Drug News
藥 物 情 報

Issue Number 45

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in July 2013 with relevant information update before publish. 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: Change of labelling for Olmesartan medoxomil to include intestinal problems (Sprue-Like Enteropathy)

On 3 July 2013, the Food and Drug Administration (FDA) of the United States (US) warned that the blood pressure drug Olmesartan medoxomil can cause intestinal problems known as sprue-like enteropathy. Symptoms of sprue-like enteropathy include severe, chronic diarrhoea with substantial weight loss. FDA has approved changes to the labels of these drugs to include this safety information.

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) approved for the treatment of high blood pressure, alone or with other antihypertensive agents, and is one of the eight marketed ARB drugs in the US. Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan. FDA will continue to evaluate the safety of olmesartan-containing products and will communicate again if additional information becomes available. Healthcare professionals should tell patients to contact them if they develop severe, chronic diarrhoea with substantial weight loss while taking an olmesartan-containing product, even if it takes months to years for symptoms to develop.

In Hong Kong, there are 14 registered pharmaceutical products containing olmesartan medoxomil. They are prescription only medicines indicated for the treatment of hypertension. The Department of Health (DH) had not received any adverse drug reaction report in relation to the drug. In view of FDA's recommendation, a letter to healthcare professionals was issued on 4 July 2013, and the matter will be discussed in the meeting of the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certificate of Clinical Trial/Medicine Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board.

US: Halt of clinical trial on Revlimid (lenalidomide) for chronic lymphocytic leukemia due to safety concerns

On 18 July 2013, FDA halted a clinical trial of the anti-cancer drug Revlimid (lenalidomide) because of significant safety concerns. The study was called ORIGIN and it was a study on the safety and efficacy of lenalidomide versus chlorambucil as first line therapy for patients 65 years and older with chronic lymphocytic leukemia (CLL). It showed higher rates of death in patients treated with lenalidomide compared to those treated with chlorambucil. In addition, FDA determined that the clinical trial was unlikely to achieve its main objective in reducing the amount of time for the leukemia to progress or extending the time for the patient to die. FDA was continuing to review the trial results and would communicate any additional important information from its investigation. Healthcare professionals should be aware that Revlimid is not approved to treat CLL and tumor flare reactions have occurred during investigational use of Revlimid for CLL.

Revlimid is still considered safe and effective for the following approved uses:

- treatment of patients with multiple myeloma who have received at least one prior medicine, when taken along with the medicine dexamethasone;

- treatment of patients who have a type of myelodysplastic syndrome (MDS) known as deletion 5q MDS, where part of chromosome 5 is

missing. Patients with this type of MDS may have low red blood cell counts that require treatment with blood transfusions; and

- treatment of patients with mantle cell lymphoma whose disease does not respond to or comes back after treatment with two prior medicines, one of which was bortezomib. Mantle cell lymphoma is a cancer of a type of white blood cell called lymphocytes that are in the lymph nodes.

In Hong Kong, there are four registered pharmaceutical products containing lenalidomide, namely Revlimid Cap 5mg (HK-59190), 10mg (HK-59193), 15mg (HK-59191) and 25mg (HK-59192). All of them are registered by Celgene Ltd. and are prescription only medicines. According to the registered packaging inserts, they are indicated to be used in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy. The study indication as an initial therapy for CLL is not a registered indication of the above products in Hong Kong. DH had not received any clinical trial certificate application for the study and any adverse drug reactions in connection with the drug. DH will keep vigilant against any safety updates of the drug.

