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, Canada, EU: Updates on the safety review of Actos (pioglitazone) with the potential increased risk of bladder cancer

Subsequent to the previous announcements on the safety review of Actos (pioglitazone) by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) as reported in Issue No. 12 and 20 of Drug News, further updates were released in June 2011.

16 June 2011 – FDA decided to include safety information that the use of Actos for more than one year may be associated with an increased risk of bladder cancer on the drug label for pioglitazone-containing medicines. This decision was based on FDA's review of data from a five-year interim analysis of an ongoing, ten-year epidemiological study which showed that an increased risk of bladder cancer was noted among patients with the longest exposure to pioglitazone, and in those exposed to the highest cumulative dose of pioglitazone. FDA recommended that healthcare professionals should not use pioglitazone in patients with active bladder cancer, and use pioglitazone with caution in patients with a prior history of bladder cancer.

18 June 2011 - In light of research suggesting an increased risk of bladder cancer with pioglitazone and subsequent actions taken by other regulatory agencies, Health Canada announced that the agency was undertaking a review of the drug's status. At this moment, Health Canada considered the benefits of pioglitazone outweigh the risks when used as directed in the Canadian Product Monograph. Patients with questions or concerns about their diabetes treatment were advised to consult their physician or pharmacist.

24 June 2011 - The EMA initiated a benefit-risk review of pioglitazone-containing medicines and the occurrence of bladder cancer in March 2011. The Committee for Medicinal Products for Human Use (CHMP) discussed at its meeting on 20-24 June 2011 the results of the retrospective cohort study on pioglitazone carried out in France, and its potential impact on the use of these medicines across the whole EU. The CHMP found that the study had several methodological limitations, which limited its strength of evidence. These data would have to be evaluated in the context of the overall available data. The Committee requested its Scientific Advisory Group on Diabetes/Endocrinology (SAG-D/E) to discuss the place of pioglitazone-containing medicines in the treatment of diabetes and the clinical relevance of the available data on the bladder cancer risk, and to identify risk-minimisation measures for patients in clinical practice. The CHMP would discuss the recommendations of SAG-D/E at its next meeting in July 2011 and give its final opinion on the benefits and risks of these medicines.

In Hong Kong, there are 24 registered pharmaceutical products containing pioglitazone (including Actos) and all are prescription medicines. Pioglitazone is an antidiabetic medicine used to manage Type II diabetes mellitus primarily by decreasing insulin resistance. In view of the recent FDA's announcement, DH has issued letters to inform healthcare professionals about this matter on 16 June 2011. At its meeting dated 6 September 2011, the Registration Committee of the Pharmacy and Poisons Board decided that the sales pack label and/or package insert of the pioglitazone-containing products should include additional information including the small increased risk of bladder cancer associated with the drug and the related precautions. DH remains vigilant to any new safety updates about pioglitazone.

US and Canada: Potential increased risk of certain cardiovascular adverse events in patients with cardiovascular disease associated with the use of Chantix (varenicline)

17 June 2011 - FDA notified the public that the smoking cessation aid Chantix (varenicline) might be associated with a small, increased risk of certain cardiovascular adverse events in patients who had cardiovascular disease. This safety information would be added to the Chantix physician labeling and the patient Medication Guide. The decision was made based on a review of a randomized clinical trial involving 700 smokers with cardiovascular disease who were treated with Chantix or placebo. Although cardiovascular adverse events were found to be infrequent overall, certain events, including heart attack, angina pectoris, nonfatal myocardial infarction, peripheral vascular disease, etc were reported more frequently in patients treated with Chantix than in patients treated with placebo. The evaluation of the cardiovascular safety of Chantix was ongoing and FDA requested the manufacturer to conduct a large, combined analysis (meta-analysis) of randomized, placebo-controlled trials. Healthcare professionals were reminded that smoking was an independent and major risk factor for cardiovascular disease and smoking cessation was of particular importance in this patient population. They were advised to weigh its benefits against its potential risk when prescribing the drug to smokers with cardiovascular disease. Patients taking Chantix were advised to consult their healthcare professionals if they experienced new or worsening symptoms of cardiovascular disease.

28 June 2011 – In light of the recent FDA's alert on Chantix, Health Canada announced that it was also reviewing the risk of heart-related side effects in smoking-cessation aid Champix (the brand name for the prescription drug varenicline tartrate). At this moment, the agency considered Champix as an effective smoking-cessation aid when used as part of a support program.

