



Drug News

藥物情報

Issue No. 23 : September 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

Singapore: Risk of venous and arterial thromboembolism associated with Revlimid (lenalidomide) and thalidomide

22 August 2011 – After a review of overseas post-marketing data, the Health Sciences Authority (HSA) of Singapore updated healthcare professionals that both the use of thalidomide and the combination of lenalidomide and dexamethasone had been associated with an increased risk of venous and arterial thromboembolism. According to HSA, the Celgene pharmacovigilance database recorded a total of 493 medically confirmed reports of arterial thromboembolic events associated with lenalidomide. Healthcare professionals were advised to take into consideration the above safety information, the presence of venous and arterial thromboembolic risk factors (eg, smoking, hypertension, hyperlipidaemia) as well as the need for thrombo-prophylaxis, when evaluating if their patients are suitable for treatment with thalidomide or lenalidomide.

In Hong Kong, there is no registered pharmaceutical product containing thalidomide. For lenalidomide, it is registered as Revlimid Cap 5mg, 10mg, 15mg and 25mg by Celgene Ltd and they are prescription medicines used in combination with dexamethasone for the treatment of multiple myeloma. DH issued letters to inform healthcare professionals about the safety updates on 23 August 2011.

Singapore: Label updates on fluoroquinolones and QT prolongation

22 August 2011 - HSA highlighted the recent amendments on the labelling of fluoroquinolones relating to the risk of QT interval prolongation. After a literature review, the Committee for Medicinal Products for Human Use (CHMP) of the European

Medicines Agency (EMA) decided to categorise fluoroquinolones into three groups according to their potential for inducing QT interval prolongation. In response, HSA was working with drug companies to update the package inserts of all oral and intravenous formulations of fluoroquinolones to strengthen the warnings regarding the potential of QT interval prolongation associated with its use. Healthcare professionals were encouraged to take account of this possible effect when selecting fluoroquinolone as a treatment for their patients, especially in patients with risk factors.

In Hong Kong, there are about 230 registered pharmaceutical products containing fluoroquinolones. All these products are prescription medicines. In view of the safety update, DH issued letters to inform healthcare professionals on 23 August 2011. The Registration Committee of the Pharmacy and Poisons Board decided at its meeting on 6 September 2011 that the sales packs or package inserts of fluoroquinolones in oral or intravenous formulations should be updated to include safety information of QT interval prolongation in accordance with the recommendations of EMA.

Singapore: Serious skin reactions associated with Protos (strontium ranelate)

22 August 2011 – HSA alerted healthcare professionals about local reports of serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with Protos (strontium ranelate) received over the past four years, out of which two were associated with a fatal outcome. Healthcare professionals were advised to educate their patients on the early

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recognition of allergic reactions and to seek medical attention promptly because early signs of rash and skin reactions might be indicative of a more serious reaction such as SJS and TEN. In addition, patients who had stopped treatment due to hypersensitivity reactions should be advised not to re-start therapy with strontium ranelate.

In Hong Kong, Protos Granules for Oral Suspension 2g (HK-53835) is registered by Servier Hong Kong Ltd., and is a prescription medicine used for treatment of osteoporosis in postmenopausal women to reduce the risk of fracture at spine and hips. DH issued letters to inform healthcare professionals on 23 August 2011. Any further updates made by other regulatory authorities will be kept in view.

US: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide)

24 August 2011 – US Food and Drug Administration (FDA) notified healthcare professionals and patients that the antidepressant Celexa (citalopram hydrobromide) should no longer be used at doses greater than 40 mg per day because it could cause abnormal changes in the electrical activity of the heart. (prolongation of the QT interval of the electrocardiogram [ECG]) which in turn may lead to fatal arrhythmias including Torsade de Pointes. Patients at particular risk for developing prolonged QT interval included those with underlying heart conditions and those who are predisposed to low serum levels of potassium and magnesium. Furthermore, studies did not show a benefit in the treatment of depression at daily doses higher than 40 mg. Previously, the citalopram drug label stated that certain patients might require a dose of 60 mg per day. The citalopram drug label had been revised to include the new drug dosage and usage recommendations, as well as information about the potential for QT interval prolongation and Torsade de Pointes.

In Hong Kong, a total of 17 registered pharmaceutical products contain citalopram and all are prescription medicines used for treatment of depression. In view of FDA's recommendation, DH issued letters to inform healthcare professionals on 25 August 2011. The Registration Committee of the Pharmacy and Poisons Board decided at its meeting on 6 September 2011 that the maximum daily

dosage of citalopram should be limited to 40mg and the sales pack label and/or package insert of citalopram-containing products should be updated to include information regarding the abnormal heart rhythm associated with high doses of citalopram.

