# Drug News
# 藥 物 情 報

**Issue No. 22 : August 2011**

***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: Ongoing safety review of oral bisphosphonates and potential increased risk of esophageal cancer

21 July 2011 - The Food and Drug Administration (FDA) was evaluating the association between the use of oral oestoporosis drugs (bisphosphonates) and an increased risk of esophageal cancer. The studies under evaluation showed conflicting findings. The largest studies that FDA had reviewed, thus far, were two epidemiologic studies using one patient database (the U.K. General Practice Research Database or GPRD). One study found no increase in the risk of esophageal cancer. The second study found a doubling of the risk of esophageal cancer among patients who had 10 or more prescriptions of the drugs, or who had taken the drugs over 3 years. Other external researchers, using different patient databases, had reported no increase or a decrease in risk. At this juncture, FDA believed that the benefits of oral bisphosphonate drugs in reducing the risk of serious fractures in people with osteoporosis continue to outweigh their potential risks. The agency stressed that the review was ongoing and the conclusion had not been arrived. It was also important to note that esophageal cancer was rare, especially in women.

In Hong Kong, bisphosphonates approved for osteoporosis include alendronate, ibandronate, risedronate and zoledronic acid. All are prescription drugs. In December 2010, the package inserts of these products in Hong Kong were updated as a possible risk of atypical thigh bone fracture with the use of bisphosphates was identified overseas. In view of the recent safety information about the risk of esophageal cancer, the Department of Health (DH) issued letters to inform healthcare professionals on 22 July 2011. DH will keep vigilance against any updated safety information in relation to the drug.

### Worldwide: Safety update on Multaq (Dronedarone) and increased risk of cardiovascular side effects

Sanofi Aventis, the manufacturer of Multaq, conducted a clinical trial, the Permanent Atrial fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS), to evaluate the effectiveness of Multaq in patients aged 65 years of age or above with permanent atrial fibrillation (AF). In July 2011, the trial was stopped prematurely because the data monitoring committee noted a two-fold increase in death, stroke and hospitalization for heart failure in patients receiving Multaq as compared with those taking a placebo. In response, different countries released safety updates concerning Multaq.

*Situation in US*

FDA was reviewing data from the PALLAS. Currently Multaq is approved for use in patients with non-permanent AF, also known as paroxysmal or persistent AF. The approval was based on another placebo-controlled, double-blind study, ATHENA trial, which showed that the use of dronedarone significantly reduced the risk of hospitalization due to cardiovascular events or death in patients with paroxysmal or persistent AF or atrial flutter. At this juncture, FDA advised those patients taking Multaq should talk to their healthcare professional about whether they should continue to take Multaq for non-permanent AF. Patients were advised not to stop taking Multaq without talking to a healthcare professionals. Healthcare professionals were advised not to prescribe Multaq to patients with permanent AF.

*Situation in EU*

The European Medicines Agency (EMA) was also reviewing the benefits and risks of Multaq in view of the preliminary data from PALLAS study which could affect its approved indication, "adult clinically stable patients with a history of, or current, non-permanent AF, to prevent recurrence or to lower ventricular rate". Prescribers in the EU were reminded to follow the recommendations in the product information with respect to the indication, contraindications and warnings. Specifically, prescribers were advised to monitor patients regularly in order to ensure that they remained within the authorised indication and did not progress to permanent AF. The Committee for Medicinal Products for Human Use (CHMP) would continue to assess those data in depth, together with all other available data on the benefits and risks of Multaq and finalise the review in September 2011. Further advice would be issued at the time of the final assessment in September.

*Situation in Canada*

Health Canada was evaluating the available information with respect to Multaq and the potential for an increased risk of cardiovascular events. The Product Monograph of Multaq would be revised by Sanofi-aventis Canada Inc. to include the following new safety information:

1) Multaq should be prescribed only in patients with a history of, or current non-permanent AF to reduce the risk of cardiovascular hospitalization due to AF.

2) Multaq must not be prescribed in patients with permanent AF (duration for at least 6 months or duration unknown) and in whom an attempt to restore sinus rhythm is no longer considered.

3) It is recommended to closely monitor patients taking Multaq. If patients treated with Multaq develop permanent AF, treatment with Multaq should be discontinued.

*Situation in Hong Kong*

In Hong Kong, Multaq (dronedarone) is registered by Sanofi-Aventis HK Ltd. and is a prescription medicine indicated to reduce the risk of cardiovascular hospitalization in patients with AF or atrial flutter. The risk of liver injury associated with the use of Multaq was previously released by FDA, UK Medicines and Healthcare products Regulatory Agency (MHRA), EMA, Health Canada and Singapore earlier this year. DH issued letters to inform healthcare professionals on 15 January 2011 and reported the matter in Issue No. 15 and 16 of Drug News. The package insert of Multaq had been updated to include the appropriate warnings of liver injury. In view of the new information concerning the risk of cardiovascular events, DH issued letters again to inform healthcare professionals on 12 and 22 July 2011. According to Sanofi-Aventis HK Ltd., the package insert will be revised to include the above updated safety information. DH will keep vigilance against any updated safety information in relation to the drug.