In Hong Kong, varenicline is registered as Champix Tab 0.5mg and 1mg by Pfizer Corporation HK Ltd. They are prescription medicines indicated for smoking-cessation. DH issued letters to inform healthcare professionals about this matter on 17 June 2011 and would keep vigilant against any related safety updates.

US: Recall of Risperdal (risperidone) and Risperidone due to uncharacteristic odour

21 June 2011 - Ortho-McNeil-Janssen Pharmaceuticals notified healthcare professionals and the public of a recall of specific lots of Risperdal (risperidone) 3mg tablets 60's (lot. no.: 0GG904 expiry date: May 2012) and risperidone 2mg tablets 60's (lot no.: OIG175 expiry date: August 2012). The recall stemed from consumer reports of an uncharacteristic odour thought to be caused by trace amounts of TBA (2,4,6 tribromoanisole). In fact, the company had initiated recall of two lots of Topamax (topiramate) Tablets in US and Puerto Rico in April 2011 due to the same reason as reported in Issue No. 19 of Drug News. TBA is a byproduct of a chemical preservative sometimes applied to wood used in the construction of pallets on which materials are transported and stored. Although TBA was not considered as toxic, it could generate an offensive odour and a small number of patients had reported temporary gastrointestinal symptoms. Patients were advised not to stop taking their medication. Those who noted an uncharacteristic odor associated with the drug recalled were advised to return them to their pharmacist and contact their healthcare professionals for queries.

In Hong Kong, Risperdal Tablets 3mg and 2 mg (risperidone) are registered by Johnson & Johnson (HK) Ltd. and they are prescription medicines. Risperidone is used for treatment of schizophenia and bipolar disorder. The company confirmed that the recalled batches have not been imported into Hong Kong.

UK: Recall of two batches of Canesten Pessary

22 June 2011 - Bayer plc, Consumer Care Division recalled two batches (BXFWKG1 and BXFTDV1) of the Pharmacy Medicine ("P"), Canesten Pessary 500mg, because they had contained the Patient Information Leaflet (PIL) intended for the Prescription Only Medicine ("POM") product. In UK, the "P" product can be purchased under the supervision of a pharmacist in a pharmacy without prescription. Additional safety information are thus required in the PIL for the "P" pack which are not

present in the "POM" leaflet.

In Hong Kong, Canesten 1 Vaginal Tab 0.5g (clotrimazole) is registered by Bayer Healthcare Ltd. It is used for treatment of candidal vaginitis. While the package insert requirements are different between UK and Hong Kong, the company also confirmed that the recalled batches have not been marketed in Hong Kong.

EU: Conclusion on review of systemic nimesulide-containing medicines

24 June 2011 – CHMP of EMA concluded that the benefits of systemic nimesulide-containing medicines continued to outweigh their risks in treating patients with acute pain and primary dysmenorrhoea. However, these medicines should no longer be used for the symptomatic treatment of osteoarthritis. The Committee started a full assessment of the benefits and risks of systemic nimesulide-containing medicines at the request of the European Commission in January 2010, because of ongoing concerns over their gastrointestinal and hepatic safety. Having reviewed all available data, the CHMP noted that nimesulide demonstrated the same risk of gastrointestinal toxicity but an increased risk of liver toxicity as compred with other NSAIDs. In fact, the Committee had previously imposed several restrictions on the use of systemic nimesulide to reduce risks of liver injury. As a further restriction, the Committee recommended that systemic nimesulide should no longer be used for the treatment of painful osteoarthritis because this would pose the risk of chronic use of systemic nimesulide and thus increase the risk of liver injury.

In Hong Kong, there are 18 registered pharmaceutical products containing nimesulide and all are prescription medicines. The approved indications in Hong Kong are for treatment of acute pain, symptomatic treatment for osteoarthritis and primary dysmenorrheal. DH has all along closely monitored the safety concerns of nimesulide**.** The Registration Committee of the Pharmacy and Poisons Board previously decided to restrict the use of nimesulide on patients 12 years of age or above and to include additional safety information, including the possible risk of liver damage on the sales packs or package insert of all oral nimesulide-containing medicines. The details were reported in Issue No. 17 & 20 of Drug News. In view of the EMA's latest decision, DH issued letters to inform healthcare professionals about the new restriction in EU on 24 June 2011. The Registration Committee of the Pharmacy and Poisons Board decided at its meeting on 6 September 2011 that in order to ensure the safe use of pharmaceutical products containing nimesulide, the indication for the treatment of painful osteoarthritis should be removed and the indications of the product should be restricted to second line treatment of acute pain or primary dysmenorrhoea only.