Canada: Pulmonary arterial hypertension (PAH) associated with the use of Sprycel (dasatinib)

26 August 2011 - Bristol-Myers Squibb Canada (BMS), in collaboration with Health Canada, informed healthcare professionals of safety information regarding reports of serious pulmonary arterial hypertension (PAH) in patients treated with a protein-tyrosine kinase inhibitor Sprycel (dasatinib). From June 2006 to June 2011, a total of 60 serious pulmonary hypertension (PH) cases associated with Sprycel treatment had been reported worldwide and 12 of them were reported as PAH confirmed by right heart catheterization. In response, the Canadian Product Monograph for Sprycel had been revised to include this important new safety finding. Healthcare professionals were recommended to follow current clinical guidelines for the diagnosis and management of patients on dasatinib with signs and symptoms suggestive of PAH.

In Hong Kong, there are 3 dasatinib-containing products registered by Bristol-Myers Squibb Pharma (HK) Ltd., Sprycel Tab 20mg, 50mg and 70mg. They are all prescription medicines used for treatment of adults with chronic, accelerated, myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib, and adults with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy. According to the company, the package insert would be updated to include the new safety finding. In addition, DH issued letters to inform healthcare professionals on 31 August 2011.

China: Potential severe liver toxicity associated with the use of oral Ketoconazole

31 August 2011 – The State Food and Drug Administration (SFDA) of China alerted the healthcare professionals and public about the safety concern of severe liver toxicity in patients treated

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with an oral anti-fungal medicine, ketoconazole. According to the National Center for Adverse Drug Reaction (ADR) Monitoring database, there were 1,621 reports of ADRs associated with the use of oral ketoconazole from 1 January 2004 to 12 July 2011 and 116 of them were classified as severe cases. Among the 116 severe cases, 157 adverse events were reported and 92 of them were related to liver toxicity. The major ADRs related to liver toxicity included liver function abnormalities, liver damage, hepatitis and hepatotoxicity.

Healthcare professionals were advised to prescribe oral ketoconazole preparations only when there were no better alternatives, and the benefits outweighed the risks. They were advised to be vigilant to any symptoms or signs of liver toxicity during treatment and monitor patient's liver function prior to the treatment and regularly during treatment. Patients were advised to strictly follow the dosage regimen in accordance with the product label, discontinue treatment and seek medical advice promptly if they developed symptoms of liver toxicity, such as dark yellow coloured urine, jaundice, loss of appetite, malaise, liver pain and nausea.

In Hong Kong, there are 24 registered oral pharmaceutical products containing ketoconazole and all are prescription medicines for treatment of fungal infections. In view of the SFDA's recommendation, DH issued letters to remind healthcare professionals on 1 September 2011 and the issue would be discussed in the next meeting of the Registration Committee of the Pharmacy and Poisons Board.

US: New contraindication and updated warning on renal impairment for Reclast (zoledronic acid)

1 September 2011 - FDA had approved an update to the drug label for Reclast (zoledronic acid) to better inform healthcare professionals and patients of the risk of renal failure. Renal failure is a rare, but serious, condition associated with the use of Reclast in patients with a history of or risk factors for renal impairment. In 2009, the Warning and Precautions section of the Reclast label was amended with a recommendation to monitor serum creatinine before each dose of Reclast and included reports of renal impairment from clinical studies after post-market review by FDA identified five deaths from acute

renal failure following Reclast infusion. However, FDA continued to note reports of renal failure requiring dialysis after the label revision in 2009. The latest revised label would state that Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment. As renal toxicity and dose reductions for renal impairment patients were already addressed in the Warnings and Precautions section of Zometa, another zoledronic acid, these labeling changes were made to Reclast label only. The Reclast Medication Guide for patients was also being updated to include information about the risk of severe renal problems. Healthcare professionals were advised to screen patients for at-risk group prior to prescribing Reclast and monitor their renal function during treatment.

In Hong Kong, Reclast is registered under the name of Aclasta Solution for Infusion 5mg/100ml (HK-54084) by Novartis Pharmaceutical (HK) Ltd. and is a prescription medicine used for treatment of osteoporosis and Paget's bone disease. The existing package insert of the medicine has already contained renal safety information. Relevant news released by HSA and Health Canada in 2010 had been reported in Issue No. 6 and 12 of Drug News and DH issued letters to inform healthcare professionals on 15 October 2010 accordingly. The Registration Committee of the Pharmacy and Poisons Board considered the renal safety of Aclasta at its meeting on 29 December 2010 and decided that the safety information included in the registered package insert of Aclasta was sufficient. In view of the latest FDA's action, DH sent another letters to remind healthcare professionals on 2 September 2011 about the issue. The matter would be further discussed in the next meeting of the Registration Committee of the Pharmacy and Poisons Board.

