Drug News
藥 物 情 報

Issue Number 40

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in February 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

Singapore: Safety update on proton pump inhibitors

Health Sciences Authority (HSA) of Singapore announced that a review of important safety information related to the class of proton pump inhibitors (PPIs) had been completed recently, and the local package inserts would be strengthened to include new safety updates. These updates include: 1) an increased risk of Clostridium difficile-associated diarrhoea (CDAD) may be associated with the use of PPIs; 2) a modest increase in risk for osteoporosis-related fractures, especially if PPIs were used in high doses and over long duration; and 3) a potential interaction between PPIs and methotrexate, leading to elevation and prolonged serum levels of methotrexate and/or its metabolites that result in methotrexate toxicities. Healthcare professionals were advised to take into consideration the above safety issues when prescribing PPIs to their patients.

In Hong Kong, there are 157 registered products that contain proton pump inhibitors, which include esomeprazole, lansoprazole, dexlansoprazole, omeprazole, pantoprazole and rabeprazole. All these products are prescription medicines except the products containing omeprazole which is pharmacy only medicine. They are used as antacids, antireflux and antiulcerants with indications including gastroesophageal reflux, gastric ulcers, duodenal ulcers, prevention of nonsteroidal anti-inflammatory agent-induced ulcers, pathologic gastrointestinal hypersecretory conditions and Crohn's disease-associated ulcers. For products containing methotrexate, 14 are registered and they are all prescription medicines indicated for the treatment of malignant tumours and autoimmune diseases. The news had been reported in Drug News Issues No. 28 and 36. Letters to healthcare professionals regarding the risks of fractures, CDAD and the interaction between PPIs and methotrexate were issued on 26 May 2010, 9 February 2012 and 22 October 2012 respectively. These issues had been discussed in meetings 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 and the Registration Committee decided that the sales pack label and/or package insert of products containing PPIs should include the appropriate safety information. Regarding the drug interaction between PPIs and methotrexate, the Registration Committee decided that the sales pack or package insert of products containing PPIs and methotrexate should be updated to include the information such as an example given as below:

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant use of PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with PPIs have been conducted. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Safety Update

The Mainland: Injectable iopromide may be assoicated with serious adverse drug reactions

On 6 February 2013, the State Food and Drug Administration (SFDA) of the Mainland alerted on the risk of serious adverse drug reactions associated with injectable iopromide. In the year of 2012, the National Centre for Adverse Drugs Reaction (ADR) Monitoring of China received 709 cases of ADRs related to injectable iopromide, among them 157 were severe cases. The main presenting clinical features included anaphylactic shock, laryngeal oedema, hypersensitivity and dyspnoea. Healthcare professionals were reminded that injectable iopromide should be used cautiously in patients with history of hypersensitivity and allergy, and they should ask patients for their history of allergy. The use of injectable iopromide was contraindicated in patients who were allergic to iopromide. Patients should be closely observed during administration, and treatment should be immediately discontinued if there were presented with any allergy symptoms. In addition, the package insert of injectable iopromide should be read carefully, particularly the indications, contraindications and precautions. In order to respond quickly for any serious adverse reactions, health institutions should strengthen the rescue training process and furnished with rescue equipment and medicines.

In Hong Kong, two injectable iopromide products, namely Ultravist 300 Inj 300mgI/ml (HK-43948) and Ultravist 370 Inj 370mgI/ml (HK-43949) are registered by Bayer Healthcare Ltd. They are prescription medicines and are iodinated radiographic contrast medium used in procedures including angiography, arthrography, hysterosalpingography and urography. The product inserts of the products have included the warning on the above risks. The Department of Health (DH) had not received any adverse event report in connection with the use of the products, and will keep vigilant on any safety updates of the drugs and actions taken by overseas regulatory authorities for consideration of any action deemed necessary.

Singapore / Canada: MabThera® / Rituxan® (Rituximab) may be associated with toxic epidermal necrolysis and Stevens-Johnson syndrome

On 8 February 2013, HSA announced that Roche Singapore Pte. Ltd. (Roche) informed healthcare professionals on cases of severe skin reactions such as Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) associated with the use of MabThera® (Rituximab). Rare cases with fatal outcomes had been reported in patients with autoimmune diseases and haematological malignancies following MabThera® infusions. A total of 67 post-marketing cases of TEN and SJS were received by Roche. The package insert for MabThera® in Singapore would be updated to include the safety information on the occurrence of TEN and SJS, with fatal outcomes, following MabThera® administration. Healthcare professionals were advised to discontinue MabThera® treatment in case of the occurrence of severe skin reactions and to carefully assess the decision to re-administer MabThera® based on individual patient's benefit-risk profile.

