Drug News
藥 物 情 報

Issue No. 25 : November 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: Updated information about drug interaction of Zyvox (linezolid) and Methylene Blue with serotonergic psychiatric medications

20 October 2011 – The Food and Drug Administration (FDA) provided additional information about the possible serotonin syndrome in patients taking serotonergic psychiatric medications and linezolid/ methylene blue. It was found that not all serotonergic psychiatric drugs had an equal capacity to cause serotonin syndrome with use of linezolid/ methylene blue. According to the FDA's Adverse Event Reporting System (AERS), most cases of serotonin syndrome with linezolid or methylene blue occurred in patients taking specific serotonergic psychiatric drugs, namely a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI); and for cases associated with methylene blue, also clomipramine . It was still unclear whether linezolid or intravenous methylene blue administration in patients receiving other psychiatric drugs with lesser degrees of serotonergic activity posed a comparable risk. Besides, cases associated with methylene blue mostly occurred in the context of parathyroid surgery which involved the intravenous administration of methylene blue as a visualizing agent with dose ranging from 1 mg/kg to 8 mg/kg. The risk in patients taking methylene blue by other routes or at intravenous doses lower than 1 mg/kg remained unknown.

In Hong Kong, Zyvox (linezolid) is registered by Pfizer Corp. HK Ltd., and is a prescription medicine used for treatment of infections, including pneumonia and infections of skin. Methylene blue injection is registered by Sino-Asia Pharmaceutical Supplies Ltd. It is a non-poison used for treatment of methemoglobinemia. Earlier this year, both Health Canada and FDA released similar alerts on the interaction between methylene blue and serotonin reuptake inhibitors. At the same time, FDA also released alert on the interaction between linezolid and serotonin reuptake inhibitors. The news had been reported in Issue No. 17 and 22 of Drug News respectively. In addition, the Department of Health (DH) issued press statement on 18 February 2011 and letters were also sent to healthcare professionals in February 2011 and July 2011.

The product certificate holders of the pharmaceutical products containing methylene blue, linezolid and serotonergic psychiatric medications have been requested to update the sales pack and/or package insert of these products to include information about the potential drug interactions. DH will keep vigilance against this issue.

EU: Safety review of Protelos and Osseor (strontium ranelate)

20 October 2011 –The Committee for Medicinal Products for Human Use (CHMP) of the The European Medicines Agency (EMA) was reviewing data on the cardiovascular and cutaneous safety concerns, taking into account existing risk-minimisation measures to determine whether the cases of venous thromboembolism and drug rash with eosinophilia and systemic symptoms would have an impact on the benefit-risk profile and conditions of use for Protelos and Osseor. At this juncture, there were no changes to the recommendations on the conditions for use of these two drugs in Europe.

In Hong Kong, Protos Granules for Oral Suspension 2g containing strontium ranelate is registered by Servier Hong Kong Ltd. and is a prescription medicine used for treatment of osteoporosis in postmenopausal women and to reduce the risk of

fracture at spine & hips. As reported in Issue No. 23 of Drug News, safety alert about serious skin reactions, namely Stevens-Johnson syndrome and toxic epidermal necrolysis, with Protos had been released by the Health Sciences Authority (HSA) of Singapore in August 2011. DH will keep vigilance against this issue.

EU: Positive benefit-risk balance of angiotensin II receptor antagonists remained

20 October 2011 – CHMP reviewed all available data in patients taking angiotensin II receptor antagonists (ARBs) and concluded that the evidence did not support any increased risk of cancer in patients using these medicines. The review was initiated as a meta-analysis which showed a small increased risk of new cancers (particularly lung cancer) with ARBs compared with placebo and other heart medicines (7.2% versus 6%). However, the CHMP found that the evidence from the meta-analysis was weak as there were several problems with the quality of the data and there was a possibility of publication bias. The CHMP also reviewed data from other studies and the results did not show an increased risk of cancer with ARBs.

In Hong Kong, there are about 130 registered pharmaceutical products containing ARBs. They are prescription medicines used to treat hypertension. They may also be used in the management of heart failure and diabetic nephropathy. FDA had also announced similar conclusion in June 2011 as reported in Issue No. 20 of Drug News. DH remains vigilant to any new findings about ARBs.