UK: Recall of several batches of Fludarabine phosphate 25mg/ml due to detection of high level of impurity

24 June 2011 - Ebewe Pharma Ges.m.b.H.Nfg.KG recalled all remaining stock of Fludarabine phosphate 25mg/ml with the batch numbers of 92497908, 92627304 and 92627309 as a precautionary measure because routine testing showed that a known impurity was present at higher levels than expected. These batches were last distributed in August 2010 and was expected to have very little stock remaining in the supply chain.

In Hong Kong, Fludarabin Ebewe Sol for Inj 50mg/2ml (fludarabine phosphate) is registered by Novartis Pharmaceuticals (HK) Ltd. and is a prescription medicine. Fludarabin is used for treatment of chronic lymphocytic leukemia of B-cell type with sufficient bone marrow function. The company confirmed that the affected batches had not been marketed in Hong Kong.

EU: Restriction on the use of dexrazoxane -containing medicines

25 June 2011 – CHMP of EMA completed a review of dexrazonxane and recommended additional restriction on the use of dexrazoxane to adult patients with advanced or metastatic breast cancer who had received anthracyclines doxorubicin and epirubicin.

The review was initiated because of concerns about the associated risk of acute myeloid leukaemia and myelodysplastic syndrome with dexrazoxane. The CHMP concluded that its benefits only outweigh its risks in those with advanced or metastatic breast cancer who have already received a minimum cumulative dose of 300mg/m2 of doxorubicin or 540mg/m2 of epirubicin. While the dose ratio of dexrazoxane to epirubicin on concomitant use

remained unchanged (10:1), the dose ratio of dexrazoxane to doxorubicin was recommended to decrease from 20:1 to 10:1. Furthermore, there was evidence that the benefits of the medicine did not outweigh the risks in children and adolescents. The CHMP therefore recommended contraindicating the use of this medicine in patients under the age of 18. Healthcare professionals were advised to carefully weigh the benefits against its risk when prescribing dexrazoxane.

In Hong Kong, there is one registered pharmaceutical product containing dexrazoxane which is a prescription medicine. Dexrazoxane is used for prevention of cardiotoxicity resulting from cytotoxic therapy with anthracycline-containing chemotherapy regimens. There is currently no restriction on its use with respect to the amount of previous anthracycline treatment and the drug is not contraindicated for use in children. In view of the recommendation of the EMA, DH issued letters to inform healthcare professionals about this matter on 27 June 2011. The issue was discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board on 6 September 2011 and the Committee decided to restrict the use of dexrazoxane-containg products so that they should not be used in children and adolescents up to 18 years of age.

US: Modified dosing recommendations for Erythropoiesis-Stimulating Agents

25 June 2011 – FDA recommended to revise the dosing guidelines of Erythropoiesis-Stimulating Agents (ESAs) for treating anemia in patients with chronic kidney disease (CKD) because of the increased risks of cardiovascular events with the current recommendation. The revision was initiated following the review of clinical trials which showed an increased risk of cardiovascular events, such as heart attack and stroke, without additional benefits to patients when ESAs were dosed to achieve a normal or nearly normal blood hemoglobin level. Until the day of FDA's announcement, the recommended dosing of ESAs as listed in the product label was to achieve and maintain hemoglobin levels within the range of 10 to 12 grams/deciliter (g/dL) in patients with CKD. The modified recommendation removed the concept of a "target hemoglobin range" and set the treatment goal as to individualize therapy and use the lowest dose of ESA to reduce the need for red blood cell transfusions. The package insert was revised to include this recommendation. In addition, FDA issued a Drug Safety Communication to inform healthcare professionals about the changes. The evaluation of ESAs safety was ongoing and the agency was requesting the manufacturer to conduct additional trials. FDA also approved modifications to the existing Risk Evaluation and Mitigation Strategy (REMS) for ESAs.

In Hong Kong, there are 57 registered pharmaceutical products containing eryrthropoiesis-stimulating agents. These are all prescription medicines. They include epoetin alfa, epoetin beta, methoxy polyethylene glycol-epoetin beta and darbepoetin alfa. In view of FDA's action, DH issued letters to inform healthcare professionals about this matter on 27 June 2011. At its meeting dated 6 September 2011, the Registration Committee of the Pharmacy and Poisons Board decided that the sales pack and/or package insert of the pharmaceutical products containing erythropoiesis-stimulating agents should include additional warning and dosing guidelines.

Canada and US: Increased risk of impaired cognitive development in children exposed in utero (during pregnancy) with valproate products.