## Singapore: Detection of a higher incidence of new cases of ovarian failure in premenopausal women treated with Avastin (bevacizumab)

25 July 2011 - Roche, in consultation with the Health Sciences Authority (HSA), was informing healthcare professionals of the higher incidence of new cases of ovarian failure observed in premenopausal women treated with Avastin (bevacizumab). In a randomized phase III trial to study the adjuvant treatment of patients with colon cancer, NSABP C-08, a higher incidence of new cases of ovarian failure was noted in premenopausal women treated with Avastin + mFOLFOX6 as compared to those with FOLFOX6 alone. The causal role of Avastin, however, could not be ruled out in these cases. Healthcare professionals were advised to discuss fertility preservation strategies with women of child-bearing potential prior to starting treatment with Avastin. The package insert of Avastin would be updated to reflect that latest finding from the study NSABP C-08.

In Hong Kong, bevacizumab, an antineoplastic drug, is registered under the name of Avastin Roche by Roche HK Ltd. and is a prescription medicine. The above safety information has been included in the package insert in Hong Kong. DH issued letters to inform healthcare professionals on 26 July 2011 and will keep vigilance against any safety information related to the drug.

## US: Possible serious central nervous system reactions in patients taking serotonergic psychiatric medications associated with the use of Methylene Blue and Zyvox (linezolid)

26 July 2011 - FDA had received reports of serious central nervous system reactions when either methylene blue or linezolid (Zyvox) were given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications). Both of them are reversible monoamine oxidase inhibitor (MAOI) which could inhibit the action of monoamine oxidase A — an enzyme responsible for breaking down serotonin in the brain. Although the exact mechanism of the drug interactions were unknown, it is believed that when methylene blue or linezolid was given to patients taking serotonergic psychiatric medications, high levels of serotonin would build up in the brain, causing toxicity. This was referred to as Serotonin Syndrome and typical signs and symptoms included mental changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination and/or fever. Safety information about the potential drug interactions and important drug usage recommendations for emergency and non-emergency situations were being added to the drug labels for serotonergic psychiatric medications and linezolid.

In Hong Kong, Methylene Blue Inj is registered by Sino-Asia Pharmaceutical Supplies Ltd and it is a non-poison used for treatment of methemoglobinemia. As for Zyvox (linezolid), three dosage forms, namely tablet, injectable and granule, were registered by Pfizer Corp. HK Ltd and they are all prescription items used for treatment of infections, including pneumonia and infections of the skin.

Similar alert on the interaction between methylene blue and serotonin reuptake inhibitors which was released by Health Canada in February 2011 had been reported in Issue No. 17 of Drug News. DH had already issued letters and press statement to inform healthcare professionals and general public respectively on 18 February 2011. Sino-Asia Pharmaceutical Supplies Ltd had also updated the package insert of Methylene Blue Inj accordingly. In view of FDA's recommendation regarding the interaction of serotonin reuptake inhibitors with methylene blue and linezolid, DH issued another letters to inform healthcare professionals on 27 July 2011.

The Registration Committee of the Pharmacy and Poisons Board decided at its meeting dated 6 September 2011 that the sales pack and/or package insert of the pharmaceutical products containing either methylene blue or linezolid should include information about the potential drug interactions with serotonergic psychiatric medications as well as drug usage recommendations for emergency and non-emergency situations.

In addition, the Committee also decided that the sales pack and/or package insert of the serotonergic psychiatric medications should include the following safety information:

"Serotonergic psychiatric drugs should not be started in a patient receiving linezolid. Wait until 24 hours after the last dose of linezolid before starting the serotonergic psychiatric drugs."

## US: Potential risk of birth defects associated with long-term, high-dose use of Diflucan (Fluconazole) during pregnancy

3 August 2011 - FDA was informing the public that chronic treatment with high-dose (400-800mg/day) Diflucan (fluconazole) during the first trimester of pregnancy might be associated with a rare and distinct set of birth defects in infants. This risk did not appear to be associated with a single, low dose (150mg) of fluconazole to treat vaginal yeast infection (candidiasis). Currently, FDA risk classification system uses single letters A, B, C, D or X for describing and interpreting the teratogenic risk of drugs. Based on the above information, the pregnancy category for fluconazole indications (other than vaginal candidiasis) had been changed from category C to category D while that for a single, low dose of fluconazole had not been changed and remained category C. Category C and category D are defined respectively as "animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks" and "there is positive evidence of human fetal risk based on

adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks".