Singapore / Canada: Communication on updated recommendations for management of hepatitis B reactivation in patients treated with MabThera® / Rituxan® (rituximab)

On 20 June 2013, DH was informed by Roche HK Ltd. (Roche) that a Direct Healthcare Professional Communication would be issued on the update management of hepatitis B activation in patients treated with MabThera® (rituximab). Hepatitis B virus (HBV) screening was initially recommended in patients at risk for HBV infection before initiation of treatment with MabThera®. As of August 2012, the crude reporting rates of hepatitis B reactivation associated with the use of MabThera® were 0.017% and 0.006% in haemato-oncology and in autoimmune diseases, respectively. Based on current data and updated clinical guidelines, Roche recommends HBV screening in all patients before the initiation of treatment with MabThera® in all indications, and that patients with positive HBV serology should consult with a liver disease specialist before start of treatment.

On 25 July 2013 and 29 July 2013, similar letters were also issued by the local agencies of Roche in Singapore and Canada and were reported in their websites. The local package inserts of MabThera® in Singapore and Rituxan® in Canada will also be updated to reflect the new recommendations.

In Hong Kong, there are 4 rituximab-containing pharmaceutical products registered, namely MabThera Inj 100mg/10ml (HK-46232), 500mg/50ml (HK-46231), MabThera Concentrate for Solution for Infusion 100mg/10ml (Germany) (HK-59248) and 500mg/50ml (Germany) (HK-59249). They are prescription only medicines registered by Roche and indicated in adults for non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis. Regarding this issue, Roche had submitted the application to change the package insert by including the relevant safety information. DH had not received any adverse drug reaction report against rituximab and will keep vigilant on any safety updates of the drug.

Canada / US / EU / UK: Updates on Ketoconazole regarding the risk of liver toxicity

On 19 June 2013, the manufacturers of oral ketoconazole, in collaboration with Health Canada, announced about the revisions to the Product Monograph (PM) for ketoconazole regarding the risk of potentially fatal liver toxicity. Ketoconazole has been associated with rare cases of serious hepatotoxicity including liver failure and death. This risk was also observed in patients with no pre-existing liver disease and no serious underlying medical conditions. Hepatotoxicity and death had been reported to occur at recommended doses and with treatment courses longer than 10 days. The Warnings' sections of the PMs had been updated to include the following additional instructions:

- ketoconazole tablets are indicated for the treatment of serious or life threatening systemic fungal infections and should not be considered for mild to moderate infections;
- oral ketoconazole has been associated with hepatic toxicity, including cases with fatal outcomes;

- liver function tests should be performed in all patients before starting treatment, at week 2 and 4, and monthly thereafter; and
- treatment should be stopped if liver parameters are elevated (> 3 times the normal limit) or if patients develop clinical signs or symptoms consistent with liver disease such as anorexia, nausea, vomiting, jaundice, fatigue, abdominal pain, dark urine, or pale stools.

On 26 July 2013, FDA took several actions related to Nizoral (ketoconazole) oral tablets, including limiting the drug's use, warning that it can cause severe liver injuries and adrenal gland problems (adrenal insufficiency) and advising that it can lead to harmful drug interactions with other medications. FDA approved label changes and added a new Medication Guide to address these safety issues. As a result, Nizoral oral tablets should not be a first -line treatment for any fungal infection, and should only be used for the treatment of certain fungal infections, known as endemic mycoses, when alternative antifungal therapies are not available or tolerated.

Apart from the decisions made by the Health Canada and FDA, the European Medicines Agency (EMA)'s Committee on Medicinal Products for Human Use (CHMP) recommended that the marketing authorisations of oral ketoconazole-containing medicines should be suspended throughout the European Union (EU). The CHMP assessed the available data on the risks with oral ketoconazole and concluded that, although liver injury such as hepatitis is a known side effect of antifungal medicines, the incidence and the seriousness of liver injury with oral ketoconazole were higher than with other antifungals. The CHMP was concerned that reports of liver injury occurred early after starting treatment with recommended doses, and it was not possible to identify measures to adequately reduce this risk. Thus, the CHMP concluded that the risk of liver injury is greater than the benefits in treating fungal infections; and the clinical benefit is uncertain as data on its effectiveness are limited and do not meet current standards, and alternative treatments are available.

The Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) followed CHMP's decision on suspension of ketoconazole, and issued a press release stating that oral ketoconazole-containing medicines should no longer be used for fungal infections.

In Hong Kong, there are 24 oral ketoconazole-containing pharmaceutical products registered and all are prescription only medicines for the treatment of fungal infections. The risk of severe liver toxicity had been released by China Food and Drug Administration and was reported in Drug News Issue No. 23. A letter to healthcare professionals was issued on 1 September 2011. The matter was discussed by the Registration Committee in the meeting in February 2012, and the Committee decided that DH should keep vigilant about this safety issue. In view of the latest recommendations from Health Canada, FDA, EMA and MHRA, another letter was issued on 29 July 2013, and the matter will be further discussed in the Registration Committee.

EU: Recommendation on the changes to the use of metoclopramide

On 26 July 2013, the EMA's CHMP recommended changes to the use of metoclopramide-containing medicines in the EU, including restricting the dose and duration of use of the medicine to minimise the known risks of potentially serious neurological (brain and nerve) side effects.

The review of metoclopramide was carried out at the request of the French Medicines Agency (ANSM), following continued safety concerns over side effects and concerns over efficacy. ANSM asked the CHMP to review the benefits and risks of these medicines in all age groups and to recommend consistent indications across the EU. The review confirmed the well-known risks of neurological effects such as short-term extrapyramidal disorders, a group of involuntary movement disorders that may include muscle spasms (often involving the head and neck), and tardive dyskinesia (uncontrollable movements such as grimacing and twitching). The risk of acute neurological effects is higher in children, although tardive dyskinesia is reported more often in the elderly, and the risk is increased at high doses or with long-term treatment. The evidence indicated that these risks outweighed the benefits of metoclopramide in conditions requiring long-term treatment.

The CHMP recommended that:-

- metoclopramide should only be prescribed for short-term use of up to 5 days,

- it should not be used in children below 1 year of age,

- for children over 1 year of age, it should only be used as a second-choice treatment for the prevention of delayed nausea and vomiting after chemotherapy and for the treatment of post-operative nausea and vomiting,

- for adults, it may be used for the prevention and treatment of nausea and vomiting such as that associated with chemotherapy, radiotherapy, surgery and in the management of migraine,

- the maximum recommended doses in adults and children should be restricted, and

- higher strength formulations be removed from the market.

In Hong Kong, there are 32 metoclopramide-containing registered pharmaceutical products and they are all prescription only medicines. In view of the recommendations from EMA, a letter to healthcare professionals was issued on 29 July 2013, and the matter will be discussed by the Registration Committee.

EU: Conclusion on the investigation into GLP-1 based diabetes therapies

In March 2013, EMA announced the findings of an increased risk of pancreatitis and pre-cancerous cellular changes in patients with type 2 diabetes treated with incretin mimetics (glucagon-like-peptide-1 (GLP-1) agonists), which was reported in Drug News Issue No. 41. The EMA's CHMP and the Pharmacovigilance Risk Assessment Committee (PRAC) further investigated the information provided by the researchers to assess the need for possible further regulatory action. On 26 July 2013, the CHMP finalised the review of GLP-1 based diabetes therapies (comprises GLP-1 agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors) and concluded that presently available data do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines.

The review was initiated following the publication of a study by a group of independent academic researchers that suggested an increased risk of pancreatitis and pancreatic-duct metaplasia in patients with type-2 diabetes treated with GLP-1 based therapies. The findings were based on examination of a small number of pancreatic tissue samples obtained from organ donors with and without diabetes mellitus, who died due to causes other than diabetes. The CHMP considered that the study itself had a number of methodological limitations and potential sources of bias, most importantly differences between the studied groups with respect to age, gender, disease duration and treatments, which precluded a meaningful interpretation of the results.