EU: Precautionary recall of Advagraf 0.5 mg capsule batches (tacrolimus)

20 October 2011 – EMA agreed to the immediate recall of some batches of 0.5 mg prolonged-release hard capsules of Advagraf (tacrolimus) from pharmacies and wholesalers across EU because an unexpected increase in release of active substance from the capsules was detected during routine testing by the marketing-authorisation holder, Astellas. The company found that an average of 70% of the tacrolimus in the capsules was released during the first 1.5 hours of dissolution testing which was above the permitted range of 48% to 68%. The available information did not suggest that the defect was linked to clinical adverse events. However, the recall was conducted as a precautionary measure because the defect could have led to slightly higher levels of tacrolimus in the blood of patients taking the affected capsules.

In Hong Kong, Advagraf Prolonged-release Hard Capsule 0.5mg is registered by Astellas Pharma Hong Kong Company Ltd., and is a prescription medicine used as an immunosuppressant for adult in preventing transplant rejection in kidney or liver allograft recipients and treatment of allograft rejection that are resistant to treatment with other immunosuppressants. The company confirmed that the affected batches have not been distributed in Hong Kong.

Canada, Australia, Singapore and US: Risk of increased blood pressure and heart rate associated with Strattera (atomoxetine)

A recent analysis of combined data from Eli Lilly sponsored controlled and uncontrolled clinical trials indicated that in 8417 pediatric patients treated with Strattera (atomoxetine), a selective norepinephrine reuptake inhibitor, approximately 25% experienced an increase in blood pressure of 10 mmHg and 5-8% an increase of 20 mmHg while heart rate increased by 10 bpm in 33% of patients and by 20 bpm in 12% of patients. These increases had also been observed in similar proportion of adult patients with Attention Deficit Hyperactivity Disorder (ADHD) which could be a potential risk for some patients. Following its release, safety alerts were issued by Health Canada, TGA and HSA on 21 October, 2 November and 8 November 2011 respectively.

Healthcare professionals were advised to observe the following recommendations:

- Atomoxetine is contraindicated in patients with symptomatic cardiovascular diseases, moderate to severe hypertension or severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or in heart rate that could be clinically important.
- Atomoxetine should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with

hypertension, tachycardia, or cardiovascular or cerebrovascular disease.

- Atomoxetine should be used with caution in patients with congenital or acquired long QT syndrome or a family history of QT prolongation.
- Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with atomoxetine and monitored during the course of treatment.
- Heart rate and blood pressure should be measured in all patients before atomoxetine is started, after the dose is increased, and periodically during treatment, particularly during the first few months of therapy.

In addition, FDA made a public announcement on 1 November 2011 that a large, recently-completed cohort study in 1,200,438 children and young adults treated with medications for ADHD (atomoxetine, amphetamine products, methylphenidate and pemoline which was no longer marketed) had not shown an association between use of those ADHD medications and adverse cardiovascular events including stroke, myocardial infarction and sudden cardiac death. Healthcare professionals were recommended to prescribe these medications according to the professional prescribing label. They were also advised to take special caution when using these stimulant products and atomoxetine and periodically monitored their patients for changes in heart rate or blood pressure.

In Hong Kong, Strattera Cap 10mg, 18mg, 25mg, 40mg and 60mg are registered by Eli Lilly Asia, Inc. and are prescription medicines indicated for treatment of ADHD in children and adults. Current product insert has already included a warning that atomoxetine may cause an increase in pulse and blood pressure. DH issued letters to inform healthcare professionals about the news on 25 October 2011 and the matter will be discussed in the next meeting of the Registration Committee of the Pharmacy and Poisons Board to decide if revision of label or product insert is indicated.

US: Presence of DNA fragments is expected

21 October 2011 – FDA had recently received inquiries following an unpublished report about the detection of recombinant HPV L1-specific DNA sequences in 13 vials of Gardasil from different lots. The Agency reassured that the presence of DNA fragments was expected in Gardasil and not evidence of contamination. FDA considered that Gardasil continued to be safe and effective and its benefits continued to outweigh its risks. The review of all reports related to Gardasil vaccination in the Vaccine Adverse Event Reporting System showed no evidence of unusual clinical patterns or high reporting rates of adverse events, including autoimmune diseases. FDA would continue to monitor the safety of Gardasil.

In Hong Kong, Gardasil Vaccine Injection available in pre-filled syringes and vials are registered by Merck Sharp & Dohme (Asia) Ltd. and are prescription medicines used for prevention of cervical, vulvur and vaginal cancer and genital warts. DH will keep vigilance against any updated safety issues related to the vaccine.