US: Inclusion of warnings about infection with Legionella and Listeria bacteria on the drug labels for the Tumor Necrosis Factor-alpha (TNF α) blockers

7 September 2011 - FDA notified healthcare professionals that the Boxed Warning for the entire class of Tumor Necrosis Factor-alpha (TNF α) blockers had been updated to include the risk of infection from two bacterial pathogens, Legionella and Listeria. In addition, the Boxed Warning and Warnings and Precautions sections of the labels for

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all of the TNF α blockers had been revised so that they contained consistent information about the risk for serious infections and the associated disease-causing pathogens. Patients treated with TNF α blockers are at increased risk for developing serious infections involving multiple organ systems and sites that may lead to hospitalization or death due to bacterial, mycobacterial, fungal, viral, parasitic, and other opportunistic pathogens. Healthcare professionals were advised to consider the risks and the benefits of TNF α blockers before initiating therapy in patients with chronic or recurrent infection and patients with underlying conditions that might predispose them to infection.

In Hong Kong, there are 11 registered pharmaceutical products containing TNF α blockers and all are prescription medicines used for treatment of Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and/or juvenile idiopathic arthritis. In view of FDA's action, DH issued letters to inform healthcare professionals on 8 September 2011 and the matter would be discussed in the next meeting of the Registration Committee of the Pharmacy and Poisons Board.

UK: Reduced effectiveness of Tamoxifen when used with CYP2D6 inhibitors

September 2011 - MHRA issued a public assessment report discussing the effectiveness of tamoxifen in treating breast cancer may be reduced by drugs that inhibit an enzyme CYP2D6. A published study had shown that women treated with tamoxifen for breast cancer had a higher risk of death from breast cancer if they, at the same time, were also receiving paroxetine, an SSRI antidepressant which is also a potent CYP2D6 inhibitor. Although another study found no evidence that the use of CYP2D6 inhibitors reduced the effectiveness of tamoxifen, there was still a strong biological rationale supporting this interaction. It was thus recommended that the use of any strong or potent CYP2D6 inhibitors should be avoided wherever possible in patients taking tamoxifen.

On the other hand, 19 relevant published clinical studies were reviewed which showed mixed and inconclusive association between CYP2D6 polymorphism and clinical outcomes in patients treated with tamoxifen for breast cancer. Therefore,

there was currently no recommendation for genetic testing to determine CYP2D6 status in patients before beginning tamoxifen treatment.

In Hong Kong, a total of 12 registered pharmaceutical products contains tamoxifen and all are prescription medicines for treatment of breast cancer. In view of MHRA's recommendation, DH issued letters to inform healthcare professionals on 14 September 2011 and the matter would be discussed in the next meeting of the Registration Committee of the Pharmacy and Poisons Board.

UK: Potential increased risk of congenital heart defects in an unborn child associated with the use of Fluoxetine during pregnancy

September 2011 – MHRA issued a public assessment report about the potential increased risk of heart defects in fetus with the use of fluoxetine, a selective serotonin reuptake inhibitors (SSRIs) for treating depression, in the first three months of pregnancy after the MHRA and the Pharmacovigilance Working Party of EMA reviewed related published clinical studies. Analysis of data from five studies with cardiac defects reported that fluoxetine was associated with a small increased risk of cardiac congenital defects. In conclusion, use of fluoxetine in early pregnancy might cause a small increased risk of heart defects in the fetus and there were insufficient data at this juncture to conclude whether there was a similar risk with other SSRIs. In view of the findings, the warnings on the risk of congenital cardiac defects were included in the product information and patient information leaflets for all medicines containing fluoxetine in the UK.

In Hong Kong, there are a total of 30 registered pharmaceutical products containing fluoxetine and all are prescription medicines used for treatment of depression, obsessive-compulsive disorder and bulimia nervosa. In view of MHRA's recommendation, DH issued letters to inform healthcare professionals on 14 September 2011 and the matter would be discussed in the next meeting of the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Recall of Neurolite for Inj with Buffer Vial (HK-43086)

On 2 September 2011, the Department of Health (DH) instructed a licensed drug importer, Global Medical Solutions Hong Kong Ltd (GMS), to recall two batches (Lot no: 0200U and 0200U1) of Neurolite for Inj with Buffer Vial (Neurolite) from users as the drug's US manufacturer, Ben Venue Laboratories Inc (BV) had initiated an international recall after the detection of particulate matter, likely to be stainless steel, in the product.

Neurolite is a prescription drug. GMS imported it to prepare Technetium Tc-99m Bicisate for Injection, a radiopharmaceutical for diagnostic radiology use.