On 25 February 2013, Hoffmann-La Roche Ltd., in consultation with Health Canada, also announced the new safety information of TEN and SJS with Rituxan® (Rituximab). Health Canada advised healthcare professionals that in case of the occurrence of severe skin reactions, Rituxan® treatment should be discontinued; and the decision to re-administer Rituxan® must be carefully assessed based on individual patient’s benefit–risk profile.

In Hong Kong, MabThera Inj 100mg/10ml (HK-46232), MabThera Inj 500mg/50ml (HK-46231), MabThera Concentrate for Solution for Infusion 100mg/10ml (Germany) (HK-59248) and MabThera Concentrate for Solution for Infusion 500mg/50ml (Germany) (HK-59249) are registered by Roche HK Ltd. They are prescription medicines indicated in adults for non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis. In view of HSA's recommendation, a letter to healthcare professionals was issued on 14

February 2013. DH had not received any adverse event report in connection with the use of the products. In view of the recommendations from HSA and Health Canada, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

US: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy

As reported in Drug News Issue No. 34, the Food and Drug Administration (FDA) of the US reminded healthcare professionals about the risks of death and respiratory depression of using codeine in children, particularly in those who had undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea. These children, who were two to five years old, had evidence of an inherited ability to convert codeine into life-threatening or fatal amounts of morphine in the body. On 20 February 2013, FDA updated the public about labelling changes of codeine-containing products to address the issue. Healthcare professionals should prescribe an alternate analgesic for post-operative pain control in children who were undergoing tonsillectomy and/or adenoidectomy. In the US, a new Boxed Warning would be added to the drug label of codeine-containing products about the risk of codeine in post-operative pain management in children following tonsillectomy and/or adenoidectomy. A Contraindication would be added to restrict codeine from being used in this setting. The Warnings/ Precautions, Paediatric Use, and Patient Counselling Information sections of the drug label would also be updated.

In Hong Kong, there are about 360 registered codeine-containing pharmaceutical products and most of them are in syrup form. Majority are indicated to relieve cough and a few are used as pain reliever. DH had not received any adverse event report in connection with the use of the products. A letter to healthcare professionals was issued on 16 August 2012 regarding this issue. In view of FDA's recommendations, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

US / Canada: FDA suspends paediatric clinical trials of Sensipar (cinacalcet hydrochloride) after report of death

On 26 February 2013, FDA announced that all paediatric clinical trials of Sensipar (cinacalcet hydrochloride) were stopped after the recent death of a 14-year-old patient in a trial. FDA had not concluded whether Sensipar had a role in the patient's death, and was evaluating the information. FDA would communicate their final conclusions and recommendations when the review was completed. Sensipar was approved for use in adults but not in children (less than 18 years of age), and the clinical trials were to determine if the drug was effective and could be used safely in children.

At this time, FDA would like to remind healthcare professionals of the following:

- patients should be monitored for the development of low serum calcium levels (hypocalcemia) since Sensipar lowered calcium levels in the blood;
- the potential signs of low serum calcium levels included muscular problems such as muscle cramping, tetany, convulsions, paresthesias, and myalgias;
- if serum calcium levels decreased below the normal range, appropriate steps should be taken to increase calcium levels, such as by providing supplemental calcium, initiating or increasing the dose of a calcium-based phosphate binder, initiating or increasing the dose of vitamin D sterols, or temporarily withholding treatment with Sensipar; and
- serum calcium levels should be measured within one week after initiation or dose adjustment of Sensipar. Once a maintenance dose had been established, serum calcium should be measured monthly.

Health Canada also announced on 7 March 2013 that Sensipar was not approved for use in patients under 18 years of age. Health Canada was reviewing available safety information and would consider updating the labelling information, as appropriate.

Safety Update

In Hong Kong, cinacalcet is registered under the brand name Regpara. Two Regpara products, namely Regpara Tab 25mg (HK-58066) and Regpara Tab 75mg (HK-58067) are registered by Kyowa Hakko Kirin (HK) Co. Ltd. They are prescription medicines indicated for secondary hyperparathyroidism in adult patients undergoing maintenance dialysis. Relevant safety information relating to hypocalcemia is mentioned in the approved package insert. DH had not received any adverse event report in connection with the use of the products, and will keep vigilant on any safety updates of the drugs and actions taken by overseas regulatory authorities for consideration of any action deemed necessary.