A small number of cases of pancreatitis have been reported in clinical trials. All these medicines already carry warnings in their product information but the CHMP considered that there would be value in harmonising the wording of these warnings across all GLP-1 based therapies so that patients and healthcare professional receive consistent advice. With regard to pancreatic cancer, data from clinical trials do not indicate an increased risk with these medicines. However, the number of events is too small to draw to any final conclusions and thus more data collection efforts are needed and are under way.

In Hong Kong, there are 20 registered products that belong to the class of incretin mimetic drugs, including the ingredients exenatide, linagliptin, liraglutide, saxagliptin, sitagliptin, and vildagliptin. All these products are prescription only medicines indicated for diabetic mellitus. The registered package inserts of the products have included safety warnings about the risk of acute pancreatitis. DH will keep vigilant on any safety updates of the drugs by other overseas regulatory authorities, and will bring up to Registration Committee for consideration when necessary.

US: Labelling changes for mefloquine hydrochloride due to the risk of serious psychiatric and nerve side effects

On 29 July 2013, FDA announced the strengthened and updated warnings regarding neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride. A boxed warning, the most serious kind of warning about these potential problems, has been added to the drug label. FDA has revised the patient

Medication Guide dispensed with each prescription and wallet card to include this information and the possibility that the neurologic side effects may persist or become permanent. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations. Neurologic side effects can occur at any time during drug use, and can last for months to years after the drug is stopped or can be permanent. If a patient develops neurologic or psychiatric symptoms while taking the drug, it may be necessary to stop mefloquine and take an alternate medicine, but do not do so without first talking with your healthcare professionals.

In Hong Kong, there are two registered pharmaceutical products containing mefloquine, namely Lariam Tab 250mg (HK-36373) and Mephaquin Lactab 250mg (HK-36557). Both are prescription only medicines indicated for prophylaxis and treatment of malaria. In view of the latest FDA's recommendations, a letter to healthcare professionals was issued on 30 July 2013, and the matter will be discussed in the meeting of the Registration Committee.

EU: Advice on the use of colistin and tigecycline in animals due to issues of antimicrobial resistance

On 30 July 2013, EMA announced with respect to the advice on the use of antibiotics colistin and tigecycline in animals. The emergence and steady increase in the occurrence of bacteria that are resistant to multiple antibiotics has become a global public health threat due to the lack of therapeutic options to treat certain infections in man. Colistin and tigecycline are amongst the antibiotics that have become life-saving treatments for human patients suffering from different kinds of infections caused by multidrug-resistant bacteria.

Colistin has been used in veterinary medicine for over 50 years. There is no available evidence on the transfer of resistance to colistin from animals to man; however, EMA acknowledged that there is limited information on the subject and more research and surveillance should be done. EMA advised that the use of colistin in veterinary medicine should be maintained but to restrict its use to the treatment of infected animals and those in contact with them, and to remove all indications for preventive (or prophylactic) use. The systems for surveillance for resistance to colistin would be strengthened in order to increase the likelihood of early detection of any rise. The benefit-risk balance for colistin would need to be re-evaluated should a substantial increase be detected in rates of resistance.

Tigecycline, an antibiotic of the glycylcycline class, is not currently approved for use in animals. The extent of off-label use of this antibiotic in veterinary medicine cannot currently be quantified. EMA advised that currently no need is foreseen for the authorisation of tigecycline for use in animals. If the need for an approval of tigecycline as a veterinary medicine should ever arise in the future, authorisations should only be considered on the basis of a positive benefit-risk assessment which would take into account the risk of transfer of resistance to humans. However, based on the current situation, it is unlikely that a marketing authorisation could be granted in light of the need for this antibiotic in human medicine.