2 July 2011 - FDA notified healthcare professionals that children born to mothers who took the anti-seizure medication valproate sodium or related products (valproic acid and divalproex sodium) during pregnancy had an increased risk of lower cognitive test scores (IQ and other tests) than children exposed to other anti-seizure medications during pregnancy. This conclusion was based on the results of epidemiologic studies. Healthcare professionals were advised to inform women of childbearing age of the increased risk for adverse effects on cognitive development with prenatal valproate exposure. In addition, they were advised to weigh the benefits and risks of valproate when prescribing this drug to women of childbearing age, particularly when treating a condition not usually associated with permanent injury or death. They were encouraged to consider alternative medications that had a lower risk of adverse birth outcomes. Patients were reminded not to stop taking valproate without talking to a healthcare professional.

Safety Update

On 9 July 2011, Health Canada also reminded Canadians, particularly women of child-bearing age, of the concerned risks.

In Hong Kong, there are 16 registered pharmaceutical products containing valproate sodium, divalproex sodium and valproic acid. These are all prescription medicines. In view of FDA's action, DH has issued letters to inform healthcare professionals about this matter on 4 July 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 pharmaceutical products containing valproate sodium and related drugs (valproic acid, divalproex sodium) should include information regarding the increased risk of impaired cognitive development (lower cognitive test scores) in children born to mothers who take the anti-seizure medication valproate sodium or related products (valproic acid and divalproex sodium) during pregnancy.

Australia: The TGA and the US FDA agreed about problems at CSL Biotherapies

9 July 2011 – TGA of Australia confirmed that it agreed FDA's comment on the deficiencies of Commonwealth Serum Laboratories (CSL) Ltd. as mentioned in the warning letter issued by FDA to the company on 15 June 2011. The letter was sent following FDA audit of CSL's manufacturing facility in Australia in March 2011. The deficiencies identified by FDA were about inadequate documentation and investigation procedures by CSL in handling concerns about the quality of its influenza vaccine, Fluvax. Apart from the routine audit, TGA had conducted five additional audits of CSL in the last 12 month after a higher than average rate of adverse reactions was reported in children immunised with CSL's flu vaccine 'Fluvax' in 2010. Neither TGA nor FDA had identified manufacturing deficiencies that would warrant product recall or a change to the vaccine production process. The two agencies were working with CSL to resolve the identified deficiencies and to ensure CSL remained fully compliant with manufacturing standards.

In Hong Kong, Fluvax Vaccine, manufactured by CSL Ltd, Australia, is registered by Luen Cheong Hong Ltd. The company confirmed that Fluvax Vaccine has not been imported into Hong Kong since 2010.

Drug Recall

Recall of Vitamin B-6 Tab 50mg (HK-49333) and Natural E-200 Cap (vitamin E) (HK-26966)

On 17 June 2011, the Department of Health (DH) instructed Winsor & Co. (Winsor), a licensed drug wholesaler, to recall Vitamin B-6 Tab 50mg (HK-49333) and Natural E-200 Cap (vitamin E) (HK-26966) from consumers, as the products were suspected to have a number of irregularities.

The incident began when Matilda International Hospital reported to DH that the appearance of several bottles of Vitamin B-6 Tab that had been supplied by Winsor was different from previous stocks. Vitamin B-6 Tab used to be a white tablet, but was found as a yellow gel capsule. DH launched investigation immediately. Preliminary investigation revealed that Winsor had the habit of reproducing labels of returned goods and products with worn-out labels, and re-labelling them for re-sale on the market. Records in Winsor indicated that the yellow gel capsules should be Natural E-200 Cap, another drug also registered under Winsor. DH suspected that Winsor had mixed up the two products in the course of relabelling and hence led to the incident. Winsor set up a hotline for public enquiries.

Both Vitamin B-6 Tab 50mg and Natural E-200 Cap are supplement products. They were manufactured by Natural Wealth Nutrition Corp, USA and imported and distributed by Winsor & Co for local sale as well as re-export to Macao. Mislabelling of vitamin E for vitamin B6 can have serious health consequences. The product mix-up may delay the treatment. Healthcare professionals and retailers were advised to stop supplying and customers were advised to stop consuming all batches of the said products immediately. Those who had taken the affected products were advised to consult their healthcare providers if in doubt or feeling unwell. DH has not received any adverse event report related to the two products at the time of press release.