Though BV also recalled another radiopharmaceutical called Cardiolite in the US, there was no information showing that Hong Kong had ever imported the affected batch.

On the other hand, GMS' sales record showed that it imported 80 vials of Neurolite from the US in 2011. Of these, it used 56 vials to make Technetium Tc-99m Bicisate for Injection which was then supplied to both public and private hospitals. 17 vials were re-exported to Thailand, while GMS kept the remaining 7 vials.

DH had immediately communicated with the hospitals, including issuing letters, to inform healthcare providers of the international recall, the reason behind and also urged them to stop using the affected batches. They were also reminded to report on any related side effect. Press release was issued on 2 September 2011. DH closely monitored the recall and had not received any related adverse incident report.

Members of the public were advised to consult their attending healthcare providers when in doubt or feeling unwell after using the product.

Recall of one batch of Duoflue Cold Tablet 1000's (HK-37595)

On 12 September 2011, DH instructed a licensed drug manufacturer, Advance Pharmaceutical Co Limited (Advance), to recall one batch (Batch No: 35262) of its product Duoflue Cold Tablet 1000's from the market because the new revised label wrongly listed the quantity for the ingredient paracetamol as 500mg instead of 150mg.

Using the DH's surveillance network for manufactured drugs, Advance reported the mistake of listing the incorrect quantity of paracetamol after investigating a customer's enquiry. Each tablet of the product should contain 150mg of paracetamol together with other active ingredients, namely salicylamide, phenylephrine, brompheniramine and caffeine. However, the label of the above batch of Duoflue Cold Tablet 1000's stated that the product contained 500mg of paracetamol per tablet.

Duoflue Cold Tablet 1000's is indicated for the symptoms of cold and influenza. According to the records of Advance, a total of 267 affected bottles were distributed to private practitioners and pharmacies. Press statement was issued on 12 September 2011. DH closely monitored the recall and had not received any related adverse incident report.

Health-care providers and retailers were advised to stop supplying the product immediately. Members of the public who were in doubt or feeling unwell after using the product should consult their health-care providers.

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.

Drug Incident

Public urged not to buy or consume unknown or doubtful slimming products sold on Internet

On 17 August 2011, the Department of Health (DH) received a notification from the Hospital Authority (HA) that a 30-year-old woman sought medical treatment at the Accident and Emergency

Department (AED) of Queen Elizabeth Hospital on 24 July 2011 for hand tremors, palpitations, dry mouth, dizziness and shortness of breath. The patient was treated and discharged on the same day.

The patient had consumed two slimming products, named "Tianran Zuanshi Xianweisu(天然鑽石纖維

素)”和 “Paidusu(排毒素)”, before the onset of symptoms. Both products were purchased from an Internet website in May 2011. Her symptoms subsided after she stopped taking the products. Laboratory tests conducted by HA on the product samples submitted by the patient showed the presence of two banned ingredients, sibutramine and phenolphthalein, and another ingredient, thyroxine.

On 19 August 2011, DH received another notification from HA that a 21-year-old woman sought medical treatment at the AED of United Christian Hospital on 1 August 2011 for insomnia and psychiatric symptoms of persecutory delusion and auditory hallucination. The patient was admitted to psychiatric ward for treatment and discharged on August 17.

The patient had consumed two slimming products, named "US ALL Nature" and another product in the form of orange-purple capsule, for several months. Both products were purchased from an Internet auction website several months ago. Laboratory tests conducted by HA on the product samples submitted by the patient showed the presence of the banned ingredient, sibutramine.

Warning on slimming product from an Indonesian shop

On 19 August 2011, DH received a notification from HA of a case involving a 34-year-old Indonesian woman, who was admitted to Prince Margaret Hospital on 14 August 2011 for dizziness and head injury resulting from a fall from bed.

During admission, the patient revealed that she had earlier taken a slimming product called "2008 Slim Baby (康壽堂 2008 瘦身寶貝)" purchased from an Indonesian shop in Tsuen Wan. Laboratory testing on the product remnant showed the presence of banned drug ingredients, sibutramine and phenolphthalein.

The finding was incidental as the clinical presentation of the patient was unrelated to the product. Subsequently, the patient made a recovery and was discharged home on 17 August 2011.

DH has also conducted investigation immediately and a quantity of the concerned product was found and seized in the Indonesian shop.

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.

Phenolphthalein was once used for treating constipation but has been banned for its cancer-causing effect. Thyroxine and sibutramine are both Part I poisons. 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. Thyroxine is used for treating hypothyroidism, inappropriate use could cause severe side effects such as hypertension and irregular heart rate, which might be fatal.

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

The products mentioned in the above drug incidents 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***