In Hong Kong, there are three registered pharmaceutical products containing colistin. They are prescription only medicines and are indicated in the treatment of severe Gram-negative infections in animals only. There is also one registered pharmaceutical product containing tigecycline. It is a prescription only medicine and is indicated for complicated skin and skin structure infections, complicated intra-abdominal infections and community-acquired bacterial pneumonia in human adults. In view of the EMA's advice, a letter to veterinarians was issued on 31 July 2013, and the matter will be discussed in the meeting of the Registration Committee.

Batch recall of Thymoglobuline for IV Injection 25mg/5ml (HK-33039)

On 2 July 2013, DH endorsed a licensed drug wholesaler, Sanofi-Aventis HK Ltd. (Sanofi) to recall from shelves one batch (imported as two sub-batches namely C1270H03 and C1270H18) of Thymoglobuline for IV Injection 25mg/5ml, because of a stability issue detected during routine testing. Thymoglobuline is an immune globulin indicated for the prophylaxis and treatment of graft rejection in transplantation. It is a prescription only medicine and should only be used under medical advice.

DH received notification from Sanofi of a global recall of one batch (No. C1270) of Thymoglobuline for IV Injection 25mg/5ml because the product's manufacturer in France, Genzyme Polyclonals SAS, found that it fell out of specification in aggregation level during ongoing stability study. Although the elevated aggregation level may theoretically lead to an increased risk of immune reactions such as anaphylaxis and serum sickness, such risk is considered low.

According to Sanofi, a total of 365 vials of the affected batch of products were imported into Hong Kong as two sub-batches (No. C1270H03 and No. C1270H18). One hundred and twenty-six vials were supplied to the Hospital Authority (HA) and 50 vials of one sub-batch (No. C1270H03) were exported to Macau. All the remaining stock is kept in the wholesaler's warehouse. DH had closely monitored the recall. As of 2 July 2013, DH had not received any adverse drug reaction reports in connection with the product. A press statement was released on the same day to alert the public of the recall.

Total recall of Triloxane-V Suspension (HK-60248)

On 10 July 2013, DH instructed a licensed drug manufacturer, Vickmans Laboratories Ltd. (Vickmans), to recall from shelves all batches of Triloxane-V Suspension due to a quality issue. Triloxane-V Suspension is an over-the-counter pharmaceutical product used for the relief of heartburn and indigestion.

Under the DH's market surveillance, samples of two batches of Triloxane-V Suspension were taken for analysis. Laboratory test on both samples revealed that the content of one of the active ingredients, simethicone, was found to be lower than the labelled claim. The quality defect may affect the efficacy of the product. As a precautionary measure, DH instructed Vickmans to recall all batches of the product.

The information revealed that Vickmans had manufactured 25 batches of the above product since mid-2011. The product has been supplied mainly to private hospitals, private doctors and pharmacies in Hong Kong. DH had closely monitored the recall. As on 10 July 2013, DH had not received any adverse drug reaction reports in connection with the product. A press statement was released on the same day to alert the public of the recall.

Members of the public who are taking the above product should consult their healthcare providers if in doubt or when symptoms persist.

Selling any drug not of the nature, substance or quality demanded by the purchaser is an offence under Section 52(1) of the Public Health and Municipal Services Ordinance (Cap 132). The maximum penalty is a $10,000 fine and three months' imprisonment.

Total recall of three pharmaceutical products: Sertraline Tablet 50mg (HK-59873), Totamol Tablet 50mg (HK-44512) and 100mg (HK-44513)

On 12 July 2013, DH instructed two licensed drug wholesalers, namely Swedish Trading Co. Ltd. (Swedish Trading) and Luen Cheong Hong Ltd. (LCH), to conduct a recall from shelves all batches of Sertraline Tablet 50mg, and all batches of Totamol Tablet 50mg and 100mg respectively, as these products have not been manufactured in line with Good Manufacturing Practice (GMP) requirements. Sertraline Tablet 50mg is used for the treatment of depression while Totamol Tablets, containing atenolol, are used for the treatment of hypertension. They are both prescription only medicines and can only be supplied at pharmacies under the supervision of a registered pharmacist upon doctors' prescription.