Drug Recall

Recall of Welfore Senna Forte Tab 17mg (HK-60017), Wel Health Strong Senna Tab 17mg (HK-60018), Legend Senna Extra Tab 17mg (HK-60019) and Senno Forte Tab 17mg (HK-60020)

On 28 June 2011, DH instructed Welfore Co Ltd, a licensed drug wholesaler, to recall four of its sennosides drugs, namely Welfore Senna Forte Tab 17mg (HK-60017), Wel Health Strong Senna Tab 17mg (HK-60018), Legend Senna Extra Tab 17mg (HK-60019) and Senno Forte Tab 17mg (HK-60020), from shelves as market surveillance conducted by DH found that a sample failed the disintegration test.

The four drugs are actually with the same formula marketed in different names. They were manufactured in the United States and imported into Hong Kong for sale over the counter for the relief of constipation. According to the product specifications, the drugs should disintegrate within 30 minutes. Welfore set up a hotline for public enquiries.

Recall of three batches of Navelbine Injection (HK-44009)

On 11 July 2011, DH endorsed Orient Europharma Co Ltd, a licensed drug wholesaler, to voluntarily recall three batches of Navelbine Injection (HK-44009) after the announcement of a worldwide recall of the affected batches of the product following an out-of-trend result in content of S/D6 (or epoxyvinorelbine or vinorelbine-3,6-ether) found during the review of routine stability data conducted by the product's French manufacturer Pierre Fabre Medicament. S/D6 is one major degradation substance in the product.

According to the investigation result by the product's manufacturer Pierre Fabre Medicament, the out-of-trend content of S/D6 originated from the use of a single batch of tartaric acid, a raw material in the manufacturing of Navelbine. An increased content of iron in the tartaric acid was found to be the cause. In Hong Kong, only three batches of the products were manufactured from the problematic batch of tartaric acid. The affected three batches were therefore recalled.

S/D6 had been shown to have equal toxic potential as the active ingredient of Navelbine Injection based on acute toxicity studies. Notwithstanding the out-of-trend content of S/D6, the product after retesting was still within the product specification.

In Hong Kong, Navelbine Injection is a prescription medicine with indication for lung cancer and breast cancer. The product has two pack sizes for sale in Hong Kong, namely as 10mg/1ml and 50mg/5ml. The three batches under recall in Hong Kong were Navelbine Injection 10mg/1ml (Batch 1P109), Navelbine Injection 50mg/5ml (Batch P507) and Navelbine Injection 50mg/5ml (Batch P508). These products had been distributed to public hospitals, private hospitals and private doctors. Orient Europharma Co Ltd set up a hotline for public enquiries.

Healthcare professionals and retailers were advised to stop supplying the abovementioned products or batches to their clients. Member of public who had the products in hand were advised to cease using them and seek advice from healthcare professionals if they felt unwell or were in doubt. So far, DH has not received any adverse event report related to the use of the products.

Drug Incident

Woman arrested for selling slimming products with undeclared and banned drug ingredients

On 24 June 2011, a joint operation was conducted by the Department of Health (DH) and the Police resulting in the arrest of an 18-year-old woman for suspected sale of two slimming products known as "8 Slimming Effects – All in One（Qing Chun Shao Nu Xing）" and "8 Slimming Effects – All in One（Guai Fu Ren Xing）", which were found to contain undeclared Part I poison.

Earlier on, through the DH's surveillance programme, the affected products were discovered to be on sale on an Internet auction website and tested to contain undeclared and banned drug ingredients, sibutramine and its analogue, as well as

phenolphthalein.

Sibutramine was once a western medicine used as appetite suppressant. In November 2010, sibutramine-containing products have been banned because of the increased cardiovascular risk. Sibutramine analogues, being chemically similar to sibutramine, are expected to have the same side effects as sibutramine. Phenolphthalein was once used for treating constipation but has been banned for its cancer-causing effect.

DH appealed to members of the public not to buy or consume unknown or doubtful slimming products from the Internet as they may contain undeclared and banned drug ingredients that are dangerous to health. Weight control should be achieved through good diet and appropriate exercise. People should consult healthcare professionals before using any medication for weight control. DH issued a press statement on the day of joint operation.

The products mentioned in the above drug incident were not registered pharmaceutical products under the Pharmacy and Poisons Ordinance in Hong Kong. A product containing any western drug ingredient must be registered under the Ordinance before it can be sold in Hong Kong. Under the Pharmacy and Poisons Ordinance, possession or sale of unregistered pharmaceutical product is an offence liable to the maximum penalties of a $100,000 fine and two year's imprisonment. Members of the public were exhorted not to sell products of unknown or doubtful composition. Members of the public should stop using the aforementioned products that contained undeclared western drug ingredients and they should see doctors if they feel unwell after using 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:

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