US: Updated study data of the risk of neuropsychiatric events associated with Chantix (varenicline)

24 October 2011 - FDA had reviewed the results from two FDA-sponsored epidemiological studies that evaluated the risk of neuropsychiatric adverse events associated with the smoking cessation drug Chantix (varenicline). The safety review was initiated when FDA received reports of suicidal thoughts and aggressive and erratic behavior in patients taking Chantix in 2007. At that time, the Chantix label was updated to include the possible neuropsychiatric events with unclear links. As the ongoing review of FDA suggested that the severe changes in mood and behaviour might be related to Chantix, the prescribing information and Medication Guide for patients were eventually updated accordingly in 2008. From the current review, neither study found a difference in risk of neuropsychiatric hospitalizations between Chantix and nicotine replacement therapy. However, both studies had a number of limitations, including only assessing neuropsychiatric events that resulted in hospitalization, and not having a large enough sample size to detect rare adverse events. In this connection, healthcare professionals and patients were advised to continue to follow the recommendations in the physician label and the

patient Medication Guide, and to monitor for neuropsychiatric symptoms when prescribing or using Chantix. The drug manufacturer was conducting a large safety clinical trial of Chantix to assess neuropsychiatric adverse events, and results from this study were expected in 2017.

In Hong Kong, Champix Tab 0.5mg and 1mg are registered by Pfizer Corporation HK Ltd. and are prescription medicines indicated for smoking cessation. DH will keep vigilance against any new safety information related to the drug.

Worldwide: Withdrawal of Xigris (drotrecogin alfa) due to lack of efficacy

25 October 2011 – Eli Lilly decided to commence a worldwide withdrawal of Xigris and discontinuation of all ongoing relevant clinical trials because the clinical trial, PROWESS-SHOCK study, failed to show a survival benefit in patients with severe sepsis and septic shock. The study was conducted as part of a regulatory commitment of European Union (EU) to confirm the benefit-risk profile of the drug. The results called into question the overall benefit-risk balance of Xigris for the indicated patient population.

Eli Lily had informed the drug regulatory authorities in different countries (e.g. USA, EU, UK, Australia, Canada and Singapore), as well as DH of Hong Kong, about the withdrawal of Xigris. In response, various regulatory authorities had made announcements on the issue.

In Hong Kong, Xigris for Inj. 5mg (HK-51126) and Xigris for Inj. 20mg (HK-51125) have been registered by Eli Lilly Asia Inc. since year 2003. They are prescription medicines and are indicated for treatment of adult patient with sepsis with multiple organ failure. After receiving the notification from Eli Lily, DH issued letters to inform healthcare professionals on 26 October 2011. The company confirmed that they has already completed the recall of Xigras from the market.

US: Recall of Gammagard Liquid [Immune Globulin Intravenous (Human)]

26 October 2011 - Baxter Healthcare Corporation (Baxter) recalled 6 batches of Gammagard Liquid [Immune Globulin Intravenous (Human)] 10%, 1g size. The recall was conducted as a precautionary measure after the supplier of the glass vials that contain Gammagard Liquid notified Baxter of the possibility that metallic particles might be partially embedded in the glass on the interior surface of the vial.

In Hong Kong, the product is registered as Kiovig Solution for Infusion 10% (HK-56576) by Baxter Healthcare Ltd., and is a prescription medicine. It is used to treat immune system disorders e.g. hypogammaglobulinaemia and common variable immunodeficiency. The company confirmed that the pack size of 1g has never been imported into Hong Kong.

US: Labeling error of Recombinate [Antihemophilic Factor (Recombinant)]

27 October 2011 - Baxter Healthcare Corporation notified customers that there was an labeling error affecting the expiration date of the Sterile Water for Injection that is packaged as a diluent with Recombinate [Antihemophilic Factor (Recombinant)]. The Sterile Water for Injection was labeled with a shelf life which was longer than what was approved. Customers were advised to use the Recombinate product as labeled on the kit, rather than the label on the Sterile Water for Injection.

In Hong Kong, Recombinate Antihemophilic Factor 250IU, 500IU and 1000IU are registered by Baxter Healthcare Ltd. and are prescription medicines. The company confirmed that the batches concerned have not been imported into Hong Kong.

US: Update on Tumor Necrosis Factor blockers and risk for pediatric malignancy

3 November 2011 – FDA updated the public that it has requested the manufacturers of Tumor Necrosis Factor (TNF) blockers to perform enhanced safety surveillance for those products in relation to malignancy in children, adolescents, and young adults (30 years of age or younger). In 2009, an analysis of US reports of cancer in children and adolescents treated with TNF blockers showed an increased risk of cancer. According to the enhanced surveillance, the manufacturers have to conduct in-depth follow-up of reports of malignancy cases and submit all reports of malignancy to FDA as expedited reports (within 15 days of becoming aware of the report) for pediatric and young adult patients. They were also required to provide FDA with annual summaries and assessments of malignancies and TNF blocker utilization data.