In Hong Kong, Diflucan (fluconazole), an antifungal drug, is registered by Pfizer Corporation HK Ltd. and there are about 60 fluconazole-containing products registered and all are prescription medicines. In view of FDA's recommendation, DH issued letters to inform healthcare professionals on 4 August 2011. The Registration Committee of the Pharmacy and Poisons Board decided at its meeting on 6 September 2011 that the sales pack label and/or package insert of the fluconazole-containing products should include information on the risk of birth defects associated with chronic use of high-dose fluconazole in accordance with the approved labeling by FDA. The following wording would be used:

"A few published case reports describe a rare pattern of distinct congenital anomalies in infants exposed in-utero to high dose maternal fluconazole (400-800 mg/day) during most or all of the first trimester. These reported anomalies are similar to those seen in animal studies. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus."

### Canada: Potential rare risk of breast cancer in men associated with the use of Propecia and Proscar (finasteride)

4 August 2011 - Health Canada was informing healthcare practitioners and patients of a labelling update for finasteride drugs to add safety information on rare reports of breast cancer in men. Breast cancer had been reported in a small number of male patients worldwide with both the 1 mg and 5 mg formulations of finasteride. Most of the reports had been in association with the 5mg formulation. The current available evidence could not establish or rule out the causal relationship between finasteride and breast cancer. The labelling for Propecia, Proscar and several of the generic finasteride products had already been updated to include information on the potential risk of male breast cancer. Updates to the remaining generic drugs would follow.

In Hong Kong, there are about 20 finasteride-containing products (including Propecia 1mg and Proscar 5mg) registered and are prescription medicines for use in men. Finasteride 1mg formulation is used for treatment of male pattern hair loss, while 5mg formulation is used in the treatment and control of benign prostatic hyperplasia (BPH). In view of Health Canada's recommendation, DH issued letters to inform healthcare professionals on 5 August 2011. The issue was discussed at the meeting of the Registration Committee of the Pharmacy and Poisons Board on 6 September 2011 and it was decided that the sales pack labels and/or package inserts of the finasteride-containing products should be updated to include the following new information:

"Post-marketing cases of male breast cancer have been reported with the use of finasteride."

# Drug Recall

### Recall of one batch of 0.3% Potassium Chloride and 0.9% Sodium Chloride IV Infusion (HK-43987) due to suspected microbial contamination

On 3 August 2011, the Department of Health (DH) endorsed a licensed drug wholesaler Luen Cheong Hong Ltd (LCH)'s voluntary recall of a batch of pharmaceutical product called "0.3% Potassium Chloride and 0.9% Sodium Chloride IV Infusion" (Batch: OG705) after the user, the Hospital Authority (HA), detected failure in the preliminary sterility test performed as part of a routine in-house quality assurance programme. Neither HA nor DH had received related adverse event report.

The product was used for replenishment of electrolytes in patients. According to LCH's sales record, the affected batch OG705 was imported from Thailand into Hong Kong last year. Apart from a lot of 400 units which was re-exported to Macao, the batch was otherwise supplied solely to HA hospitals.

The implication of a failed sterility test was that the

infusion might have microbial contamination. Thus, it was prudent that the wholesaler recalled from end-users or else it would risk infecting patients if administered. LCH set up a hotline for public enquiry. Members of the public were advised to consult their healthcare providers when in doubt and in particular if they felt unwell after using the product. All healthcare providers were also advised to report suspected adverse incidents to DH. Meanwhile, DH notified the Macao drug authority to take necessary action.

## Recall of one batch of Coldrex+C Tablet 20's (HK-50258)

On 11 August 2011, DH endorsed the proposal of the GlaxoSmith Kline Limited (GSK) to recall one batch (batch no.: XPN161R) of its product, Coldrex+C Tablet 20's from consumers because the batch's dosage instruction in Chinese was found to have an error during the GSK routine in-house check.

The dosage as appeared in the original English insert and unit carton was correct. However, the insert in Chinese, worded as two tablets every four to six hours as required for children aged 6 and above, had doubled the recommended dosage.

GSK's sales record showed that the affected batch was imported from Ireland in form of 20-tablet packs. 1,398 packs were then distributed by L F Asia (Hong Kong) Ltd, another licensed drug wholesaler, which was responsible to include a paracetamol package warning label and an insert in Chinese before sale in Hong Kong, while 240 packs were re-exported to Macao. That only one batch was likely to be involved because it was the only one distributed since the introduction of the new paracetamol package warning label since July 2011.

Coldrex+C Tablet 20's contains paracetamol, phenylephrine, terpin hydrate, caffeine and ascorbic acid as ingredients and is an over-the-counter drug used to relieve cold and flu symptoms in both adults and children aged 6 and above. Paracetamol overdose is known to be associated with serious health consequences such as liver injury and gastrointestinal discomfort, with children being particularly vulnerable. Healthcare professionals and retailers were urged to stop supplying and customers were advised to stop consuming the said batch of the product immediately. For those who had taken the affected product and were either in doubt or feeling unwell, they were advised to consult their healthcare providers. GSK set up a hotline for public enquiry. DH had not received any related adverse incident report so far. Meanwhile, DH notified the Macao drug authority to take necessary action.

Labelling error is an offence under the Public Health and Municipal Services Ordinance (Cap 132). The maximum penalty is a fine of $50,000 and six months' imprisonment.

## *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,***