Singapore: Vertical transmission of hepatitis B despite immunoprophylaxis

HSA updated healthcare professionals on several cases of vertical transmission of hepatitis B (HB) despite immunoprophylaxis with both HB immunoglobulin (HBIG) and HB vaccine. The infants were born to HB carrier mothers and had received a single dose of HBIG at birth and completed a three-dose regimen of HB vaccine. The root cause of vertical transmission of HB could not be ascertained in view of incomplete data and multi-factorial nature of immunoprophylaxis failure. Based on these reports, the rates of immunoprophylaxis failure from 2009 to 2011 were estimated to be within the expected incidences reported in literature. Healthcare professionals were encouraged to report all cases of HB infection despite immunoprophylaxis to HSA for on-going monitoring of this issue.

In Hong Kong, there are 2 and 13 pharmaceutical products containing hepatitis B immunoglobulin and hepatitis B antigen respectively. All are prescription medicines and are indicated for the immunisation against infection caused by all known subtypes of hepatitis B virus. DH had not received any adverse event report in connection with the use of the products, and will keep vigilant on any updates of the drugs and actions taken by overseas regulatory authorities for consideration of any action deemed necessary.

Drug Recall

Batch recall of Fensinemix cough syrup (HK-38911)

On 18 February 2103, DH instructed a licensed drug manufacturer, Loyal Advance Ltd. (Loyal Advance), to recall from shelves one batch (AAC18B) of Fensinemix cough syrup, due to a labelling error.

Following an investigation to a public enquiry, DH found that some bottles, but not the outer boxes, of the batch (AAC18B) of Fensinemix cough syrup were wrongly labelled as Ammocol cough syrup (HK-43200). This error only appeared on some bottle labels.

Fensinemix cough syrup is an over-the-counter medicine containing chlorpheniramine, noscapine and guaiphenesin indicated for the relief of cough. On the other hand, Ammocol cough syrup contains codeine and ephedrine that can only be sold at a pharmacy under the supervision of a registered pharmacist.

According to Loyal Advance, about 400 bottles of the affected batch of Fensinemix cough syrup had been supplied to local pharmacies and medicine stores since October 2012. DH had alerted the relevant parties about the matter and closely monitored the recall. So far, DH had not received any adverse 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 should consult healthcare providers if in doubt or feeling unwell.

Wrong labeling 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.

Safety Recall

Batch recall of Simvastatin-Teva 10mg Tablets (HK-51049)

On 22 February 2013, DH instructed a licensed medicine wholesaler, The International Medical Co. Ltd. (International Medical), to recall from consumers three batches (batch numbers: 3560612, 3590612 and 3610612) of Simvastatin-Teva 10mg tablets 「善脂健」, due to a packaging error. Simvastatin-Teva tablets, containing simvastatin, is a prescription medicine indicated for hypercholesterolaemia.

International Medical informed DH that it had received a complaint from its client that a box (30 tablets per box) of Simvastatin-Teva 10mg tablets (batch number 3560612) was found to contain Simvastatin-Teva 20mg tablets. After preliminary investigation, the product's manufacturer, Teva Pharmaceutical Works Private Ltd. Co. in Hungary, suspected the printing error might be caused by a mix-up of at least one cardboard box of Simvastatin -Teva 10mg tablets into one lot of cardboard boxes of Simvastatin-Teva 20mg tablets supplied by the printing company. The problematic lot of 20mg cardboard boxes was later used to pack several batches of Simvastatin-Teva 20mg tablets. The packaging error thus might also involve two other batches, i.e. 3590612 and 3610612. As a precautionary measure, all Simvastatin-Teva 10mg tablets bearing any of the above three batch numbers were recalled. So far, only one box of Simvastatin-Teva 10mg tablets was found to have such packaging error.

According to International Medical, the affected batches were imported into Hong Kong in December 2012, and were mainly supplied to hospitals of the Hospital Authority (HA), DH clinics, private doctors and pharmacies. DH had alerted the relevant parties about the matter and closely monitored the recall. So far, DH had not received any adverse 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 using Simvastatin-Teva tablets should take extra caution and check if the strip pack label of the tablets matches the box label and the prescriber's dispensing label. Simvastatin-Teva 20mg tablets are tan in colour with the figure '20' debossed on one side while the 10mg tablets are peach in colour with the figure '10' debossed on one side. Members of the public should consult healthcare providers if in doubt or feeling unwell.

