hormonal birth control products (contraceptives) which preliminarily suggested an approximately 1.5-fold increase in the risk of blood clots for women who used drospirenone-containing birth control pills compared to users of other hormonal contraceptives. In view of the conflicting findings, FDA had scheduled a joint meeting with the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in December to discuss the benefits and risks, especially the risk of blood clots, of drospirenone-containing birth control pills. At this juncture, the Agency had not yet reach a conclusion on the risk of blood clots with drospirenone-containing oral contraceptives but remained concerned about the risk.

In Hong Kong, there are three registered products containing drospirenone. They are Yasmin Tab, Angeliq Tab and Yaz Tab and all are registered by Bayer Healthcare Ltd. As reported in Issue No. 20 of Drug News, MHRA recommended in May 2011 on update of information on the higher risk of VTE for combined oral contraceptives (COCs) containing

drospirenone in comparison to the risk for levonorgestrel-containing second generation COCs, and may be similar to the risk for desogestrel-containing or gestodene-containing third generation COCs. The Registration Committee of the Pharmacy and Poisons Board decided at its meeting on 15 June 2011 that the sales pack or package insert of these products should add the above safety information. The current package inserts of Yasmin Tab and Yaz Tab had already been updated. DH will follow the progress of package insert updating of Angeliq Tab and keep vigilant against any updated safety issue of the drug.

UK: Non-steroidal anti-inflammatory drugs (NSAIDs) and risk of heart problems

28 September 2011 – In response to an international review by Hull York Medical School about an increased risk of heart attack or stroke with NSAIDs, MHRA considered the findings were not new as the risk had been well recognised for some years, particularly with long-term use of high doses and in patients who were already at high risk. In fact, information about its restriction on use had already been included in the information for healthcare professionals and the leaflet for patients that accompanied the medicine. The MHRA 's advice on using the medicine for the shortest time and lowest dose necessary to control symptoms remained.

In Hong Kong, NSAIDs-containing products are registered pharmaceutical products with ingredients such as diclofenac, ibuprofen, indomethacin, mefenamic acid and piroxicam. They are indicated for the treatment of arthritis and many other painful conditions, including headache, fever, and minor ailments. Selective COX-2 inhibitors (including celecoxib, etoricoxib and parecoxib) have been required to include a warning about the increased risk of cardiovascular adverse effects in their package inserts. In view of MHRA's recommendation, DH issued letters to remind healthcare professionals on 30 September 2011. Additional labeling requirements regarding the issue on non-selective NSAIDs products except aspirin will be discussed in the next meeting of the Registration Committee of the Pharmacy and Poisons Board.

Australia: Adverse events associated with the off-label use of Topiramate in weight reduction

4 October 2011 –TGA had received a case report involving a patient who developed acute closed angle glaucoma soon after commencing topiramate for weight reduction. This was a serious and known side effect of topiramate therapy. TGA had not approved the use of topiramate to assist with weight loss and reminded health professionals and consumers that its use for this indication was associated with serious adverse events. In Australia, topiramate was only indicated for the treatment of epilepsy and the prevention of migraine headaches.

In Hong Kong, there are 15 registered topiramate-containing pharmaceutical products and are prescription medicines. The approved indications include treatment of epilepsy and prophylaxis of migraine headache. In view of TGA's action, DH issued letters to remind healthcare professionals on the same day about the risks with this off-label use. DH would keep vigilance against any updated safety issues related to the drug.

Australia: Risk of bleeding relating to use of Pradaxa (Dabigatran)

5 October 2011 – TGA received an increase number of bleeding-related adverse events reports related to Pradaxa after its use to prevent stroke and other blood clots in people with atrial fibrillation (AF) had been approved in April 2011. As with warfarin, another oral anticoagulant, there is a risk of bleeding when using Pradaxa. The TGA analysis of these reports showed that: some of the bleeding adverse events occurred during the transition from warfarin to dabigatran and many of the adverse events were found in patients on the reduced dosage regimen. The most common site of serious bleeding for Pradaxa was the gastrointestinal tract, whereas for warfarin it was intracranial. In clinical trials, the risk of bleeding per year of treatment with Pradaxa was 16.6% (1 in 6 patients) when taking 150 mg twice daily, and 14.7% (1 in 6.8 patients) taking 110 mg twice daily compared to 18.4% (1 in 5.4 patients) for warfarin. Clinicians were advised to carefully consider the suitability of their patients for Pradaxa, particularly with regard to the risks of bleeding and their current stability on warfarin or other anticoagulants. They were advised to study the product information before prescribing.