According to FDA, the enhanced surveillance plan would be re-evaluated periodically over the next ten years.

In Hong Kong, there are 11 registered TNF blockers and all are prescription medicines. In 2009, the Registration Committee of the Pharmacy and Poisons Board requested product registration certificate holders of TNF blockers to update the product label and /or package insert to include information about the increased cancer risk in children and adolescents. In response to a FDA's safety update related to Hepatosplenic T-cell Lymphoma in adolescents and young adults associated with TNF blockers, DH issued letters on 15 April 2011 to remind healthcare professionals and reported the alert in Issue No. 18 of Drug News. DH will keep vigilant against any updated safety news of this class of drugs.

Australia : New recommendations for monitoring kidney function of patients on Pradaxa (dabigatran)

3 November 2011 – After publishing a safety advisory on the risk of bleeding relating to the use of Pradaxa (dabigatran) in 5 October 2011, TGA further evaluated the international reports of bleeding with Pradaxa and recommended healthcare professionals to assess kidney function before starting this medicine and during its use.

Patients with severe kidney impairment (i.e. CrCL<30 mL/min) are recommended not to start Pradaxa. Furthermore, kidney function should be assessed before staring Pradaxa and during the treatment particularly in clinical situations where a decline in kidney function is suspected, such as low blood volume, dehydration and concomittant use of medications that may impair kidney function. For elderly patients older than 75 years of age or in patients with moderate kidney impairment, kidney function should be assessed at least once a year.

The sponsor of Pradaxa in Australia, Boehringer-Ingelheim Pty Limited, would work with TGA to update the Product Information and Consumer Medicine Information.

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. and is a prescription medicine. In view of TGA's new recommendations, letters to inform healthcare professionals were issued on 4 November 2011. The matter will be discussed in the next meeting of the Registration Committee of the Pharmacy and Poisons Board.

Canada: Risk of potential patient harm associated with brand name confusion of Pradax (dabigatran) and Plavix (clopidogrel)

3 November 2011 - Boehringer Ingelheim (Canada) Ltd., and Sanofi-Aventis Canada Inc. issued an alert on the risk of medication errors associated with name confusion between the anticoagulant Pradax (which is marketed as Pradaxa in Hong Kong) from Boehringer Ingelheim (Canada) Ltd. and the antiplatelet drug Plavix (clopidogrel) from Sanofi-Aventis Canada Inc. Since January 2011, a total of 5 Canadian cases, associated with drug name confusion between Pradax and Plavix, had been received by Boehringer Ingelheim (Canada) Ltd. and Health Canada, including 1 case resulting in patient harm (non-serious bleeding after a medical procedure). An additional 2 reports of concern were received from healthcare professionals about the potential for confusion between the names of these two drugs. The companies, in consultation with Health Canada, were working on measures to reduce the risk associated with medication errors related to name confusion issues between Pradax and Plavix.

In Hong Kong, dabigatran is registered under the name of Pradaxa by Boehringer Ingelheim (HK) Ltd. and Plavix is registered by Sanofi-Aventis HK Ltd. Both are prescription medicines. In view of Health Canada's action, DH issued letters to alert healthcare professionals on 9 November 2011.

Canada: Increased risk of muscle weakness in patients with myasthenia gravis taking fluroquinolone antibiotics

7 November 2011 – Health Canada alerted the public that patients with myasthenia gravis taking fluoroquinolone might have a rare but serious risk of worsening of their symptoms, including muscle weakness or breathing problems. Based on available data, the risk appeared to occur for oral or intravenous formulation and did not appear to apply to ear or eye drops. Healthcare professionals were advised to avoid the use of fluoroquinolone in patients with a known history of myasthenia gravis. Health Canada had requested the Canadian

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manufacturers of fluoroquinolone to update the labelling with a relevant warning.

In Hong Kong, there are about 180 registered pharmaceutical products containing fluoroquinolones in oral or IV dose forms. All are prescription medicines. In view of Health Canada's recommendation, DH issued letters to inform healthcare professionals on 8 November 2011 and will discuss the matter in the next meeting of the Registration Committee of the Pharmacy and Poisons Board.

US: Label change of Trilipix (fenofibric acid)

9 November 2011 - FDA notified healthcare professionals that Trilipix (fenofibric acid), a cholesterol-lowering drug, might not lower a patient's risk of having a heart attack or stroke after a review of a clinical trial. The clinical trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial. did not show a significant difference in the risk of experiencing a major adverse cardiac event between the group treated with fenofibrate plus simvastatin and the group with simvastatin alone. The label and the patient Medication Guide of Trilipix have been updated to include this information. Healthcare professionals were advised to consider the benefits and risks of Trilipix when deciding to prescribe the drug to patients, and counsel patients about those benefits and risks.