Through DH's drug surveillance system, it is noted that the United Kingdom's drug regulatory

Drug Recall

authority, Medicines and Healthcare Products Regulatory Agency (MHRA), had initiated a precautionary recall of various medicines manufactured by Wockhardt Ltd. (Wockhardt). The recall was due to the identification of manufacturing deficiencies by the MHRA at the manufacturing site in India. According to MHRA, although the affected medicines have not been manufactured in line with GMP requirements, there is no evidence of a risk to patient safety from the products.

In Hong Kong, three pharmaceutical products manufactured by Wockhardt are being marketed in Hong Kong.

According to the wholesalers, Sertraline Tablet 50mg have been supplied to private doctors and local pharmacies while Totamol Tablet 50mg and 100mg have been supplied to public and private hospitals, DH's clinics, private doctors, local pharmacies, and also exported to Macao. DH had closely monitored the recall. As on 12 July 2013, DH had not received any adverse drug reaction reports in connection with the products. A press statement was released on the same day to alert the public of the recall.

Healthcare professionals and pharmacies are advised to stop supplying the products to patients. However, members of the public who are taking the products should not stop taking their medicines as there is no evidence of a risk to patient safety from the products. If in doubt or feeling unwell, they should seek advice from their healthcare providers.

Total recall of Red Forrest Cal-600 Calcium with D Tablet (HK-58212)

On 19 July 2013, DH instructed a licensed drug wholesaler, Welfore Co. Ltd. (Welfore), to recall from shelves a pharmaceutical product, namely Red Forrest Cal-600 Calcium with D Tablet, as the product was sold in an unapproved sales pack and label, rendering the product unregistered. Red Forrest Cal-600 Calcium with D Tablet is a vitamin supplement product.

DH had closely monitored the recall. As on 19 July 2013, DH had not received any adverse drug reaction reports in connection with the product. A press statement was released on the same day to alert the public of the recall.

Drug Incident

Woman arrested for suspected illegal sale of slimming products with banned drug ingredient on the Internet

On 11 July 2013, a joint operation was conducted by DH and the Police resulting in the arrest of a 63-year-old woman for suspected illegal sale and possession of Part I poisons and unregistered pharmaceutical products. The products concerned were suspected to contain banned drug ingredient and other Western medicines.

Upon the DH's investigation of a public complaint, samples of products claiming to be for slimming purposes were purchased via the Internet for analysis. Test results showed that four products contained Western medicines. One of them contained sibutramine and hydrochlorothiazide, while the remaining three contained fluoxetine, chlorpheniramine and bisacodyl respectively. The seller alleged that the slimming products were obtained from Thailand.

Sibutramine is a Part I poison and was once used as an appetite suppressant. Since November 2010, products containing sibutramine have been banned because of an increased cardiovascular risk. Hydrochlorothiazide is a diuretic used for the treatment of hypertension and it may cause hypotension and electrolyte imbalance. Fluoxetine is used for depression and may cause diahorrea and insomnia. Hydrochlorothiazide and fluoxetine are Part I poisons which should only be supplied at pharmacies under the supervision of a registered pharmacist upon a doctor's prescription. Chlorpheniramine is an antihistamine sold over-the-counter which may cause drowsiness. Bisacodyl is a laxative sold over-the-counter that may cause abdominal pain.

Weight control should be achieved through a balanced diet and appropriate exercise. The public should consult healthcare professionals before using any medication for weight control.

Drug Incident

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part I poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part I poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 3904 1224

E-mail: pharmgeneral@dh.gov.hk

Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920

Fax: 2186 9845

E-mail: adr@dh.gov.hk

Link: http://www.drugoffice.gov.hk/adr.html

Post: ***Pharmacovigilance Unit,***
Drug Office, Department of Health,
Rm 1856, 18/F, Wu Chung House,
213 Queen's Road East,
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The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.