Safety Update

In Hong Kong, dabigatran is an anticoagulant registered under the brand name of Pradaxa as 75mg, 110mg and 150mg capsules by Boehringer Ingelheim (HK) Ltd. It is a prescription medicine.

DH was notified by Boehringer Ingelheim (HK) Ltd. about this risk on 19 August 2011 and letters were sent to healthcare professionals on the same day. The package insert has been updated to include the above warnings.

Advice to Health Professionals

Requirement of record-keeping and proper storage of Dangerous Drugs under the Dangerous Drugs Ordinance

Record-keeping

Every person authorized by or licensed under the Dangerous Drugs Ordinance (Cap. 134) to supply a dangerous drug[1], including a registered medical practitioner, a registered dentist, a registered veterinary surgeon, a registered pharmacist who is employed at a prescribed hospital or health centre or clinic maintained by the government, an authorized seller of poisons and a holder of Wholesale Dealer's Licence to supply Dangerous Drugs, should comply with regulations 5 and 6 of the Dangerous Drugs Regulations to keep a register in the form specified in the First Schedule to the Regulations. A copy of the register is attached at Table 1.

Major requirements regarding dangerous drug record -keeping included:

- A separate register or separate part of register should be used for different dangerous drug and different strengths of its preparation. The register shall not be used for any purpose other than the purposes of the Ordinance.
- All relevant and applicable information should be filled in the register. The exact quantity of the dangerous drug that was obtained and supplied should be entered.
- The dangerous drug and its strength should be specified at the head of any page of the respective register.
- Every entry in the register should be recorded in chronological sequence. It should be made on the day when the dangerous drug is received or supplied or , if that is not reasonably practicable, on the day next following the said day.
- No cancellation, obliteration or alteration of any entry should be made. Every correction of the entry can only be made by a marginal note or footnote specified with the date of correction.
- Every entry and every correction should be made in ink or other indelible form.
- Registers, books or other like records pursuant to the requirement of the Dangerous Drugs Ordinance and Regulations should be kept for a period of two years from the date on which the last entry is made, while other documents should be kept for a period of two years from the date on which it is issued or made.
- All the registers, stock and documents related to any dealings in dangerous drugs should be kept at the premises to which it related and be available for inspection by authorized officers at all times. The register should only be used for the purpose of the Dangerous Drugs Ordinance.

Failing to keep a proper register of dangerous drugs in accordance with the statutory provisions as stated in the Dangerous Drugs Ordinance and its Regulations is an offence punishable by a fine of $450,000 and 3 years imprisonment under regulation 5(7) of the Dangerous Drugs Regulations.

Upon request of inspectors authorized by Department of Health, the person should

(i) furnish the particulars with respect to the obtaining or supplying by him of any dangerous drug, or with respect to any stock of dangerous drugs in his possession;

(ii) produce any stock of dangerous drugs in his possession for the purpose of confirming those particulars; and

(iii) produce such register and such other books or documents in his possession relating to any dealings in dangerous drugs as may required.

[1] According to the Dangerous Drugs Ordinance, dangerous drug means any of the drugs or substances specified in Part I of the First Schedule.

Table 1. Copy of a "Dangerous Drug Register"

Date of receipt/ supply	Name and address of person* or firm from whom received/to whom supplied	Patient's identity card number+	Amount		Invoice No.	Balance
			received	supplied		

*Cross reference of the person to whom supplied may be made in which case only the reference number of the person's treatment record needs to be given.

+ For a patient who is not resident in Hong Kong, the reference number of any proof of identity, other than an identity card, specified in section 17B(1) of the Immigration Ordinance (Cap 115) shall be inserted.

Proper Storage

Every dangerous drug in the custody of a person authorized by the Dangerous Drugs Ordinance to be in possession should be kept in a locked receptacle which can only be opened by him or by some other person authorized to be in possession of the dangerous drug, except when the necessities of the practice or exercise of the profession, function or employment by virtue of which that person is authorized otherwise require.

Failing to keep dangerous drugs in a locked receptacle is an offence punishable by a fine of $5,000 under section 23(6) of the Dangerous Drugs Ordinance.

The above advice serves as general guidance only. Please refer to the specific legal requirements of the respective Ordinance/ Regulation which can be downloaded from http://www.legislation.gov.hk/eng/home.htm. In addition, medical practitioners are advised to follow the Guidelines on Proper Prescription and Dispensing of Dangerous Drugs promulgated by the Medical Council of Hong Kong and listed in the Code of Professional Practice for the Guidance of Registered Medical Practitioners.

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 2147 0457 & 2123 1996

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

You are encouraged to report any suspected or confirmed ADR cases to our office by:

Fax: 2147 0457

E-mail: adr@dh.gov.hk

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