In Hong Kong, a total of 15 fenofibrate-containing products are registered and all are prescription medicines. In view of FDA's recommendation, DH issued letters to inform healthcare professionals on 10 November 2011 and will discuss the matter in the next meeting of Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Recall of Algikey injection 3% (HK-52919) due to quality defect

On 20 October 2011, DH instructed a licensed drug wholesaler, Hind Wing Co. Ltd (Hind Wing), to recall a pharmaceutical product called "Algikey Inj 3%" from consumers in view of a quality defect. It is a prescription medicine and is indicated for treatment of moderate to severe pain.

The incident began in August 2011 when the Hospital Authority (HA) noted particles in some of its Algikey ampoules in stock. Hind Wing conveyed to HA in early October 2011 that the product's manufacturer in Spain, Farma Mediterrania (FM), reported the cause as isolated, due to carbonization of the liquid content during sealing of the ampoules. HA subsequently resumed use of the injection and found particles again in at least three other ampoules.

According to Hind Wing's sales record, 500 boxes had been imported into Hong Kong in January 2011. 477 boxes were supplied to HA and 15 boxes were sold to three private doctors. As the scale of the defect was found to be more than isolated, FM's manufacturing process was opened to question. Though the defect was reported to be qualitative in nature and no related adverse report had been received, it was prudent for public health protection to recall the product from consumers. The incident had been referred to the Spanish counterpart for their upstream follow up. For the product to resume sale in Hong Kong, the wholesaler needed to demonstrate to the satisfaction of DH that the cause had been found and remedial measures had been instituted. Press statement was issued on 20 October 2011. DH closely monitored the recall.

Batch recall of Ternolol tablet 100mg (HK-41860) on quality ground

On 25 October 2011, DH instructed licensed drug wholesaler Hovid Ltd to recall one batch of Ternolol Tablet 100mg (batch number AJ12560) from shelves on quality grounds as market surveillance by the DH found that the sample had failed the disintegration test. Laboratory analysis suggested that the problem was limited to that single batch.

The drug contains atenolol and is used for the treatment of hypertension. It can only be sold by

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prescription and under the supervision of pharmacists at registered pharmacies. It is manufactured by Hovid Sdn Bhd (Malaysia) and had been imported for sale to private doctors and pharmacies and exported to Macao.

Press statement was issued on 25 October 2011. DH closely monitored the recall.

Members of the public were advised to consult their healthcare providers if they were in doubt or felt unwell after using the above products.

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

Drug Incident

Warning on slimming products with banned drug ingredients

During the period between late October and early November 2011, DH received notifications from the HA about four women feeling unwell after consumption of slimming products. Banned and/ or undeclared drug ingredients were detected in these products by the Government laboratory. While three patients obtained their products outside Hong Kong, the source of product from one patient could not be verified. The details of these four cases are listed as follows.

Patient	Slimming products consumed	Symptoms developed	Drug ingredients detected in laboratory test
48-year old woman	SlimEasy Herbs Capsule (輕姿綠茶膠囊)	shortness of breath and ankle swelling with diagnosis of heart failure	sibutramine and phenolphthalein
37-year old woman	Super Fat Burning Bomb (51 左旋肉碱)	palpitation, dizziness, nausea and chest discomfort	sibutramine and phenolphthalein
43-year old woman	Unlabelled greenish capsules	hepatitis which was later confirmed to be unrelated to consumption of the product	sibutramine, phenolphthalein and diclofenac
32-year old woman	Omine 15	thyrotoxicosis which was later confirmed to be unrelated to consumption of the product	sibutramine

Sibutramine is a Part I poison and was once a western medicine used as appetite suppressant. In November 2010, sibutramine-containing products were banned because of the increased cardiovascular risk. Phenolphthalein was once used for treating constipation but was banned for its cancer-causing effect.

Diclofenac is also a Part I poison used as a painkiller. Its side effects include gastro-intestinal disturbances such as gastric pain, nausea, diarrhoea, vomiting, peptic ulcer and bleeding. Under the Pharmacy and Poisons Ordinance, products containing diclofenac can only be sold with a doctor's prescription and under the supervision of a pharmacist.

Press statements related to these four cases were issued. Members of the public were advised to stop using the above products immediately if they had them in their possession. They were also advised to consult healthcare professionals if they felt unwell or were in doubt after taking the products.

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