Drug Incident

Public urged not to buy or consume slimming product of unknown composition

On 1 February 2013, DH appealed to members of the public not to buy or consume a slimming product called Brazilian Slimming Coffee 「巴西減肥咖啡」 as it was found to contain an undeclared and banned drug ingredient that is dangerous to health.

DH was notified by HA about a 33-year-old female patient who was hospitalized for having headache, insomnia and psychiatric symptoms of persecutory delusion and auditory hallucination. It was found that she had a history of consuming the above slimming product. The laboratory test on the product sample submitted by the patient showed the presence of sibutramine, which is a banned medicine. The patient purchased the product from a grocery shop in Tsuen Wan.

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.

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

Pharmacies raided for illegal sale of antibiotics and prescription medicine

In February 2013, three joint operations were conducted by DH and the Police against registered pharmacies resulting in the arrests of various persons. Press statements related to the cases were issued on the days of the operations. The details of these cases were summarized as follows:

Drug Incident

Case No.	Products concerned	Drug ingredients	Indications / Side effects	Arrested persons
1.	Cephalexin Capsules 250mg	Cephalexin (an antibiotic)	* Indicated for the treatment of infections including the respiratory and genito-urinary tracts, bones, and skin. * Side effects include gastrointestinal (GI) disturbances and hypersensitivity reactions, including skin rashes, urticaria, eosinophilia, and fever .	30-year-old salesman
2.	Product containing dexamethasone and indomethacin	Dexamethasone and indomethacin (prescription medicines)	* Dexamethasone is commonly used for the treatment of inflammatory diseases. * Side effects of dexamethasone include GI discomfort, osteoporosis and Cushing's syndrome. * Indomethacin is commonly used for the treatment of mild to moderate pain. * Side effects of indomethacin include GI discomfort and headache.	48-year-old salesman
3.	Product containing clarithromycin	Clarithromycin (an antibiotic)	* Indicated for the treatment of respiratory-tract infections and in skin and soft-tissue infections. * Side effects include GI disturbances, stomatitis, glossitis, tongue and tooth discoloration, and headache.	37-year-old salesman

Prescription medicines and antibiotics should only be used under the advice of a doctor. The products can only be sold at pharmacies upon a doctor's prescription, by a registered pharmacist or under his or her supervision.

Members of the public should only take antibiotics prescribed by a doctor and follow the health professionals' instructions. Inappropriate and irrational use of antibiotics would result in the emergence and spreading of resistant microorganisms in the community.

Retail shops raided for selling unregistered pharmaceutical products with controlled drug ingredients

In February 2013, two joint operations were conducted by DH and the Police against two retail shops, which were raided for selling unregistered pharmaceutical products with undeclared controlled drug ingredients. Press statements related to the cases were issued on the days of the operations. The details of these cases were summarized as follows:

Case No.	Products concerned	Drug ingredients	Indications / Side effects	Locations
1.	a. Maxman-II b. Jolex c. Shenghe Zunbao d. Procomil Spray	a. Sildenafil and tadalafil b. Tadalafil c. Sildenafil d. Lidocaine (all Part I poisons)	* Sildenafil and tadalafil are for the treatment of erectile dysfunction. * Side effects of sildenafil and tadalafil are similar, including low blood pressure, headache, vomiting, dizziness and transient vision disturbances. They may interact with some drugs (such as nitroglycerin for treatment of angina) and cause a decrease in blood pressure to dangerous levels. * Lidocaine is a local anaesthetic for the relief of pain or to desensitise skin before minor operations. * Common side effects of lidocaine include hypersensitive reactions.	Tsuen Wan
2.	GlucoTranz Patch 「化糖貼」	Ephedrine and pseudoephedrine (Part I poisons)	* Commonly used for treatment of cold and blocked nose. * Side effects include hypertension and tachycardia, especially in patients with cardiovascular problems.	Causeway Bay

Drug Incident

Improper use of sildenafil and tadalafil may pose serious health risks, especially for patients with heart problems.

People who have a high blood sugar level or diabetes mellitus should refrain from self-medication and consult their healthcare providers for proper treatment. Diabetic patients who are on medication should not stop using or adjust their medications without consulting their medical practitioners.

Possession or sale of unregistered pharmaceutical products and possession or sale of Part I poisons 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. Illegal sale of antibiotics is an offence under the Antibiotics Ordinance (Cap 137) and the maximum penalty is a $30,000 fine and one year's imprisonment.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. 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

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Adverse Drug Reaction (ADR) Reporting:

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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.